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ORIGINAL ARTICLE

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The impact of a physical exercise program on quality of life, fatigue, physical performance, and level of physical activity in patients with cancer

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Brazilian Society of Physical Medicine and Rehabilitation

SUMMARY

OBJECTIVE: Increasing evidence suggests that exercise programs are of great value in the rehabilitation and survivorship of patients with cancer. However, challenges remain regarding maintaining patients more physically active. This study aimed to evaluate the impact of a supervised exercise program on quality of life, fatigue, physical performance, and levels of physical activity of patients with cancer.

METHODS: An observational longitudinal study, with a 1-year prospective follow-up, was developed.

SETTING: This is a university-based outpatient rehabilitation program in a high-complexity cancer care center in Sao Paulo.

RESULTS: After the program, patients showed a significant gain in quality of life ($p<0.0001$), physical performance ($p<0.0001$), and improvement in fatigue ($p<0.0001$). After 12 months, 81.1% of the patients remained active, and only 4.5% declared themselves to be sedentary.

CONCLUSION: The results of this study confirm that exercise programs are an important tool in the rehabilitation of patients with cancer and that an initial supervised exercise program, in combination with follow-ups, can help increase the levels of physical activity of this population.

CLINICAL REHABILITATION IMPACT: This study provides additional information on the outcomes that are expected with the provision of a supervised physical exercise program in the rehabilitation care of patients with cancer and that additional follow-ups could further benefit this population.

KEYWORDS: Neoplasms. Rehabilitation. Physical activity. Fatigue. Quality of life.

INTRODUCTION

Cancer rehabilitation should be integrated throughout the oncology care continuum to maintain or restore function, reduce symptom burden, maximize independence, and improve quality of life in this medically complex population. In many countries around the world, cancer is one of the most frequent causes of morbidity and mortality. According to the World Health Organization, cancer is the second leading cause of death in the world and was responsible for 9.96 million deaths in 2020. The estimated number of new cases (incidence) of different types of cancers, worldwide, is around 10 million a year[1].

Similar to the incidence of cancer worldwide, the population of cancer survivors continues to grow. Improvements in care are responsible for longer life expectancy and better survival. However, the disease itself and its treatment can have both physical and psychological negative effects, including muscle atrophy, altered body weight, pain, depression, fatigue, an overall reduction in quality of life, bone loss, and functional decline[2]. For this reason, physical activity has been increasingly recognized as an important tool for the recovery and rehabilitation of individuals with cancer[2-6]. There is abundant evidence on the benefits of rehabilitation interventions and physical exercise for patients with cancer, with significant impact on functionality, mobility, physical capacity, mood, self-image, and management of lymphedema[2-7].

For physical activity to function as a determinant of health promotion and the prevention and reduction of risks associated with diseases in patients with cancer, it must be performed regularly and consistently[8]. The last Physical Activity Guidelines for Americans and many guidelines published earlier recommend at least 150 min per week of aerobic activity of moderate intensity or 75 min of vigorous activity for good health, which

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was also recommended in the last World Health Organization guidelines on physical activity and sedentary behavior[9,10].

Exercise, particularly supervised exercise, effectively improves quality of life and physical function in patients with cancer across different demographic and clinical characteristics during and following treatment[4]. However, cancer survivors tend to decrease their level of physical activity following diagnosis, and most never return to their pre-diagnosis levels after treatment[11].

Thus, measures of physical activity are important because they can provide indicators to assess the health situation of patients with cancer, enabling the planning of interventions that can both promote physical activity and reduce exposure to other risk factors for sedentary behaviors. The objective of this study was to evaluate the impact of a physical exercise program on the quality of life, physical performance, and fatigue levels of patients with cancer and to verify the continuity of their post-discharge levels of physical activity.

METHODS

A prospective observational longitudinal study was developed, involving cancer outpatients of a university-based high-complexity cancer care center in Sao Paulo. A total of 600 adult patients with cancer who participated in an outpatient physical rehabilitation program at the Cancer Institute of the State of São Paulo were recruited for this study. After completing the 3-month exercise program and education, the patients were referred to three post-discharge meetings: 521 patients attended the first meeting (3 months after discharge), 350 patients attended the second meeting (6 months after discharge), and 310 patients attended the third meeting (12 months after discharge). The total data available for analysis involved 287 patients (Figure 1). All the procedures of this study were approved by the Research Ethics Committee of the University of Sao Paulo School of Medicine (approval no: 1.306.807).

Inclusion criteria: the study included patients with cancer who participated in an outpatient physical rehabilitation program and who completed the physical exercise program consisting of 1-h sessions, twice per week, for 3 consecutive months. Exclusion criteria: patients who did not complete the physical fitness program or had an adherence of less than 80% were excluded.

The structured supervised exercise program in this study involved two 1-h sessions per week, for 3 months, and consisted of aerobic, resistance, and flexibility exercises. Patients received specialized medical evaluation by a physiatrist and were referred to a supervised exercise program taking into consideration their clinical and functional conditions and rehabilitation needs. The aerobic exercises were performed on a treadmill, stationary bike, and/or step machine for up to 25 min. Resistance exercises included exercises for major muscle groups (chest, back, arms, and legs), which varied according to the patient's limitations and condition, with a maximum of five muscle groups being exercised per session using weights, dumbbells, and pulleys for up to 25 min. Weekly progression was considered, according to performance and tolerance. The flexibility exercises were performed at the end of each session for up to 10 min, and each position was maintained for 30 s and repeated three times. During all exercises, the patients were monitored for heart rate, blood pressure, scale of perceived exertion (Borg), and oxygen saturation. Patients also received education on the importance of a regular amount of 150 min of moderate to vigorous exercise every week and a booklet with additional information on the benefits of physical exercise and the different types of exercises that should be practiced.

The patients participated in two assessments: one prior to beginning the exercise program and the other at the end of the 3-month program. In both assessments, the patients completed the Revised Piper Fatigue Scale (PFS-R). The PFS-R has 22 items, each rated on a 0–10 numeric scale, and four subscales that assess four dimensions of fatigue: sensory, affective, cognitive-emotional, and behavioral. Both the total score and each subscale score range from 0 to 10, with fatigue scores being categorized as mild (1–3), moderate (4–6), or severe (7–10 points)[12]. Quality of life was assessed using the Short Form-36 Health Survey (SF-36) questionnaire, which is a multidimensional questionnaire consisting of 36 items sorted into eight domains[13]. The 6-min walk test (6MWT) was also performed to evaluate the global and integrated responses of all the systems involved in exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. The self-paced 6MWT assesses the patient's submaximal level of physical capacity[14]. In addition, at 3, 6, and 12 months after discharge from the physical exercise program, the short version of the International Physical Activity Questionnaire (IPAQ) was given to patients. The short version of the IPAQ consists of seven open-ended questions, and the resulting information enables estimating the time spent per week in different dimensions of physical activity (e.g., moderate and vigorous walking and physical exertion) and inactivity (e.g., a sitting position)[15].

The main outcome was the level of physical activity (IPAQ) and the secondary outcomes were fatigue (PFS-R), quality of life (SF-36), and physical capacity (6MWT). Convenience sampling was adopted. Regarding statistical analysis, the normality of the data was tested using the Shapiro-Wilk test, and

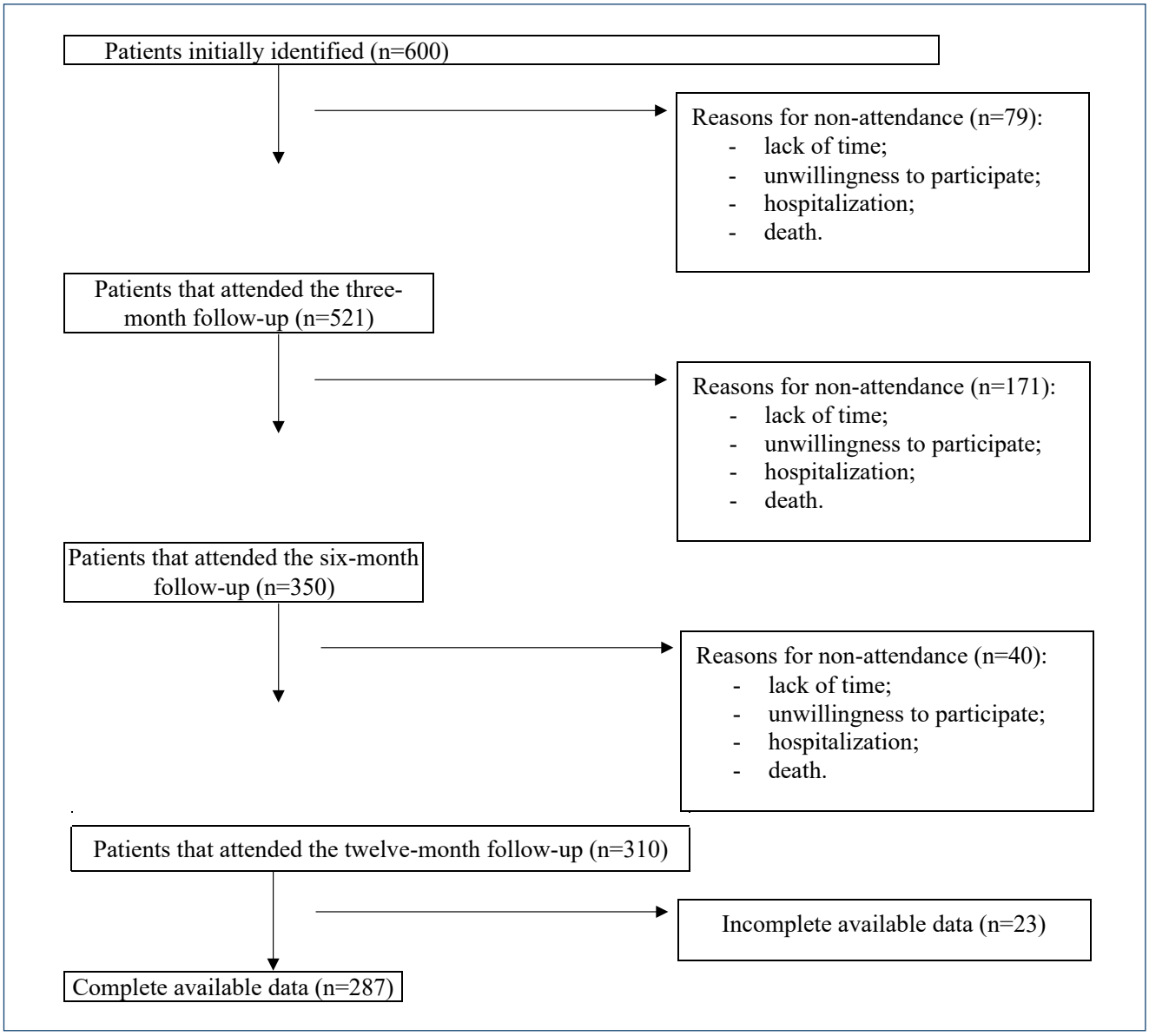

Figure 1. Participants' follow-up attendance throughout the study.

the Wilcoxon test was used to compare assessments before and after treatment. The chi-square test was used to analyze the level of physical activity. The alpha level was set at $p<0.05$.

RESULTS

The mean age of the participants in this study was 58 years, 70% of participants were women, and breast cancer was the most prevalent diagnosis, comprising almost 60% of the cases (Table 1). Patients were either in the active treatment phase or up to 5 years after cancer treatment. After the 3-month program, the patients showed significant differences in their levels of cancer-related fatigue ($p<0.0001$), quality of life ($p<0.0001$), and distance walked in the walking test ($p<0.0001$) (Table 2). We only considered the data of the patients who had at least 80% adherence to the supervised program and of the 287 patients who were successfully followed for 12 months.

There was no significant difference in the IPAQ questionnaires between the third and sixth months ($p=0.8472$), the third and twelfth months ($p=0.9806$), and the sixth and twelfth months ($p=0.8491$). At 3 months post-discharge, 7.6% of participants were very active, 72.8% were active, 14.9% were irregularly active, and 4.5% were sedentary. At 6 months post-discharge, 7.3% were very active, 74.5% were active, 14.9% were irregularly active, and 3.1% were sedentary. At 12 months post-discharge, 6.9% were very active, 74.2% were active, 14.2% were

irregularly active, and 4.5% were sedentary (Table 3). Patients were all sedentary when they started the supervised exercise program. The application of the questionnaires was done by the team of physical educators of the Cancer Institute of the State of Sao Paulo Rehabilitation Center (Figure 2), and the analysis was done by the main researcher.

DISCUSSION

This study evaluated the impact of a physical exercise program on quality of life, physical performance, fatigue, and adherence to a more active lifestyle in patients with cancer. The results showed statistically significant benefits in most of these aspects. Some researchers claim that the effects of a 12-week exercise program may persist for up to 3 months after the intervention, resulting in a substantial improvement in muscle strength and a decrease in abdominal adipose tissue[16]. Another study showed that 3 months in a physical exercise program can improve cardiovascular capacity, fatigue, and depression symptoms in patients with breast cancer. That study also stated that additional benefits are possible if the exercise is maintained for 6 months[17].

The literature suggests that although there are some specific risks for patients with cancer that must be considered, physical exercise is generally safe during and after cancer treatment[4,5]. This study corroborates the authors above, showing improvement in the quality of life, a decrease in the oncologic fatigue levels, and improvement in the physical performance of oncology patients. Comparing the results of the final evaluation with those of the initial evaluation clearly demonstrates the importance of a program of exercise in cancer rehabilitation and shows no adverse effects in this studied group. In a systematic review and meta-analysis of 48 randomized clinical trials (3,632 patients), it was shown that aerobic exercise was associated with an increase in cardiorespiratory fitness suggesting that patients with cancer maintain the ability to adapt to the exercise stimulus and

Table 1. Medical and demographical data.

Patients	n=287	%
Age in years (mean, range, and standard deviation—SD)	58 (21–89; SD 11.7)	
Gender		
Men	86	30
Women	201	70
Diagnosis		
Breast cancer	172	59.9
Head and neck cancer	30	10.5
Hematological cancer	18	6.3
Other tumors	67	23.3

Table 2. Values of the Revised Piper Fatigue Scale, Short Form-36 Health Survey (SF-36) questionnaire, and the 6-min walk test.

Variable	Pre	Post	p-value
Fatigue Scale	4.6 ±2.2	1.8±2.1	0.0001
SF-36	464±157	573±144	0.0001
6-min walk test			
(Distance in meters)	452±95	523±93	0.0001

Data are mean±standard deviation. Statistically significant p<0.05.

Figure 2. Therapeutic gymnasium of the Cancer Institute of the State of Sao Paulo Rehabilitation Center.

Table 3. Classification of the level of physical activity.

Physical activity status	3 months		12 months		x^2	p
	n	%	n	%		
Very active	22	7.6	20	6.9		
Active	209	72.8	213	74.2		
Irregularly active	43	14.9	41	14.2		
Sedentary	13	4.5	13	4.5	0.1808	0.9806

IPAQ: International Physical Activity Questionnaire. Comparing months 3 and 12. Values are expressed as absolute numbers and percentages. X^2 chi-square test. Statistically significant p<0.05.

that exercise can be effectively combined with other cancer therapies[18]. Similarly, a meta-analysis of 11 randomized controlled trials of resistance training showed that cancer survivors retain the ability to gain muscle strength, increase their lean body mass, and lose body fat in response to this type of exercise while undergoing treatment or long-term follow-up for breast, prostate, or head and neck cancer. It is of clinical relevance to note that no deleterious effects of the exercise program were noted[19].

Most of the studies in exercise oncology involve patients in the post-adjuvant therapy setting, and the vast majority of studies were conducted in women with breast cancer. The majority of patients in our study also presented breast cancer. In our service, patients with breast cancer are the main group that is referred. The novel aspect of our study was to show the impact of additional follow-ups by specialized physical educators on patients' behaviors in regard to their level of physical activity. Literature states that the adoption of regular practice of physical exercise after initial supervised programs remains a great challenge[6,11,20].

In relation to IPAQ data, we must consider that it is a questionnaire that measures different dimensions of physical activity, not just physical exercise. However, for some authors, the limitations of IPAQ include its size, low follow-up adherence, and difficulties completing the questionnaire. These difficulties may be of even greater magnitude for patients with cancer suffering from treatment-related illnesses and side effects, such as fatigue, loss of interest, and cognitive difficulties. In fact, we observed low adherence in response to IPAQ during the 12-month follow-up period, with 87% responding to the IPAQ after 3 months of discharge, 58% responding to IPAQ 6 months after discharge, and only 51% responding to the IPAQ 12 months post-discharge. This might have influenced the results, overestimating the positive effect of the initial supervised program, as the patients exhibiting greater adherence to the follow-up program were probably those more likely to follow orientations and be active. This study showed that after 3, 6, and 12 months post-discharge, a little more than 80% of the patients remained active, and less than 5% declared themselves to be sedentary. Another limitation of our study is that, ideally, physical activity levels should be obtained with more objective measurement systems, such as accelerometers and pedometers, which were not available in this study. Moreover, we opted to consider solely the data regarding the 287 that were successfully followed for 12 months and that had good adherence to the supervised program, which resulted in a selection bias. On the contrary, it also points to the possibility that those with better adherence to the supervised program might probably present higher chances of increasing their physical activity levels in the long run.

In general, our study indicates that a supervised exercise program can encourage the continuity of post-discharge levels of physical activity in patients with cancer, but additional studies are necessary. A recent study with 392 cancer outpatients evidenced that although the great majority of patients (93%) were insufficiently active, 80% declared an interest in exercise programs[21]. In our study, most of the patients declared themselves to be sedentary when starting the rehabilitation program, but our meetings showed that less than 5% of our patients declared themselves to be sedentary during the follow-up period. It is estimated that one-third of adults in the world population do not meet the minimum recommendations for physical activity[22]. Moreover, it is estimated that between only 17 and 58% of cancer survivors adhere to physical activity guidelines[23,24].

CONCLUSION

The findings of this study suggest that exercise programs are an important tool in the rehabilitation of patients with cancer and that an initial supervised exercise program, in combination with follow-ups, might contribute to increasing the level of physical activity of some individuals. This study provides additional information on the outcomes that are expected with the provision of a supervised physical exercise program in the rehabilitation care of patients with cancer and that additional follow-ups could further benefit this population.

AUTHORS' CONTRIBUTIONS

FR: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. **ACCP:** Data curation, Formal Analysis, Investigation, Project administration, Software, Visualization, Writing – original draft. **RBC**: Formal Analysis, Project administration, Supervision, Validation, Visualization, Writing – original draft. **CMMB:** Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **EPMA:** Formal Analysis, Project administration, Supervision, Validation, Visualization, Writing – original draft.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
2. Cheville AL, Mustian K, Winters-Stone K, Zucker DS, Gamble GL, Alfano CM. Cancer rehabilitation: an overview of current need, delivery models, and levels of care. Phys Med Rehabil Clin N Am. 2017;28(1):1-17. https://doi.org/10.1016/j.pmr.2016.08.001
3. Santa Mina D, Rooijen SJ, Minnella EM, Alibhai SMH, Brahmbhatt P, Dalton SO, et al. Multiphasic prehabilitation across the cancer continuum: a narrative review and conceptual framework. Front Oncol. 2021;10:598425. https://doi.org/10.3389/fonc.2020.598425
4. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: an individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev. 2017;52:91-104. https://doi.org/10.1016/j.ctrv.2016.11.010
5. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc. 2019;51(11):2375-90. https://doi.org/10.1249/MSS.0000000000002116
6. Schmitz KH, Campbell AM, Stuiver MM, Pinto BM, Schwartz AL, Morris GS, et al. Exercise is medicine in oncology: engaging clinicians to help patients move through cancer. CA Cancer J Clin. 2019;69(6):468-84. https://doi.org/10.3322/caac.21579
7. Leclerc AF, Foidart-Dessalle M, Tomasella M, Coucke P, Devos M, Bruyère O, et al. Multidisciplinary rehabilitation program after breast cancer: benefits on physical function, anthropometry and quality of life. Eur J Phys Rehabil Med. 2017;53(5):633-42. https://doi.org/10.23736/S1973-9087.17.04551-8
8. Rogers LQ, McAuley E, Anton PM, Courneya KS, Vicari S, Hopkins-Price P, et al. Better exercise adherence after treatment for cancer (BEAT cancer) study: rationale, design, and methods. Contemp Clin Trials. 2012;33(1):124-37. https://doi.org/10.1016/j.cct.2011.09.004
9. U.S. Department of Health and Human Services. Physical activity guidelines for Americans. 2nd ed. Washington (DC): U.S. Department of Health and Human Services; 2018. Available from: https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf
10. World Health Organization. WHO guidelines on physical activity and sedentary behavior. 2020. Available from: https://www.who.int/publications/i/item/9789240015128
11. Elshahat S, Treanor C, Donnelly M. Factors influencing physical activity participation among people living with or beyond cancer: a systematic scoping review. Int J Behav Nutr Phys Act. 2021;18(1):50. https://doi.org/10.1186/s12966-021-01116-9
12. Mota DD, Pimenta CA, Piper BF. Fatigue in Brazilian cancer patients, caregivers, and nursing students: a psychometric validation study of the piper fatigue scale-revised. Support Care Cancer. 2009;17(6):645-52. https://doi.org/10.1007/s00520-008-0518-x
13. Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36). Rev Bras Reumatol. 1999;39(3):143-50.
14. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7. https://doi.org/10.1164/ajrccm.166.1.at1102
15. Hallal PC, Victora CG. Reliability and validity of the international physical activity questionnaire (IPAQ). Med Sci Sports Exerc. 2004;36(3):556. https://doi.org/10.1249/01.mss.0000117161.66394.07
16. Rogers LQ, Hopkins-Price P, Vicari S, Markwell S, Pamenter R, Courneya KS, et al. Physical activity and health outcomes three months after completing a physical activity behavior change intervention: persistent and delayed effects. Cancer Epidemiol Biomarkers Prev. 2009;18(5):1410-8. https://doi.org/10.1158/1055-9965.EPI-08-1045
17. Sprod LK, Hsieh CC, Hayward R, Schneider CM. Three versus six months of exercise training in breast cancer survivors. Breast Cancer Res Treat. 2010;121(2):413-9. https://doi.org/10.1007/s10549-010-0913-0
18. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, et al. Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. J Clin Oncol. 2018;36(22):2297-305. https://doi.org/10.1200/JCO.2017.77.5809
19. Strasser B, Steindorf K, Wiskemann J, Ulrich CM. Impact of resistance training in cancer survivors: a meta-analysis. Med Sci Sports Exerc. 2013;45(11):2080-90. https://doi.org/10.1249/MSS.0b013e31829a3b63
20. Hudis CA, Jones L. Promoting exercise after a cancer diagnosis: easier said than done. Br J Cancer. 2014;110(4):829-30. https://doi.org/10.1038/bjc.2014.12
21. Avancini A, Pala V, Trestini I, Tregnago D, Mariani L, Sieri S, et al. Exercise levels and preferences in cancer patients: a cross-sectional study. Int J Environ Res Public Health. 2020;17(15):5351. https://doi.org/10.3390/ijerph17155351
22. Kohl HW, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, et al. The pandemic of physical inactivity: global action for public health. Lancet. 2012;380(9838):294-305. https://doi.org/10.1016/S0140-6736(12)60898-8
23. Troeschel AN, Leach CR, Shuval K, Stein KD, Patel AV. Physical activity in cancer survivors during "re-entry" following cancer treatment. Prev Chronic Dis. 2018;15:E65. https://doi.org/10.5888/pcd15.170277
24. Coletta AM, Basen-Engquist KM, Schmitz KH. Exercise across the cancer care continuum: why it matters, how to implement it, and motivating patients to move. Am Soc Clin Oncol Educ Book. 2022;42:1-7. https://doi.org/10.1200/EDBK_349635

ORIGINAL ARTICLE

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Biomarkers and prediction of anthracyclic cardiotoxicity in breast cancer

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Brazilian Society of Cardiology

SUMMARY

BACKGROUND: Chemotherapy with doxorubicin may lead to left ventricular dysfunction. There is a controversial recommendation that biomarkers can predict ventricular dysfunction, which is one of the most feared manifestations of anthracycline cardiotoxicity.

OBJECTIVE: The aim of this study was to evaluate the behavior of biomarkers such as Troponin I, type B natriuretic peptide, creatine phosphokinase fraction MB, and myoglobin in predicting cardiotoxicity in a cohort of women with breast cancer undergoing chemotherapy with anthracycline.

METHODS: This is an observational, prospective, longitudinal, unicentric study, which included 40 women with breast cancer, whose therapeutic proposal included treatment with doxorubicin. The protocol had a clinical follow-up of 12 months. Biomarkers such as Troponin I, type B natriuretic peptide, creatine phosphokinase fraction MB, and myoglobin were measured pre-chemotherapy and after the first, third, fourth, and sixth cycles of chemotherapy.

RESULTS: There was a progressive increase in type B natriuretic peptide and myoglobin values in all chemotherapy cycles. Although creatine phosphokinase fraction MB showed a sustained increase, this increase was not statistically significant. Troponin, type B natriuretic peptide, myoglobin, and creatine phosphokinase fraction MB were the cardiotoxicity markers with the earliest changes, with a significant increase after the first chemotherapy session. However, they were not able to predict cardiotoxicity.

CONCLUSION: Troponin I, type B natriuretic peptide, myoglobin, and creatine phosphokinase fraction MB are elevated during chemotherapy with doxorubicin, but they were not able to predict cardiotoxicity according to established clinical and echocardiographic criteria. The incidence of subclinical cardiotoxicity resulting from the administration of doxorubicin was 12.5%.

KEYWORDS: Biomarkers. Cardiotoxicity. Chemotherapy. Anthracyclines. Breast cancer. Heart failure.

INTRODUCTION

One of the most feared clinical presentations of cardiotoxicity resulting from cancer (CA) treatment is left ventricular dysfunction. In recent years, there has been a growing interest in the use of cardiac biomarkers (BMK) to guide the management of CA patients who will receive or are undergoing chemotherapy (CT) treatment against CA.

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of a normal, pathological, biological process or pharmacological response[1]. BMK, in addition to assisting in the diagnosis of cardiotoxicity in the pre-clinical phase, play a key role in guiding treatment strategies, including the initiation of "cardioprotection" during oncological treatment without compromising the therapeutic efficacy of CA[2].

The literature relates cardiotoxicity to the occurrence of cardiomyopathy resulting from CT, radiotherapy (RT), and immunotherapy. In patients treated with anthracyclines (ANT), the measurement of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) calculated by echocardiography have been the most commonly used tools in the assessment of cardiac function, although there is no consensus on whether the percentage decline in contractile function would represent a clinically relevant change that justifies prevention and intervention measures. In the last decade, the measurement of troponin I (TnI), type B natriuretic peptide (BNP), and its precursor, NT-pro-BNP, before and during CT treatment, proved to be a promising alternative in the early detection of cardiotoxicity as it is minimally invasive, easy to perform, without interobserver variability, and less expensive than imaging tests.

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The European Society of Cardiology, in its recent Cardio-Oncology Guideline, recommended the measurement of BMK in the initial assessment of the risk of cardiotoxicity in patients with CA and cardiovascular disease or with previous ventricular dysfunction[3].

This study aimed to evaluate the behavior of BMK such as TnI, BNP, creatine phosphokinase fraction MB (CK-MB), and myoglobin in predicting cardiotoxicity in a cohort of women with breast CA undergoing CT with ANT.

METHODS

This is an observational, prospective, longitudinal, unicentric study, which included 40 women over 18 years old, with breast CA, whose therapeutic proposal included treatment with doxorubicin, from two high-complexity public oncology units, both in the State of Rio de Janeiro, Brazil. Patients with previous CT and/or RT, previous myocardial infarction, chronic obstructive pulmonary disease, chronic renal failure, and metastatic CA were excluded.

Study population

A total of 202 patients were referred and evaluated, with 40 patients included in the final analysis. However, 72 patients were excluded from the study protocol in the initial assessment, of which 49 did not agree to participate. Furthermore, seven had an inadequate "echocardiographic window"; seven due to a low level of understanding of the study protocol; four because the inclusion criteria were not met; three due to ulceration of the left breast tumor, making echocardiographic examination unfeasible; and two due to recent surgery on the left breast, a reason that also makes the acquisition of echocardiographic images difficult. Among the 130 patients included, 90 subsequent exclusions occurred: 51 patients participating in another study underway at the same institution using carvedilol and 39 due to segment losses (Figure 1).

Study protocol

The study protocol had a clinical follow-up of 12 months. BMK such as TnI, BNP, CK-MB, and myoglobin were measured pre-CT and after the first, third, fourth, and sixth cycles of CT in a time interval between 24 h and 48 h after CT. BMK were not measured 12 months after starting CT, and 17 patients had only four sessions. Five patients did not undergo the 12-month evaluation: 3 deaths resulting from CA complications and 2 lost to follow-up (Figure 2).

Biomarkers

To measure BMK, 5 mL of blood was collected from a peripheral vein and immediately added to the test panel on a point-of-care

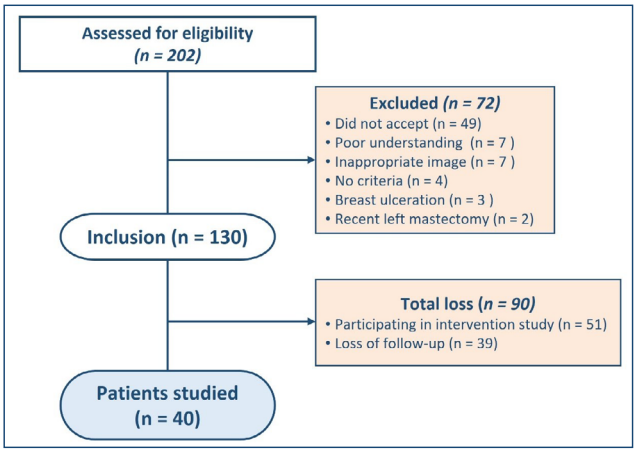

Figure 1. Study population.

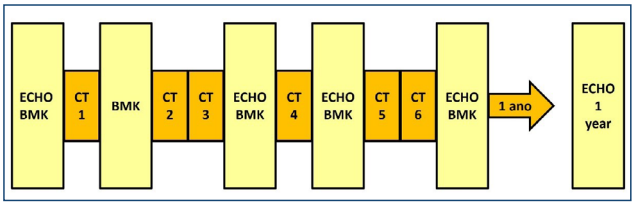

Figure 2. Study protocol. ECHO: echocardiography; BMK: biomarkers; CT: chemotherapy.

platform. The Alere Triage® Cardiac Panel kit was used to measure CK-MB and TnI, and the Alere Triage® BNP Test kit (Alere Inc., San Diego, California, USA) was used for BNP, using immunoassay methodology. The results were expressed in pg/mL for BNP and ng/mL for TnI, CK-MB, and myoglobin measurements.

Ethical aspects

This study was conducted in accordance with the principles set out in the Declaration of Helsinki, revised in 2000. The study protocol was approved and monitored by the Research Ethics Committee, under the authorization of the National Research Committee, registration number 0084.0.258.000-11. All patients signed free, informed consent.

Data analysis

Statistical analysis was performed using the SPSS version 21.0 software (Chicago, Illinois, USA). Continuous variables were expressed as means±standard deviation. Categorical variables were expressed as absolute numbers or percentages. For comparison between groups, the chi-square test was used to evaluate differences between proportions, the analysis of variance (ANOVA) between groups, and the Student's t-test to evaluate differences in means. In all comparisons, two-sided tests were considered with a significance level of 5%.

RESULTS

Demographic and clinical characteristics

Forty women with breast CA studied had a mean age of 55.9±10.8 years, with 42.5% white, 32.5% Afro-descendant, and 25.0% mixed race. The majority (77.5%) had a family income of up to two minimum wages. The patients presented high (77.5%), intermediate (12.5%), and low (10.0%) cardiovascular global risks. Among the cardiovascular risk factors studied, they had a sedentary lifestyle (85.0%), obesity and overweight (80.0%), hypertension (50.0%), dyslipidemia (37.5%), family history of arterial disease and premature coronary disease (37.5%), smoking (30.0%), and diabetes mellitus (20.0%).

The average systolic and diastolic blood pressure values found in the studied population were 143.9±19.3 mmHg and 87.6±13.2 mmHg, respectively. The average body mass index was 32.1±4.3 kg/m^2.

The medications with cardiovascular and metabolic action most frequently used by the study patients were diuretics (32.5%), calcium channel blockers (22.5%), angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) (17.5%), oral hypoglycemic agents (17.5%), and statins (12.5%).

Cancer treatment data

Most patients (57.5%) used the FAC protocol (5-Fluoruracil+doxorubicin+cyclophosphamide), and 42.5% used the doxorubicin+cyclophosphamide+docetaxel protocol. The average dose of doxorubicin per session was 87.0±13.4 mg/m^2, and the average cumulative dose used was 423.0±119.0 mg/m^2. Cumulative doses ³400 mg/m^2 were used in 24 patients (60%).

Biomarker behavior

There was a progressive increase in BNP and myoglobin values in all CT cycles. Although CK-MB showed a sustained increase, this increase was not statistically significant. TnI had an increasing behavior during CT cycles, only reaching statistical significance in the last cycle of doxorubicin administration when compared to pre-CT values. For data analysis purposes, the mean biomarker values in CT4 and CT6 were grouped at the same time as they correspond to the last cycle of doxorubicin (Table 1).

Biomarkers as predictors of cardiotoxicity

Echocardiogram examinations were performed in all patients pre-CT, post-CT3, post-CT4, post-CT6, and 12 months after the start of CT. In the present series, 5 patients (12.5%) developed asymptomatic systolic ventricular dysfunction with a drop in Simpson LVEF≥10% to values lower than 53%, 12 months after CT. GLS was also reduced by ≥10% in 2 patients, and TnI was positive during all CT sessions in only one patient, and none of the patients presented clinical heart failure syndrome.

The serum BMK such as troponin, BNP, myoglobin, and CK-MB were the cardiotoxicity markers with the earliest changes, with a significant increase after the first CT session. However, they were not able to predict cardiotoxicity in the studied population according to current clinical and echocardiographic criteria.

DISCUSSION

There is still less evidence regarding the true predictive power of BMK for cardiotoxicity in different situations in cardio-oncology. Most recommendations are based on expert opinion. The largest clinical trial with BMK evaluated 703 patients treated with high doses of CT, including ANT, and followed them for an average of 20 months. TnI measurement was performed before the start of CT, after each cycle and 1 month after treatment, a methodology similar to that used in our study. This study demonstrated that patients who did not have TnI elevation during treatment and 1 month later had fewer outcomes related to cardiotoxicity (heart failure, asymptomatic LV dysfunction, or any other cardiac event) than those who had transient TnI elevations or who persisted with elevated TnI throughout clinical follow-up (1%, 37%, and 84%, respectively)[4].

Type B natriuretic peptide has been used as a marker of ventricular dysfunction in CA-induced cardiotoxicity, with

Table 1. Comparison of mean biomarker values throughout treatment.

Variables	Pre-CT	Post-CT1	p-value	Post-CT3	p-value	Post-CT4/6	p-value
BNP (pg/mL)	33.7±22.8	52.6±41.2	0.003	68.6±66.7	0.010	72.9±56.6	**<0.0001**
Myoglobin (ng/mL)	47.9±26.9	60.2±22.7	0.017	62.4±28.1	0.007	64.5±24.3	**<0.008**
CK-MB (ng/mL)	0.77±0.59	0.85±0.62	0.511	0.92±0.56	0.083	0.95±0.63	0.067
TnI (ng/mL)	0.01±0.00	0.08±0.28	0.097	0.07±0.23	0.091	0.21±0.51	**0.030**

Statistically significant p-value are denoted in bold. CT: chemotherapy; CT1: first CT; CT3: third CT; CT4/6: fourth and sixth CT; BNP: type B natriuretic peptide; CK-MB: creatine phosphokinase MB fraction; TnI: troponin I.

conflicting results[5]. Data from the Framingham study population demonstrate a progressive increase in the risk of cardiovascular death, heart failure (HF), stroke, and atrial fibrillation with a progressive increase in BNP levels, even within normal values[6]. Our study showed an ascending curve of BNP levels with statistical significance in all CT cycles (p<0.0001), despite not exceeding the cutoff value used to rule out HF in the emergency room, which is 100 pg/m. This behavior was also consistently reflected in the levels of myoglobin (p=0.008) and TnI (p=0.030). CKMB, despite having an ascending curve similar to the other BMK, did not reach statistical significance (p=0.067). These changes did not correlate with clinical cardiovascular outcome or with any echocardiographic parameter evaluating systolic or diastolic function throughout treatment. Only one of the five patients who presented asymptomatic ventricular dysfunction had a progressive increase in TnI throughout the treatment (pre-CT= 0.01 ng/mL; post-CT1=0.6 ng/mL; post-CT3=0.8 ng/mL; post-CT6=1.9 ng/mL).

The mean BNP value in the pre-CT assessment was 33.7±22.8 pg/mL, reaching significantly higher values immediately after the last cycle of doxorubicin (72.9±56.6 pg/mL, p<0.001). These values, despite being lower than 100 pg/mL, should be interpreted, considering current knowledge, as a high value for patients with stage A of HF. In a cross-sectional study that included 633 individuals from a primary healthcare program in the city of Niterói (RJ), Jorge et al.[7] found 230 individuals (36.6%) in stage A of HF with an average BNP value of 19.7±21.2 pg/mL and a cutoff value of 42 pg/mL to exclude HF (negative predictive value of 99%). In our study, a higher mean BNP value may be related to the presence of a high global cardiovascular risk in 77.5% of patients and an intermediate global cardiovascular risk in 12.5% of patients.

BNP has been recommended in the most recent HF guidelines as a tool for detecting individuals predisposed to developing HF. The update of the first Brazilian Cardio-Oncology Guideline recommended the monitoring of BNP and TnI BMK for the purpose of early detection of cardiotoxicity at Class IIa level of evidence B[8].

In our study, the mean BNP value in the pre-CT assessment of 33.7±22.8 pg/mL and its sustained increase during CT already signaled a population at risk for developing HF. Similar to what was observed in our study, Sawaya et al.[9] demonstrated that high levels of NT-pro-BNP were not a predictor of reduced LVEF or the occurrence of symptomatic HF in a group of 81 women with HER2+ breast CA who used ANT followed by therapy adjuvant with taxanes and trastuzumab. Likewise, Fallah-Rad et al.[10] in a prospective study using echocardiography, BMK [TnT, C-reactive protein (CRP), and NT-pro-BNP], and cardiac resonance in 42 patients undergoing adjuvant CT with trastuzumab, found no differences in the dosages of the three BMK studied between patients who developed cardiotoxicity (n=10) compared to those who did not have this complication.

Several other BMKs have been studied to detect cardiotoxicity. Putt et al.[11] in a multicenter cohort study with 78 women with breast CA receiving doxorubicin and trastuzumab, evaluated the behavior of eight BMKs: TnI, NT-pro-BNT, Galectin 3, myeloperoxidase (MPO), factor placental growth factor (PIGF), growth differentiation factor-15 (GDF-15), soluble fms-like tyrosine kinase receptor 1 (sFlt-1), and high-sensitivity polymerase chain reaction (PCR), before the start of CT and every 3 months with a maximum follow-up of 15 months. All BMK, except NT-pro-BNP, increased in the third month after starting CT, persisting until the 15th month for GDF-15, PIGF, and TnI. Elevations of MPO, PlGF, and GDF-15 correlated with the occurrence of cardiotoxicity, with MPO being the biomarker that presented a more robust correlation with the occurrence of cardiotoxicity in all assessments.

Several studies that included patients receiving CT with ANT followed by taxanes and trastuzumab did not demonstrate an association between BMKs CRP, Galectin-3, interleukin-1 receptor (ST-2), and GDF-15 and cardiotoxicity[12].

In this study, the early and sustained rising behavior of BNP was the only parameter studied which was found to be correlated with the progression of the cumulative dose of doxorubicin administered.

CONCLUSION

The cardiac BMK such as TnI, BNP, myoglobin, and CK-MB are elevated during CT with doxorubicin but they were not able to predict cardiotoxicity according to the established clinical and echocardiographic criteria.

The incidence of subclinical cardiotoxicity resulting from the administration of doxorubicin was 12.5%.

AUTHORS' CONTRIBUTIONS

ENS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **MLR:** Conceptualization, Data curation, Investigation, Methodology. **LCC:** Data curation. **AJLJ:** Data curation, Formal Analysis, Methodology. **MLGR:** Data curation, Formal Analysis, Methodology. **ETM:** Conceptualization, Supervision. **HV:** Conceptualization, Supervision. **WAM:** Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol. 2010;28(25):3910-6. https://doi.org/10.1200/JCO.2009.27.3615
2. Ananthan K, Lyon AR. The Role of Biomarkers in Cardio-Oncology. J Cardiovasc Transl Res. 2020;13(3):431-50. https://doi.org/10.1007/s12265-020-10042-3
3. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European hematology association (EHA), the European society for therapeutic radiology and oncology (ESTRO) and the international cardio-oncology society (IC-OS). Eur Heart J. 2022;43(41):4229-361. https://doi.org/10.1093/eurheartj/ehac244
4. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004;109(22):2749-54. https://doi.org/10.1161/01.CIR.0000130926.51766.CC
5. Friedewald VE, Burnett JC, Januzzi JL, Roberts WC, Yancy CW. The editor's roundtable: B-type natriuretic peptide. Am J Cardiol. 2008;101(12):1733-40. https://doi.org/10.1016/j.amjcard.2008.03.017
6. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med. 2004;350(7):655-63. https://doi.org/10.1056/NEJMoa031994
7. Jorge AL, Rosa ML, Martins WA, Correia DM, Fernandes LC, Costa JA, et al. The prevalence of stages of heart failure in primary care: a population-based study. J Card Fail. 2016;22(2):153-7. https://doi.org/10.1016/j.cardfail.2015.10.017
8. Hajjar LA, Costa IBSDSD, Lopes MACQ, Hoff PMG, Diz MDPE, Fonseca SMR, et al. Brazilian Cardio-oncology Guideline - 2020. Arq Bras Cardiol. 2020;115(5):1006-43. https://doi.org/10.36660/abc.20201006
9. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging. 2012;5(5):596-603. https://doi.org/10.1161/CIRCIMAGING.112.973321
10. Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. J Am Coll Cardiol. 2011;57(22):2263-70. https://doi.org/10.1016/j.jacc.2010.11.063
11. Putt M, Hahn VS, Januzzi JL, Sawaya H, Sebag IA, Plana JC, et al. Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. Clin Chem. 2015;61(9):1164-72. https://doi.org/10.1373/clinchem.2015.241232
12. Bloom MW, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L, et al. Cancer therapy-related cardiac dysfunction and heart failure: part 1: definitions, pathophysiology, risk factors, and imaging. Circ Heart Fail. 2016;9(1):e002661. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002661

ORIGINAL ARTICLE

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Quality of emergency oncological surgery: time for advanced oncological life support

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Brazilian Society of Oncologic Surgery; Brazilian College of Surgeons

SUMMARY

In the emergency care of cancer patients, in addition to cancer-related factors, two aspects influence the outcome: (1) where the patient is treated and (2) who will perform the surgery. In Brazil, a significant proportion of patients with surgical oncological emergencies will be operated on in general hospitals by surgeons without training in oncological surgery.

OBJECTIVE: The objective was to discuss quality indicators and propose the creation of an urgent oncological surgery advanced life support course.

METHODS: Review of articles on the topic.

RESULTS: Generally, nonelective resections are associated with higher rates of morbidity and mortality, as well as lower rates of cancer-specific survival. In comparison to elective procedures, the reduced number of harvested lymph nodes and the higher rate of positive margins suggest a compromised degree of radicality in the emergency scenario.

CONCLUSION: Among modifiable factors is the training of the emergency surgeon. Enhancing the practice of oncological surgery in emergency settings constitutes a formidable undertaking that entails collaboration across various medical specialties and warrants endorsement and support from medical societies and educational institutions. It is time to establish a national registry encompassing oncological emergencies, develop quality indicators tailored to the national context, and foster the establishment of specialized training programs aimed at enhancing the proficiency of physicians serving in emergency services catering to cancer patients.

KEYWORDS: Cancer care facility. Healthcare quality assessment. Healthcare quality indicators. Medical emergency services. Surgical oncology. Operative procedures.

INTRODUCTION

Cancer currently stands as the second-leading cause of death worldwide. In parallel with the estimated 50% increase in incidence and 62% rise in mortality by 2040, the care of oncology patients has become increasingly complex[1]. In many countries, due to the lack of large-scale screening programs, a significant portion of patients will receive a cancer diagnosis following an acute event in an emergency setting. In this scenario, apart from the aspects related to the underlying disease, two factors influence the outcome: (1) where the patient is treated and (2) who will perform the surgery. In Brazil, most cancer patients seeking emergency care undergo surgery in general hospitals, with access to specialized hospitals limited to patients with previously confirmed diagnoses. Consequently, surgical oncology emergencies are often managed by nonspecialized surgeons. Adding to this challenge is the difficulty of accessing tertiary and quaternary hospital emergency services, which consequently leads to emergency surgeries being performed predominantly in smaller hospitals, where the on-call surgeon, quite often, is in the early stages of their career.

Certainly, emergencies introduce conditions that impact clinical outcomes and the prognosis of oncology patients; however, it is essential to analyze the potential factors that justify

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the poorer results. Are the technical principles of oncological surgery being adhered to? Do patients exhibit distinct sociodemographic and clinical characteristics? Is there a lack of hospital infrastructure and/or professional expertise to address surgical oncology emergencies? It is intuitive to think that the ideal professional to attend to cancer patients seeking emergency care would be someone with experience in emergency surgery and a deep understanding of the fundamentals and principles of oncological surgery. However, it is foreseeable that the number of surgeons with this profile will be limited to meet demand.

Working to enhance the practice of oncological surgery in emergency conditions is a formidable task that involves various specialties and deserves support and encouragement from medical societies and educational institutions. In this paper, we analyze how to evaluate the quality of oncological surgery in an emergency setting and discuss proposals for improving outcomes.

QUALITY INDICATORS IN ONCOLOGICAL SURGERY

Quality in healthcare is defined as safe, effective, patient-centered, timely, efficient, and equitable medical care. Quality reflects how medical care increases the likelihood of desired outcomes and reduces the likelihood of undesired outcomes[1]. However, measuring the quality of oncological surgery is not an easy task. Some challenges include the lack of a specific definition and the constant change in quality indicators (QIs) due to advances in oncological treatment[2]. QIs are standardized measures used to quantify and track the quality of care. QIs enable the assessment of aspects related to structure (e.g., number of board-certified physicians, nurse-to-bed ratio, hospital size), process (diagnostic, e.g., completeness of staging, adequacy of pathological specimen examination; treatment, e.g., completeness of neoadjuvant therapy, an adequate number of harvested lymph nodes), and outcome (morbidity, mortality, survival, quality of life, preservation of organ function)[3]. Other indicators are based on rates (e.g., anastomotic leak rate) and sentinel events, which are individual undesirable events requiring further investigation.

The collection and analysis of QI that illustrate the degree of compliance with predefined standards define the assessment of quality. Particularly in an emergency setting, the issue is that data is not always of high quality or readily available. Some services use administrative data, including postoperative mortality rate, postoperative hospital transfer rate, and hospital length of stay, but there is a lack of planning for prospective data collection. In practice, there is a need to establish management programs with a predefined QI adjusted to the national context so that issues can be identified and solutions discussed. Among patients seeking emergency services in Brazilian general hospitals, how many are oncology cases? What are the most common conditions? How many cases qualify as surgical emergencies? What are the rates of operative morbidity and mortality? What are the infection rates? How many patients have the minimum number of sampled lymph nodes? What is the percentage of non-oncological resections, and why? Among surgeons working in emergency settings, how many have supplementary training in surgical oncology? What is the volume-outcome relationship? Questions like these serve as QI and need to be part of management strategies so that we can conduct a proper analysis of reality and take appropriate actions.

ACCREDITATION, VOLUME-OUTCOME RELATIONSHIP, AND SPECIALIZATION

Participation in accreditation programs demonstrates a commitment to quality objectives and goals; however, in an emergency setting, adherence to established standards is more vulnerable. In practice, due to demand, many patients are treated at low-volume centers by early-career surgeons with no basic training in surgical oncology, which increases the likelihood of undesirable outcomes.

A positive relationship between higher volume and better outcomes (volume-outcome relationship) has consistently been demonstrated in complex cases in surgical oncology. To understand the observed gain in the volume-outcome relationship, we must examine which specific attributes justify better results in high-volume centers, i.e., what are the routines, guidelines, and practices applied to each oncological condition, including emergencies. However, how can we replicate these results nationally given the heterogeneity in quality-of-service delivery? If achieving results in high-volume oncological centers is challenging to replicate in smaller centers for elective cases, certainly the emergency condition adds additional complexity when considering the variety of clinical situations and the greater difficulty in standardizing practices. Drawing a parallel with the care of traumatic emergencies, the collaborative efforts of medical societies, educational institutions, and private initiatives in organizing and disseminating guidelines for the management of trauma victims were notable, resulting in more balanced outcomes despite the significant disparities in emergency care conditions nationwide. In the case of emergency oncological surgery, besides the lack of minimal standardization, there is no proper notification or recording, rendering the assessment of the volume-outcome relationship imprecise or unavailable.

In any surgical field, specialization adds knowledge that translates into improved outcomes, which also applies to emergency and oncological surgery. However, unlike what happened with trauma surgery, which was organized to provide specialized training in the care of polytrauma patients, oncological surgery has not yet directly addressed this issue. Evidence of this is the lack of any formal curriculum requirement in surgical oncology for the hiring of surgeons working in emergency settings.

These issues pave the way for discussing the training of surgeons working in emergency services, as the 3 years of general surgery residency do not include official systematic rotations in surgical oncology. Therefore, one cannot demand enhanced technical knowledge from newly graduated surgeons who did not choose a specialization, many of whom will often be at the forefront of surgical oncological emergencies. This fact highlights the need for attention to training programs that provide qualifications for work in emergency surgery services, including courses such as Advanced Trauma Life Support (ATLS), Advanced Cardiac Life Support (ACLS), Pediatric Advanced Life Support (PALS), and Basic Life Support (BLS), among others, which have become formal requirements for employment in some hospitals seeking quality certification, including the need for periodic updates. It is time to create a certification program aimed at improving the training of surgeons working in emergency services and caring for cancer patients.

SPECIFICITIES OF ONCOLOGICAL SURGERY IN THE EMERGENCY SETTING

In the emergency setting, there is often not a suitable condition for a comprehensive diagnostic investigation, either due to technical impossibility stemming from clinical limitations or due to a lack of infrastructure. Many emergency services lack the necessary imaging resources for minimal staging, and only a few have the privilege of having high-quality computed tomography or 24-h endoscopy services available.

The concept of the importance of multidisciplinarity in oncology, based on the results produced by the cooperative work approach adopted in major world reference centers, has become synonymous with good medical practice. However, in an emergency setting, how can multidisciplinary discussion be promoted? Depending on the workplace and the urgency of the situation, the multidisciplinary team will often be limited to the on-call surgical team. While complex cases are discussed in "tumor boards" in elective situations, in emergencies, solitary decision-making becomes common, where oncological complexity is compounded by unfavorable clinical conditions and a lack of adequate preparation time. In a population with unique clinical characteristics, including a significant fraction of elderly patients with comorbidities and advanced-stage cancer, this is a challenging reality to transform.

The knowledge and skill of the surgeon are crucial in oncological surgery; however, assessing a surgeon's actions in an emergency setting in terms of quality metrics is not an easy task. Small acts that occur within the operating room have the potential to impact the outcome and may not always be transparently recorded. In most cases, when analyzing a description of an oncological procedure in an emergency setting, it is inadequate. There is a need to raise awareness among emergency surgeons about the importance of proper documentation containing a description of findings and surgical staging (sTNM), explicitly stating findings related to the primary tumor, lymph node status, and the presence or absence of metastases. In addition to the technical details that confirm or deny adherence to oncological principles, it must be clear whether the operation was curative or palliative. This topic warrants collective effort from medical entities involved in emergency surgery and surgical oncology to establish national standardizations and minimal requirements. Only then can we identify the regions and services that require more investment in training and capacity-building, with the ultimate beneficiary being the cancer patient.

From this analysis, it is evident that the equation for assessing the quality of emergency oncological surgery is not resolved. The rationale is to maintain adherence to technical principles; however, the emergency condition adds obstacles.

QUALITY OF EMERGENCY ONCOLOGICAL SURGERY: COLORECTAL CANCER AS AN ANALYTICAL MODEL

Approximately 15–40% of colorectal cancer (CRC) patients seek emergency services due to complications arising from undiagnosed disease, 8–40% due to obstruction, and 3–10% with intestinal perforation[4-6]. Both the demand for emergency services and the availability of data for comparison with elective surgery conditions make CRC a suitable model to answer the question about the quality of oncological surgery in the emergency setting. Are CRC patients well operated on in the emergency setting? Fundamental aspects involve the quality of diagnosis and staging, choice of surgical approach, selection of the type of operation concerning the extent of resection, primary anastomosis or external diversion, the number of sampled lymph nodes, the status of surgical margins, as well as clinical and oncological short- and long-term outcome indicators:

morbidity rates, mortality, disease-free survival (DFS), and overall survival (OS). Additionally, the impact of surgeon training, the volume-outcome relationship, and the sociodemographic characteristics of the CRC patient population seeking emergency care need to be analyzed.

A literature review highlights differences in management and outcomes when comparing elective and nonelective surgery scenarios. CRC patients undergoing emergency surgery are less likely to undergo staging examinations and are less likely to be approached laparoscopically[7]. The type of operation is also influenced by the emergency setting, with a significantly higher number of Hartmann's procedures, stoma creation, and segmental resections at the expense of classic colectomies with primary anastomoses[8,9]. In emergencies, there is a higher likelihood of positive margins, a lower number of sampled lymph nodes[10,11], and a higher anastomotic dehiscence rate[9].

Morbidity and mortality rates are consistently higher in the emergency setting, as are hospitalization stays and rates of readmissions and reoperations[7,10,11]. In most studies, 5-year DFS and OS rates are significantly lower in the emergency group[8,10]. It is a fact that cases in emergencies are more advanced[12], and there is a high proportion of elderly patients (including octogenarians) with clinical and socioeconomic problems[11,13]. Some authors even suggest that the worse outcomes are a consequence of patient profiles and clinical circumstances rather than the emergency itself[14].

In emergencies, there is a lower likelihood that the patient will be operated on by a surgeon with a specialization in oncological or colorectal surgery, and resections are more likely to occur in community hospitals and low-volume centers[10]. In the analysis by Patel et al.[15], elective surgeries were performed by colorectal surgeons (37%), oncological surgeons (10%), and general surgeons (53%); in emergencies, the proportion was: colorectal surgeons (19%), oncological surgeons (10%), and general surgeons (70%). The data reinforce the observation that the majority of CRC cases are operated on by general surgeons, both electively and in an emergency setting, emphasizing the importance of training emergency surgeons in oncological surgery.

This analysis demonstrates that nonelective resection for CRC is associated with a higher likelihood of short-term adverse outcomes, including higher rates of postoperative complications, mortality, stoma creation, admission to intensive care units, as well as poorer DFS and OS rates[16-18]. In this context, among the potentially modifiable factors are the training of emergency surgeons to handle CRC cases and the referral of more complex cases to higher-volume centers[19].

WHAT CAN BE DONE?

One of the suggestions to make the quality management process feasible is applying the plan-do-check-act (PDCA) cycle[1]. The planning phase could involve a joint effort by entities such as the Brazilian Society of Oncological Surgery (SBCO) and the Brazilian College of Surgeons (CBC) to establish QIs of recognized importance in emergency oncological surgery. Once the QIs are defined and a data recording platform is created, teaching and educational strategies focused on surgical skills training will be established in partnership with these entities. The next steps would involve verifying the results of the initial measures and directing actions to strengthen the training of surgeons in managing oncological emergencies, starting in regions and hospitals where the indicators point to the greatest problems.

The success of quality improvement initiatives depends on the validity of the collected data and the reliability of the selected measures. Therefore, quality improvement programs that provide high-quality data are necessary. In the United States, the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP)[20] and the Agency for Healthcare Research and Quality Patient Safety Indicators (AHRQ-PSIs) have been established as tools for measuring surgical quality[21]. The ACS NSQIP is a nationally validated, risk-adjusted outcomes-based program for quality measurement and improvement with more than 600 participating hospitals. There is solid evidence that enrollment in quality improvement programs helps hospitals improve surgical quality over time. An analysis of 118 hospitals from the private sector participating in the ACS NSQIP showed that 66% of the hospitals reduced risk-adjusted mortality and 82% had a decreased complication rate[20]. The American Society of Clinical Oncology (ASCO) has established an infrastructure with more than 70 specific quality measures for cancer treatment[22]. The European Organization for Research and Treatment of Cancer (EORTC) initiated the first quality assurance projects in the 1980s[23]. In 2007, EURECCA (EUropean REgistry of Cancer CAre or EURopEan CanCer Audit) was created with the aim of improving the quality of cancer patient care[24]. In addition to programs focused on quality assessment, numerous Operative Standards Manuals for Cancer Surgery have been created under the supervision of the American College of Surgeons (ACS)[25]. This is an idea that could be developed by the SBCO in partnership with the CBC: the creation of manuals with guidelines for managing the most common oncological emergencies.

The quality of oncological surgical care is a priority in various healthcare systems, with ongoing efforts to reliably measure surgical outcomes. Particularly in the emergency setting, knowledge of oncological surgical principles can assist

in decision-making and, above all, positively influence the outcomes of cancer patients. It is time to establish a national registry that encompasses oncological emergencies; it is time to promote the creation of the "Advanced Oncological Life Support" ("AOLS") with the aim of training surgeons working in emergency services and caring for cancer patients.

AUTHORS' CONTRIBUTIONS

FOF: Conceptualization, Writing – original draft, Writing – review & editing. **TMAL:** Writing – original draft. **EMU:** Supervision, Writing – review & editing. **AFO:** Writing – review & editing. **LCB:** Writing – review & editing. **HSCR:** Writing – review & editing.

REFERENCES

1. Hardt JL, Merkow RP, Reissfelder C, Rahbari NN. Quality assurance and quality control in surgical oncology. J Surg Oncol. 2022;126(8):1560-72. https://doi.org/10.1002/jso.27074
2. Wong SL. The state of quality indicators in surgical oncology. J Surg Oncol. 2009;99(1):7-8. https://doi.org/10.1002/jso.21172
3. Donabedian A. Evaluating the quality of medical care. Milbank Mem Fund Q. 1966;44(3):S166-206. PMID: 5338568
4. Biondo S, Kreisler E, Millan M, Fraccalvieri D, Golda T, Martí Ragué J, et al. Differences in patient postoperative and long-term outcomes between obstructive and perforated colonic cancer. Am J Surg. 2008;195(4):427-32. https://doi.org/10.1016/j.amjsurg.2007.02.027
5. Kermani R, Coury JJ, Dao H, Lee JH, Miller PE, Yee D, et al. A practical mortality risk score for emergent colectomy. Dis Colon Rectum. 2013;56(4):467-74. https://doi.org/10.1097/DCR.0b013e31827d0f93
6. Chen TM, Huang YT, Wang GC. Outcome of colon cancer initially presenting as colon perforation and obstruction. World J Surg Oncol. 2017;15(1):164. https://doi.org/10.1186/s12957-017-1228-y
7. Guidolin K, Withers R, Shariff F, Ashamalla S, Nadler A. Quality of colon cancer care in patients undergoing emergency surgery. Curr Oncol. 2021;28(3):2079-86. https://doi.org/10.3390/curroncol28030192
8. Wanis KN, Ott M, Koughnett JAM, Colquhoun P, Brackstone M. Long-term oncological outcomes following emergency resection of colon cancer. Int J Colorectal Dis. 2018;33(11):1525-32. https://doi.org/10.1007/s00384-018-3109-4
9. Biondo S, Gálvez A, Ramírez E, Frago R, Kreisler E. Emergency surgery for obstructing and perforated colon cancer: patterns of recurrence and prognostic factors. Tech Coloproctol. 2019;23(12):1141-61. https://doi.org/10.1007/s10151-019-02110-x
10. Xu Z, Becerra AZ, Aquina CT, Hensley BJ, Justiniano CF, Boodry C, et al. Emergent colectomy is independently associated with decreased long-term overall survival in colon cancer patients. J Gastrointest Surg. 2017;21(3):543-53. https://doi.org/10.1007/s11605-017-3355-8
11. Zielinski MD, Merchea A, Heller SF, You YN. Emergency management of perforated colon cancers: how aggressive should we be? J Gastrointest Surg. 2011;15(12):2232-8. https://doi.org/10.1007/s11605-011-1674-8
12. Borba MR, Brochado MCRT, Alcântara PSM, Lima TMA, Arantes TS, Otoch JP. Ressecções eletiva e de urgência para tratamento de neoplasia maligna do cólon em hospital universitário: estudo de 66 casos. Rev Bras Coloproct. 2011;31(2):120-5. https://doi.org/10.1590/S0101-98802011000200002
13. Gunnarsson H, Ekholm A, Olsson LI. Emergency presentation and socioeconomic status in colon cancer. Eur J Surg Oncol. 2013;39(8):831-6. https://doi.org/10.1016/j.ejso.2013.04.004
14. Weixler B, Warschkow R, Ramser M, Droeser R, Holzen U, Oertli D, et al. Urgent surgery after emergency presentation for colorectal cancer has no impact on overall and disease-free survival: a propensity score analysis. BMC Cancer. 2016;16:208. https://doi.org/10.1186/s12885-016-2239-8
15. Patel SV, Patel SV, Brackstone M. Emergency surgery for colorectal cancer does not result in nodal understaging compared with elective surgery. Can J Surg. 2014;57(5):349-53. https://doi.org/10.1503/cjs.019313
16. Teixeira F, Akaishi EH, Ushinohama AZ, Dutra TC, Netto SD, Utiyama EM, et al. Can we respect the principles of oncologic resection in an emergency surgery to treat colon cancer? World J Emerg Surg. 2015;10:5. https://doi.org/10.1186/1749-7922-10-5
17. Mullen MG, Michaels AD, Mehaffey JH, Guidry CA, Turrentine FE, Hedrick TL, et al. Risk associated with complications and mortality after urgent surgery vs elective and emergency surgery: implications for defining "quality" and reporting outcomes for urgent surgery. JAMA Surg. 2017;152(8):768-74. https://doi.org/10.1001/jamasurg.2017.0918
18. Aquina CT, Becerra AZ, Xu Z, Boscoe FP, Schymura MJ, Noyes K, et al. Nonelective colon cancer resection: a continued public health concern. Surgery. 2017;161(6):1609-18. https://doi.org/10.1016/j.surg.2017.01.001
19. Schrag D, Cramer LD, Bach PB, Cohen AM, Warren JL, Begg CB. Influence of hospital procedure volume on outcomes following surgery for colon cancer. JAMA. 2000;284(23):3028-35. https://doi.org/10.1001/jama.284.23.3028
20. Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, Ko CY. Does surgical quality improve in the American college of surgeons national surgical quality improvement program: an evaluation of all participating hospitals. Ann Surg. 2009;250(3):363-76. https://doi.org/10.1097/SLA.0b013e3181b4148f
21. Braxton CC. Defining, measuring, and improving surgical quality: beyond teamwork and checklists to systems redesign and transformation. Surg Infect (Larchmt). 2012;13(5):312-6. https://doi.org/10.1089/sur.2012.182
22. Landercasper J, Bailey L, Buras R, Clifford E, Degnim AC, Thanasoulis L, et al. The American society of breast surgeons and quality payment programs: ranking, defining, and benchmarking more than 1 million patient quality measure encounters. Ann Surg Oncol. 2017;24(10):3093-106. https://doi.org/10.1245/s10434-017-5940-1
23. Tanis E, Caballero C, Collette L, Verleye L, Dulk M, Lacombe D, et al. The European organization for research and treatment for cancer (EORTC) strategy for quality assurance in surgical clinical research: assessment of the past and moving towards the future. Eur J Surg Oncol. 2016;42(8):1115-22. https://doi.org/10.1016/j.ejso.2016.04.052
24. EJSO. Quality assurance in surgical oncology the EURECCA platform. Eur J Surg Oncol. 2014;40(11):1387-90. https://doi.org/10.1016/j.ejso.2014.08.478
25. Katz MHG, Francescatti AB, Hunt KK, Cancer surgery standards program of the American college of surgeons. technical standards for cancer surgery: commission on cancer standards 5.3-5.8. Ann Surg Oncol. 2022;29(11):6549-58. https://doi.org/10.1245/s10434-022-11375-w

ORIGINAL ARTICLE

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Training in oncoplastic surgery for mastologists

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Brazilian Society of Mastology

SUMMARY

OBJECTIVE: The radical change in the treatment of breast cancer has promoted the necessity for more comprehensive training of the professionals involved, ensuring the preservation of oncological safety while also allowing for cosmetic interventions to benefit breast cancer survivors. The aim of this study was to present the methods employed in the training of breast surgeons, highlighting the importance of oncoplasty and breast reconstruction.
METHODS: A literature review was conducted in two databases, identifying articles related to medical education in the context of oncoplastic surgery and breast reconstruction. We also assessed the Brazilian experience in oncoplastic centers.
RESULTS: The basis for educational discussions was derived from 16 articles. We observed approaches that included hands-on courses utilizing simulator models, porcine models, cadaver labs, and fellowship programs. Positive outcomes were observed in Brazil, a fact based on seven oncoplasty training centers for senior mastologists and five training centers for junior mastologists. From 2009 to 2023, an estimated 452 seniors and 42 juniors received training, representing approximately 30% of mastologists in Brazil who have acquired training and experience in oncoplasty.
CONCLUSION: Despite the limited number of publications on training methods, oncoplastic centers have made significant progress in Brazil, establishing a successful model that can be replicated in other countries.
KEYWORDS: Segmental mastectomy. Mammaplasty. Oncoplastic breast surgery. Medical education. Fellowships and scholarships.

INTRODUCTION

The surgical treatment of breast cancer has undergone a radical transformation in recent years. We have transitioned from radical mastectomies to breast-conserving therapy (BCT), which has been demonstrated to be as safe as radical surgery[1,2] in the long term. Initially, conservative treatment was indicated for tumors up to 3 cm in size, with subsequent expansion to 5 cm and a favorable breast-to-tumor ratio. Simultaneously, for invasive carcinomas, the ideal margin changed from 1 cm to the absence of tumor at the inked margin[3].

In the beginning, patients who underwent mastectomies often underwent delayed breast reconstructions with myocutaneous flaps, and now we perform immediate reconstructions. Implants typically used for breast augmentation became an integral part of immediate reconstruction[4], facilitated by techniques such as skin and nipple-sparing mastectomies[5]. These reconstructions, traditionally performed by plastic surgeons, have also become part of the skill set of breast surgeons.

Concerning BCT, the need for tactics to preserve the breast and avoid unsatisfactory outcomes presented a challenge. The concept of oncoplastic breast surgery (OBS) emerged nearly a decade ago, initially met with resistance, but is now widely accepted by breast surgeons[6-9]. Techniques have been categorized based on breast location[10,11], multicentricity/multifocality, and breast-to-tumor ratio[12]. Current literature shows that oncoplastic surgery (OPS) is safe, has acceptable recurrence rates, and is associated with improved cosmetic outcomes and greater patient satisfaction[13,14].

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As the paradigm shifted, it became necessary to prepare breast surgeons for breast or skin preservation, focusing on cosmetic quality and achieving acceptable local recurrence rates without compromising survival. Senior breast surgeons needed to enhance their skills. Although the literature on training methodologies is limited, this challenge was initially discussed only as a perspective[8]. In 2009, the first international consensus on this subject was established[15]. There are reports of hands-on courses on OPS[16], simulator models[17,18], porcine models[19], and cadaver labs[20,21]. For the new breast surgeon, fellowship programs in OPS were also established[22,23].

In Brazil and other countries, the advancement of mastology as a specialty has contributed to significant progress in surgical techniques. This has complemented existing techniques and fostered the substantial development of oncoplasty and breast reconstruction[24]. The concept of OPS has been embraced by the Brazilian Society of Mastology, leading to the creation of training courses for senior mastologists[20,21]. These courses have taken various formats, including biennial, annual, or modular. Consequently, the Brazilian Oncoplasty Journey, a national symposium organized by the Brazilian Society of Mastology, was established. Additionally, there has been a notable increase in the number of fellows in OPS. Simultaneously, OPS has been recognized as a necessary component of mastology medical residency programs throughout Brazil.

However, the literature on experiences with education in oncoplasty is limited[25]. Despite witnessing a quantitative growth in the number of mastologists performing OPS in Brazil, much of this experience remains undocumented. There is a shortage of studies discussing OPS training in both Brazil and abroad, a gap that justifies the present study.

METHODS

This study is a systematic integrative review designed to analyze training methodologies in OPS for breast surgeons. To identify relevant literature, the PICO methodology was employed, with the following components: P=breast reconstruction or OPS or oncoplasty; I=medical education or fellowship; C=all articles; and O=all articles.

For keyword selection, two databases, PubMed and Lilacs, were utilized. The chosen keywords were drawn from Mesh terms or words deemed relevant to the study. No language restrictions were imposed, and the search was extended until September 30, 2023. In PubMed, the following search query was applied: ("Mammaplasty" [Mesh] OR "Mastectomy, Segmental" [Mesh] OR "oncoplastic surgery" OR "oncoplasty" OR "oncoplastic breast surgery") AND ("Education, Medical" [Mesh] OR "Fellowships and Scholarships" [Mesh]). In Lilacs, the following query was employed: "Educação Medica" (subject descriptor) and "neoplasias da mama" (subject descriptor).

Following the initial search, articles were selected based on their titles and abstracts. Selected articles were then obtained in full and evaluated for their relevance to the study's focus. In cases where there were multiple publications from the same research group addressing the same topic, the most recent publication was included. Figure 1 illustrates the application of the PRISMA methodology in article selection. To improve the information on oncoplasty training in Brazil, records from the Brazilian Society of Mastology and information obtained from Training Center Coordinators were examined. This examination aimed to provide a retrospective analysis of oncoplasty training for both senior mastologists (Table 1) and junior mastologists (Table 2). Information was directly collected from the training centers.

This study reports a literature review and uses publicly available data. In accordance with Resolution 466/2012 of the National Research Ethics Committee (CONEP) in Brazil, this research does not require evaluation by an Ethics Committee.

RESULTS

Using the PRISMA methodology, we initially identified 88 studies, with 81 coming from PubMed and 7 from LILACS. To expand the dataset, 11 additional studies were incorporated,

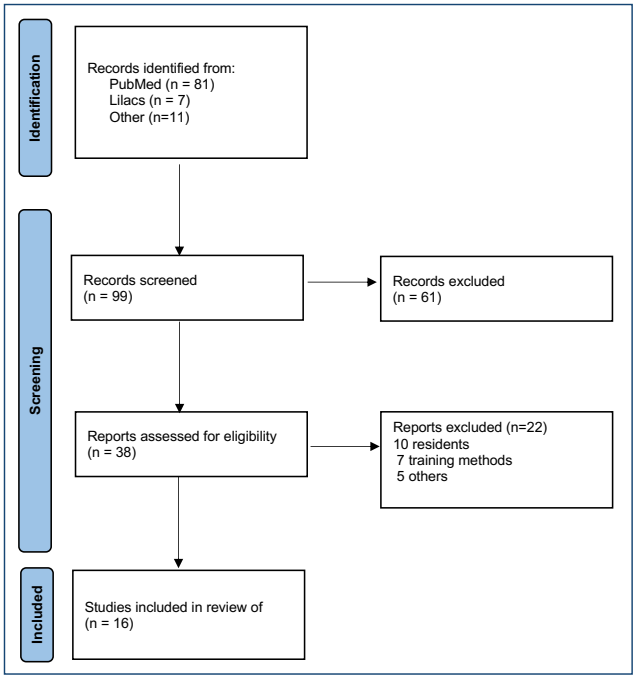

Figure 1. PRISMA flowchart.

Table 2. Oncoplastic training centers in Brazil for junior mastologists.

Course	H.C. Araújo Jorge	S.C.M. de Belo Horizonte	H.C. Barretos	H.G. de Fortaleza	H.G. in Universidade de Caxias
Location	Goiânia/GO	Belo Horizonte/MG	Barretos/SP	Fortaleza/CE	Caxias do Sul/RS
Beginning	2014	2015	2016	2017	2023
End	Current	Current	Current	Paused	Current
Residency in hospital	Mastology/surgical oncology	Mastology/plastic surgery	Mastology/surgical oncology	Mastology/plastic surgery	Mastology
Attendees/year	1	1–3	2	2	1
Activities	Breast reconstruction	Mastology/breast reconstruction	Mastology/breast reconstruction	Mastology/breast reconstruction	Mastology/breast reconstruction
Frequency	Annual	Annual	Annual	Annual	Annual
Certification	Fellow	Fellow	Lato-sensu in oncology	Fellow	Fellow
No. of graduated	9	7	13	7	0
No. of current attendees	1	3	1	0	1

H.C.: Hospital do Câncer (Cancer Hospital); S.C.M.: Santa Casa de Misericórdia (Holy House of Mercy); H.G.: Hospital Geral (General Hospital).

Table 1. Oncoplastic training centers in Brazil for senior mastologists.

Course	H.C. Porto Alegre	H.C. Barretos[20]	S.C.M. de São Paulo[21]	S.C.M. de Belo Horizonte[27]	H.C. Araújo Jorge[27]	H.C. Amaral Carvalho	H.C. Pernambuco
Location	Porto Alegre/RS	Barretos/SP	São Paulo/SP	Belo Horizonte/MG	Goiania/GO	Jaú/SP	Recife/PE
Beginning	2008	2009	2010	2011	2014	2016	2023
End	Current	2018	Current	2018	Current	Current	Current
Format	Theoretical-practical	Theoretical-practical	Theoretical-practical	Theoretical-practical	Theoretical-practical	Theoretical-practical	Theoretical-practical
Format	Modular	Continuous	Continuous	Continuous	Continuous	Continuous	Continuous
Duration	4 modules/course	21 months	10 months	9–15 months	11 months	11 months	12 months
Total number of hours/month	40 h/module	12–20 h	20 h	36 h	25 h	20 h	30 h
Total hours	160/year	252–420	200	320–540	240–275	220	360
Attendees/class	46 modules	12	10	12	12	12	12
Classes	2008–2019 2021–2023	5	13	5	9	7	1
Graduated*	13 years/4 modules/4 students	60	130	60	108	60	–
Current face-to-face attendees	4×4	Finished in 2018	Paused in 2023	Finished in 2018	12	12	12
Observation	Modular/thematic	8 h: 2009 20 h: 2015	Beneficência Portuguesa		2022: 15 online 2023: 23 online		

H.C.: Hospital do Câncer (Cancer Hospital); S.C.M.: Santa Casa de Misericórdia (Holy House of Mercy). *Estimation.

resulting in a total of 99 studies. No duplicate articles were encountered. Applying the selection criteria, 16 articles were ultimately chosen for comprehensive examination, representing the primary focus of this article. These articles were categorized as follows: consensus[15], hands-on OPS courses[16], simulators[17,18,26], porcine models[19], or practical courses in humans/

cadaver labs[20,21], fellows in OPS[22,23,27,28], medical residency[29,30], learning curve[31], and limitations and perspectives[32].

Regarding the oncoplasty training centers for senior mastologists in Brazil, we identified a total of seven centers, two of which had published their results[20,21]. In the context of training senior mastologists (Table 1), seven courses were conducted in Brazil. The first course started in 2008, and at present, five courses remain ongoing. These programs are distributed across five capital cities and two medium-sized city in Interior of São Paulo State. Additionally, five of them are held in cancer hospitals, while the other two take place in general hospitals. Six of these programs feature monthly meetings, with the number of total hours varying from 200 h to 540 h. A modular course format was also observed, featuring four independent modules: (1) oncological mammoplasty; (2) myocutaneous flaps and fat grafting; (3) reconstruction with implants and fat grafting; and (4) fat grafting in conservative surgery and refinements. In 2022, one of the courses adopted a dual-track format, offering both face-to-face and virtual sessions, thereby accommodating participants from numerous countries and providing simultaneous translation into Portuguese, English, and Spanish (www.oncoplasticsurgerycourse.com). Adding up all the attendees, besides those who started in 2023, we will have about 452 students who completed the course.

Assessing the training of junior mastologists (fellowship program) who have recently concluded their residencies, we identified five training centers (Table 2). These centers run annual programs located in hospitals that offer medical residency programs in mastology, surgical oncology, or plastic surgery. Among these centers, three are situated in capital cities, while two are affiliated with cancer hospitals. Including all the centers that started in 2023, there will be 42 graduates.

DISCUSSION

In the 1990s, Audretsch coined the term "oncoplasty"[27] to describe a new approach to breast cancer surgery that combined oncological principles with plastic surgery techniques. However, it was not until 2003 that a publication discussing the importance of training breast surgeons in reconstructive procedures[8] was observed. In 2007, EUSOMA recommended that breast surgeons receive training in OPS[33]. In 2009, there was a consensus on oncoplastic training, emphasizing the need for collaboration between plastic surgeons and breast surgeons in various scenarios and the accreditation of training centers[15].

Audretsch used the term "oncoplasty" as a synonym for tumor-specific breast reconstruction, so it was used as associated with reconstruction after mastectomy and BCT[15]. AndradeUrban[9] proposed three levels of competencies for OPS: Level I for basic procedures that do not require specific training in plastic surgery; Level II for mastopexy, breast augmentation, lipofilling, Grisotti flap, reconstruction with implants, and bilateral procedures; and Level III for complex procedures with flaps. Clough et al.[10] introduced a classification based on resection volume, distinguishing between Level I (resections less than 20% of breast volume) and Level II (extensive resections, representing 20–50% of breast volume). In 2019, a consensus by the American Society of Breast Surgeons[7,11] introduced the terms "volume replacement" and "volume displacement." In the volume replacement group, techniques such as Level I (<20% volume excision) and Level II (20–50% techniques) were included. Techniques for volume replacement (>50%) include local/regional flaps, myocutaneous flaps, and implant-based reconstruction. This categorization is crucial for evaluating publications related to OPS training.

A study compared surgeons who performed oncoplastic procedures with those who did not. Factors associated with the use of oncoplastic techniques included male sex, fewer years of practice (<10 years), previous training in oncoplasty, and greater availability of plastic surgeons. Surprisingly, plastic surgeons were less related to breast preservation studies than oncoplastic breast surgeons[34]. Questionnaires were applied to surgeons who participated in an oncoplastic course in Australia and New Zealand that lasted two years, consisting of monthly classes. For the 59% (33/56) respondents, cost and time constraints were identified as negative factors affecting course participation[35]. Several barriers to surgeon training in oncoplasty were observed, including a lack of time to access oncoplastic educational material or courses[36] the lengthy training period for breast surgeons, the non-recognition of the breast sub-specialty in some countries, and the necessity for dual (oncological and reconstructive) training[32].

One of the great problems with different learning models is the establishment of methodologies for evaluating learning outcomes, such as knowledge or skill retention. Therefore, in order to evaluate potential methodologies that can assist in OPS training, we observed the results in the simulators made in Montreal[17] in a hands-on course held in Canada[16]. This study compared senior and junior surgeons' skills in the procedure of subpectoral breast augmentations[17]. They concluded that a hands-on course helps surgeons adopt OPS in their clinical practice[17]. A randomized study conducted in Singapore compared the performance of OPS performed on humans and in simulators. It was noted that although surgeons initially showed superior knowledge using the simulator, the results were similar[26] after six months.

There is no defined minimum number of procedures to achieve expertise in oncoplasty. The British Association of Surgical Oncology suggested a minimum number of procedures for oncoplasty, with 25 for Level I and 50 for Level II[37]. The regional Australian experience was published in 2012, showing quantitative data in which the fellow performed 91 procedures as the first surgeon and 73 as an assistant[22]. A retrospective study evaluating the learning curve observed that 58 procedures were needed to reduce surgical time[31].

In England, training courses in cadaver labs were started, and oncoplasty became a sub-specialty after breast surgery or plastic surgery[33]. In 2002, an investment was made in nine centers, creating 100 training and qualification scholarships for fellows for a 12-month period[27,28]. They selected breast or plastic surgeons with a minimum of 15 years of training in breast surgery, as they were considered for breast center accreditation[33] and the formation of disciples. A later publication reported that many surgeons applied their new expertise in private practice, while few remained in public reconstructive services, highlighting the importance of educating not only fellows but also including oncoplasty in the curriculum of all breast surgeons[23].

In Brazil, in 2012, the first report of an oncoplasty training course for senior mastologists was observed, showing positive results for attendees in 2009 and 2010[20]. Over time, other courses were created[27]. Table 1 synthesizes information about the courses up to the present date. The model positively impacted clinical practice[20,21]. Among the continuous courses held in Brazil, the number of classes varied from 200 h to 540 h. Theoretical discussions were associated with clinical practice, in which multiple simultaneous surgical rooms, various types of surgery, and bilateral surgeries helped enhance surgical skills. From the available information, the shortest course was 200 h, and it yielded satisfactory[21] results. As a criterion for participation in the courses, breast surgeons should be board certified. Initially, student selection was based on decentralization, academic relevance, and the potential to train new surgeons, aiming to maximize the impact of the training.

This hands-on course model in Brazil has inspired similar courses in other countries, such as Argentina and Peru, with live surgeries conducted in both face-to-face and virtual formats but in a more concise format with less workload and fewer surgeries at each meeting. Similar hands-on courses with live surgery sessions lasting 1 or 2 days are being offered in other countries, including Colombia, Mexico, Spain, and Germany. International collaboration can benefit developed countries since low- and middle-income countries have shown astonishing ease in training breast specialists and developing new surgical techniques[24].

There is no predefined duration for training junior surgeons[28]. In Brazil, since 2014, there have been 42 fellows in OPS, all breast surgeons, who were trained for one year by other breast oncoplastic surgeons. From 2009 to 2023, an estimated 452 seniors and 42 juniors were trained, representing approximately 30% of mastologists in Brazil.

Internationally, various basic training courses for breast surgeons exist, which may follow training in general surgery, oncological surgery, or gynecology. OPS training is considered a secondary surgical skill[38] In Brazil, breast cancer surgeries are performed by mastologists and oncological surgeons. Mastology is a two-year specialty, with initial two- or three-year training in general surgery or gynecology[39]. Oncoplasty training was initially secondary to general mastology training but is gradually being integrated into residency programs, a process that will take more time to consolidate.

Evaluating the training of the breast surgeon in Spain[29], OPS is a part of the competencies required for breast surgeon training, although publications on this subject were not observed. In Spain, there has been a traditional course for several years that includes lectures, video presentations, and surgeries on pigs[19], attracting attendees from various countries. In Brazil, oncoplasty is integrated into the training program for mastology residents. By the end of the first year, residents should have mastered level I oncoplastic procedures, and by the end of the second year, they should have attained competency in level II and breast reconstructions[39]. Medical residency programs must adapt to these guidelines. A survey conducted among mastology residents from 2015 to 2016 found that 60% of residents had training in oncoplasty throughout their residency. In breast units where mastologists perform oncoplasty, residents are better prepared to perform oncoplasty and reconstruction techniques[30].

In Brazil, the Brazilian Society of Mastology offers an official oncoplasty course (https://oncoplasticsurgerycourse.com/en) with live broadcasting of 100 reconstructive procedures, held over two days per month for 11 months. The course provides simultaneous translation in Portuguese, English, and Spanish for breast surgeons, surgical oncologists, and plastic surgeons. In the United States, an online course with home study tools and simulator models organized by the Oncoplastic Surgery Society is available (https://oncoplasticmd.org). In India, the International School of Oncoplasty offers theoretical courses, simulator courses, and a 2-year master's program in oncoplastic surgery (www.breastoncoplasty.org). The European Institute of Oncology in Italy organizes a two-day course with live broadcasting of reconstructive procedures once a year (www.ieo-oncoplastic.com). The American College of Surgeons is planning

a course on oncoplastic breast surgery (https://learning.facs.org/content/oncoplastic-breast-surgery). However, there are no publications reporting their outcomes, and there is no standardization of methods and types of procedures.

Additional measures that should be taken include continuing education through the inclusion of an oncoplasty section in national and regional congresses or events, as well as hosting specific oncoplasty congresses. The Brazilian Congress of Mastology and São Paulo Mastology Journey dedicate a period to discussing oncoplasty, offering 4 h of content for about 1000 mastologists each year. The Brazilian Journey of Oncoplasty, initiated by the Brazilian Society of Mastology in 2012, has allowed mastologists to discuss the topic for over a decade, with an average annual participation of more than 300 attendees.

From future perspectives, there is a need to conduct more studies that evaluate learning curves in training breast surgeons and the impact of different methodologies. Additionally, there is a need to increase the number of training centers with associated publications and study trend curves. Oncoplasty is becoming increasingly integrated into daily practice due to increase in both the learning curve and the rate of BCT secondary to neoadjuvant chemotherapy. Reconstructions, initially performed through myocutaneous flaps, have transitioned to implant-based techniques, significantly simplifying the procedures. OPS depends on training, and the more training one receives, the broader the range of potential indications and availability. This is evident in the increasing number of publications related to oncoplasty, in which breast surgeons play a significant role[25]. There is gradually an increase in the number of reconstructions in the public health system in Brazil[40]. To further improve results, it is essential to focus on various aspects such as residency programs, fellowships, oncoplasty training centers, and continuing education. These efforts will ultimately lead to better treatment for breast cancer patients, who are vulnerable and deserving of high-quality care, thereby justifying the need for educating breast surgeons.

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AUTHORS' CONTRIBUTIONS

ATH: Conceptualization, Project administration, Visualization, Writing – review & editing. **CAU:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **GF:** Conceptualization, Project administration, Writing – review & editing. **RFJ:** Conceptualization, Project administration, Validation, Writing – original draft, Writing – review & editing. **RRP:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **JVB:** Data curation, Methodology, Writing – review & editing. **VMO:** Data curation, Methodology, Writing – review & editing. **RACV:** Conceptualization, Data curation, Investigation, Project administration, Writing – original draft, Writing – review & editing.

REFERENCES

1. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227-32. https://doi.org/10.1056/NEJMoa020989
2. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233-41. https://doi.org/10.1056/NEJMoa022152
3. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol. 2014;21(3):717-30. https://doi.org/10.1245/s10434-014-3480-5
4. Yang X, Zhu C, Gu Y. The prognosis of breast cancer patients after mastectomy and immediate breast reconstruction: a meta-analysis. PLoS One. 2015;10(5):e0125655. https://doi.org/10.1371/journal.pone.0125655
5. Mota BS, Riera R, Ricci MD, Barrett J, Castria TB, Atallah ÁN, et al. Nipple- and areola-sparing mastectomy for the treatment of breast cancer. Cochrane Database Syst Rev. 2016;11(11):CD008932. https://doi.org/10.1002/14651858.CD008932.pub3
6. Oliveira-Junior I, Haikel RL, Vieira RAC. Breast-conserving treatment in oncoplastic times: indications, cosmesis, and quality of life. Mastology. 2021;31(1):e20200040. https://doi.org/10.29289/2594539420200040
7. Chatterjee A, Gass J, Patel K, Holmes D, Kopkash K, Peiris L, et al. A consensus definition and classification system of oncoplastic surgery developed by the American Society of Breast Surgeons. Ann Surg Oncol. 2019;26(11):3436-44. https://doi.org/10.1245/s10434-019-07345-4
8. Rainsbury D. Training in breast reconstruction: a new chapter in breast surgery. Hosp Med. 2003;64(12):700-1. https://doi.org/10.12968/hosp.2003.64.12.2358
9. Andrade Urban C. New classification for oncoplastic procedures in surgical practice. Breast. 2008;17(4):321-2. https://doi.org/10.1016/j.breast.2007.11.032
10. Clough KB, Ihrai T, Oden S, Kaufman G, Massey E, Nos C. Oncoplastic surgery for breast cancer based on tumour location and a quadrant-per-quadrant atlas. Br J Surg. 2012;99(10):1389-95. https://doi.org/10.1002/bjs.8877
11. Patel K, Bloom J, Nardello S, Cohen S, Reiland J, Chatterjee A. An oncoplastic surgery primer: common indications, techniques, and

complications in level 1 and 2 volume displacement oncoplastic surgery. Ann Surg Oncol. 2019;26(10):3063-70. https://doi.org/10.1245/s10434-019-07592-5

12. Silverstein MJ, Savalia N, Khan S, Ryan J. Extreme oncoplasty: breast conservation for patients who need mastectomy. Breast J. 2015;21(1):52-9. https://doi.org/10.1111/tbj.12356
13. Losken A, Dugal CS, Styblo TM, Carlson GW. A meta-analysis comparing breast conservation therapy alone to the oncoplastic technique. Ann Plast Surg. 2014;72(2):145-9. https://doi.org/10.1097/SAP.0b013e3182605598
14. Mohamedahmed AYY, Zaman S, Zafar S, Laroiya I, Iqbal J, Tan MLH, et al. Comparison of surgical and oncological outcomes between oncoplastic breast-conserving surgery versus conventional breast-conserving surgery for treatment of breast cancer: a systematic review and meta-analysis of 31 studies. Surg Oncol. 2022;42:101779. https://doi.org/10.1016/j.suronc.2022.101779
15. Cardoso MJ, Macmillan RD, Merck B, Munhoz AM, Rainsbury R. Training in oncoplastic surgery: an international consensus. The 7th Portuguese Senology Congress, Vilamoura, 2009. Breast. 2010;19(6):538-40. https://doi.org/10.1016/j.breast.2010.03.030
16. Angarita FA, Leroux ME, Palter VN, Richardson J, Arnaout A, Hanrahan RM, et al. Assessing the effect of a hands-on oncoplastic surgery training course: a survey of Canadian surgeons. Surg Oncol. 2020;35:428-33. https://doi.org/10.1016/j.suronc.2020.10.003
17. Kazan R, Viezel-Mathieu A, Cyr S, Hemmerling TM, Gilardino MS. The montreal augmentation mammaplasty operation (MAMO) simulator: an alternative method to train and assess competence in breast augmentation procedures. Aesthet Surg J. 2018;38(8):835-49. https://doi.org/10.1093/asj/sjx267
18. Zucca-Matthes G, Lebovic G, Lyra M. Mastotrainer new version: realistic simulator for training in breast surgery. Breast. 2017;31:82-4. https://doi.org/10.1016/j.breast.2016.08.009
19. Acea Nebril B, García Novoa A, Bouzón Alejandro A, Centeno Cortes A. Porcine model for training in oncoplastic breast surgery technical description and results of its application in a training course in oncoplastic and reconstructive techniques in breast surgery. J Plast Reconstr Aesthet Surg. 2019;72(6):1030-48. https://doi.org/10.1016/j.bjps.2018.12.049
20. Zucca Matthes AG, Viera RA, Michelli RA, Ribeiro GH, Bailão A, Haikel RL, et al. The development of an oncoplastic training center – OTC. Int J Surg. 2012;10(5):265-9. https://doi.org/10.1016/j.ijsu.2012.03.009
21. Businaro Fernandes João T, Oliveira VM, Bagnoli F, Bastos MCS, Rinaldi JF, Brenelli FP, et al. How well are Brazilian mastologists (breast surgeons) trained in breast reconstruction and oncoplastic surgery? A study of the impact of a breast reconstruction and oncoplastic surgery improvement course. Front Oncol. 2023;13:1139461. https://doi.org/10.3389/fonc.2023.1139461
22. Yunaev M, Hingston G. Oncoplastic breast surgery: a regional Australian 2012 fellowship experience. ANZ J Surg. 2013;83(9):624-9. https://doi.org/10.1111/ans.12318
23. Audisio RA, Chagla LS. Oncoplastic fellowship: can we do better? Breast. 2007;16(1):11-2. https://doi.org/10.1016/j.breast.2006.07.001
24. Freitas-Junior R, Ferreira-Filho DL, Soares LR, Paulinelli RR. Oncoplastic breast-conserving surgery in low- and middle-income countries: training surgeons and bridging the gap. Global Breast Cancer. 2019;11:136-42. https://doi.org/10.1007/s12609-019-00317-3
25. Freitas-Junior R, Faria SS, Paulinelli RR, Martins E. Trends in oncoplastic breast surgery and breast reconstruction over the past 35 years. Breast J. 2018;24(3):432-4. https://doi.org/10.1111/tbj.12922
26. Lim GH, Wang X, Allen JC, Ng RP, Tan BK, McCulley S, et al. Evaluating the feasibility of a novel Marking Breast Oncoplastic Surgery Simulator (MBOSS) as a training tool for marking: a randomised trial. Gland Surg. 2020;9(5):1227-34. https://doi.org/10.21037/gs-20-476
27. Pires DM, Gazoto-Junior O, Valadares CN, Andrade RL. Training in oncoplastic and reconstructive breast surgery: analysis of training in America and in the European Union with the Brazilian reality. Mastology. 2017;27(2):164-71. https://doi.org/10.5327/Z2594539420170000185
28. Liem AA, Iqbal A. Oncoplastic breast surgery in Britain. Plast Reconstr Surg. 2011;127(2):1012-3. https://doi.org/10.1097/PRS.0b013e318200acb9
29. Miguelena JM, Domínguez Cunchillos F. Training in breast surgery in Spain. Cir Esp. 2016;94(6):323-30. https://doi.org/10.1016/j.ciresp.2016.01.007
30. Urban C, Gazoto-Junior O, Pires DM, Garcia GN, Paulinelli RR, Amoroso V, et al. Trends and attitudes toward oncoplastics training in mastology in Brazil. Mastology. 2017;27(3):182-6. https://doi.org/10.5327/Z2594539420170000221
31. Lai HW, Lin J, Sae-Lim C, Lin YJ, Chen DR, Lai YC, et al. Oncoplastic and reconstructive breast surgeon performance and impact on breast reconstructions: clinical outcomes, learning curve, and patients' satisfaction. Surg Oncol. 2023;47:101920. https://doi.org/10.1016/j.suronc.2023.101920
32. Malycha PL, Gough IR, Margaritoni M, Deo SV, Sandelin K, Buccimazza I, et al. Oncoplastic breast surgery: a global perspective on practice, availability, and training. World J Surg. 2008;32(12):2570-7. https://doi.org/10.1007/s00268-008-9635-4
33. Rainsbury R. Oncoplastic training in the UK and perspectives for the future. Mastology. 2017;27(4):265-70. https://doi.org/10.29289/Z259453942017EDIT274
34. Maxwell J, Roberts A, Cil T, Somogyi R, Osman F. Current practices and barriers to the integration of oncoplastic breast surgery: a Canadian perspective. Ann Surg Oncol. 2016;23(10):3259-65. https://doi.org/10.1245/s10434-016-5318-9
35. Spillane AJ, Flitcroft KL, Warrier S, Katelaris AG. Evaluation of a structured clinical program and formal coursework in breast surgeon training in Australia and New Zealand. Eur J Surg Oncol. 2019;45(10):1821-6. https://doi.org/10.1016/j.ejso.2019.05.014
36. Chatterjee A, Gass J, Burke MB, Kopkash K, El-Tamer MB, Holmes DR, et al. Results from the American society of breast surgeons oncoplastic surgery committee 2017 survey: current practice and future directions. Ann Surg Oncol. 2018;25(10):2790-4. https://doi.org/10.1245/s10434-018-6586-3
37. Association of Breast Surgery at BASO, Association of Breast Surgery at BAPRAS, Training Interface Group in Breast Surgery, Baildam A, Bishop H, Boland G, et al. Oncoplastic breast surgery – a guide to good practice. Eur J Surg Oncol. 2007;33(Suppl 1):S1-23. https://doi.org/10.1016/j.ejso.2007.04.014
38. Armstrong K, Maxwell J. Oncoplastic surgery for breast cancer: global perspectives and trends. J Surg Oncol. 2023;128(6):967-71. https://doi.org/10.1002/jso.27408
39. Souza WVB. Resolução CNRM No 17, de 6 de Julho de 2021. Aprova a matriz de competências dos programas de Residência Médica em Mastologia no Brasil. In: Comissão Nacional de Residência Médica, editor. Diário Oficial da União; 2021. p. 1-5.
40. Freitas-Júnior R, Gagliato DM, Moura Filho JWC, Gouveia PA, Rahal RMS, Paulinelli RR, et al. Trends in breast cancer surgery at Brazil's public health system. J Surg Oncol. 2017;115(5):544-9. https://doi.org/10.1002/jso.24572

REVIEW ARTICLE

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Acupuncture in cancer care: a narrative review

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INTRODUCTION

Cancer is the main public health problem worldwide, being one of the main causes of death and, consequently, one of the main barriers to the increase in life expectancy[1]. The impact of cancer, based on estimates by the Global Cancer Observatory (Globocan)[2], prepared by the International Agency for Research on Cancer (IARC), points out that there were 19.3 million new cases of cancer in 2020 worldwide. One in five individuals will have cancer during their lifetime[2,3]. Notably, 10 main types of cancer represent more than 60% of all new cases. Female breast cancer is the most common cancer worldwide, with 2.3 million (11.7%) new cases, followed by lung cancer, with 2.2 million (11.4%); colon and rectum, with 1.9 million (10.0%); prostate, with 1.4 million (7.3%); and non-melanoma skin, with 1.2 million (6.2%) new cases. In Brazil, the estimate for the 3-year period from 2023 to 2025 indicates that there will be 704,000 new cases of cancer, 483,000 if cases of non-melanoma skin cancer are excluded[1].

Systemic treatment or combined therapies are commonly used for cancer patients, among which palliative care may be used for the alleviation of cancer-related symptoms, side effects related to conventional treatment, as well as the healthcare of cancer survivors[4,5].

Acupuncture, a therapy originating from the system of traditional Chinese medicine (TCM), has been in use for at least 2500 years. Fine needles are inserted and stimulated, either manually or electrically, to treat specific symptoms or health conditions. According to the World Health Organization (WHO), acupuncture is used in at least 103 countries, some of which have established regulations for providers[6,7]. In the United States, about 3.5 million adults receive acupuncture for each ear[4,7].

Acupuncture is also widely used for palliative and supportive care for cancer patients, and it has not only been limited to manual acupuncture but has also incorporated electrical acupuncture, auricular acupuncture, laser acupuncture, etc[8-10]. Based on a large number of recommendations made by clinical practice guideline development groups and expert groups from 13 countries, acupuncture has been recommended for chemotherapy-induced and post-operative nausea and vomiting, cancer pain, fatigue, insomnia, xerostomia, hot flashes, lymphoedema, and chemotherapy-induced neuropathy, as well as to improve the quality of life (QoL) of these patients[11,12]. In addition, acupuncture has been considered a safe therapy for cancer patients when practiced by qualified practitioners, and although mild adverse events (AE) like dizziness, fatigue, and nausea may appear, they generally improve without any extra measures[13,14].

In this narrative literature review, we will briefly address the main clinical evidence for the use of acupuncture in cancer patients and cancer survivors, ending with aspects related to the safety of the procedure and implications for healthcare policy in these patients.

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CLINICAL EVIDENCE FOR ACUPUNCTURE IN CANCER CARE

Emerging research has found promising evidence for the role of acupuncture in oncology, especially to control symptoms where existing standard options remain a challenge. Three relatively recent reviews[6,11,12] synthesized data across several systematic reviews (SR) for effects on symptoms such as pain, fatigue, hot flashes, nausea/vomiting, xerostomia, insomnia, lymphoedema, bone marrow suppression, and QoL (central illustration).

In the following sections, we will show a summary of the data presented in these and other reviews on the above-mentioned cancer-related conditions.

Pain

The prevalence of pain in cancer patients varies widely depending on the type of cancer and the stage of the disease. A SR and meta-analysis published in 2016 analyzed 117 articles that addressed the prevalence of pain in cancer patients, which was approximately 39.3% [95% confidence interval (CI) 33.3–45.3%] after the end of curative treatment, 55% (95%CI 45.9–64.2%) during treatment, and 66.4% (95%CI 58.1–74.7%) in cases of advanced disease, with a combined prevalence in all stages of treatment of 50.7% (95%CI 37.2–64.1%)[15]. The same study also analyzed 52 articles that reported pain intensity and indicated that moderate to severe pain is present in 38% (95%CI 32.8–43.3%) of patients. In another review, around 90% of cancer patients in advanced stages have moderate to severe pain, and in those with early and intermediate stages, the prevalence reaches 40%[16]. Unfortunately, management ends up being inadequate for up to 70% of individuals with cancer, damaging their QoL[16].

Pain in this context has different origins, including factors related to the presence of the tumor itself and the treatments performed. Nociceptive pain is often caused by the compression or invasion of tissues by tumor cells. Neuropathic pain can occur due to injuries induced by surgical, radiotherapy, and/or chemotherapy treatments. Clinical studies highlight the heterogeneous nature of cancer pain, with mixed pain being considered the most common[17].

The use of acupuncture in the treatment of pain in oncology has been investigated over the last few decades, making it possible to carry out some reviews. However, the methodological quality of the publications still hinders the analysis of their value. A review published in 2017 included 29 articles that addressed patients over 18 years and indicated that acupuncture has a moderate effect on pain induced by the tumor lesion as well as by surgical treatments (-0.7 and -0.4; 95%CI -0.94 to -0.48 and -0.69 to -0.1, respectively)[18].

Despite the doubts that still linger on the subject, based on the evidence available in the literature, the study group "*International Trustworthy Traditional Chinese Medicine Recommendations (TCM Recs) Working Group*" published an article with three recommendations in 2022[19]:

1. Strong recommendation for the use of acupuncture when not treating moderate to severe pain in cancer patients.
2. Weak recommendation for the combination of acupuncture and acupressure in pain management treatments with the aim of reducing the use of opioids and the incidence of side effects induced by such drugs in patients with moderate to severe pain who are using analgesics.
3. Strong recommendation for the use of acupuncture to relieve arthralgia induced by aromatase inhibitors in patients with breast cancer.

A SR conducted by Yang et al., concluded that acupuncture is a safe and effective treatment to reduce the intensity of pain in cancer patients under palliative care[20].

Therefore, we understand that pain in oncology is a significant concern that requires a multidisciplinary approach to its management. Acupuncture has been shown to be an effective option, but its usefulness must be evaluated considering the context of the disease, its staging, and the etiology of the pain.

Fatigue

Cancer-related fatigue (CRF) is one of the most frequent symptoms of cancer patients and cancer survivors. Although related to the illness process, the main reason for it is the treatment, like surgery, radiation therapy, and the most common chemotherapy[21].

In recent years, much research has been carried out to validate the efficacy of acupuncture for this disorder. From 2013 to 2023, 21 SR and 12 meta-analyses (MA) were also performed. However, 15 SR and 8 MA were performed only for acupuncture, and in 6 SR and 4 MA researchers observed other kinds of complementary and integrative therapeutics, including acupuncture.

He et al.[22] found 7 studies involving 804 patients and concluded that despite the few high-quality randomized controlled trials (RCTs), acupuncture appears to be an efficacious method for CRF. In other SR, Posadzki et al.[23] observed four trials in seven that showed effectiveness against *sham* or usual care, although most of them were small pilot studies, and concluded that it remained unclear whether the results were due to specific effects of acupuncture. Finnegan-John et al.[24], analyzing 20 studies using complementary therapies for the management of CRF, concluded that acupuncture may reduce this symptom following cancer treatments.

Choi et al.[25], analyzing 12 studies with 1,084 participants with breast cancer, observed that acupuncture was more effective than *sham*, usual care, or waiting list. They called attention to the fact that most of the studies were of low quality, mainly because of the small samples. Also in 2022, the same author[25], in an overview of SR and MA with 10 SRs, 160 RCTs, and 14,392 patients, declared that most of the SRs reached the potential benefits of acupuncture for CRF, despite the methodological quality of most of them was low. In the same year, Zhang et al.[12] published an overview of SR for many cancer-related conditions, comprising 7 SRs and 18 RCTs, which showed acupuncture's efficacy in controlling CRF. Tian et al.[26], in a Bayesian network MA and SR where 34 RCTs and 2,632 participants were included, comparing acupuncture with *sham* interventions, usual care, or waiting lists, showed that acupuncture was effective and safe for CRF treatment.

Hot flashes

Hot flashes are a subjective symptom associated with objective signs of cutaneous vasodilation and a subsequent drop in core temperature with sweating, flushing, palpitations, anxiety, panic, and irritability, which appear in women with hypoestrogenism during climacteric and menopause periods. Among survivors of gynecological cancer, there is an increase in the prevalence of symptoms by up to 35%, worsening the QoL of these patients[27].

Many factors have been linked to loss of control of temperature regulation in the hypothalamus, including pituitary hormones, hormone-releasing factors, gonadotropins, and neurohumoral pathways. Menopause estrogen reductions are associated with decreased endorphin and 5-hydroxytryptamine (5-HT) levels and increased 5-HT receptors. This results in a loss of the feedback mechanism of increased norepinephrine production, which can reduce the thermoneutral zone and thus increase the likelihood of flushing. Therefore, any substance that increases 5-HT, estrogen, endorphins, or decreases norepinephrine can widen the thermoneutral zone and, therefore, reduce hot flashes[28].

Non-hormonal treatments, with selective serotonin reuptake inhibitors, serotonin reuptake inhibitors, norepinephrine, and gabapentin, provide partial relief to women, but with very frequent side effects, causing treatment abandonment[6,29].

Acupuncture has been recommended in the treatment of cancer patients due to its safety, high accessibility, and minimal risk of causing endometrial problems. Its action in increasing endorphin activity and neurotransmitter levels (serotonin, dopamine, and noradrenaline, in addition to metenkephalin and substance P) has already been proven, which may be associated with the modulation of thermoregulation in the hypothalamus and the neutralization of vasomotor symptoms[30].

Despite difficulties in scientific methodology in acupuncture trials, evidence has grown in favor of its use as an adjuvant treatment for hot flashes. Lund et al.[31] report that standardized, brief acupuncture treatment can produce a rapid and clinically relevant reduction in moderate to severe menopausal symptoms during a six-week intervention. Li et al.[32] state that the effectiveness of the combination acupuncture and electroacupuncture was superior to that of *sham* acupuncture and significantly superior to placebo pills, with electroacupuncture being superior to traditional acupuncture, significantly superior to *sham* acupuncture, and comparable to the results of selective serotonin inhibitors, serotonin reuptake/selective serotonin-norepinephrine reuptake inhibitors, and neuroleptic agents, with reports in the literature of therapeutic effects that persisted for six months or more and did not require continued treatment[29,33].

Nausea/vomiting

Nausea and vomiting are very common conditions in the universe of gastrointestinal dysfunctions or pathologies. In general, they are triggered by emetic stimuli not only through the central nervous system (CNS) and/or peripheral nervous system (PNS), affected by toxins, drugs, bacteria, viruses, or fungi, enterally or parenterally, but also through the skin and respiratory system[34,35].

Noxious stimuli, or those recognized as such, initiate the emetic reflex coordinated by the dorsal vagal complex in the brain stem, composed of the area postrema, the nucleus of the solitary tract, and the dorsal motor nucleus of the vagus[34,35], frequent therapeutic targets of acupuncture, whether systemic or auricular.

Stimulation of deep tissues through afferent sensory nerves is the initial event that leads to the activation of pathways involved in sensory modulation in the CNS and autonomic regulation[6].

The therapeutic potential that emerges from some known mechanisms, pathways of action, and therapeutic targets of acupuncture is effective in a relatively robust body of clinical research. Data related to post-surgical nausea and vomiting suggest a biological effect through stimulation of the acupuncture point with a needle and electrical stimulation and demonstrate benefits in controlling vomiting induced by chemotherapy[36].

In a SR and MA published in 2022, Xi et al., considered acupuncture to be promising, both post-surgery and post-chemotherapy, to treat symptoms related to cancer. Acupuncture, in this review, in relation to side effects caused by chemotherapy or

radiotherapy, such as nausea and vomiting specifically, proved to be a viable, safe, and cost-effective alternative[37].

Considering that the aim of cancer treatment is not only to eliminate the tumor lesion but also to promote the patient's QoL during treatment and beyond, therapeutic approaches that contribute to this aspect are obviously welcome. Significantly, in this sense, acupuncture has proven particularly useful in controlling gastrointestinal dysfunctions[38].

We can conclude that acupuncture can be an option for cancer survivors with relevant suffering conditions, including nausea and vomiting, that acutely affect the QoL and nutritional capacity of these individuals[12].

Insomnia

About a third to even more than half of cancer patients have insomnia[39-42]. The prevalence of insomnia differs across different types of cancer but is higher than in the general population[43]. A review by Choi et al.[44] including six RCTs, demonstrated that acupuncture was superior to *sham* acupuncture, drugs, or hormone therapy for insomnia treatment. A recent RCT with blinded data collectors and using the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines found a significant benefit of acupuncture in improving sleep quality in women with climacteric-like symptoms associated with breast cancer treatment[45].

Xerostomia

For patients with head and neck cancer undergoing combined chemoradiation treatment, xerostomia is one of the most common and debilitating side effects[6]. Recent reviews have analyzed the effect of acupuncture in the treatment of xerostomia in cancer patients[46,47]. Although several studies present a risk of bias, acupuncture had a favorable effect on patient-reported xerostomia compared with *sham* acupuncture or no treatment. The most relevant common finding in more recent papers was that acupuncture treatment was significantly associated with less severe patient-reported symptoms of salivary impairment compared with standard supportive measures up to 1 year from the end of treatment[47].

Lymphoedema

Acupuncture has been explored as a potential treatment for breast cancer-related lymphoedema (BCRL). BCRL is a common complication after breast cancer treatment, involving the accumulation of lymph fluid and swelling in the arm. The mechanisms by which acupuncture may help treat BCRL are not fully understood but likely involve enhancement of lymphatic circulation. According to TCM principles, acupuncture can restore the flow of *qi* and blood, thereby reducing stagnation and swelling. From a Western perspective, acupuncture may reduce inflammation, induce the release of neuropeptides, and modulate autonomic nervous system activity to improve lymphatic drainage[48].

Evidence for the efficacy of acupuncture in BCRL has been examined in several RCTs. A SR by Chien et al.[48] included 6 trials with 178 patients and found acupuncture did not significantly reduce arm circumference versus control but appeared safe. The heterogeneity of acupuncture techniques, outcome measures, and lack of symptom monitoring were limitations. A larger trial by Bao et al.[49] with 73 patients did not find a significant difference in arm circumference or bioimpedance between acupuncture and waitlist control. However, a 2016 study by Yao et al.[50] did report significantly greater improvement in arm circumference and range of motion with acupuncture versus medication. Overall, existing studies show promising results for acupuncture but are limited by small sample sizes.

While acupuncture may not significantly decrease limb size, it may still provide subjective symptom relief in BCRL. A pilot study by Cassileth et al.[51] found acupuncture was associated with symptom improvement in 9 patients. A trial by Jeong et al.[52] showed reduced pain and improved QoL with acupuncture in 9 patients. Though limited by the lack of control groups, these studies indicate acupuncture could benefit patient-reported symptoms. Larger studies using validated symptom surveys are needed.

Accumulating evidence shows that acupuncture is safe for BCRL patients, but uncertainty remains regarding its efficacy in limb size reduction. Potential benefits for patient symptoms have been reported, though high-quality randomized trials are still needed. Future research should utilize larger sample sizes, standardized acupuncture protocols, objective swelling assessments, and patient-reported outcomes. Elucidating the mechanisms of acupuncture in BCRL may help optimize techniques. Overall, acupuncture shows promise for integration into multimodal BCRL treatment.

Bone marrow suppression

Acupuncture has emerged as a promising supportive therapy to help mitigate myelosuppression from chemotherapy. Animal studies show acupuncture helps to regulate cytokines, growth factors, and proteins vital to hematopoiesis and immune function in models of chemotherapy-induced leukopenia and cytopenia[53,54]. Clinical studies, including a few randomized trials, indicate acupuncture reduces the severity of leukopenia and related side effects like fatigue in cancer patients undergoing chemotherapy[55,56].

Proposed mechanisms include immunomodulation, anti-inflammatory effects, and regulating hematopoiesis. Specific actions include enhancing DNA repair in bone marrow cells[54], increasing

hematopoietic cytokines like granulocyte-macrophage colony-stimulating factor (GM-CSF)[53], stimulating hematopoietic stem cell proliferation[54], and modulating regulatory proteins like cyclin D1 that influence marrow cell cycling[54]. Acupuncture may also improve the bone marrow microenvironment by promoting angiogenesis and energy metabolism.

Clinical research indicates acupuncture is well-tolerated and improves symptoms like fatigue and QoL in chemotherapy patients[56]. Adding acupuncture to usual care significantly reduced the severity of leukopenia[55]. While animal models suggest immune and hematopoietic effects, rigorous evidence in humans is needed. There is also debate around optimal acupuncture points and techniques for managing cytopenia.

Quality of life

Acupuncture has been shown to be effective in treating physical and mental conditions related to cancer patients' health. The QoL of these patients is often compromised, not only by the symptoms of the disease itself but also by the side effects of therapeutic interventions, whether radiotherapy or chemotherapy.

There are a variety of scales for judging the improvement of QoL. Two recent reviews focused on QoL[57,58]. The first one included only two RCTs of low quality and concluded that acupuncture was superior to conventional treatment[57]. The second, comprising 14 RCTs and 1,225 participants, pooled the results of different scales to evaluate the improvement of QoL and showed that acupuncture improved overall QoL compared with *sham* or no intervention.

SAFETY OF ACUPUNCTURE IN CANCER CARE

Needling performed in an acupuncture session is generally considered safe, with publications indicating a higher incidence restricted to low-risk AE and very rare serious events when performed by trained practitioners[59,60]. However, some particularities of the oncological context must be observed.

The greatest concern is the greater risk of infections and bleeding, since the interventions used to treat this population often alter both their immunity and clotting factors and modify the usual anatomy with tissue resections and prosthetic implants. Another point of attention is adequate communication between the acupuncturist, the team that conducts the oncological treatment, the patient, and their loved ones to avoid conflicts and guarantee the integration of this therapy as a complement and not a replacement for the usual treatment.

A recent SR and MA managed to include 65 articles that addressed the occurrence of AE in this context[14]. Their results indicate that there is no increase in the incidence of AE when comparing groups undergoing acupuncture and their controls (*sham* or active) but indicate a greater risk of the occurrence of low-risk events such as small bleeding, hematomas, pain at the needling site, and syncope when compared with groups undergoing usual treatment. The authors' conclusion, however, highlights the great heterogeneity in the quality of the data analyzed and suggests greater attention to the method used when reporting the AE that occurred.

Based on the data available in the literature and the experience of these authors, we suggest avoiding needling in situations of neutropenia with neutrophils below 1,000/mm^3, thrombocytopenia with platelets below 25,000/mm^3, and changes in clotting times with an international normalized ratio (INR)>2.0 or partial thromboplastin time (PTT)>60 s. Regarding the puncture site, we suggest avoiding needling adjacent to places with surgical synthesis material, metal rods, plates, and similar, the presence of tumors, and, in the case of bone lesions in the spine, avoiding needling in the muscular layer adjacent to the puncture site due to the risk of altering any muscle contractions that may be keeping the spine stable.

IMPLICATIONS FOR CLINICAL PRACTICE

For clinical practice, some SR support the use of acupuncture for cancer-related pain, CRF, breast cancer-related hot flashes, nausea, and vomiting, which is in line with clinical practice guidelines[11,19].

Clinical studies should be recommended on conditions that commonly use acupuncture in routine clinics, but lack high-quality or well-reported evidence, such as xerostomia, lymphoedema, and insomnia. Clinical trials are strongly recommended to be reported by the CONSORT Statement and its extension to acupuncture trials (STRICTA)[61], to maintain a high methodological quality.

For SR and meta-analysis, many have been conducted in the last few years for different cancer-related conditions. It is recommended that the authors who wish to perform a SR or a MA stick to the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA)[62], registering protocol before conducting, providing an exclusion list if possible, and reporting by acknowledged criteria.

CONCLUSION

This narrative review showed that acupuncture can be used for various cancer-related conditions, such as cancer-related pain, CRF, insomnia, QoL, nausea and vomiting, bone marrow

suppression, lymphoedema, and xerostomia. It is a safe method, with no serious adverse effects reported. Future reviews reporting according to the acknowledged reporting standards are recommended to improve the quality of evidence.

AUTHORS' CONTRIBUTIONS

FMS: Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **AWWT:** Conceptualization, Writing – original draft. **ED:** Conceptualization, Methodology, Writing – original draft. **SB:** Data curation, Project administration, Validation. **JBGS:** Methodology, Writing – original draft. RMB: Methodology, Writing – original draft. **JSB:** Validation, Writing – review and editing. **MYBP:** Methodology, Writing – original draft. **AH:** Supervision, Validation, Writing – original draft. **AVS:** Methodology, Visualization, Writing – original draft.

REFERENCES

1. Santos MO, Lima FCS, Martins LFL, Oliveira JFP, Almeida LM, Cancela MC. Estimativa de incidência de câncer no Brasil, 2023-2025. Rev Bras Cancerol. 2023;69(1):e-213700. https://doi.org/10.32635/2176-9745.RBC.2023v69n1.3700
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
3. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: an overview. Int J Cancer. 2021. https://doi.org/10.1002/ijc.33588
4. Dans M, Kutner JS, Agarwal R, Baker JN, Bauman JR, Beck AC, et al. NCCN guidelines® insights: palliative care, version 2.2021. J Natl Compr Canc Netw. 2021;19(7):780-8. https://doi.org/10.6004/jnccn.2021.0033
5. Wu X, Chung VC, Hui EP, Ziea ET, Ng BF, Ho RS, et al. Effectiveness of acupuncture and related therapies for palliative care of cancer: overview of systematic reviews. Sci Rep. 2015;5:16776. https://doi.org/10.1038/srep16776
6. Zia FZ, Olaku O, Bao T, Berger A, Deng G, Fan AY, et al. The National cancer institute's conference on acupuncture for symptom management in oncology: state of the science, evidence, and research gaps. J Natl Cancer Inst Monogr. 2017;2017(52):lgx005. https://doi.org/10.1093/jncimonographs/lgx005
7. World Health Organization. WHO Traditional medicine strategy: 2014-2023. Geneva: World Health Organization; 2013.
8. Zeng Y, Xia J, Chen Z, Tian X, Ren Y. Transcutaneous electrical acupoint stimulation (TEAS) for cancer-related fatigue: study protocol for a systematic review and meta-analysis. BMJ Open. 2021;11(11):e049318. https://doi.org/10.1136/bmjopen-2021-049318
9. Yang Y, Wen J, Hong J. The Effects of auricular therapy for cancer pain: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2020;2020:1618767. https://doi.org/10.1155/2020/1618767
10. Alimi D, Rubino C, Pichard-Léandri E, Fermand-Brulé S, Dubreuil-Lemaire ML, Hill C. Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial. J Clin Oncol. 2003;21(22):4120-6. https://doi.org/10.1200/JCO.2003.09.011
11. Birch S, Lee MS, Alraek T, Kim TH. Evidence, safety and recommendations for when to use acupuncture for treating cancer related symptoms: a narrative review. Integr Med Res. 2019;8(3):160-6. https://doi.org/10.1016/j.imr.2019.05.002
12. Zhang XW, Hou WB, Pu FL, Wang XF, Wang YR, Yang M, et al. Acupuncture for cancer-related conditions: an overview of systematic reviews. Phytomedicine. 2022;106:154430. https://doi.org/10.1016/j.phymed.2022.154430
13. Wang CC, Tan JY, Williams A. Safety and side effects of acupuncture therapy in Australia: a systematic review. Eur J Int Med. 2019;27:81-9. https://doi.org/10.1016/j.eujim.2019.03.004
14. Höxtermann MD, Haller H, Aboudamaah S, Bachemir A, Dobos G, Cramer H, et al. Safety of acupuncture in oncology: a systematic review and meta-analysis of randomized controlled trials. Cancer. 2022;128(11):2159-73. https://doi.org/10.1002/cncr.34165
15. Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage. 2016;51(6):1070-90.e9. https://doi.org/10.1016/j.jpainsymman.2015.12.340
16. Paley CA, Johnson MI, Tashani OA, Bagnall AM. Acupuncture for cancer pain in adults. Cochrane Database Syst Rev. 2015;2015(10):CD007753. https://doi.org/10.1002/14651858.CD007753.pub3
17. Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, et al. Management of cancer pain in adult patients: ESMO clinical practice guidelines. Ann Oncol. 2018;29(Suppl 4):iv166-91. https://doi.org/10.1093/annonc/mdy152
18. Chiu HY, Hsieh YJ, Tsai PS. Systematic review and meta-analysis of acupuncture to reduce cancer-related pain. Eur J Cancer Care (Engl). 2017;26(2). https://doi.org/10.1111/ecc.12457
19. Ge L, Wang Q, He Y, Wu D, Zhou Q, Xu N, et al. Acupuncture for cancer pain: an evidence-based clinical practice guideline. Chin Med. 2022;17(1):8. https://doi.org/10.1186/s13020-021-00558-4
20. Yang J, Wahner-Roedler DL, Zhou X, Johnson LA, Do A, Pachman DR, et al. Acupuncture for palliative cancer pain management: systematic review. BMJ Support Palliat Care. 2021;11(3):264-70. https://doi.org/10.1136/bmjspcare-2020-002638
21. Iop A, Manfredi AM, Bonura S. Fatigue in cancer patients receiving chemotherapy: an analysis of published studies. Ann Oncol. 2004;15(5):712-20. https://doi.org/10.1093/annonc/mdh102
22. He XR, Wang Q, Li PP. Acupuncture and moxibustion for cancer-related fatigue: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2013;14(5):3067-74. https://doi.org/10.7314/apjcp.2013.14.5.3067
23. Posadzki P, Moon TW, Choi TY, Park TY, Lee MS, Ernst E. Acupuncture for cancer-related fatigue: a systematic review of randomized clinical trials. Support Care Cancer. 2013;21(7):2067-73. https://doi.org/10.1007/s00520-013-1765-z
24. Finnegan-John J, Molassiotis A, Richardson A, Ream E. A systematic review of complementary and alternative medicine interventions

for the management of cancer-related fatigue. Integr Cancer Ther. 2013;12(4):276-90. https://doi.org/10.1177/1534735413485816

25. Choi TY, Ang L, Jun JH, Alraek T, Birch S, Lu W, et al. Acupuncture for managing cancer-related fatigue in breast cancer patients: a systematic review and meta-analysis. Cancers (Basel). 2022;14(18):4419. https://doi.org/10.3390/cancers14184419
26. Tian H, Chen Y, Sun M, Huang L, Xu G, Yang C, et al. Acupuncture therapies for cancer-related fatigue: a Bayesian network meta-analysis and systematic review. Front Oncol. 2023;13:1071326. https://doi.org/10.3389/fonc.2023.1071326
27. Horesh D, Kohavi S, Shilony-Nalaboff L, Rudich N, Greenman D, Feuerstein JS, et al. Virtual reality combined with artificial intelligence (VR-AI) reduces hot flashes and improves psychological well-being in women with breast and ovarian cancer: a pilot study. Healthcare (Basel). 2022;10(11):2261. https://doi.org/10.3390/healthcare10112261
28. Sturdee DW. The menopausal hot flush--anything new? Maturitas. 2008;60(1):42-9. https://doi.org/10.1016/j.maturitas.2008.02.006
29. Mao JJ, Bowman MA, Xie SX, Bruner D, DeMichele A, Farrar JT. Electroacupuncture versus gabapentin for hot flashes among breast cancer survivors: a randomized placebo-controlled trial. J Clin Oncol. 2015;33(31):3615-20. https://doi.org/10.1200/JCO.2015.60.9412
30. Li H, Schlaeger JM, Jang MK, Lin Y, Park C, Liu T, et al. Acupuncture Improves multiple treatment-related symptoms in breast cancer survivors: a systematic review and meta-analysis. J Altern Complement Med. 2021;27(12):1084-97. https://doi.org/10.1089/acm.2021.0133
31. Lund KS, Siersma V, Brodersen J, Waldorff FB. Efficacy of a standardised acupuncture approach for women with bothersome menopausal symptoms: a pragmatic randomised study in primary care (the ACOM study). BMJ Open. 2019;9(1):e023637. https://doi.org/10.1136/bmjopen-2018-023637
32. Li T, Zhang Y, Cheng Q, Hou M, Zheng X, Zheng Q, et al. Quantitative study on the efficacy of acupuncture in the treatment of menopausal hot flashes and its comparison with nonhormonal drugs. Menopause. 2021;28(5):564-72. https://doi.org/10.1097/GME.0000000000001767
33. Lesi G, Razzini G, Musti MA, Stivanello E, Petrucci C, Benedetti B, et al. Acupuncture as an integrative approach for the treatment of hot flashes in women with breast cancer: a prospective multicenter randomized controlled trial (AcCliMaT). J Clin Oncol. 2016;34(15):1795-802. https://doi.org/10.1200/JCO.2015.63.2893
34. Zhong W, Shahbaz O, Teskey G, Beever A, Kachour N, Venketaraman V, et al. Mechanisms of nausea and vomiting: current knowledge and recent advances in intracellular emetic signaling systems. Int J Mol Sci. 2021;22(11):5797. https://doi.org/10.3390/ijms22115797
35. Heckroth M, Luckett RT, Moser C, Parajuli D, Abell TL. Nausea and vomiting in 2021: a comprehensive update. J Clin Gastroenterol. 2021;55(4):279-99. https://doi.org/10.1097/MCG.0000000000001485
36. Ezzo J, Vickers A, Richardson MA, Allen C, Dibble SL, Issell B, et al. Acupuncture-point stimulation for chemotherapy-induced nausea and vomiting. J Clin Oncol. 2005;23(28):7188-98. https://doi.org/10.1200/JCO.2005.06.028
37. Xi Z, Wei X, Ye Z, Wang K, Zhou J. Acupuncture for adult lung cancer of patient-reported outcomes: a systematic review and meta-analysis. Front Oncol. 2022;12:921151. https://doi.org/10.3389/fonc.2022.921151
38. Lin D, Ou Y, Li L, Wu K, Zhang Q, Yan J, et al. Acupuncture for postoperative gastrointestinal dysfunction in cancer: a systematic review and meta-analysis. Front Oncol. 2023;13:1184228. https://doi.org/10.3389/fonc.2023.1184228
39. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol. 2001;19(3):895-908. https://doi.org/10.1200/JCO.2001.19.3.895
40. Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. Soc Sci Med. 2002;54(9):1309-21. https://doi.org/10.1016/s0277-9536(01)00043-0
41. Chen ML, Yu CT, Yang CH. Sleep disturbances and quality of life in lung cancer patients undergoing chemotherapy. Lung Cancer. 2008;62(3):391-400. https://doi.org/10.1016/j.lungcan.2008.03.016
42. Liu L, Ancoli-Israel S. Sleep disturbances in cancer. Psychiatr Ann. 2008;38(9):627-34. https://doi.org/10.3928/00485713-20080901-01
43. Anderson KO, Getto CJ, Mendoza TR, Palmer SN, Wang XS, Reyes-Gibby CC, et al. Fatigue and sleep disturbance in patients with cancer, patients with clinical depression, and community-dwelling adults. J Pain Symptom Manage. 2003;25(4):307-18. https://doi.org/10.1016/s0885-3924(02)00682-6
44. Choi TY, Kim JI, Lim HJ, Lee MS. Acupuncture for managing cancer-related insomnia: a systematic review of randomized clinical trials. Integr Cancer Ther. 2017;16(2):135-46. https://doi.org/10.1177/1534735416664172
45. D'Alessandro EG, Silva AV, Cecatto RB, Brito CMM, Azevedo RS, Lin CA. Acupuncture for climacteric-like symptoms in breast cancer improves sleep, mental and emotional health: a randomized trial. Med Acupunct. 2022;34(1):58-65. https://doi.org/10.1089/acu.2021.0073
46. Ni X, Tian T, Chen D, Liu L, Li X, Li F, et al. Acupuncture for radiation-induced xerostomia in cancer patients: a systematic review and meta-analysis. Integr Cancer Ther. 2020;19:1534735420980825. https://doi.org/10.1177/1534735420980825
47. Bonomo P, Stocchi G, Caini S, Desideri I, Santarlasci V, Becherini C, et al. Acupuncture for radiation-induced toxicity in head and neck squamous cell carcinoma: a systematic review based on PICO criteria. Eur Arch Otorhinolaryngol. 2022;279(4):2083-97. https://doi.org/10.1007/s00405-021-07002-1
48. Chien TJ, Liu CY, Fang CJ. The effect of acupuncture in breast cancer-related lymphoedema (BCRL): a systematic review and meta-analysis. Integr Cancer Ther. 2019;18:1534735419866910. https://doi.org/10.1177/1534735419866910
49. Bao T, Iris Zhi W, Vertosick EA, Li QS, Rito J, Vickers A, et al. Acupuncture for breast cancer-related lymphedema: a randomized controlled trial. Breast Cancer Res Treat. 2018;170(1):77-87. https://doi.org/10.1007/s10549-018-4743-9
50. Yao C, Xu Y, Chen L, Jiang H, Ki CS, Byun JS, et al. Effects of warm acupuncture on breast cancer-related chronic lymphedema: a randomized controlled trial. Curr Oncol. 2016;23(1):e27-34. https://doi.org/10.3747/co.23.2788
51. Cassileth BR, Zee KJ, Chan Y, Coleton MI, Hudis CA, Cohen S, et al. A safety and efficacy pilot study of acupuncture for the treatment of chronic lymphoedema. Acupunct Med. 2011;29(3):170-2. https://doi.org/10.1136/aim.2011.004069
52. Jeong YJ, Kwon HJ, Park YS, Kwon OC, Shin IH, Park SH. Treatment of lymphedema with saam acupuncture in patients with breast cancer: a pilot study. Med Acupunct. 2015;27(3):206-15. https://doi.org/10.1089/acu.2014.1071
53. Cui J, Yan J. Effect of moxibustion or acupuncture at Geshu acupoint on the granulocyte-macrophage colony stimulating factor of cylophosphamide induced leukopenic rats. J Clin Rehabili Tissue Eng Res. 2007;11(28):5473-6.

54. Lu M, Cao DM, Zhao XX. [Study on dynamic effect of acupuncture on marrow cell cycle regulatory protein cyclin D1 expression and cell cycle in mice with cyclophosphamide induced myelosuppression]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2011;31(2):238-43. PMID: 21425582

55. Shih YW, Su JY, Kung YS, Lin YH, To Anh DT, Ridwan ES, et al. Effectiveness of acupuncture in relieving chemotherapy-induced leukopenia in patients with breast cancer: a systematic review with a meta-analysis and trial sequential analysis. Integr Cancer Ther. 2021;20:15347354211063884. https://doi.org/10.1177/15347354211063884

56. Molassiotis A, Bardy J, Finnegan-John J, Mackereth P, Ryder DW, Filshie J, et al. Acupuncture for cancer-related fatigue in patients with breast cancer: a pragmatic randomized controlled trial. J Clin Oncol. 2012;30(36):4470-6. https://doi.org/10.1200/JCO.2012.41.6222

57. Lian WL, Pan MQ, Zhou DH, Zhang ZJ. Effectiveness of acupuncture for palliative care in cancer patients: a systematic review. Chin J Integr Med. 2014;20(2):136-47. https://doi.org/10.1007/s11655-013-1439-1

58. Zhang Y, Sun Y, Li D, Liu X, Fang C, Yang C, et al. Acupuncture for breast cancer: a systematic review and meta-analysis of patient-reported outcomes. Front Oncol. 2021;11:646315. https://doi.org/10.3389/fonc.2021.646315

59. Melchart D, Weidenhammer W, Streng A, Reitmayr S, Hoppe A, Ernst E, et al. Prospective investigation of adverse effects of acupuncture in 97 733 patients. Arch Intern Med. 2004;164(1):104-5. https://doi.org/10.1001/archinte.164.1.104

60. Ernst E, White AR. Prospective studies of the safety of acupuncture: a systematic review. Am J Med. 2001;110(6):481-5. https://doi.org/10.1016/s0002-9343(01)00651-9

61. Hughes JG, Lewith G, MacPherson H, Witt CM, Cummings M, Fisher P. Assessment of the quality of reporting in studies of acupuncture for patients with cancer using the STRICTA guidelines. Acupunct Med. 2019;37(4):223-7. https://doi.org/10.1136/acupmed-2017-011592

62. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71

REVIEW ARTICLE

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Anesthesia and cancer

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INTRODUCTION

Major surgeries have an influence on the neuroendocrine system [hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS)], leading to cytokine-mediated stress responses that cause immunosuppression. During surgical procedures, tumor cells are released, and tumor emboli are disseminated. Hence, the surgery itself appears to be associated with an increased risk of cancer metastasis and recurrence[1] (Figure 1).

PERIOPERATIVE IMMUNOSUPPRESSION

Th1-type responses, including $CD8^+$ T lymphocytes and natural killer (NK) cells, are required for immunity against tumor growth. However, the dominant Th2 status, yet not Th1, develops in cancer patients. In this context, surgical stress further induces Th1/Th2 balance toward Th2[2]-type immune responses.

The main causes of responses toward immunosuppression in surgical patients relate to the neuroendocrine stress exerted by SNS and HPA axis activation[1].

The immune system is innervated with sympathetic nerve fibers and catecholamines (adrenaline and noradrenaline) released from the nerve terminal, binding to b2-adrenergic receptors expressed in T cells, NK cells, and macrophages[1].

These interactions between catecholamines and b2-adrenoreceptors increase intracellular cyclic adenosine monophosphate (cAMP), inhibit NK cell activity, and polarize T cells and macrophages in Th2 cytokine production, leading to a shift toward the Th2 response, although catecholamines are known to mobilize b2-adrenoreceptors. Therefore, sympathetic activation during surgery suppresses antitumor immunity[1].

HPA axis activation leads to the increased production of adrenocorticotropic hormone (ACTH) in the pituitary gland,

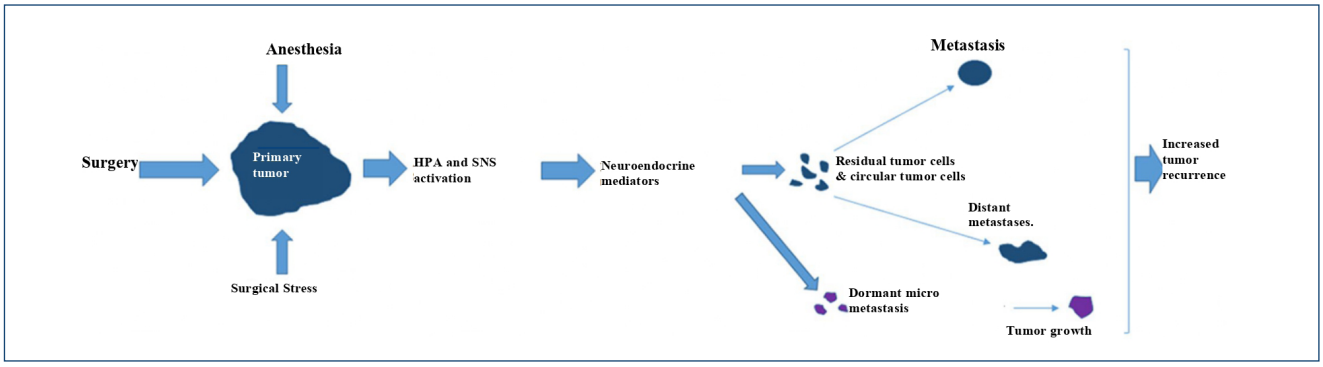

Figure 1. Hypothesis to explain cancer metastasis and recurrence caused by surgery and perioperative anesthetic-induced immunosuppression. Surgery, anesthesia, and analgesia stimulate the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system during the perioperative period. Activated neuroendocrine mediators lead to increases in several soluble immunosuppressive factors that promote tumor progression and metastasis, resulting in increased cancer recurrence. Adapted from Kim[1].

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releasing glucocorticoids from the adrenal glands. The interaction between glucocorticoids and receptors expressed on immune cells prevents the production of Th1 cytokines on macrophages and T cells, promoting Th2[1] polarization.

HYPOTENSION, HYPOVOLEMIA, AND HYPOXIA

Hypotension and hypovolemia activate the SNS and HPA axes; they also cause decreased tissue perfusion and cellular hypoxia, which induce increased adhesion molecule expression in the vascular endothelium, initiating a systemic inflammatory response that results in reduced Th1 activity. Hypoxia impulses generate hypoxia-induced factor (HIF) activation in the immune cells and tumor cells[3].

Increasing HIF production in T cells induces a change from a Th1 to a Th2 phenotype by increasing interleukin-10 (IL-10) production and decreasing IFN-γ, as well as stimulating Treg cell differentiation and proliferation. Expression of HIF on tumor cells promotes tumor cell proliferation and induces angiogenic factor[3] secretion.

HYPOTHERMIA

In vitro experimental studies demonstrate that monocytes incubated at low temperatures reduce human leukocyte antigen-DR isotype (HLA-DR) antigen expression and increase tumor necrosis factor-α (TNF-α) and IL-10 release, generating chronic inflammation. *In vivo* animal studies have revealed that hypothermia suppresses NK cell activity and increases tumor metastasis risk[4].

HYPERGLYCEMIA

Acute perioperative hyperglycemia inhibits glucose-6-phosphate dehydrogenase, the enzyme responsible for forming nicotinamide adenine dinucleotide phosphate, suppressing monocyte and neutrophil functions. The degree of hyperglycemia required to impair phagocytosis is about 200 mg dL^{-1}. However, hyperglycemia can evoke leukocyte adhesion-triggered microvascular inflammation in the endothelium through the generation of adhesion molecules. Microvascular inflammation, depending on high glucose- and NF-κB activation-associated increased osmolarity, leads to increased inflammatory cytokine production in addition to HPA axis activation. Thus, insulin can reduce the levels of these cytokines and inhibit the NF-κB pathway in monocytes, playing an anti-inflammatory role[5].

BLOOD TRANSFUSION

Allogeneic blood transfusion is known to cause transfusion-related immunomodulation (TRIM). TRIM can be mediated by allogeneic mononuclear cells, soluble mediators derived from white blood cells, and allogeneic plasma-soluble HLA peptides. However, removal of leukocytes from allogeneic blood failed to reduce TRIM because transfusion of packed red blood cells also suppresses immunity in patients receiving allogeneic blood transfusions[6].

While the mechanisms by which allogeneic blood transfusion suppresses recipients' immunity remain unclear, deleucotized donor red blood cells may have direct suppressive effects. Red blood cells contain constituent substances such as metabolically active arginase, an enzyme of the urea cycle that is expressed in cells throughout the body and limits the availability of arginine, which is an amino acid needed for T cell proliferation and expression of the functional ς chain of cytotoxic lymphocytes. Therefore, arginase-mediated arginine depletion can strongly suppress the function of T-cell receptors[7].

In addition, allogeneic blood transfusion-related immunosuppression is mediated by the induction of Treg, which can suppress $CD4^+$ and $CD8^+$ T cells and inhibit dendritic cell function. Therefore, for reducing both transfusion and blood loss in surgeries, the use of cell saver and erythropoietin is worthy of consideration[7].

NUTRITIONAL STATUS

Preoperative malnutrition, present with some frequency in cancer patients, leads to immunosuppression. Therefore, some authors advocate the practice of the so-called "immunonutrition", in which the administration of arginine and omega-3 fatty acids may favor Th1 polarization and thus have a beneficial effect on these patients[8].

DRUGS

Inhaled anesthetics

A study investigated the effects of isoflurane on the expression of tumor markers, including insulin-like growth factor (IGF-1) and proliferative capacity in ovarian cancer cells, and demonstrated that isoflurane significantly increased IGF-1 receptor expression, cell cycle progression, and cell proliferation in ovarian cancer cells. It also showed increased expression of the angiogenic markers, namely, vascular endothelial growth factor (VEGF) and angiopoietin-1. Cancer cell migration after exposure to isoflurane has been associated with an increased

production of metalloproteinases 2 and 9, enzymes that ease local dissemination of tumor cells[9]. A small study with 40 patients presenting for colon cancer surgery showed that serum levels of pro-angiogenic VEGF-C factors and transforming growth factor beta-1 increased significantly in patients receiving inhalational anesthesia versus propofol-epidural anesthesia[10].

Another study evaluating the response of glioma stem cell exposure to varying durations and concentrations of sevoflurane compared to controls showed increased cancer cell proliferation and a capacity for self-renewal following sevoflurane use[11].

Kvolik et al., investigated the cytotoxic and antiproliferative effects of sevoflurane on different *in vitro* human cancer cell lines and found that the apoptotic rate significantly increased 24 h after anesthesia and was associated with the increased expression of the p53 and caspase-3 genes in colon cancer cells. They also noted a decrease in laryngeal cancer cell expression, suggesting any potential beneficial effect of this volatile agent on increasing cell apoptosis in this cancer and that it may be tumor cell line-dependent[12].

Although conflicting evidence remains on the potential deleterious effects of volatile agents based on the in vitro study evidence to date, there is insufficient evidence to justify avoiding these agents in cancer patients[13].

Nitrous oxide

The immunosuppressive effect of nitrous oxide, mediated through selective inhibition of methionine synthase and, therefore, purine and thymidylate synthesis, causes macrophage and NK cell function depression[14]. The ENIGMA-II trial found that the use of nitrous oxide did not interfere with cancer recurrence or mortality[15].

Another study with a specific focus on nitrous oxide and cancer evaluated the recurrence rate of colon cancer in a randomized trial with 204 patients undergoing 65% nitrous oxide or oxygen concentration during surgery and found a similar recurrence rate in both groups[16].

Propofol

Some of the direct effects of propofol include inhibition of proliferation, migration, invasion, and induction of apoptosis based on micro-RNA changes and influence on signaling pathways such as inhibition of mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB), and HIF-1α[17]. On the contrary, propofol has been described to activate erythroid nuclear factor-related factor 2 (Nrf2) in bladder cancer, which leads to apoptosis inhibition. Propofol indirectly interferes with tumor progression by increasing chemosensitivity and maintaining immune function. Increased chemosensitivity was found for trastuzumab in breast cancer, paclitaxel and cisplatin in ovarian cancer, and gemcitabine in pancreatic cancer. Propofol conserves immune function compared to sevoflurane, which suppresses T1-lymphocytes in cervical and colorectal cancer[18].

However, another *in vivo* study showed a depletion of tumor-associated macrophages from the tumor microenvironment and an upregulation of immune checkpoint-programmed death ligand-1 (PD-L1) by sevoflurane in melanomas, indicating a possible positive effect of sevoflurane in combination with the checkpoint-programmed death-1 (PD-1)[19] inhibitor.

Several retrospective analyses indicate a beneficial effect of propofol compared to inhaled agents. A meta-analysis carried out by Jin et al.[20] summarized 12 studies with an overall mortality hazard ratio of 0.73% [95% confidence interval (CI) 0.60–0.89] for total intravenous anesthesia (TIVA). However, when divided into subgroups of different types of cancer, only a statistical analysis of breast and colorectal cancer could be run, showing a positive trend for TIVA in colorectal cancer but not in breast cancer. The limitations of this study are numerous: retrospective design, lack of statistical strength, and uncertain control of confounding factors. Still, a large cohort study in Japan (166,966 inhalational anesthesia, 29,337 TIVA) showed no difference in survival compared to any digestive tract cancer surgery. There was, however, a slight advantage in recurrence-free survival for TIVA upon analyzing instrumental variables (95%CI 0.87–0.98; p=0.01)[21].

Few well-designed clinical trials have prospectively investigated the use of propofol and tumor recurrence. A large multicenter randomized controlled trial (n=2108) compared recurrence rates (7-year follow-up) after curative breast cancer resection and found no difference between a paravertebral block combined with propofol and general anesthesia with sevoflurane and opioids[22].

Ketamine

Ketamine as an anesthetic or at higher doses (up to 80 mg kg^{-1}) has been shown to suppress NK cell activity, possibly via sympathetic activation. Additionally, low-dose ketamine as an adjuvant to general anesthesia reduced inflammatory responses and pain after cancer surgery, which could be advantageous for mitigating NK cell activity suppression. Ketamine can exert a direct influence on NK cell activity as its use leads to N-methyl-D-aspartate (NMDA) receptor activation suppression and subsequent changes in intracellular calcium and reactive oxygen species[23].

A study by Duan et al.[24] demonstrated that ketamine decreased intracellular calcium levels, leading to a reduction of VEGF1 expression and cell migration. It concluded that the

antitumor effect of ketamine can be achieved by blocking the NMDA receptor. A meta-analysis also showed the anti-inflammatory property of ketamine on cytokines, especially IL-6[25].

In another study carried out by Forget et al.[26] which evaluated the use of analgesics on tumor recurrence after mastectomy, the use of ketamine was not associated with an improvement in cancer patient outcome.

Alpha agonists

Despite their frequent use as sedatives and analgesic agents, very few studies focus on the effects of α-2 adrenoceptor agonists on cancer. Given the overall pro-tumor effects of catecholamines, it can be postulated that agents that similarly activate adrenoceptors should also promote carcinogenic effects. On the other hand, a small, randomized trial with patients undergoing radical gastrectomy for dexmedetomidine or saline infusion demonstrated that dexmedetomidine resulted in reduced levels of catecholamines and pro-inflammatory cytokines, suggesting a potentially beneficial antitumor effect[27].

While animal studies have shown potential for promoting cancer recurrence and metastasis due to their role in facilitating angiogenesis, thus leading to metastasis, randomized human studies have not shown conclusive results[28].

Evidence suggests that dexmedetomidine may reduce the degree of immune function suppression and keep the number of CD3+ cells, NK cells, the CD4+/CD8+ ratio, and the Th1/Th2 ratio stable by decreasing the level of pro-inflammatory cytokines (IL-6 and TNF-α) during cancer operations. However, dexmedetomidine exhibits different roles in cell biology behavior depending on the types of cancer cells. Therefore, this is still a new area that needs further exploration.

Opioids

There is conflicting evidence from experimental studies investigating the role of opioids in tumor growth and metastases. Several animal studies have found that some opioids promote immunosuppression and, in turn, postoperative tumor recurrence, with effects on immune function varying between different types of opioids. Namely, morphine has been shown to suppress NK cell cytotoxicity and T cell proliferation. However, a few studies contradict these findings by proposing that morphine has antitumor effects. Similarly, fentanyl has shown the inhibition of NK cells and the promotion of lymphocyte and macrophage apoptosis in several laboratory studies. Still, a recent retrospective cohort study with 1,679 patients with stage I-III colorectal cancer showed no association between fentanyl and oncological or prognostic outcomes. Alternatively, tramadol has been shown to have immunostimulatory properties by increasing the cytotoxicity of NK[29] cells.

A special interest emerged in methadone, which has been shown to increase the apoptosis and chemosensitivity of *in vitro* and *in vivo* leukemic and glioblastoma cells through a reduction of cAMP, which leads to caspase activation. However, these preclinical findings have not yet been found in well-designed clinical studies, and the adverse effects of methadone, especially in pain-free patients, should be considered with caution[30].

There is also evidence that mu opioid receptors (MOR) are overexpressed in certain cancers. As a consequence, opioid binding in MOR directly promotes cancer cell growth via growth factor-induced receptor signaling and angiogenesis potentiation. A lung sample study with 34 lung cancer patients demonstrated a twofold increase in MOR expression in patients with metastatic lung disease. Clinical studies further support the role of MOR in cancer progression. In a retrospective study with 113 patients with prostate cancer, MOR overexpression was associated with reduced overall survival and progression-free survival, especially in those with metastatic disease. In line with these results, two randomized clinical trials showed that treatment with methylnaltrexone (a MOR antagonist) is associated with increased overall survival in terminal cancer patients[31,32].

Overall, the role of opioids in facilitating tumor recurrence and metastasis is variable and influenced by opioid type, dosage, and form of administration. More controlled, randomized, and prospective studies are still needed for higher-quality clinical evidence.

LOCAL ANESTHETICS

If administered epidurally, local anesthetics are partially absorbed into the bloodstream, reaching concentrations of 1–10 μM. This concentration of local anesthetics also reaches tumor cells. *In vitro* data showed a dose-dependent antiproliferative effect of local anesthetics in various cancer types. For example, inhibition of migration, invasion, and progression of colorectal cancer cells in response to lidocaine (10 μM), ropivacaine (10 μM), and bupivacaine (1 mM). Similar results were found in gastric cancer. Low bupivacaine concentrations (10 μM) reduced the migration of gastric cancer cells, while high concentrations (1 mM) also increased apoptosis[33].

The most recent evidence points to a possible synergistic effect of LA along with chemotherapy. *In vitro*, lidocaine appears to have a potentiating effect on cisplatin chemotoxicity through demethylation of retinoic acid receptor beta 2 (RAR beta 2), located in the cell nucleus, and the Ras association domain-containing tumor suppressor 1 (RASSF1) protein in breast cancer cells. In another recent study by Chamaraux-Tran et al.[34] lidocaine demonstrated a direct cytotoxic effect on *in vitro* breast cancer cells and in an *in vivo* mouse model.

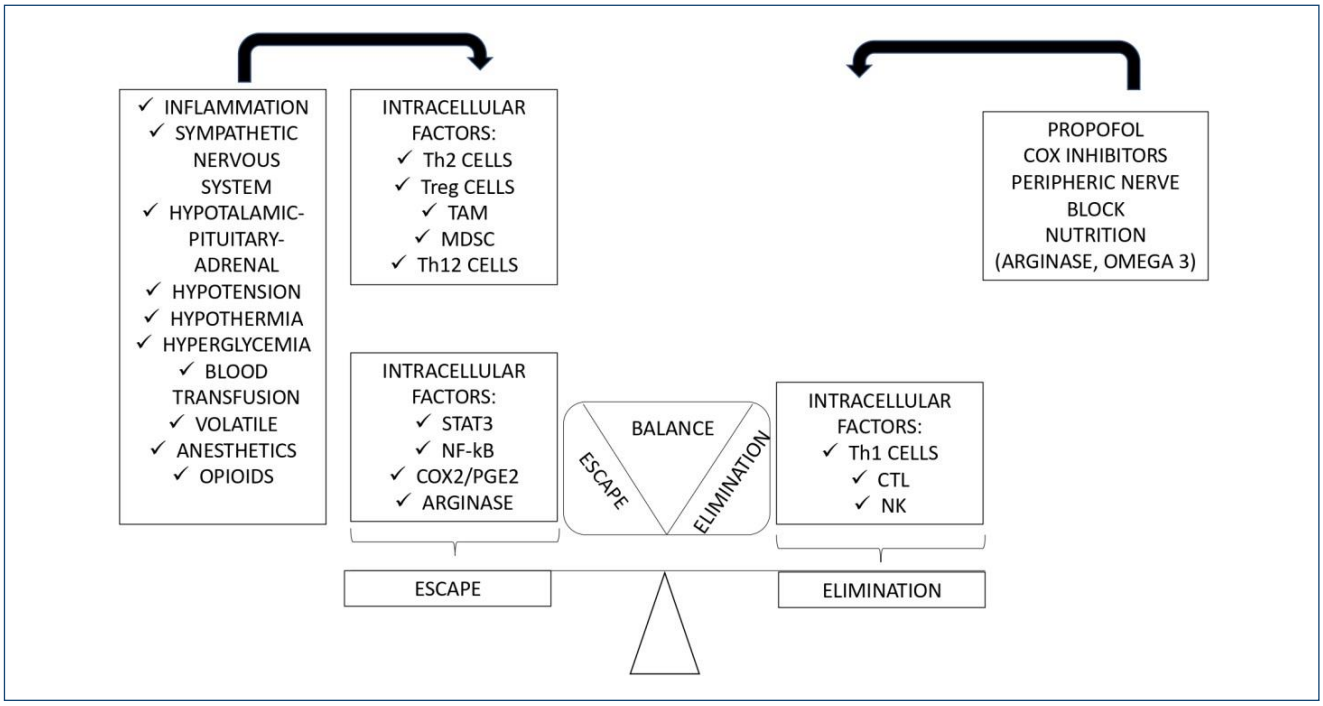

Figure 2. Mechanisms related to TH1 or TH2 polarization and their relationship with factors present in the perioperative period. Adapted from Junqueira et al.[8]. Th2: helper 2 type cells; Treg cells: regulatory cells; TAM cells: macrophage-associated tumor cells; MDSC cells: myeloid suppressor cells; NK cells: natural killer cells; STAT3: signal transducer and activator of transcription 3; NF-κB: nuclear factor kappa light-chain enhancer of activated B cells; COX-2: cyclooxygenase 2; PGE2: prostaglandin 2.

LA can also induce apoptosis in cancer cells by activating caspases and regulating the MAPK signaling pathway. The inhibitory effect of lidocaine on Src tyrosine-protein kinase indicates that systemically administered local anesthetics can potentially prevent tumor cell metastasis[35].

A retrospective analysis of intraoperative IV lidocaine use in pancreatic surgery (n=915 in each group) revealed an improvement in overall survival after 1 (68% vs. 62.6%, p<0.001) and 3 years (34.1% vs. 27.2%, p=0.011)[36]. A controlled, randomized, prospective study identified a reduction of myeloperoxidase, histone H3, and matrix metalloproteinase MMP3 via intraoperative infusion of IV lidocaine during breast cancer surgery. These findings support the hypothesis of an antimetastatic effect of lidocaine[37].

Another study compared the rate of breast cancer recurrence after curative surgery in more than 2,000 patients who received propofol-based anesthesia in combination with a paravertebral nerve block or general anesthesia with sevoflurane and an opioid-based analgesic regimen. There was no difference in relation to the primary outcome between these two groups[38].

Current evidence supports the use of intraoperative lidocaine IV infusion as a supplement in pain therapy when epidural anesthesia is not possible or desired. In addition, the hypothesis of lidocaine having an anticancer effect has been formulated, but benefits in terms of survival and recurrence rates have not yet been demonstrated in prospective randomized clinical trials.

CONCLUSION

With the increasing number of patients undergoing oncological surgeries and the number of studies suggesting possible long-term effects of the anesthetic technique on tumor growth, there is an increased need for more multicenter studies that can address these issues more clearly.

A summary of what was exposed in this article can be seen in Figure 2.

AUTHORS' CONTRIBUTIONS

PCL: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **MACA**: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **LASD**: Validation, Visualization, Writing – original draft, Writing – review & editing. **MÂT**: Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. J Transl Med. 2018;16(1):8. https://doi.org/10.1186/s12967-018-1389-7
2. Kuroda E, Yamashita U. Mechanisms of enhanced macrophage-mediated prostaglandin E2 production and its suppressive role in Th1 activation in Th2-dominant BALB/c mice. J Immunol. 2003;170(2):757-64. https://doi.org/10.4049/jimmunol.170.2.757
3. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. N Engl J Med. 2011;364(7):656-65. https://doi.org/10.1056/NEJMra0910283
4. Ben-Eliyahu S, Shakhar G, Rosenne E, Levinson Y, Beilin B. Hypothermia in barbiturate-anesthetized rats suppresses natural killer cell activity and compromises resistance to tumor metastasis: a role for adrenergic mechanisms. Anesthesiology. 1999;91(3):732-40. https://doi.org/10.1097/00000542-199909000-00026
5. Turina M, Miller FN, Tucker CF, Polk HC. Short-term hyperglycemia in surgical patients and a study of related cellular mechanisms. Ann Surg. 2006;243(6):845-51; discussion 851-3. https://doi.org/10.1097/01.sla.0000220041.68156.67
6. Weber RS, Jabbour N, Martin RC. Anemia and transfusions in patients undergoing surgery for cancer. Ann Surg Oncol. 2008;15(1):34-45. https://doi.org/10.1245/s10434-007-9502-9
7. Ng T, Ryder BA, Chern H, Sellke FW, Machan JT, Harrington DT, et al. Leukocyte-depleted blood transfusion is associated with decreased survival in resected early-stage lung cancer. J Thorac Cardiovasc Surg. 2012;143(4):815-9. https://doi.org/10.1016/j.jtcvs.2011.12.031
8. Kurosawa S. Anesthesia in patients with cancer disorders. Curr Opin Anaesthesiol. 2012;25(3):376-84. https://doi.org/10.1097/ACO.0b013e328352b4a8
9. Luo X, Zhao H, Hennah L, Ning J, Liu J, Tu H, et al. Impact of isoflurane on malignant capability of ovarian cancer in vitro. Br J Anaesth. 2015;114(5):831-9. https://doi.org/10.1093/bja/aeu408
10. Xu YJ, Chen WK, Zhu Y, Wang SL, Miao CH. Effect of thoracic epidural anaesthesia on serum vascular endothelial growth factor C and cytokines in patients undergoing anaesthesia and surgery for colon cancer. Br J Anaesth. 2014;1:113(Suppl 1):i49-55. https://doi.org/10.1093/bja/aeu148
11. Shi QY, Zhang SJ, Liu L, Chen QS, Yu LN, Zhang FJ, et al. Sevoflurane promotes the expansion of glioma stem cells through activation of hypoxia-inducible factors in vitro. Br J Anaesth. 2015;114(5):825-30. https://doi.org/10.1093/bja/aeu402
12. Kvolik S, Dobrosevic B, Marczi S, Prlic L, Glavas-Obrovac L. Different apoptosis ratios and gene expressions in two human cell lines after sevoflurane anaesthesia. Acta Anaesthesiol Scand. 2009;53(9):1192-9. https://doi.org/10.1111/j.1399-6576.2009.02036.x
13. Yoo S, Lee HB, Han W, Noh DY, Park SK, Kim WH, et al. Total intravenous anesthesia versus inhalation anesthesia for breast cancer surgery: a retrospective cohort study. Anesthesiology. 2019;130(1):31-40. https://doi.org/10.1097/ALN.0000000000002491
14. Sanders RD, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anesthesiology. 2008;109(4):707-22. https://doi.org/10.1097/ALN.0b013e3181870a17
15. Myles PS, Leslie K, Chan MT, Forbes A, Peyton PJ, Paech MJ, et al. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. Lancet. 2014;384(9952):1446-54. https://doi.org/10.1016/S0140-6736(14)60893-X
16. Fleischmann E, Marschalek C, Schlemitz K, Dalton JE, Gruenberger T, Herbst F, et al. Nitrous oxide may not increase the risk of cancer recurrence after colorectal surgery: a follow-up of a randomized controlled trial. BMC Anesthesiol. 2009;9:1. https://doi.org/10.1186/1471-2253-9-1
17. Jiang S, Liu Y, Huang L, Zhang F, Kang R. Effects of propofol on cancer development and chemotherapy: potential mechanisms. Eur J Pharmacol. 2018;831:46-51. https://doi.org/10.1016/j.ejphar.2018.04.009
18. Yu J, Han M, Geng J. Influence of propofol intravenous anesthesia on hemorheology, haemodynamics and immune function of colorectal carcinoma patients undergoing radical resection. Pak J Med Sci. 2019;35(3):780-5. https://doi.org/10.12669/pjms.35.3.590
19. Sztwiertnia I, Schenz J, Bomans K, Schaack D, Ohnesorge J, Tamulyte S, et al. Sevoflurane depletes macrophages from the melanoma microenvironment. PLoS One. 2020;15(5):e0233789. https://doi.org/10.1371/journal.pone.0233789
20. Jin Z, Li R, Liu J, Lin J. Long-term prognosis after cancer surgery with inhalational anesthesia and total intravenous anesthesia: a systematic review and meta-analysis. Int J Physiol Pathophysiol Pharmacol. 2019;11(3):83-94. PMID: 31333811
21. Makito K, Matsui H, Fushimi K, Yasunaga H. Volatile versus total intravenous anesthesia for cancer prognosis in patients having digestive cancer surgery. Anesthesiology. 2020;133(4):764-73. https://doi.org/10.1097/ALN.0000000000003440
22. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. Lancet. 2019;394(10211):1807-15. https://doi.org/10.1016/S0140-6736(19)32313-X
23. Cho JS, Kim NY, Shim JK, Jun JH, Lee S, Kwak YL. The immunomodulatory effect of ketamine in colorectal cancer surgery: a randomized-controlled trial. Can J Anaesth. 2021;68(5):683-92. https://doi.org/10.1007/s12630-021-01925-3
24. Duan W, Hu J, Liu Y. Ketamine inhibits colorectal cancer cells malignant potential via blockage of NMDA receptor. Exp Mol Pathol. 2019;107:171-8. https://doi.org/10.1016/j.yexmp.2019.02.004
25. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. Anesth Analg. 2012;115(4):934-43. https://doi.org/10.1213/ANE.0b013e3182662e30
26. Forget P, Vandenhende J, Berliere M, Machiels JP, Nussbaum B, Legrand C, et al. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. Anesth Analg. 2010;110(6):1630-5. https://doi.org/10.1213/ANE.0b013e3181d2ad07
27. Wang Y, Xu X, Liu H, Ji F. Effects of dexmedetomidine on patients undergoing radical gastrectomy. J Surg Res. 2015;194(1):147-53. https://doi.org/10.1016/j.jss.2014.10.008
28. Nair AS, Saifuddin MS, Naik V, Rayani BK. Dexmedetomidine in cancer surgeries: present status and consequences with its use. Indian J Cancer. 2020;57(3):234-8. https://doi.org/10.4103/ijc.IJC_376_19
29. Das J, Kumar S, Khanna S, Mehta Y. Are we causing the recurrence-impact of perioperative period on long-term cancer prognosis: review of current evidence and practice. J Anaesthesiol Clin Pharmacol. 2014;30(2):153-9. https://doi.org/10.4103/0970-9185.129996
30. Kreye G, Masel EK, Hackner K, Stich B, Nauck F. Methadone as anticancer treatment: hype, hope, or hazard? : a series of case reports and a short review of the current literature and recommendations of the societies. Wien Med Wochenschr. 2018;168(7-8):159-67. https://doi.org/10.1007/s10354-018-0623-5
31. Singleton PA, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased μ-opioid receptor expression in metastatic lung cancer. Br J Anaesth. 2014;113(Suppl 1):i103-8. https://doi.org/10.1093/bja/aeu165

32. Du KN, Feng L, Newhouse A, Mehta J, Lasala J, Mena GE, et al. Effects of intraoperative opioid use on recurrence-free and overall survival in patients with esophageal adenocarcinoma and squamous cell carcinoma. Anesth Analg. 2018;127(1):210-6. https://doi.org/10.1213/ANE.0000000000003428

33. Dan J, Gong X, Li D, Zhu G, Wang L, Li F. Inhibition of gastric cancer by local anesthetic bupivacaine through multiple mechanisms independent of sodium channel blockade. Biomed Pharmacother. 2018;103:823-8. https://doi.org/10.1016/j.biopha.2018.04.106

34. Chamaraux-Tran TN, Mathelin C, Aprahamian M, Joshi GP, Tomasetto C, Diemunsch P, et al. Antitumor effects of lidocaine on human breast cancer cells: an in vitro and in vivo experimental trial. Anticancer Res. 2018;38(1):95-105. https://doi.org/10.21873/anticanres.12196

35. Xing W, Chen DT, Pan JH, Chen YH, Yan Y, Li Q, et al. Lidocaine induces apoptosis and suppresses tumor growth in human hepatocellular carcinoma cells in vitro and in a xenograft model in vivo. Anesthesiology. 2017;126(5):868-81. https://doi.org/10.1097/ALN.0000000000001528

36. Zhang H, Yang L, Zhu X, Zhu M, Sun Z, Cata JP, et al. Association between intraoperative intravenous lidocaine infusion and survival in patients undergoing pancreatectomy for pancreatic cancer: a retrospective study. Br J Anaesth. 2020;125(2):141-8. https://doi.org/10.1016/j.bja.2020.03.034

37. Galoș EV, Tat TF, Popa R, Finnerty D, Buggy DJ, Ionescu DC, et al. Neutrophil extracellular trapping and angiogenesis biomarkers after intravenous or inhalation anaesthesia with or without intravenous lidocaine for breast cancer surgery: a prospective, randomised trial. Br J Anaesth. 2020;125(5):712-21. https://doi.org/10.1016/j.bja.2020.05.003

38. Zhang J, Chang CL, Lu CY, Chen HM, Wu SY. Paravertebral block in regional anesthesia with propofol sedation reduces locoregional recurrence in patients with breast cancer receiving breast conservative surgery compared with volatile inhalational without propofol in general anesthesia. Biomed Pharmacother. 2021;142:111991. https://doi.org/10.1016/j.biopha.2021.111991

REVIEW ARTICLE

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Oncovascular surgery

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INTRODUCTION

Surgical intervention is the main therapeutic method for cancer cure. Aggressive resection of malignant disease, including when vascular structures are involved, has really changed the patients' quality of life (QoL). In the past, the involvement of arteries and veins was a barrier to surgery[1,2]. Until today, many surgeons are still reluctant to operate on tumors with significant vessel involvement due to the increased inherent complexity[1,2] due to the high complexity of those operations and the uncertainty about the long-term oncological benefit. However, in the last decade, many papers suggest that survival depends on the complete elimination of the primary pathology and tumor biology, and, therefore, it has been proven that the en bloc resection technique with vascular reconstruction shows good results, which is supported by evidence in many studies in patients with multiorgan neoplastic involvement, including pancreatic, retroperitoneal, renal, and limb tumors[2]. Although many oncological surgeons are accustomed to the interventions and techniques necessary for vascular repair and also for vessel reconstruction, vascular surgeons have more practice and a bigger set of important skills that can facilitate complex oncological resolution and even reduce operative time. Careful preoperative planning by a multidisciplinary team consisting of an oncological surgeon and a vascular surgeon is essential[1,3].

CONCEPT

The term "oncoplastic surgery," "oncoplasty," or even "onco-reconstructive surgery" refers to the association of plastic surgery techniques with breast reconstruction simultaneously with the surgical treatment of breast cancer resection, and it has already been established in the medical world for a few decades[1]. The basic concept was to treat cancer and preserve aesthetics without compromising oncological efficacy. The feasibility of breast reconstruction brought comfort and self-esteem to those patients who were already depressed and distressed by the challenge of neoplasia, which is the main cause of death in women around the world, and this has a great impact on several pillars of their lives (psychological, sexual, affective, and social)[4], therefore ensuring, above all, QoL. For the success of oncoplastic surgery, multidisciplinary therapy is essential.

The vascular surgeon is dedicated to treat arterial and venous diseases using drug therapy, open surgery, endovascular surgery, or hybrid techniques, and, consequently, oncological surgery is not their main focus[1].

Oncovascular surgery (OVS) is a term similar to oncoplastic surgery that implies oncological surgery with simultaneous vascular reconstruction. OVS can be defined as surgical resection of the malignant disease with concomitant ligation or reconstruction of a large vascular structure. Experts have pointed out the increasing relevance of OVS, which includes training for surgeons who act as strategists involved in all phases of treatment: planning, execution, and post-operative follow-up[5]. The use of the term "OVS" may increase awareness of the important role of vascular surgeons in complex cancer surgeries among the public and the medical community[1].

The concept of OVS has become increasingly popular and is already considered a determining factor for quality and safety in R0 resections aimed at curing advanced cancers[6,7].

Ghosh et al., after reviewing several health electronic databases, reported that the published results about different neoplasms suggested that survival depended on the complete

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extirpation of the primary disease and the tumor's biology, instead of vessel-related complications, and concluded that a bigger vessel involvement by a tumor mass shall not be necessarily considered a barrier against block resection and, by extension, against curative surgery. The radical surgical resection may offer the only cure or palliation chance to these patients[7].

The vascular surgeon must act on all treatment phases: on preoperative planning, choosing the best technique and surgical access, or performing embolizations in order to decrease the circulatory contribution to the mass and reduce the bleeding during the resection; per-operative, performing resections and vessel reconstructions, avoiding and/or controlling important or fatal hemorrhage; and post-operative, diagnosing ischemic complications, venous thromboembolism (VTE), or lymphedema by lymphatic interruption or by radical ganglionar emptying.

THE VASCULAR SURGEON'S CURRENT ROLE IN ONCOLOGICAL SURGERY

The vascular surgeon's performance may be classified into three distinct categories: as the main surgeon of vessel-originated tumors, as a rescue surgeon against complications during the cancer surgery, and as a multidisciplinary team's consulting surgeon in cancer treatment[1].

Primary surgeon for vessel-origin tumors

Vascular surgeons must treat some rare primary malignant tumors of blood vessels, such as angiosarcoma, leiomyosarcoma, and retroperitoneal sarcoma, as well as intravenous leiomyomatosis (IVL), a rare benign tumor.

Angiosarcoma

Malignant tumors of the aorta are classified according to their originary cell: intimal angiosarcoma, medial leiomyosarcoma, and adventitial fibrosarcoma.

Angiosarcoma, an infiltrative tumor with a high rate of local recurrence and metastasis, represents less than 2% of all soft tissue sarcomas and mainly affects adult and elderly patients[8]. Reported rates of metastatic disease at presentation range from 16 to 44%, and survival ranges from 6 months to 16 months[8]. According to epidemiological research, angiosarcoma has a similar distribution between genders and can occur at any age[8].

Thromboembolic complications are the typical clinical presentation. Several authors recommend resection of the tumor-bearing aortic region[9], but it is not clear if this approach is beneficial to the patient. Chemotherapy and radiotherapy have been shown to be of less value for patient survival but may play a role in certain circumstances, such as inoperable tumors or metastatic complications[9].

These tumors are difficult to diagnose preoperatively and, in most cases, are diagnosed late, resulting in a worse prognosis. Clinical suspicion of a primary angiosarcoma of the aorta, especially in cases of atypical, rapidly growing abdominal aortic aneurysm with a thrombotic mass, is essential for early diagnosis and adequate surgical management.

Leiomyosarcoma of the vena cava

Of all types of leiomyosarcoma, vascular ones account for 2%, affecting veins five times more often[10]. Primary tumors of the inferior vena cava (IVC) are rare, and 95% of them correspond to leiomyosarcomas that present insidious, non-specific symptoms. Generally, the diagnosis is made late and, consequently, the prognosis is often poor.

Curative treatment requires aggressive surgical excision of the tumor and the involved IVC segment with clear margins. This radical approach associated with the absence of metastases can provide long-term survival and, eventually, even cure[11-13]. However, radiotherapy or chemotherapy is ineffective[1,14].

Inferior vena cava reconstruction after tumor resection can be performed in three ways: ligation without reconstruction, selective reconstruction, or routine reconstruction (Figures 1 and 2).

Choosing non-reconstruction can reduce operative time, prevent pulmonary thromboembolism from VTE of the lower limbs, avoid graft complications such as infections, and reduce

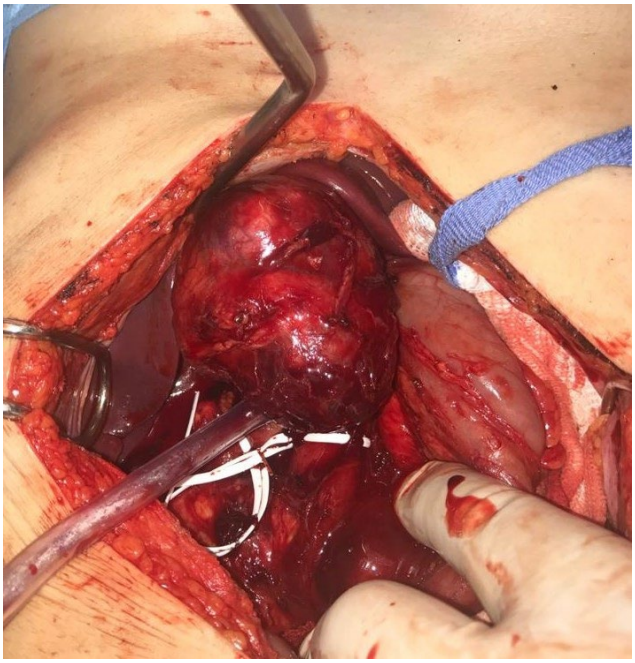

Figure 1. Caval leiomyosarcoma.

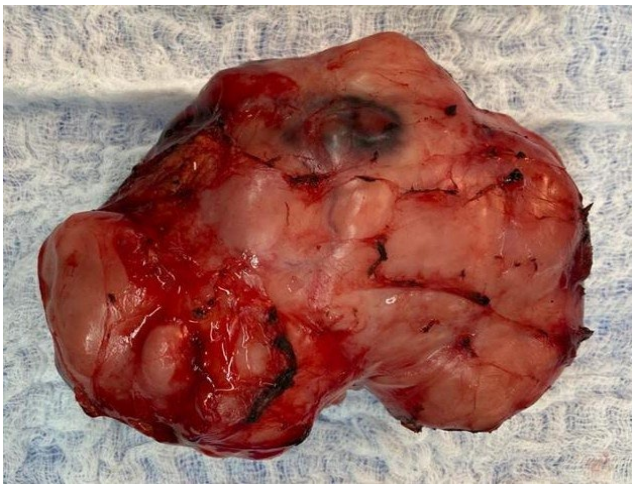

Figure 2. Operative piece leiomyosarcoma of the cava.

the risk of high-output heart failure and the need for perennial anticoagulation.

Reconstruction, when performed, can be by primary repair, patching, or graft interposition. If the expected narrowing of the IVC is less than 50%, repair may be preferred first; when it is greater than 50%, a patch can be used. In cases where complete resection of the IVC wall is necessary, graft interposition should be chosen, knowing, however, that this is the option with the lowest patency rate. The grafts used can be an autologous vein, peritoneum, cryopreserved graft, bovine pericardium, or synthetic Dacron or poly-tetra-flour-ethylene (PTFE) prosthesis. The series, which is still small, does not allow us to establish which is the best synthetic graft or which size is best.

Preservation of renal and hepatic vein flow is particularly relevant; these veins can be resected and reimplanted. Reconstruction of the left renal vein may be unnecessary due to collateral circulation via the gonadal or adrenal gland, but reconstruction of the right renal vein is generally necessary.

Intravenous leiomyomatosis

It is a rare tumor originated from intrauterine veins, characterized by the intravenous growth of smooth muscle nodules that are histologically benign, like vermiform projections proximally through the IVC until reaching the right chambers of the heart. The onset of IVL is in the fifth decade of life, and, as it is an extension of uterine leiomyomas, it occurs exclusively in women[15]. Patients diagnosed with this disease are often followed up in gynecology services due to having uterine leiomyoma or a previous history of hysterectomy months or even years ago[15].

This tumor's etiology is not completely understood, and there are two main theories: one proposes that the origin of the tumor is in the smooth muscle cells of the venous wall, where the intravenous proliferation of the tumor originates, while the other suggests that IVL appears through direct invasion of the venous system by the adjacent tumor[15].

The clinical presentation varies greatly depending on the extent of the tumor, ranging from completely asymptomatic (in most cases) to sudden death. The complaints are of hypogastric pain or metrorrhagia[15]. As soon as vascular invasion reaches larger vessels, such as the common iliac veins and the IVC, VTE and related syndromes may occur. Renal vein thrombosis, or Budd-Chiari syndrome, has also been described[15]. About 10–30% of IVL cases affect the right atrium, causing cardiac symptoms such as palpitations, syncope, dyspnea, or chest pain[15].

Surgical management includes excision of the uterine tumor, bilateral oophorectomy, and intravenous tumor removal, but which technique should be adopted to remove the tumor from the pelvis to the heart remains controversial. The intervention can be in one or two stages, with or without cardiopulmonary bypass, via laparotomy or laparotomy associated with median sternotomy.

Intravenous leiomyomatosis rarely embolizes during operative removal. These tumors adhere firmly to the hypogastric vein, where they originate and invade the systemic circulation, adhering to the IVC at the confluence of the ovarian vein. Tumor masses in the IVC and right atrium are generally mobile and do not adhere to the venous walls.

The characteristics of this tumor, as well as the biology of its growth, guarantee safety in performing the surgical procedure in a single abdominopelvic approach. The tumor mass must be accessed at the level of the hypogastric vein or distal IVC, followed by slight traction downward with its total removal. Perioperative echocardiography monitors the intracardiac portion of the tumor, ensuring its mobility and the absence of tumor residue at the end of the procedure.

Retroperitoneal soft tissue sarcoma involving large vessels

Retroperitoneal soft tissue sarcomas, although rare, are tumors that are difficult to manage due to their extension and malignancy.

Treatment is based on surgical resection, ideally complete in the first approach, targeting any potential chance of cure or prolonged survival. En bloc resection of the tumor mass, adjacent organs, and tissues is the standard procedure, with vascular resection and reconstruction often required[14].

Vascular surgeon's work allows for a safer resection margin, with a lower risk of vascular injury and a consequent reduction in bleeding and surgical time.

Rescue surgeon in the treatment of complications during cancer surgery

Another extremely important role of the vascular surgeon in oncological surgery is the treatment of complications of vascular origin or effect, often resulting from the surgical treatment of tumor masses.

Modern cancer treatment centers must provide vascular surgery teams among their human resources since these consultations are, in almost 60% of cases, unplanned. The most common causes of these consultations are bleeding (35%), vascular protection, limb ischemia, or vascular exposure.

Among the various vascular injuries resulting from these procedures, major bleeding due to vascular laceration or transection, dissection, pseudoaneurysms, arteriovenous fistulas, acute thrombosis, and vascular contusion with late thrombosis stand out (Figures 3 to 6).

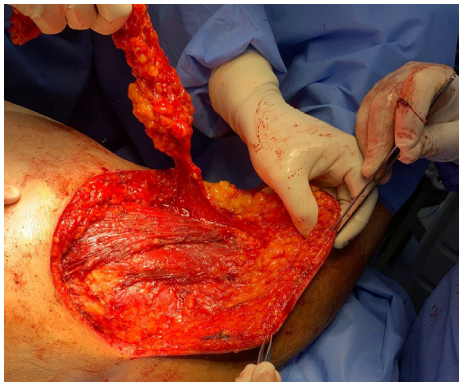

Figure 3. A large axillary sarcoma mobilized during dissection in the anterior region of the chest.

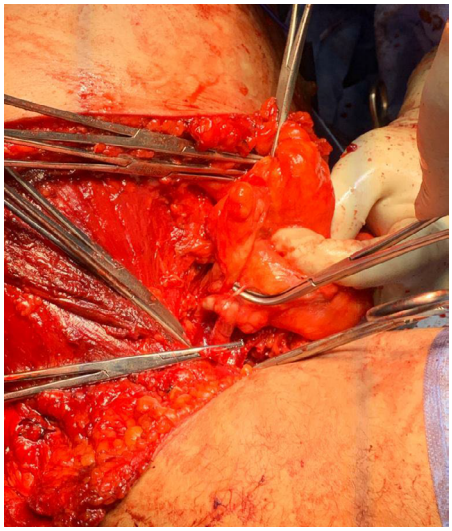

Figure 4. A large axillary sarcoma mobilized during dissection in the posterior region of the chest.

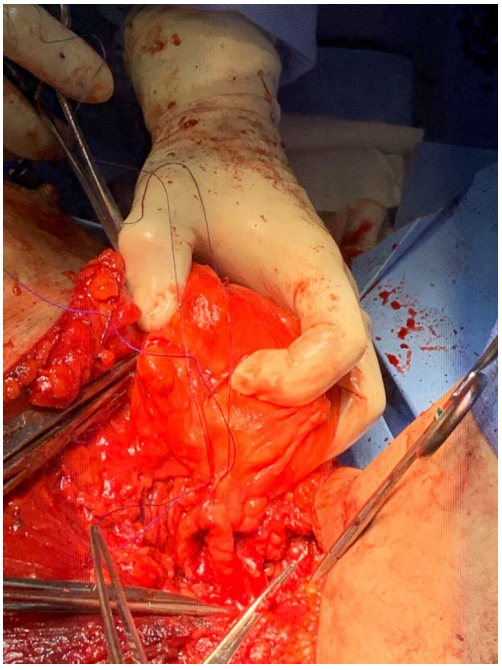

Figure 5. Manual mobilization and ligation of the pedicle of a large axillary sarcoma. An intimate relationship is noted between the tumor and the left axillary artery.

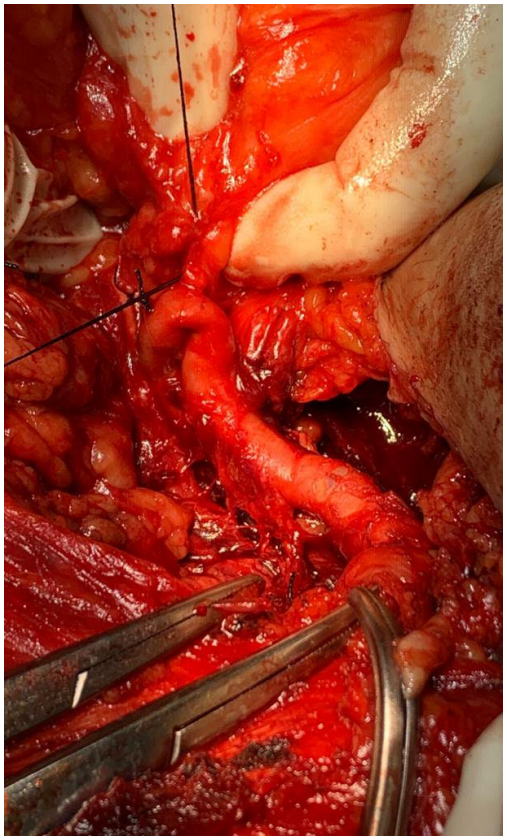

Figure 6. Skeletonization of the left axillary artery and ligation of one of the vascular pedicles of the large axillary sarcoma.

Consultant surgeon of a multidisciplinary team in cancer surgery

The vascular surgeon must form, together with other surgeons, a cancer treatment team, especially in more advanced cases where there is involvement or invasion of large vessels.

Vascular resection, whether or not associated with reconstruction, may be necessary in the surgical treatment of a wide variety of cancers (pancreatic, invading the portal vein or hepatic artery; rectal, invading iliac vessels; thyroid tumors with invasion of the jugular vein or the carotid artery; and adrenal tumors, which involve renal vessels).

In soft tissue sarcomas of the extremities, which may involve femoral, popliteal, axillary, or brachial vessels, tumor resection can become a major challenge due to the risk of amputation, tumor recurrence, and reduced long-term survival (Figures 7–14)[16].

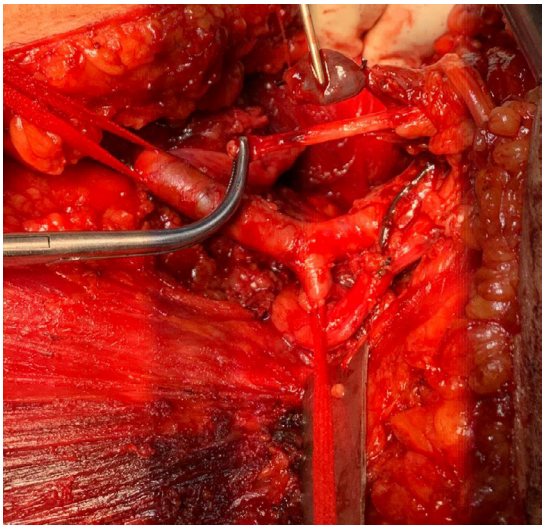

Figure 7. Overview of the operation after excision of the tumor mass that encompassed a branch of the brachial plexus and the axillary vein (ligated), which was too close to the axillary artery, requiring the removal of the adventitial layer, weakening the vascular wall.

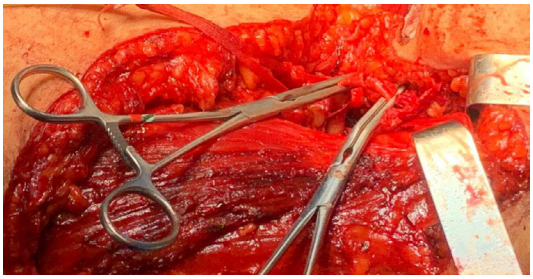

Figure 8. The axillary artery is clamped proximally and distally for vascular repair.

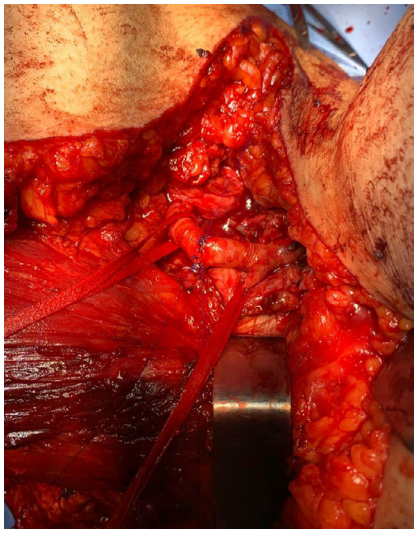

Figure 9. Final image after tumor resection and axillary arteriorrhaphy.

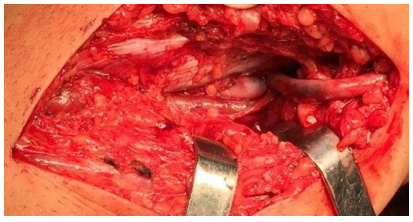

Figure 10. Surgical aspect of the distal anastomosis of the supra-popliteal-infrapatellar popliteal bypass before resection of popliteal synoviosarcoma.

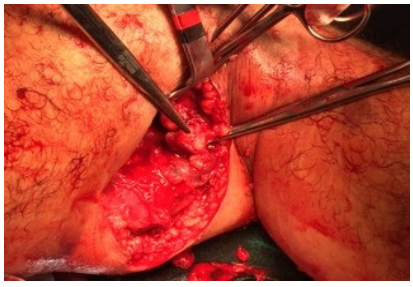

Figure 11. Posterior access to a popliteal synoviosarcoma.

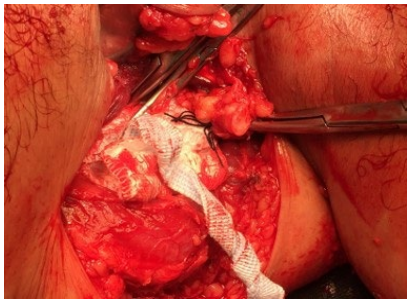

Figure 12. Dissection of a popliteal synoviosarcoma and ligation of the proximal and distal parts of the right popliteal artery.

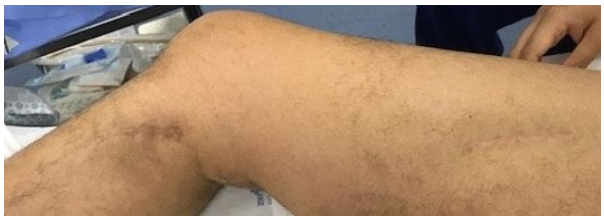

Figure 13. A photograph shows the scars of the medial accesses on the right leg for the suprapatellar popliteal bypass with an inverted ipsilateral saphenous vein.

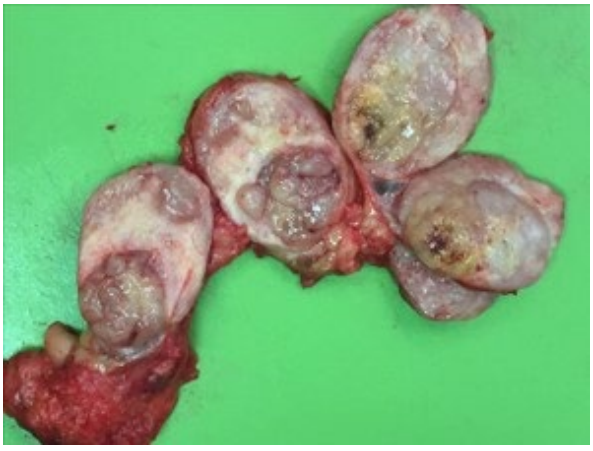

Figure 14. Synoviosarcoma.

CONCLUSION

Surgical collaboration in oncological cases is technically and professionally challenging and should be an important part of the training of new surgeons, as it encourages strong interdisciplinary relationships.

Vascular surgeons must act as co-protagonists in the practice of modern oncological surgery, allowing macroscopic resection of a tumor even in the presence of invasion of large vessels.

Currently, OVS is more than a concept, which is a new vision of the multidisciplinary management of cancer patients, highly recommended for therapeutic planning, aiming for better results for these patients.

AUTHORS' CONTRIBUTIONS

FJSDVG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ARV:** Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft. **IVGS:** Investigation, Methodology, Resources, Software, Visualization, Writing – original draft. **JCPO:** Formal analysis, Funding acquisition, Validation.

REFERENCES

1. Han A, Ahn S, Min SK. Oncovascular surgery: essential roles of vascular surgeons in cancer surgery. Vasc Specialist Int. 2019;35(2):60-9. https://doi.org/10.5758/vsi.2019.35.2.60
2. Finlay B, Bednarz J, Dawson J. A multidisciplinary approach to oncological resections with vascular surgeons improves patient outcomes. Eur J Vasc Endovasc Surg. 2020;60(2):293-9. https://doi.org/10.1016/j.ejvs.2020.04.011
3. Kotsis T, Christoforou P, Polydorou A. The contribution of oncovascular surgery in a young patient with idiopathic retroperitoneal fibrosis. J Surg Case Rep. 2022;2022(1):rjab589. https://doi.org/10.1093/jscr/rjab589
4. Brandão BL, Silva ACB, Gouvêa MM, Lobão LM. Importância da cirurgia plástica para mulheres mastectomizadas e o papel do Sistema Único de Saúde: revisão integrativa. Rev Bras Cir Plást. 2021;36(4):457-65.
5. Sallam K, Khairy H. Oncovascular surgery and the making of the oncovascular surgeon. Vasc Specialist Int. 2019;35(4):189-92. https://doi.org/10.5758/vsi.2019.35.4.189
6. Woo HY, Ahn S, Min S, Han A, Mo H, Ha J, et al. Crucial roles of vascular surgeons in oncovascular and non-vascular surgery. Eur J Vasc Endovasc Surg. 2020;60(5):764-71. https://doi.org/10.1016/j.ejvs.2020.08.026
7. Gad Z, Gamal A, Sallam K. Analysis of the onco-vascular approach in retroperitoneal sarcoma with vascular involvement. J Cancer Ther. 2019;10(8):632-41. https://doi.org/10.4236/jct.2019.108052
8. Cao J, Wang J, He C, Fang M. Angiosarcoma: a review of diagnosis and current treatment. Am J Cancer Res. 2019;9(11):2303-13. PMID: 31815036
9. Thalheimer A, Fein M, Geissinger E, Franke S. Intimal angiosarcoma of the aorta: report of a case and review of the literature. J Vasc Surg. 2004;40(3):548-53. https://doi.org/10.1016/j.jvs.2004.06.035
10. Kevorkian J, Cento DP. Leiomyosarcoma of large arteries and veins. Surgery. 1973;73(3):390-400. PMID: 4687797
11. Cantwell CP, Stack J. Abdominal aortic invasion by leiomyosarcoma. Abdom Imaging. 2006;31(1):120-2. https://doi.org/10.1007/s00261-005-0163-5
12. Drukker L, Alberton J, Reissman P. Leiomyosarcoma of the inferior vena cava: radical surgery without vascular reconstruction. Vasc Endovascular Surg. 2012;46(8):688-90. https://doi.org/10.1177/1538574412460102
13. Dew J, Hansen K, Hammon J, McCoy T, Levine EA, Shen P. Leiomyosarcoma of the inferior vena cava: surgical management and clinical results. Am Surg. 2005;71(6):497-501. https://doi.org/10.1177/000313480507100609
14. Bertrand MM, Carrère S, Delmond L, Mehta S, Rouanet P, Canaud L, et al. Oncovascular compartmental resection for retroperitoneal soft tissue sarcoma with vascular involvement. J Vasc Surg. 2016;64(4):1033-41. https://doi.org/10.1016/j.jvs.2016.04.006
15. Oliveira IF, Pedro LM, Nobre A, Freire JP, Fernandes JF. Leiomiomatose intravenosa: do útero ao coração. Angiol Cir Vasc. 2013;9(2):41-5.
16. Schwarzbach MH, Hormann Y, Hinz U, Bernd L, Willeke F, Mechtersheimer G, et al. Results of limb-sparing surgery with vascular replacement for soft tissue sarcoma in the lower extremity. J Vasc Surg. 2005;42(1):88-97. https://doi.org/10.1016/j.jvs.2005.03.017

REVIEW ARTICLE

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Malignancies in the inborn errors of immunity

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INTRODUCTION

Inborn errors of immunity (IEI) are a group of approximately 500 diseases with genetically determined changes in the immune system's development and/or function. As a group, they are considered rare diseases, affecting 1 in 2,000 individuals on average[1].

According to the periodically updated International Union of Immunology Societies (IUIS) classification, these diseases are distributed into 10 groups: combined T and B cell deficiencies; combined T and B cell deficiencies associated with syndromes; predominantly antibody deficiencies; diseases of immune dysregulation; congenital defects of phagocyte number or function; deficiencies in intrinsic and innate immunity; autoinflammatory diseases; complement system deficiencies; diseases with bone marrow failure; and phenocopies of immunodeficiencies. The most common defects worldwide are deficiencies in antibody production, with selective immunoglobulin A (IgA) deficiency being the most common oligo or asymptomatic defect and common variable immunodeficiency, the most frequent symptomatic defect[2].

The main clinical manifestations of this group of diseases, particularly the most classic defects, formerly called primary immunodeficiencies, are infections that can be repeated and/or severe, requiring venous antibiotics to resolve them, caused by common or opportunistic microorganisms. The type of infectious agent and the location of infections are related to the sector of the immune system most affected by each disease. Some infections are very characteristic of some diseases and are called sentinel infections[3].

In recent years, with the advent of genetic sequencing, the number of IEI described has increased dramatically, many of which are associated with manifestations of dysregulation of the immune system: allergies, autoimmunity, autoinflammation, benign lymphoproliferation, and malignancies[4]. Many patients begin the clinical picture of their diseases with these noninfectious manifestations, so if we use only infections as warning signs for the suspicion of an IEI, we may lose 25% of early diagnoses[5].

The loss of immune surveillance capacity, with the recognition and elimination of emerging tumor cells, is the mechanism most easily remembered to justify the risk of malignancies in IEI. However, there are other recognized mechanisms[6].

Our objective in this non-systematic literature review is to present the main mechanisms related to the development of malignancies in IEI and describe the most common malignancies found in the IEI group and associated with different types of IEI.

MECHANISMS RELATED TO PREDISPOSITION TO MALIGNANCIES IN INBORN ERRORS OF IMMUNITY

We can list four intrinsic mechanisms related to the risk of developing malignancies in several IEIs, usually involving the cell type affected by the disease. These mechanisms are not exclusive and can act simultaneously in diseases[6,7].

1. defects in the development of stem and myeloid cells;
2. defects in lymphocyte development, differentiation, and apoptosis;
3. deficiencies in the co-signaling, cytoskeleton, cytotoxicity, or metabolism of lymphocytes; and
4. defects in DNA repair, telomere maintenance, and chromosomal stability.

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Three extrinsic mechanisms of oncogenesis are relevant in some IEIs, usually involving cell types not primarily affected by the immune defect[6,7]:

1. viral infections;
2. chronic tissue inflammation; and
3. impaired immune surveillance.

In Table 1, we list some examples of malignancies and IEI for each of the oncogenic mechanisms described.

MAIN MALIGNANT DISEASES IDENTIFIED IN INBORN ERRORS OF IMMUNITY

The malignancies most identified in IEI are those related to the lymphoreticular system: lymphomas, leukemias, malignant histiocytosis, and thymus tumors. According to a survey conducted with data from the North American registry (USIDNET), these hematological malignancies corresponded to approximately 96% of the identified malignancies. Other malignant diseases corresponding to 36% of the tumors identified were skin, genitourinary, gastrointestinal, and breast cancer[8].

The overall incidence of cancer is increased by 1.42 times, being 1.91 times in males and 1.12 times in females. In patients with IEI, the pediatric age group and adults between 40 and 50 years of age are affected more often than expected[8].

Malignant diseases were the first clinical presentation in 0.8% of cases of IEI, especially between 40 and 50 years old and in ataxia telangiectasia and activated phosphoinositide 3-kinase-delta syndrome (APDS)[8].

The risk of skin cancer is 4.55 times higher than expected in men and 3.33 times higher in women. The risk of lymphoma in patients with IEI is 10 times higher in men than expected in different age groups, and in women, 8.34 times[8].

The genetic signature identified in lymphomas in patients with IEI differs from those without IEI, and germline and somatic mutations were described. Somatic mutations in *BRWD3* identified in the lymphomas of a group of patients with APDS are relevant[9].

A multicenter study in Turkey identified a prevalence of malignancies of 0.9% in patients with IEI, with a male:female ratio of 1.8, a median age at diagnosis of 10 years, and a mortality rate of 52.5%. Most patients were diagnosed with ataxia telangiectasia (32.2%), and non-Hodgkin lymphoma was the most common malignancy. The risk of malignancy, however, was higher in patients with DOCK8 deficiency[10].

Lymphoid malignancies in patients with IEI are more challenging to diagnose, especially because of previous persistent lymphoproliferation. There is also less response to treatment protocols, as well as an increased risk of toxicity related to them, which increases the complexity of the therapeutic approach for these patients. Radiotherapy is contraindicated in IEI when there is a defect in DNA repair with radiosensitivity, such as ataxia telangiectasia, Nijmegen syndrome, or combined T and B defects caused by a LIG4 mutation. Previous organic damage by the underlying disease, such as bronchiectasis, may also compromise the response to treatment[9].

A systematic review of lymphomas in IEI patients showed that T cell defects were the most associated with lymphomas (57%), with a median age of diagnosis between 9.5 and 12

Table 1. Examples of malignant diseases and inborn errors of immunity associated with oncogenesis mechanisms.

Type of malignancies	Inborn errors of immunity	Main mechanisms of oncogenesis
MDS, AML	Congenital neutropenias Chédiak-Higashi syndrome	Defects in the development of stem and myeloid cells
Lymphomas, leukemias, HLH	CVID, ALPS	Defects in lymphocyte development, differentiation, and apoptosis
	CVID, combined deficiencies of T and B cells	Defects in co-signaling, cytoskeleton, cytotoxicity, or lymphocyte metabolism
Lymphomas, leukemias, carcinomas, sarcomas	Ataxia telangiectasia, nijmegen syndrome, combined deficiencies of T and B cells, congenital dyskeratosis	Defects in DNA repair, telomere maintenance, and chromosomal stability
Lymphomas, leukemias, carcinomas, sarcomas, HLH, smooth muscle tumor	WHIM, epidermodysplasia verruciformis, combined deficiencies of T and B cells	Viral infections
Carcinomas	Innate immunity defects, IBD, virtually any IEI	Chronic tissue inflammation
	Adaptive immunity defects, virtually any IEI	Impaired immune surveillance

MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; CVID: common variable immunodeficiency; ALPS: autoimmune lymphoproliferative syndrome; HLH: hemophagocytic lymphohistiocytosis; WHIM: warts, hypogammaglobulinemia, infections, and myelocathexis; IBD: inflammatory bowel disease; IEI: inborn errors of immunity. Adapted from Hauck et al.[6].

years. The most common type was diffuse large B-cell lymphoma (33.5%). Lymphomas related to the Epstein-Barr virus were found more frequently in innate immunity deficiencies. The complete response to treatment occurred in 65.8%, with death reported in 38.2% of cases[11].

INBORN ERRORS OF IMMUNITY MOST OFTEN ASSOCIATED WITH MALIGNANCIES

In several studies, the number of described malignancies is higher in predominantly antibody production deficiencies, especially in the common variable immunodeficiency, the most common symptomatic IEI worldwide. The prevalence of lymphoma, gastric, and breast cancer in individuals with CVID was 4.1, 1.5, and 1.3%, respectively, in a study with 8,123 patients[12].

Other IEI commonly described in studies on malignancies and primary immune diseases are the combined deficiencies of T and B cells (ataxia telangiectasia mainly), APDS, hyper-IgE syndromes, Wiskott-Aldrich syndrome, and autoimmune lymphoproliferative syndrome (ALPS)[13-15].

MAIN MALIGNANT DISEASES ASSOCIATED WITH DIFFERENT TYPES OF INBORN ERRORS OF IMMUNITY

Table 2 shows the main types of cancer in several IEIs, and Table 3 shows the main IEIs to be considered for each kind of malignancy.

Table 2. Main types of cancer reported in some inborn immunity errors.

Inborn errors of immunity	Reported malignancies
Selective IgA deficiency	Gastric
	Lymphomas
CVID	Lymphomas (more frequently non-Hodgkin)
	Gastric
	Thymus
	Breast
	Bladder
	Cervical
X-linked agammaglobulinemia	Gastric
	Colorectal
Wiskott-Aldrich syndrome	Lymphoma
	Lymphoblastic leukemia
	Myelodysplasia-myeloproliferative disorders
22q11.2 deletion syndrome	Lymphoma
	Acute leukemia
Ataxia telangiectasia	Lymphoma
	Lymphoblastic leukemia
	Breast
	Liver
	Gastric
	Esophagus
	Glioma
WHIM syndrome	Lymphoma
	Genital and squamous carcinoma
	Acute myeloid leukemia

IgA: immunoglobulin A; CVID: common variable immunodeficiency; WHIM: warts, hypogammaglobulinemia, infections and myelocathexis. Adapted from Tiri et al.[13].

Table 3. Main inborn errors of immunity to be considered according to the malignancy found.

Malignancies	Inborn errors of immunity
Non-Hodgkin and Hodgkin lymphomas, ALL	Combined deficiencies of T and B cells not severe
	Defects of DNA repair
	Predominantly antibody deficiencies
	Diseases of immune dysregulation
MDS, AML	Congenital neutropenia,
	Shwachman-Diamond syndrome,
	GATA2 deficiency,
	Diseases with bone marrow failure
CNS tumors	Defects of DNA repair
Solid tumors	Defects of DNA repair
	Congenital dyskeratosis (telomeropathies)
	PTEN deficiency (APDS-like)
	CVID
Smooth muscle tumors associated with EBV	Combined deficiencies T and B not severe
	Ataxia telangiectasia
	Deficiency of GATA2
	Deficiency of CARMIL2
	Deficiency of ZAP70
Kaposi's sarcoma	Wiskott-Aldrich syndrome
	XMEN syndrome
	Deficiency of IFNg receptor 1
	Deficiency of STIM
	Deficiency of OX40
Skin cancer, not melanoma	Epidermodisplasia verruciformis
	Deficiency of DOCK8
	Cartilage hair hypoplasia
	Xeroderma pigmentosum
	Chronic mucocutaneous candidiasis

ALL: acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; CNS: central nervous system; EBV: Epstein-Barr virus; IFNg: interferon gamma. Adapted from Bosh et al.[16].

CONCLUSION

In general, malignancies have a higher incidence and are diagnosed at an earlier age in individuals with some IEI. There are several mechanisms of oncogenesis, transcending the simple impairment of immune surveillance and varying according to the type of defect in the immune system. Hematological malignancies are the most common, especially lymphomas, in patients with common variable immunodeficiency and defects in DNA repair. The response to treatment is worse than in individuals without IEI, with a higher risk of treatment-related toxicity and lower survival.

AUTHORS' CONTRIBUTIONS

ESG: Conceptualization, Writing – original draft. **FCK:** Writing – review & editing. **DS:** Writing – review & editing. **MMRF:** Writing – review & editing.

REFERENCES

1. Goudouris E, Oliva-Alonso ML. Primary immunodeficiencies (or inborn errors of immunity) for the non-specialist. Sao Paulo (SP): ASBAI RJ; 2023.
2. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human inborn errors of immunity: 2022 update on the classification from the international union of immunological societies expert committee. J Clin Immunol. 2022;42(7):1473-507. https://doi.org/10.1007/s10875-022-01289-3
3. Silva AMR, Antunes AA, Falcão ACAM, Goudouris E, Salgado RC, Napoleão SMS, et al. Innate immunity errors and infections. In: Goudouris E, Grumach AS, Neto AC, Aranda C, Solé D, editors. Inborn errors of immunity. New York (NY): Atheneu; 2023. p. 115-30.
4. Costagliola G, Peroni DG, Consolini R. Beyond infections: new warning signs for inborn errors of immunity in children. Front Pediatr. 2022;10:855445. https://doi.org/10.3389/fped.2022.855445
5. Thalhammer J, Kindle G, Nieters A, Rusch S, Seppänen MRJ, Fischer A, et al. Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. J Allergy Clin Immunol. 2021;148(5):1332-41.e5. https://doi.org/10.1016/j.jaci.2021.04.015
6. Hauck F, Voss R, Urban C, Seidel MG. Intrinsic and extrinsic causes of malignancies in patients with primary immunodeficiency disorders. J Allergy Clin Immunol. 2018;141(1):59-68.e4. https://doi.org/10.1016/j.jaci.2017.06.009
7. Baris S, Kolukisa B. Immune dysfunction in inborn errors of immunity causing malignancies. Expert Rev Clin Immunol. 2021;17(7):695-9. https://doi.org/10.1080/1744666X.2021.1925542
8. Mayor PC, Eng KH, Singel KL, Abrams SI, Odunsi K, Moysich KB, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the united states immune deficiency network registry. J Allergy Clin Immunol. 2018;141(3):1028-35. https://doi.org/10.1016/j.jaci.2017.05.024
9. Ye X, Maglione PJ, Wehr C, Li X, Wang Y, Abolhassani H, et al. Genomic characterization of lymphomas in patients with inborn errors of immunity. Blood Adv. 2022;6(18):5403-14. https://doi.org/10.1182/bloodadvances.2021006654
10. Cekic S, Metin A, Aytekin C, Edeer Karaca N, Baris S, Karali Y, et al. The evaluation of malignancies in Turkish primary immunodeficiency patients; a multicenter study. Pediatr Allergy Immunol. 2020;31(5):528-36. https://doi.org/10.1111/pai.13231
11. Herber M, Mertz P, Dieudonné Y, Guffroy B, Jung S, Gies V, et al. Primary immunodeficiencies and lymphoma: a systematic review of literature. Leuk Lymphoma. 2020;61(2):274-84. https://doi.org/10.1080/10428194.2019.1672056
12. Kiaee F, Azizi G, Rafiemanesh H, Zainaldain H, Sadaat Rizvi F, Alizadeh M, et al. Malignancy in common variable immunodeficiency: a systematic review and meta-analysis. Expert Rev Clin Immunol. 2019;15(10):1105-13. https://doi.org/10.1080/1744666X.2019.1658523
13. Tiri A, Masetti R, Conti F, Tignanelli A, Turrini E, Bertolini P, et al. Inborn errors of immunity and cancer. Biology (Basel). 2021;10(4):313. https://doi.org/10.3390/biology10040313
14. Riaz IB, Faridi W, Patnaik MM, Abraham RS. A systematic review on predisposition to lymphoid (B and T cell) neoplasias in patients with primary immunodeficiencies and immune dysregulatory disorders (inborn errors of immunity). Front Immunol. 2019;10:777. https://doi.org/10.3389/fimmu.2019.00777
15. Tavakol M, Delavari S, Salami F, Ansari S, Rasouli SE, Chavoshzadeh Z, et al. Diversity of malignancies in patients with different types of inborn errors of immunity. Allergy Asthma Clin Immunol. 2022;18(1):106. https://doi.org/10.1186/s13223-022-00747-2
16. Bosch JVWT, Hlaváčková E, Derpoorter C, Fischer U, Saettini F, Ghosh S, et al. How to recognize inborn errors of immunity in a child presenting with a malignancy: guidelines for the pediatric hemato-oncologist. Pediatr Hematol Oncol. 2023;40(2):131-46. https://doi.org/10.1080/08880018.2022.2085830

REVIEW ARTICLE

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Pericardial involvement in neoplastic diseases

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INTRODUCTION

There are several ways of pericardial involvement in neoplastic diseases: acute pericarditis, pericardial effusion, cardiac tamponade, and constrictive pericarditis[1].

Primary tumors of the pericardium, such as mesotheliomas, sarcomas, or teratomas, are very rare. Secondary involvement of the pericardium by primary tumors elsewhere is much more common, mainly from lungs, breasts, blood, and mediastinal lymph nodes. Pleural mesotheliomas and gastrointestinal cancers may also evolve with pericardial effusion[2,3]. Pericardial neoplastic involvement is a predictor of poor prognosis, and most treatments are palliative[4]. Pericardial effusion may be the first marker of occult cancer and is correlated with advanced stages of the disease[5]. A study by Fernandes et al., revealed that 16.9% of 254 cases of pericardial effusion had a neoplastic etiology[6]. Patients with neoplastic pericardial effusion typically have a life expectancy of less than 4 months[7].

Patients with neoplasms can develop pericardial disease due to non-neoplastic etiologies, such as those induced by radiotherapy, chemotherapy, infections in immunocompromised patients, and autoimmune and idiopathic causes.

PERICARDITIS

Acute pericarditis is an inflammatory process that may present effusion and has the following clinical features: (1) acute retrosternal chest pain exacerbated by breathing and relieved when sitting up; (2) a pericardial rub audible at the left sternal border; (3) diffuse ST-segment elevation and PR-segment depression on the electrocardiogram (EKG); and (4) pericardial effusion.

This condition has a self-limited evolution and is treated with acetylsalicylic acid and non-steroidal anti-inflammatory drugs. Low-dose colchicine is advised to enhance the effectiveness of the prescribed medications and to avoid recurrence. A major investigation is needed in cases involving high fever, subacute evolution, major pericardial effusion, cardiac tamponade, and no response to medical treatment[8].

PERICARDIAL EFFUSION

The majority of patients with pericardial effusion, even those with large effusions, are asymptomatic, as the effusion evolves slowly and insidiously. Diagnosis is commonly made by routine chest X-rays and echocardiogram.

Common symptoms, when present, are cough, dyspnea, and pleuritic pain. In rare cases, patients may present palpitation due to low cardiac output, dysphagia due to esophagus compression, hoarseness due to recurrent laryngeal nerve compression, and hiccups due to phrenic nerve compression[3,8].

A chest X-ray may show cardiomegaly with a flask-shaped heart and clear lungs without pleural effusion or lung congestion. EKG can be normal or present non-specific ST segment and T-wave elevation.

Echocardiogram is the most important diagnostic test for detecting pericardial effusion (Figure 1). It assesses effusion volume, location, hemodynamic impairment, and eventual cardiac tamponade. An echocardiogram can also detect neoplastic intrapericardial masses (Figure 2).

Computed tomography and magnetic resonance imaging can be used to detect and evaluate primary tumors such as lung cancer, loculated effusion, pericardial thickness, and malignant tumor deposits in the pericardial sac[1,8,9].

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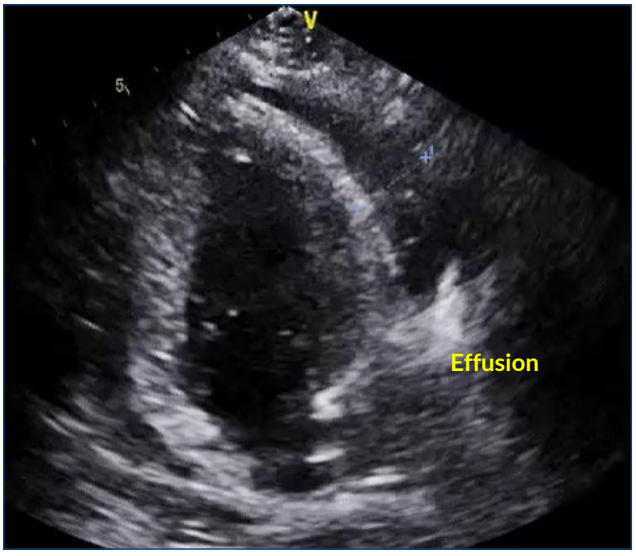

Figure 1. Pericardial effusion in a breast cancer patient (image courtesy of Dr. Márcio Mendes).

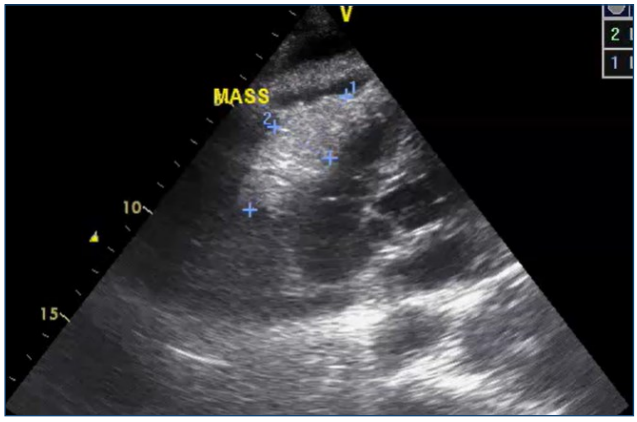

Figure 2. Pericardial metastasis from gastric cancer (image courtesy of Dr. Márcio Mendes).

CARDIAC TAMPONADE

A large pericardial effusion can lead to cardiac tamponade, which is a condition where the pericardial liquid pressure exceeds the ventricular filling pressure, resulting in low cardiac output and cardiogenic shock. As the neoplastic pericardial effusion has a subacute slow filling of the pericardial sac, only few patients present the classic Beck's triad of arterial hypotension, tachycardia, and muffled heart sounds.

Patients with cardiac tamponade commonly present neck vein distension with a rise in jugular pressure that does not decrease during deep inspiration (known as Kussmaul's sign). There is also a drop of more than 10 mmHg in systolic arterial pressure during deep inspiration (*pulsus paradoxus*)[1,9].
On an EKG, diffuse low voltage may be observed.

Echocardiography is crucial for diagnosing and evaluating the severity of pericardial tamponade. Several key echocardiographic findings in pericardial tamponade include (a) late right atrium systolic collapse; (b) early right ventricle diastolic collapse; (c) interventricular septal bulge to the left during inspiration and reversal movement during expiration; and (d) inferior vena cava dilation without inspiratory collapse.

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis can arise as a complication of radiotherapy for breast cancer, leukemia, or lymphoma. Patients usually present with fatigue, dyspnea, palpitations, and ascites. Computed tomography and cardiac magnetic resonance are very useful in the diagnosis and evaluation of constrictive pericarditis[10].

SURGICAL TREATMENT

The main objectives of the surgical treatment for neoplastic pericardial involvement with effusion or constriction are symptom relief and hemodynamic stability. Those objectives can be obtained through pericardiocentesis, pericardial window, and pericardiectomy. Adjunctive therapy is used mainly to avoid recurrence[11].

PERICARDIOCENTESIS

Pericardiocentesis is the treatment of choice for cardiac tamponade and large effusions. Besides fluid removal, another benefit of pericardiocentesis is the cytological analysis of pericardial fluid to detect neoplastic cells.

The procedure should be guided by echocardiography or fluoroscopy. A needle is advanced either subxiphoidally or near the area of major pericardial fluid collection close to the chest wall until fluid is aspirated. After the initial syringe fluid aspiration, a multiperforated pigtail catheter is introduced into the pericardial sac by the Seldinger technique to drain the remaining pericardial effusion.

The pigtail catheter is kept in the pericardial sac under low-pressure aspiration until the drainage amount is <30 mL/day, with the objective of reducing recurrence. Neoplastic pericardial effusion can have a recurrence rate of up to 70%[12].

PERICARDIAL WINDOW

The subxiphoid pericardial window is a commonly used procedure that allows pericardial fluid drainage and pericardial biopsy.

This window is created through an epigastric incision under local or general anesthesia. The pericardium can be approached in a space developed below the distal third of the sternum.

A pleuropericardial window enables drainage of pericardial tamponade and large effusions into the pleural space and pericardial biopsy. This window can be done through a small thoracotomy or preferably through video-assisted thoracoscopy. While these procedures provide palliative relief, pericardial effusion can recur, mainly due to fluid loculation[9].

A pleuropericardial window can also be achieved through percutaneous thoracic puncture and posterior balloon enlargement of the pericardial puncture site[13].

PERICARDIECTOMY

Pericardiectomy, whether partial or total, might be considered in cases of constrictive pericarditis or recurrent pericardial effusion that persists after pericardiocentesis and pericardial window. This procedure is rarely performed and is associated with a high mortality rate. The decision for pericardiectomy depends on the type of tumor, tumor stage, and surgical risk to the patient[10,14].

ADJUVANT THERAPY

Every patient with neoplastic pericardial effusion should be treated with systemic antineoplastic agents. Cytotoxic agents should be instilled into the pericardial sac to avoid recurrence. Celik et al., found that patients who underwent a pericardial window procedure plus chemotherapy fared better than those receiving pericardiocentesis plus chemotherapy[15]. For primary lung cancer, cisplatin is the preferred choice, while thiotepa is used for breast cancer. Intrapericardial tetracycline can be used as a sclerosing agent to avoid recurrence, but it often leads to arrhythmias, chest pain, and high fever[16].

Radiotherapy can be used in cases of lymphomas and leukemia[8].

KEY MESSAGES

1. Secondary pericardial involvement is common in neoplastic diseases.
2. Pericardial effusion in neoplastic patients may have other etiologies beyond cancer itself.
3. Pericardial primary tumors are rare. Pericardial secondary tumors most frequently originate from lungs, breasts, mediastinal lymphomas, and leukemias.
4. Pericardial involvement in neoplastic diseases can cause pericarditis, pericardial effusion, cardiac tamponade, and rarely constrictive pericarditis.
5. Echocardiogram is the most important test for diagnosing neoplastic pericardial disease. A definitive diagnosis is made by cytology or pericardial biopsy. Investigation of the primary tumor is mandatory.
6. The basis of the treatment includes systemic antineoplastic drugs, pericardiocentesis for diagnosis and symptom relief, and intrapericardial instillation of antineoplastic agents.
7. Pericardial effusion is treated by pericardiocentesis and pericardial window but has a high recurrence rate. In some cases, pericardiectomy may be needed.

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AUTHORS' CONTRIBUTIONS

HM: Conceptualization, Formal Analysis, Supervision, Visualization, Writing – original draft, Writing – review & editing. **JCFL:** Formal Analysis, Visualization, Writing – review & editing. **RMSSAA:** Formal Analysis, Visualization, Writing – review & editing. **VJSN:** Conceptualization, Formal Analysis, Visualization, Writing – review & editing.

REFERENCES

1. Soman B, Vijayaraghavan G. Pericardial involvement in neoplastic disease: prevalence, clinical picture, diagnosis and treatment. e-J Cardiol Pract. 2017;15(25).
2. Neves MBM, Stival MV, Neves YCS, Silva JGP, Macedo DBDR, Carnevalli BM, et al. Malignant pericardial effusion as a primary manifestation of metastatic colon cancer: a case report. J Med Case Rep. 2021;15(1):543. https://doi.org/10.1186/s13256-021-03085-w
3. Imazio M, Colopi M, Ferrari GM. Pericardial diseases in patients with cancer: contemporary prevalence, management and outcomes. Heart. 2020;106(8):569-74. https://doi.org/10.1136/heartjnl-2019-315852
4. Gornik HL, Gerhard-Herman M, Beckman JA. Abnormal cytology predicts poor prognosis in cancer patients with pericardial effusion. J Clin Oncol. 2005;23(22):5211-6. https://doi.org/10.1200/JCO.2005.00.745
5. Søgaard KK, Farkas DK, Ehrenstein V, Bhaskaran K, Bøtker HE, Sørensen HT. Pericarditis as a marker of occult cancer and a prognostic factor for cancer mortality. Circulation. 2017;136(11):996-1006. https://doi.org/10.1161/CIRCULATIONAHA.116.024041
6. Fernandes F, Luzuriaga GCJ, Dabarian A, Fernandes ID, Celano PM, Valsi IP, et al. Pericardial disease in patients with cancer. ABC

Heart Fail Cardiomyop. 2022;2(4):363-6. https://doi.org/10.36660/abchf.20220081

7. Feins EN, Walker JD. Pericardial disease in cardiac surgery in the adult. Cohn LH, Adams DH, editors. 5th ed. New York (NY): McGraw-Hill; 2018. p. 1225-42.
8. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC guidelines for the diagnosis and management of pericardial disease. Eur Heart J. 2015;36(42):2921-64. https://doi.org/10.1093/eurheartj/ehv318
9. Warren WH. Malignancies involving the pericardium. Semin Thorac Cardiovasc Surg. 2000;12(2):119-29. https://doi.org/10.1053/ct.2000.5078
10. Schwefer M, Aschenbach R, Heidemann J, Mey C, Lapp H. Constrictive pericarditis, still a diagnostic challenge: comprehensive review of clinical management. Eur J Cardiothorac Surg. 2009;36(3):502-10. https://doi.org/10.1016/j.ejcts.2009.03.004
11. Maisch B, Ristic AD, Sferovic PM, Tsang TSM. Interventional pericardiology: pericardiocentesis, pericardial biopsy, balloon pericardiotomy and intrapericardial therapy. Heidelberg: Springer; 2011.
12. Petrofsky M. Management of malignant pericardial effusion. J Adv Pract Oncol. 2014;5(4):281-9. PMID: 26110072
13. Wang HJ, Hsu KL, Chiang FT, Tseng CD, Tseng YZ, Liau CS. Technical and prognostic outcomes of double-balloon pericardiotomy for large malignancy-related pericardial effusions. Chest. 2002;122(3):893-9. https://doi.org/10.1378/chest.122.3.893
14. Maisch B, Ristic A, Pankuweit S. Evaluation and management of pericardial effusion in patients with neoplastic disease. Prog Cardiovasc Dis. 2010;53(2):157-63. https://doi.org/10.1016/j.pcad.2010.06.003
15. Çelik S, Lestuzzi C, Cervesato E, Dequanter D, Piotti P, Biasio M, et al. Systemic chemotherapy in combination with pericardial window has better outcomes in malignant pericardial effusions. J Thorac Cardiovasc Surg. 2014;148(5):2288-93. https://doi.org/10.1016/j.jtcvs.2014.04.031
16. Imazio M, Adler Y. Management of pericardial effusion. Eur Heart J. 2013;34(16):1186-97. https://doi.org/10.1093/eurheartj/ehs372

REVIEW ARTICLE

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Pre-operative imaging evaluation of renal cell carcinoma

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INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common cancers worldwide, with approximately 4,31,288 new cases and 1,79,368 deaths globally in 2020 and 81,800 new cases in the United States alone[1,2]. RCC may present with flank pain, mass, or hematuria, but its incidence has increased due to incidental diagnosis through imaging methods[3].

The standard treatment for localized RCC includes surgical and imaging-guided non-invasive procedures, such as ablation, nephron-sparing (NS) partial nephrectomy (PN), and radical nephrectomy (RN). Precise preoperative imaging is essential in determining the surgical approach, and imaging methods also play a critical role in subtype characterization and staging. Therefore, adhering to structured and updated guidelines for appropriately utilizing imaging methods in evaluating RCC is crucial[4,5].

This article aims to provide a comprehensive overview of the preoperative role of imaging, including imaging protocols, epidemiological insights, subtype characterization, staging, and structured reporting in assessing RCC.

PROTOCOLS

Computed tomography

Overview

Computed tomography (CT) is the most commonly used imaging technique for presurgical planning, detection, and post-therapy monitoring of renal masses. It also plays a significant role in detecting renal lesions incidentally. CT is faster and more readily available than MRI, is less prone to imaging artifacts, and provides better spatial resolution. Compared to ultrasound (US), which is equally functional, CT is less dependent on operator skills. It offers a better view of the perirenal space without bowel gas interposition or patient body fat composition limitations. Intravenous contrast administered during CT scans allows for better characterization of homogeneous masses and more accurate subtype prediction based on the enhancement pattern.

Computed tomography protocols

Our CT protocol follows Society of Abdominal Radiology RCC Disease-Focused Panel guidelines for pre-nephrectomy and pre-ablation mass characterization, using a combination of pre- and post-contrast imaging acquisitions (Table 1)[6].

A renal scan includes four phases, namely, precontrast, corticomedullary, nephrographic, and excretory. The precontrast phase helps detect fat, hemorrhagic content, and calcifications. The corticomedullary phase helps map the vasculature and determine lesion enhancement patterns. The nephrographic phase is most effective for detecting renal lesions and identifying poorly vascularized tumors. The excretory phase characterizes the involvement of the renal collecting system and differentiates non-renal cell subtypes such as urothelial carcinoma.

Magnetic resonance imaging

Overview

Magnetic resonance imaging (MRI) is helpful for preoperative renal mass examination. It does not emit ionizing radiation, making it suitable for pregnant women, children, and patients with prior radiation exposure. Gadolinium can replace iodinated

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Table 1. Computed tomography and magnetic resonance imaging protocol for evaluation of renal masses.

Contrast-enhanced CT protocol					
	Precontrast phase	**Corticomedullary phase**	**Nephrographic phase**	**Excretory phase**	**Technical notes**
Iodine contrast vol.	–	1.2 mL/kg	1.2 mL/kg	1.2 mL/kg	- Use a straight-back support - Patient lying flat in a supine position with both arms elevated -Axial laser: intermammillary line -Coronal laser: axillary line Sagittal laser: midline
Contrast flow	–	4 mL/s	4 mL/s	4 mL/s	
Acquisition time	–	40 s	80 s	5 min	
kV	120	120	120	120	
Range	800	800	800	800	
Rot time	0.5	0.5	0.5	0.5	
FOV	Upper abdomen	Upper abdomen	Upper abdomen and pelvis	Upper abdomen	
Pitch	Thickness 0.5×80 (Std)	Thickness 0.5×80 (Std)	Thickness 0.5×80 (Std)	Thickness 0.5×80 (Std)	
Thickness	1.0×0.8 mm	1.0×0.8 mm	1.0×0.8 mm	1.0×0.8 mm	
Dynamic MRI protocol					
	Axial T2WI fat-sat trigger	**Axial DWI trigger (B400-800)**	**2D coronal T2WI**	**CORONAL 3D pre- and post-contrast**	**Axial 3D-GRE in-out phase**
FOV (cm)	34	34	38	38	30
Thickness/GAP	6/1	6/1	5/1	3.8	5/1
Matrix (frequency/phase)	320	192/224	256/224	256/224	256/160
NEX/224	1.5	3/5	1	1	1
Band	83	250	31.5	83	83

contrast, which is beneficial for allergic patients and does not cause kidney damage (although it is contraindicated during pregnancy and linear molecule formulations of gadolinium must be avoided in patients with renal failure).

Magnetic resonance imaging protocols

Our institutional protocol for abdominal imaging follows the general MRI guidelines of the Society of Abdominal Radiology RCC Disease-Focused Panel (Table 1)[7]. We use two-dimensional (2D) T2-weighted (T2W) fast spin-echo (FSE) sequences in the axial or coronal planes of the upper abdomen, with and without fat suppression, to characterize macroscopic fat and obtain a general overview of upper abdominal structures. 3D T1-weighted (T1W) gradient-recalled echo (GRE) sequences in in-phase and out-of-phase imaging can help identify microscopic fat and hemorrhagic content, while dynamic 3D T1W fat-suppressed sequences before and after contrast administration can provide information on vascularization, subtype prediction, and renal vasculature. We use diffusion-weighted imaging (DWI) sequences with b-values of 400 and 800 to better detect small renal masses and identify lymph nodes and secondary lesions.

SUBTYPES AND HISTOLOGICAL PREDICTION

Epidemiology

The 5th edition of the World Health Organization (WHO) classification of renal tumors has introduced genetics and molecular features for subtype characterization, comprising 20 different entities[5]. While this might help tailor treatment in the future, current guidelines rely on distinguishing between clear-cell RCC (ccRCC), which represents about 75% of the lesions, and non-clear RCC[4]. Most non-clear RCC cases correspond to papillary RCC (pRCC) and chromophobe RCC (chRCC)[8,9]. Identifying the features that suggest specific subtypes, particularly ccRCC, is crucial in the imaging workup. Distinguishing between these entities can speed up the treatment of patients at higher risk and theoretically prevent disease progression or metastasis.

Clear-cell renal cell carcinoma

Clear-cell renal cell carcinoma is a malignant tumor originating from the renal cortex's tubular epithelial cells. It displays a wide range of morphological variations, making it a prevalent subtype

of sporadic RCCs in adults. It is responsible for about 75% of all cases[5,9]. It is more likely to develop in individuals over 60 years old, with a slightly higher occurrence in men and a higher prevalence among white individuals than black individuals.

The clinical behavior of ccRCC is more aggressive than other RCC subtypes and has a higher potential for metastasis, particularly for solid tumors, than those with solid-cystic characteristics. This risk is due to the potential for late-stage diagnosis and its resistance to conventional chemotherapy and radiation therapy. As a result, surgical resection is the primary therapeutic option.

Imaging features

Clear-cell renal cell carcinoma typically appears as a well-defined, hypervascular, and heterogeneous mass that grows from the cortex in a classic "ball-type" exophytic pattern on sectional imaging exams. This growth pattern tends to displace or distort the adjacent renal parenchyma rather than invade it (Figure 1). Hypervascularity of ccRCC comes from a rich network of capillaries surrounding the tumoral cell nest. The mass may contain necrosis, calcification, or hemorrhage, contributing to its variable appearance[10].

On MRI, the tumor shows a variable T2W signal intensity, usually hyperintense or isointense. It may present a characteristic opposed-phase signal intensity drop resulting from the high glycogen and lipid content of its "clear" cytoplasm. The mass appears hypointense or heterogeneous on T1W imaging, reflecting its hydrated or often necrotic and hemorrhagic content. DWI restriction is variable, and it typically presents a marked restriction.

Papillary renal cell carcinoma

Overview

Papillary renal cell carcinoma is a type of kidney cancer that is typically well defined and can be identified by its papillary or tubulopapillary architectural patterns in the renal cortex[5]. It is the second most common subtype of RCC, accounting for approximately 13–20% of renal epithelial tumors. Although it is primarily found in adults, it can also occur in children[9]. PRCC can appear as single or multiple tumors, and it is not uncommon to appear bilaterally in patients with chronic renal disease. It is usually asymptomatic and is often detected incidentally during imaging studies. Macroscopically, pRCCs can have varying appearances, ranging from yellow to red-brown or variegated, due to factors such as hemorrhage, necrosis, foamy macrophages, cholesterol, or hemosiderin. Compared to other subtypes of RCC, such as ccRCC or unclassified RCC, pRCC generally has a more favorable prognosis.

Imaging features

Papillary renal cell carcinoma often appears as a hypovascular or iso-vascular lesion that enhances less than the normal renal

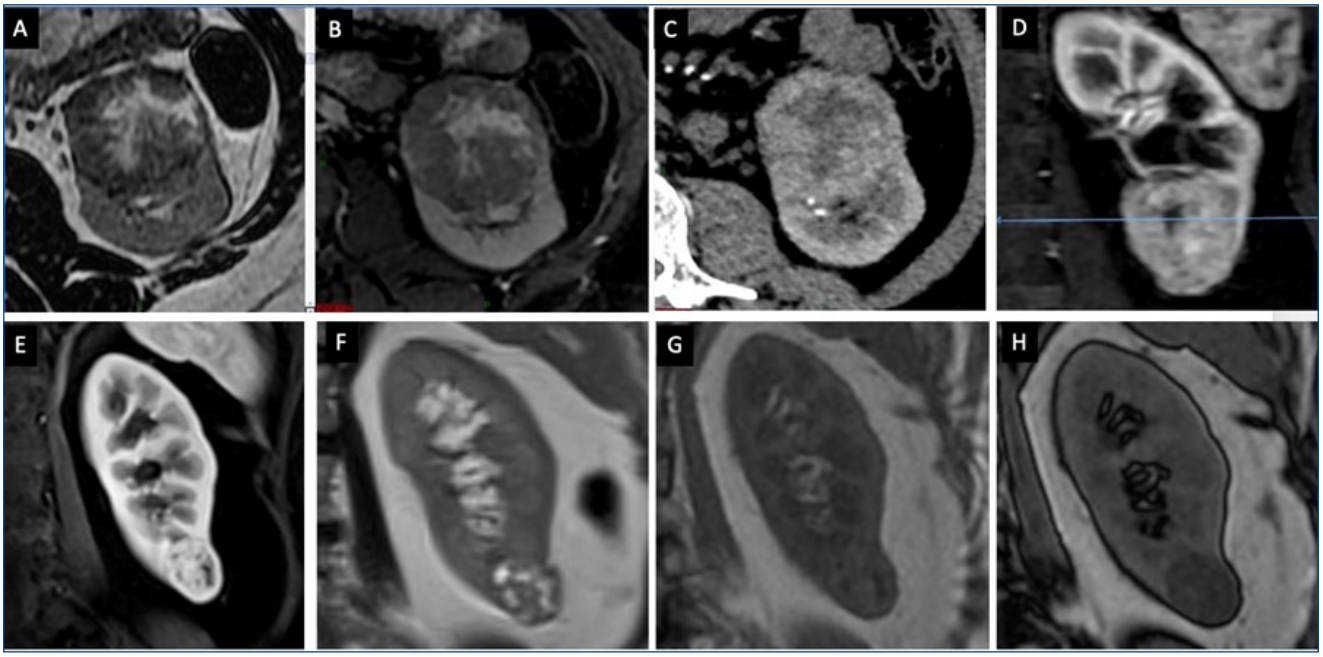

Figure 1. Imaging features of the clear-cell renal cell carcinoma subtype. (A, F) (T2WI), and (B) (fat-sat T2WI) show a heterogeneous lesion with liquefied or necrotic areas. (C) (CT) and (D) (magnetic resonance imaging) images show hyperenhancement in the corticomedullary phase, simillar to (E) (magnetic resonance imaging). (G) and (H) images demonstrate signal drop on opposed-phase imaging, demonstrating intralesional microscopic fat.

cortex and demonstrates a low signal on T2W sequences[11-13]. However, areas of hyper-vascularity can be seen, particularly at the periphery of the tumor (Figure 2). Although smaller lesions are usually homogeneous, they may display a combination of cystic and solid components, resulting in regions of low attenuation alongside enhanced solid components. Although not always present, calcifications can appear as punctate or curvilinear densities. While these imaging features can suggest pRCC, a definitive diagnosis relies on histological examination.

Chromophobe renal cell carcinoma

Overview

Chromophobe renal cell carcinoma is a distinct subtype of kidney cancer originating from the collecting duct's intercalated cells. It accounts for approximately 5% of all RCCs and is usually observed in people in their sixth decade. Patients with chRCC generally have a better prognosis than those with ccRCC, as chRCC is less aggressive and has a lower risk of metastasis[14,15].

Imaging features

Chromophobe renal cell carcinoma tumors appear as well-defined masses on sectional imaging scans. Enhancement is often equal to, or lower than, the renal parenchyma. The peripheral pattern of enhancement is often observed, and a central scar may be seen (Figure 2). On MRI, chRCC is usually isointense or slightly hypointense on the T1W and T2W sequences. Necrotic areas and calcifications are infrequently observed, consistent with the well-defined and often homogeneous nature of chRCC.

The differential diagnosis of chRCC includes oncocytomas, which are benign renal tumors. Due to overlapping imaging features, notably the central scar, the differential diagnosis is often challenging. However, avid contrast enhancement favors oncocytomas over chRCC.

Other renal cell carcinoma subtypes and renal cell carcinoma not otherwise specified

Approximately 10% of RCCs are classified as subtypes such as collecting duct, medullary, tubulocystic carcinoma, and RCC not otherwise specified (NOS)[5]. These subtypes do not have specific imaging features, and a histological diagnosis should only be suggested when well-known clinical conditions are associated with them. These clinical conditions may include falciform disease (for medullary carcinoma), genetic syndromes (such as Birt-Hogg-Dubbe and oncocytomas), and chronic kidney disease (CKD) (for acquired cystic disease-associated RCC)[16].

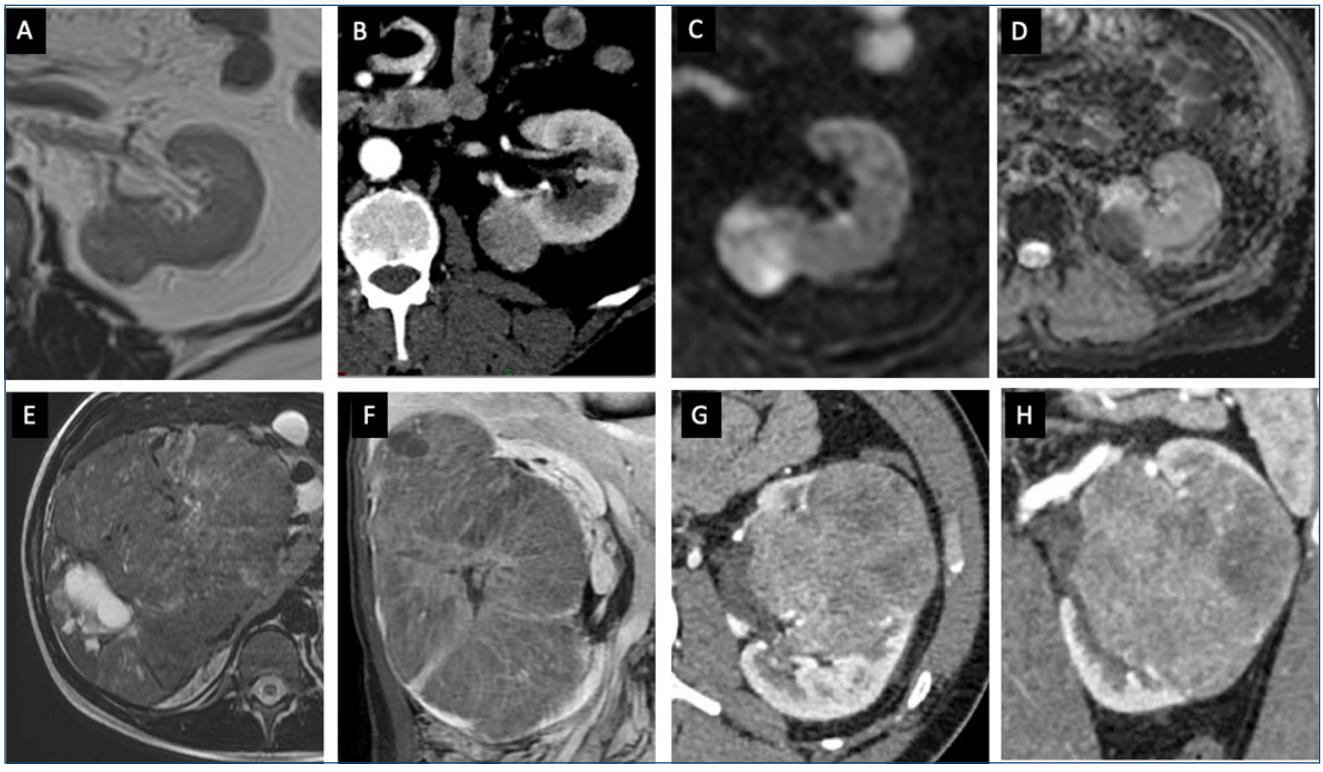

Figure 2. Papillary (A–D) and chromophobe RCC (E–H) features. PRCC is shown in (A) (T2WI imaging) as a homogeneous intermediate signal nodular lesion, hypovascular on (B) (CECT), and presenting marked diffusion-weighted imaging restriction (C) and low signal on the ADC map (D). Chromophobe RCC features are shown on (E–H) as a large heterogeneous lesion, hypovascular, with a central scar.

Clear-cell likelihood score

Although renal mass biopsy is an option for evaluating the histological nature of renal masses in selected cases, its use remains debatable due to its invasiveness, risk of bleeding, and potential complications[17]. In addition, specific masses located in the hilar region are difficult to target effectively, and even when adequately biopsied, they still have a non-diagnostic rate[18] of more than 10%.

In this sense, to identify potential ccRCC among indeterminate solid renal masses through imaging methods and avoid potential unnecessary biopsies, a Likert scale-based score called the clear-cell likelihood score (ccLS) has been introduced[19]. This scoring system can be applied only to MRI studies and has demonstrated good diagnostic performance, with a positive predictive value (PPV) and negative predictive value (NPV) of around 80% for cT1a ccRCC in several retrospective studies[20].

Assigning a ccLS score involves a six-step imaging assessment, as demonstrated in Figure 3.

STAGING

TNM staging

The tumor (T), nodes (N), and metastases (M) (TNM) system from the 8th edition of the American Joint Committee on Cancer (AJCC) is the predominant staging system for kidney cancer[21]. Radiological imaging is used to identify, classify, and determine the extent of kidney cancer. Its primary advantages are that it is non-invasive, offers precise measurement of tumor size, can visualize important landmarks for T-category assessment, and allows for the detection of pathologic lymph nodes and distant metastases. However, its limitation is that it may be unable to identify invasions into significant landmarks such as the renal capsule or Gerota fascia.

Tumor (T) staging

Computed tomography is the primary method for assessing the size and extent of the primary renal tumor. It effectively differentiates between tumors confined to the kidney (T1 and T2 stages) and those that extend beyond the renal capsule, either into the perinephric fat or renal veins (T3 stage). CT can also identify tumors that invade the surrounding adrenal gland or directly penetrate the ipsilateral renal fascia, indicative of the T4 stage. On the other hand, MRI provides superior soft tissue contrast and becomes particularly valuable when CT findings are unclear. MRI is excellent at visualizing tumor extensions into vascular structures like the renal vein or inferior vena cava. It is also preferred for patients who cannot undergo CT scans with iodinated contrast agents due to allergies or kidney issues.

Lymph node (N) staging

For RCC, regional lymph nodes primarily refer to the lymph nodes around the kidneys in the retroperitoneal space. This includes the hilar, perirenal, paracaval, and para-aortic lymph nodes. Notably, any lymph node metastasis beyond these regional nodes would

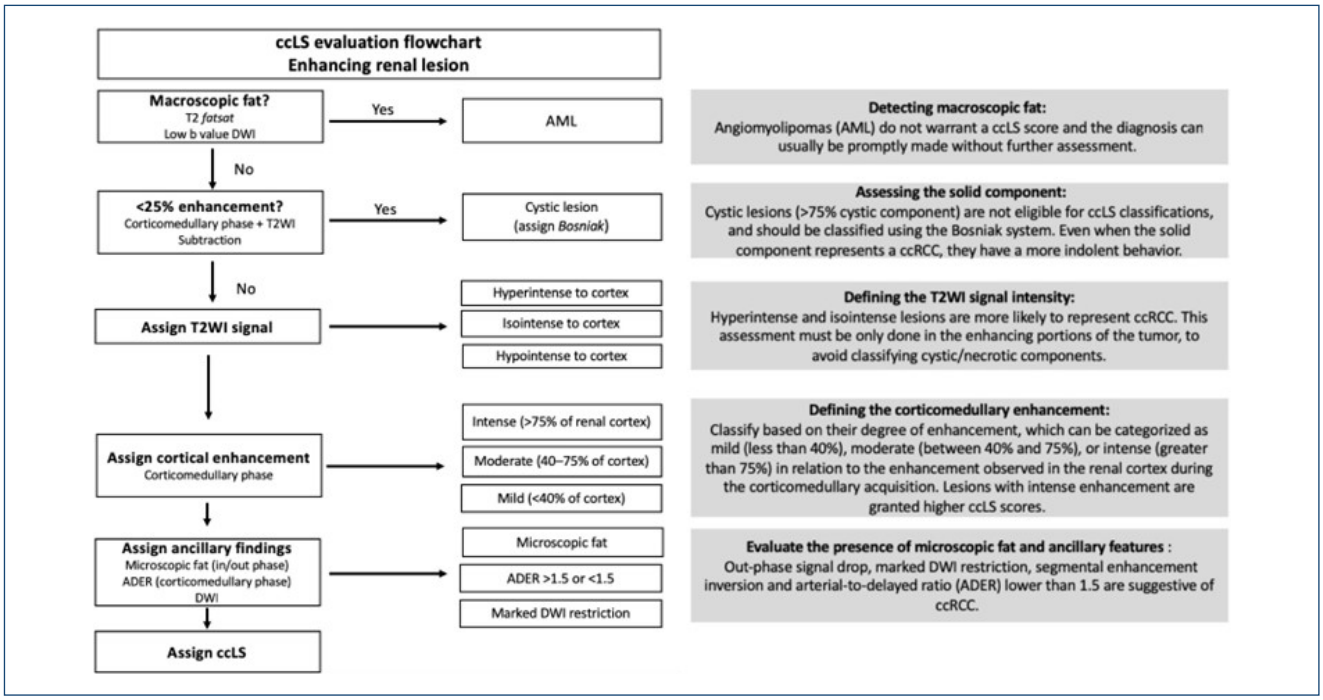

Figure 3. Clear-cell likelihood score evaluation flowchart. Adapted from Pedrosa et.al.[19].

be classified under distant metastasis, designated as "M1" in the TNM staging system. The probability of regional lymph node metastasis grows with the tumor's size. CT accuracy in detecting these metastases in RCC patients ranges between 72 and 99%, with a median sensitivity of 76% and specificity of 79%[22,23]. MRI has a performance comparable to CT. Both modalities struggle to distinguish between enlarged reactive and metastatic lymph nodes, and they cannot detect micrometastases in smaller nodes. While fluorine-2-fluoro-2-deoxy-D-glucose positron emission tomography/computerized tomography (FDG PET/CT) is not commonly used to stage RCC due to its subpar assessment of the primary tumor, it has a median sensitivity of 77% and a specificity of 100% in identifying lymph node metastases in RCC patients[24].

Distant metastatic disease (M) staging

Renal cell carcinoma metastases can spread to any organ but most commonly affect the lungs, bones, and lymph nodes. CT and MRI scans are 85% accurate in detecting lymph node metastases[25,26]. Abdominal metastases are best detected using CT scans of the arterial and venous phases. Adrenal nodules require special attention, as it can be challenging to differentiate between benign adenomas and RCC metastases.

SURGICAL MANAGEMENT

Radical nephrectomy

Radical nephrectomy was the most common treatment for RCC. It involves removing the entire kidney but is associated with reduced renal function. To avoid this, NS techniques like laparoscopic and robotic-assisted PN have been developed. These methods can be expensive and require specialized training.

For less advanced RCC, NS approaches are preferred. The National Comprehensive Cancer Network (NCCN)[4] recommends RN for Stage I-III RCC (and T1a for selected patients). The American Urological Association (AUA)[27,28] suggests considering RNs for cases with higher oncologic potential, high tumor complexity, and normal contralateral kidney function.

Partial nephrectomy and nephron-sparing surgery

Partial nephrectomy is now the standard treatment for small renal masses, removing the tumor while preserving the non-tumorous portion of the kidney. Studies have shown equivalent oncologic outcomes for T1 tumors between partial and radical nephrectomies.

The National Comprehensive Cancer Network[4] recommends PN for patients with stage I–III tumors, where technically feasible, bilateral renal masses, and familial renal cell cancer. Due to its young age or medical risk factors, it is also recommended for patients at risk of developing CKD. AUA[28] recommends PN for T1a tumors and anatomical/functional unilateral kidney, bilateral tumors, pre-existing CKD, proteinuria, multifocal masses, and comorbidities.

Renal ablation

Ablation techniques are minimally invasive alternatives to surgical removal of tumors. They are valuable for treating small renal masses and high-risk surgical patients.

Table 2. R.E.N.A.L and PADUA score parameters.

R.E.N.A.L nephrometry score					
	Radius (maximum diameter)	**Exophytic/ endophytic**	**Nearness to sinus/ colleting system**	**Anterior/ posterior**	**Location regarding polar lines**
1 point	≤4 cm	≥50% exophytic	≥7 mm	–	Entirely above or below
2 points	4–7 cm	<50% exophytic	4–7 mm		<50% between polar lines
3 points	4–7 cm	Entirely endophytic	≤4 mm		≥50% between polar lines
PADUA nephrometry score					
Longitudinal (polar) location	1 point if superior/inferior/2 points if middle				Risk categories (surgical complications)
Exophytic vs. endophytic	1 point if <50% exophytic/2 points if ≥50% exophytic/3 points if entirely endophytic				
Renal rim	1 point if lateral/2 points if medial				6–7: Low risk
Renal sinus	1 point if not involved/2 points if involved				8–9: Moderate risk
Collecting system	1 point if not involved/2 points if involved				≥10: High risk
Tumor size	1 point if ≤4 cm/2 points if 4.1–7 cm/3 points if >7 cm				

Examples include radiofrequency ablation (RFA), cryoablation, microwave ablation (MWA), and high-intensity focused ultrasound (HIFU). Renal ablation is recommended for T1a and T1b tumors, especially in patients with a solitary kidney or multiple bilateral tumors associated with hereditary syndromes[29,30].

Table 3. Reporting guidelines for renal mass evaluation.

Morphology		
	General guidance	**When to report**
Size	AP×LL×CC measures	Every report
Composition (solid/cystic)	If >75% cystic provide Bosniak	
Enhancement	Hyper, iso, or hypo compared to cortex	
Necrotic component	Provide %, if possible, to estimate	
Macroscopic fat	T2WI fat-sat or b50 or <−10 UH at CT	
Microscopic fat	In-phase/out-phase signal drop	
T2W1 signal intensity	Hyper, iso, or hypo to cortex	Provide if ccLS score is given
DWI restriction	Degree of restriction (marked)	
ADER	>1.5and <1.5	
Location		
Laterality	Left vs. right	Every report
Polar location	Upper vs. lower pole	
Relation to polar lines	If crosses either and % between lines	
Exophytic/endophytic component	Provide %	
Axial location	Anterior vs. posterior	
Bowel proximity	Useful for ablation	If candidate for ablation
Adjacency to ureter	Useful for ablation	
Staging		
Invasion of perirenal fat	Invasion vs. no invasion	Every report
Invasion/proximity with sinus fat	Invasion vs. no invasion	
Invasion/proximity with collecting system	Invasion vs. no invasion	
Invasion/proximity with venous system	Report tumoral thrombosis and extension to IVC	
Tumoral thrombosis	If present, provide length, distance to IVC, hepatic venous confluence, diaphragm, and right atrium	
Invasion of adjacent organs	Invasion vs. no invasion	
Regional lymph nodes	Provide sizes of largest ones	
Distant metastasis	Provide sizes of largest ones	
Renal anatomic relations		
Arterial anatomy	Detail anatomy and variations	If candidate for surgery/ablation
Renal venous anatomy	Detail anatomy and variations	
Collecting system anatomy	Cite variations	
Scores		
ccLS	–	Optional
R.E.N.A.L.	–	If candidate for surgery/ablation
PADUA	–	
$(MC)^2$	–	If candidate for ablation
P-RAC	–	
Ablation	–	

PREPROCEDURAL PLANNING: SCORE SYSTEMS

R.E.N.A.L. nephrometry score

The R.E.N.A.L. nephrometry[31] score assesses five critical attributes of renal tumors to determine their surgical complexity. It guides surgical planning and helps decide between PN and RN. The score predicts perioperative complications, longer operative times, and more significant blood loss. The R.E.N.A.L. score parameters are shown in Table 2.

PADUA score

PADUA classification system[32] evaluates seven anatomical features of kidney tumors (Table 2). Each feature is assigned a score, categorizing tumors based on their complexity and surgical risks.

Ablation-focused scores: $(MC)^2$ score, P-RAC, and ablation

RENAL and PADUA scores are not effective for percutaneous ablation. Three new scoring systems have been developed: $(MC)^2$ score predicts complications after cryoablation[33,34], the P-RAC score[35] considers tumors near sensitive structures, and the ABLATE algorithm[36] identifies procedural challenges. Cryoablation is recommended for tumors smaller than 3 cm. Therefore, the evaluation of the tumor's proximity to the bowel is crucial. The ABLATE algorithm suggests methods to avoid damage to adjacent structures and offers guidance based on tumor location.

Three-dimensional reconstruction

Three-dimensional reconstruction is a valuable tool in surgical planning, creating detailed models using CT or MRI data. Accurately displaying anatomical structures and tumor morphology improves surgical planning, increases surgeon confidence, and reduces risks during surgery[37]. The main goal of 3D reconstruction is to show the relationship between the tumor and hilum structures. The 3D reconstruction helps with surgical planning and the arterial clamping approach.

REPORTING RECOMMENDATIONS

Our recommended reporting guidelines are presented in Table 3, based on our experience and recommendations by the Society of Abdominal Radiology 2016 survey on radiologists' and urologists' preferences[38].

AUTHORS' CONTRIBUTIONS

PVAP: Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **FMAC:** Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. **RHB:** Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. **AS:** Methodology, Writing – review & editing. **MZ:** Methodology, Writing – review & editing.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17-48. https://doi.org/10.3322/caac.21763
3. Volpe A, Panzarella T, Rendon RA, Haider MA, Kondylis FI, Jewett MA. The natural history of incidentally detected small renal masses. Cancer. 2004;100(4):738-45. https://doi.org/10.1002/cncr.20025
4. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®) for guideline name kidney cancer.1.2024. Plymouth (PA): National Comprehensive Cancer Network, Inc©; 2023.
5. IARC Publications. Urinary and male genital tumours. WHO classification of tumours, v. 8. 5th ed. Geneva: WHO; 2022.
6. Wang ZJ, Davenport MS, Silverman SG, Chandarana H, Doshi A, Israel GM. CT renal mass protocols v1.0. 2018.
7. Wang ZJ, Davenport MS, Silverman SG, Chandarana H, Doshi A, Israel GM. MRI renal mass protocol v1.0. 2018.
8. Muglia VF, Prando A. Renal cell carcinoma: histological classification and correlation with imaging findings. Radiol Bras. 2015;48(3):166-74. https://doi.org/10.1590/0100-3984.2013.1927
9. Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, et al. Epidemiology of renal cell carcinoma. World J Oncol. 2020;11(3):79-87. https://doi.org/10.14740/wjon1279
10. World Health Organization. WHO classification of urinary and male genital tumours. Geneva: World Health Organization; 2022.
11. Vikram R, Ng CS, Tamboli P, Tannir NM, Jonasch E, Matin SF, et al. Papillary renal cell carcinoma: radiologic-pathologic correlation and spectrum of disease. Radiographics. 2009;29(3):741-54; discussion 755-7. https://doi.org/10.1148/rg.293085190
12. Couvidat C, Eiss D, Verkarre V, Merran S, Corréas JM, Méjean A, et al. Renal papillary carcinoma: CT and MRI features. Diagn Interv Imaging. 2014;95(11):1055-63. https://doi.org/10.1016/j.diii.2014.03.013
13. Herts BR, Coll DM, Novick AC, Obuchowski N, Linnell G, Wirth SL, et al. Enhancement characteristics of papillary renal neoplasms revealed on triphasic helical CT of the kidneys. AJR Am J Roentgenol. 2002;178(2):367-72. https://doi.org/10.2214/ajr.178.2.1780367

14. Marko J, Craig R, Nguyen A, Udager AM, Wolfman DJ. Chromophobe renal cell carcinoma with radiologic-pathologic correlation. Radiographics. 2021;41(5):1408-19. https://doi.org/10.1148/rg.2021200206
15. Volpe A, Novara G, Antonelli A, Bertini R, Billia M, Carmignani G, et al. Chromophobe renal cell carcinoma (RCC): oncological outcomes and prognostic factors in a large multicentre series. BJU Int. 2012;110(1):76-83. https://doi.org/10.1111/j.1464-410X.2011.10690.x
16. Northrup BE, Jokerst CE, Grubb RL, Menias CO, Khanna G, Siegel CL. Hereditary renal tumor syndromes: imaging findings and management strategies. AJR Am J Roentgenol. 2012;199(6):1294-304. https://doi.org/10.2214/AJR.12.9079
17. Choy B, Nayar R, Lin X. Role of renal mass biopsy for diagnosis and management: review of current trends and future directions. Cancer Cytopathol. 2023;131(8):480-94. https://doi.org/10.1002/cncy.22697
18. Marconi L, Dabestani S, Lam TB, Hofmann F, Stewart F, Norrie J, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. Eur Urol. 2016;69(4):660-73. https://doi.org/10.1016/j.eururo.2015.07.072
19. Pedrosa I, Cadeddu JA. How we do it: managing the indeterminate renal mass with the MRI clear cell likelihood score. Radiology. 2022;302(2):256-69. https://doi.org/10.1148/radiol.210034
20. Steinberg RL, Rasmussen RG, Johnson BA, Ghandour R, Leon AD, Xi Y, et al. Prospective performance of clear cell likelihood scores (ccLS) in renal masses evaluated with multiparametric magnetic resonance imaging. Eur Radiol. 2021;31(1):314-24. https://doi.org/10.1007/s00330-020-07093-0
21. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC cancer staging manual. 8th ed. New York (NY): Springer; 2017.
22. Elkassem AA, Allen BC, Sharbidre KG, Rais-Bahrami S, Smith AD. Update on the role of imaging in clinical staging and restaging of renal cell carcinoma based on the AJCC 8th edition, from the AJR special series on cancer staging. AJR Am J Roentgenol. 2021;217(3):541-55. https://doi.org/10.2214/AJR.21.25493
23. Griffin N, Gore ME, Sohaib SA. Imaging in metastatic renal cell carcinoma. AJR Am J Roentgenol. 2007;189(2):360-70. https://doi.org/10.2214/AJR.07.2077
24. Win AZ, Aparici CM. Clinical effectiveness of (18) f-fluorodeoxyglucose positron emission tomography/computed tomography in management of renal cell carcinoma: a single institution experience. World J Nuclear Med. 2015;14(1):36-40. https://doi.org/10.4103/1450-1147.150535
25. Elkassem AA, Allen BC, Sharbidre KG, Rais-Bahrami S, Smith AD. Update on the role of imaging in clinical staging and restaging of renal cell carcinoma based on the AJCC 8th edition, from the AJR special series on cancer staging. AJR Am J Roentgenol. 2021;217(3):541-55. https://doi.org/10.2214/AJR.21.25493
26. Vig SVL, Zan E, Kang SK. Imaging for metastatic renal cell carcinoma. Urol Clin North Am. 2020;47(3):281-91. https://doi.org/10.1016/j.ucl.2020.04.005
27. Campbell SC, Uzzo RG, Karam JA, Chang SS, Clark PE, Souter L, et al. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part II. J Urol. 2021;206(2):209-18. https://doi.org/10.1097/JU.0000000000001912
28. Campbell SC, Clark PE, Chang SS, Karam JA, Souter L, Uzzo RG. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part I. J Urol. 2021;206(2):199-208. https://doi.org/10.1097/JU.0000000000001911
29. Higgins LJ, Hong K. Renal ablation techniques: state of the art. AJR Am J Roentgenol. 2015;205(4):735-41. https://doi.org/10.2214/AJR.15.14752
30. Joe WB, Zarzour JG, Gunn AJ. Renal cell carcinoma ablation: preprocedural, intraprocedural, and postprocedural imaging. Radiol Imaging Cancer. 2019;1(2):e190002. https://doi.org/10.1148/rycan.2019190002
31. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009;182(3):844-53. https://doi.org/10.1016/j.juro.2009.05.035
32. Ficarra V, Novara G, Secco S, Macchi V, Porzionato A, Caro R, et al. Preoperative aspects and dimensions used for an anatomical (PADUA) classification of renal tumours in patients who are candidates for nephron-sparing surgery. Eur Urol. 2009;56(5):786-93. https://doi.org/10.1016/j.eururo.2009.07.040
33. McCafferty BJ, Huang JJ, Khudari H, Macha V, Bready E, Rais-Bahrami S, et al. External validation of the renal ablation-specific (MC)2 risk scoring system in predicting complications from percutaneous renal cryoablation. Cardiovasc Intervent Radiol. 2021;44(11):1763-8. https://doi.org/10.1007/s00270-021-02929-8
34. Schmit GD, Schenck LA, Thompson RH, Boorjian SA, Kurup AN, Weisbrod AJ, et al. Predicting renal cryoablation complications: new risk score based on tumor size and location and patient history. Radiology. 2014;272(3):903-10. https://doi.org/10.1148/radiol.14132548
35. Mansilla AV, Bivins EE, Contreras F, Hernandez MA, Kohler N, Pepe JW. CT-guided microwave ablation of 45 renal tumors: analysis of procedure complexity utilizing a percutaneous renal ablation complexity scoring system. J Vasc Interv Radiol. 2017;28(2):222-9. https://doi.org/10.1016/j.jvir.2016.10.013
36. Schmit GD, Kurup AN, Weisbrod AJ, Thompson RH, Boorjian SA, Wass CT, et al. ABLATE: a renal ablation planning algorithm. AJR Am J Roentgenol. 2014;202(4):894-903. https://doi.org/10.2214/AJR.13.11110
37. Wang J, Lu Y, Wu G, Wang T, Wang Y, Zhao H, et al. The role of three-dimensional reconstruction in laparoscopic partial nephrectomy for complex renal tumors. World J Surg Oncol. 2019;17(1):159. https://doi.org/10.1186/s12957-019-1701-x
38. Davenport MS, Hu EM, Smith AD, Chandarana H, Hafez K, Palapattu GS, et al. Reporting standards for the imaging-based diagnosis of renal masses on CT and MRI: a national survey of academic abdominal radiologists and urologists. Abdom Radiol (NY). 2017;42(4):1229-40. https://doi.org/10.1007/s00261-016-0962-x.

REVIEW ARTICLE

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Hand tumors

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Brazilian Society of Hand Surgery

SOFT TISSUE TUMORS

Synovial cyst on the wrist

Synovial cyst (SC) is the most common soft tissue tumor in the wrist and hand, accounting for almost 50–70% of the total. It is more frequent in women, between the second and fourth decades of life. Clinically, it presents as a nodular and superficial increase in volume, which is mostly located in the dorsal and central region of the wrist (up to 80%) and originates from the radiocarpal joint (RCJ). It can also be located in the volar and radial region, which is the second most common location, or originate from the mid-carpal joint (MCJ), mainly in the scaphotrapeziotrapezoid (STT) joint, when they are located more distally[1].

Treatment is predominantly non-surgical. However, patients with symptomatic lesions after treatment or with aesthetic complaints are candidates for invasive procedures. Aspiration, with or without corticosteroid infiltration, has a high recurrence rate, which can reach 80%, and is being less used. The surgical treatment principle consists of decompression and drainage, with resection of a portion of the joint capsule and the cyst wall, with no need for complete and extensive resection of the tumor, and with an average recurrence rate of 15%[2].

Wrist SCs can be treated through open surgery. However, large incisions present a greater risk of general complications, such as cosmetically unsatisfactory scarring and stiffness of the wrist, and especially in the case of volar cysts, injury to noble structures such as the superficial palmar branch of the radial artery, flexor tendons, superficial terminal branches and palmar cutaneous branch of the median nerve[2,3].

Currently, arthroscopy has become a consolidated technique in the treatment of orthopedic pathologies. With technological advances, arthroscopy of small joints has allowed, through direct visualization, the diagnosis and immediate treatment of intra-articular injuries. Arthroscopic resection, initially described by Osterman[3] for dorsal cysts and later for volar cysts, proved to be a minimally invasive alternative to the open technique (Figure 1). Its advantages are less post-operative pain, less scarring and stiffness, and a quicker return to work activities, without a high incidence of complications. The recurrence rate of wrist SCs arthroscopic treatment ranges from 0 to 26%[4-6].

In special situations, when we do not have the appropriate material (shaver), we can use a pink needle (1.2 mm) to open the pedicle and a portion of the capsule. Due to the risk of injury to deep structures, we only recommend this "trick" to surgeons who are already trained and used to this treatment[7].

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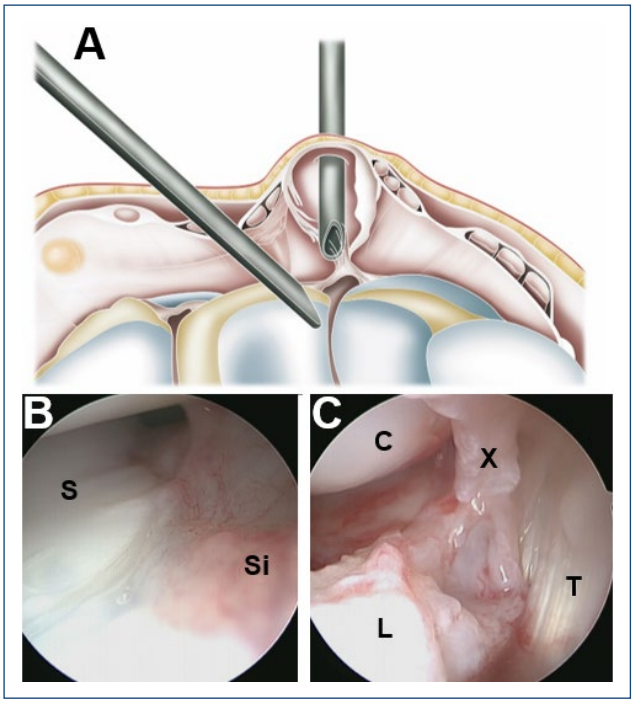

Figure 1. Schematic drawing showing arthroscopic surgical treatment, with the camera positioned in the mid-carpal joint, in its ulnar portal, and the shaver in the radial portal, located transcystic **(A)**. In an initial view, thickening of the dorsal capsule and synovial membrane is observed, typical of a patient with a symptomatic dorsal cyst **(B)**. Similar positioning of the optic after resection of the cyst pedicle and a portion of the dorsal capsule, making the extensor tendons visible **(C)**. S: scaphoid; Si; synovitis; C: capitate; L: lunate; X: dorsal capsule; T: extensor tendon.

Giant cell tumor of the tendon sheath

Giant cell tumor of the tendon sheath (GCTTS) is one of the most common soft tissue tumors of the hand, second only to ganglion cysts. It is also known as pigmented villonodular synovitis and originates from the synovial membranes, bursae, and tendon sheaths[8].

It affects young individuals, with women being the most affected (3:2), more commonly in the fingers. It rarely affects children[9].

Diagnosis is mainly based on clinical examination. The GCTTS appears as a firm, painless, slow-growing mass. Ultrasound exams usually help with the diagnosis, but MRI provides more details of the tumor's characteristics.

Diagnostic confirmation is based exclusively on anatomopathological examination. Excisional biopsy, with a safety margin, is recommended, and excision of satellite lesions is essential to avoid recurrence, which can reach up to 45% of cases. The patient should always be warned of the possibility of recurrence. Macroscopically, typical lesions are yellowish-brown and multinodular[8] (Figure 2).

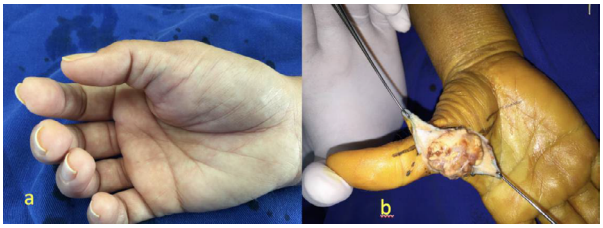

Figure 2. Giant cell tumor of the tendon sheath on the palmar aspect of the thumb. **(A)** Clinical appearance. **(B)** Surgical appearance of the tumor.

Lipoma

Lipomas are benign tumors of fatty cells that appear as soft, painless masses. Despite being the most common tumors of mesenchymal origin, they are uncommon in the hand. They can be superficial or deep, and when located in neural pathways, they can generate compressive symptoms. The etiology of lipomas is unknown[10].

Lipoma is a circumscribed fat nodule surrounded by a thin fibrous capsule that has a characteristic yellowish content typical of fatty tissue[11]. Although ultrasound has proven to be a useful diagnostic tool, magnetic resonance imaging is more informative, as the image shows fat signal intensity[12].

Lipomas can be observed or excised according to their size and the patient's complaints[11].

The definitive diagnosis is made through excisional biopsy followed by histopathological examination, which generally heals the lesion with rare recurrences.

Glomus tumor

Glomus tumors are tumors arising from the glomus body, which is a contractile neuromyoarterial structure responsible for adjusting blood pressure and temperature and regulating blood flow to the skin[13]. Glomus tumors are uncommon and mostly benign, representing approximately 2% of all soft tissue tumors in the extremities[13]. They can be single or multiple. The most frequent clinical picture found is a female patient presenting with a small, painful, thermosensitive nodule on the nail bed[14]. Patients often report throbbing pain, "as if there was a heart under your fingernail." The tumor is often visible through the nail.

Typical symptoms of the glomus tumor triad are pinpoint pain, severe pain, and cold hypersensitivity. Diagnostic tests include the paperclip test (increased pain with localized compression), Hildreth's test (the patient's arm is elevated, a tourniquet is inflated to 250 mmHg, and the tumor is palpated. Pain and sensitivity should be reduced. The test is positive when cuff release causes sudden onset of pain and tenderness in the tumor area), and cold sensitivity test[15].

Imaging exams also help us, which include X-rays, ultrasound, and, mainly, magnetic resonance[16].

The gold standard of treatment is complete excision, which often results in permanent relief of symptoms. The tumor can be accessed through the lateral route of the finger, when the tumor is lateralized, or by resecting the nail piece. Another option is to create a "window" on the nail when the tumor is easily identified (Figure 3). Malignant presentation (glomangiosarcomas) is very rare[17].

Skin tumors on the hand

The hand represents only 1–2% of the body surface area, but malignant skin tumors of the hand account for about 10–15% of all malignant skin tumors. The most common malignant tumor is squamous cell carcinoma, followed by basal cell carcinoma, and finally, melanoma[18].

Squamous cell carcinoma originates from epithelial keratinocytes and, when restricted to the epidermis, is called squamous cell carcinoma in situ or Bowen's disease. Numerous non-invasive or minimally invasive treatments are effective in this case. In invasive cases, surgical treatment is required. The American Cancer Committee recommends staging squamous cell carcinoma into low-risk tumors or high-risk tumors based on the risk of local spread or metastases. The tumors of more than 2 cm in diameter or that have at least two of the following risk factors are considered high-risk tumors: undifferentiated or poorly differentiated histology, 2 mm or more in thickness, invasion of the reticular dermis (Clark IV), or perineural invasion[19]. The study by Brodland and Zitelli[20] suggests a 4-mm margin for low-risk tumors and a 6-mm margin for high-risk tumors. However, controversy still persists regarding the type of surgical treatment and the exact safety margin required in invasive cases.

Basal cell carcinoma is the most common malignant tumor in the human body, but it is much less common in the hand than squamous cell carcinoma. The known relationship between basal cell carcinoma and solar irradiation could contribute to a high incidence in the dorsal region of the hand, which is permanently exposed, but this does not occur, probably due to the lower proportion of sebaceous glands on the dorsum of the hand[21]. This tumor is more common in white men over 60 years of age, in immunosuppressed patients, and in patients who have already had malignant hair follicle tumors in other regions[22].

Melanoma on the hand has a more invasive behavior than in other regions, with high rates of lymph node involvement and deaths. In terms of location, the most common is the subungual, followed by the back of the hand, and finally the palmar region. Treatment varies depending on location and depth, and wide resection and reconstruction or amputations with or without reconstructions can be performed[21].

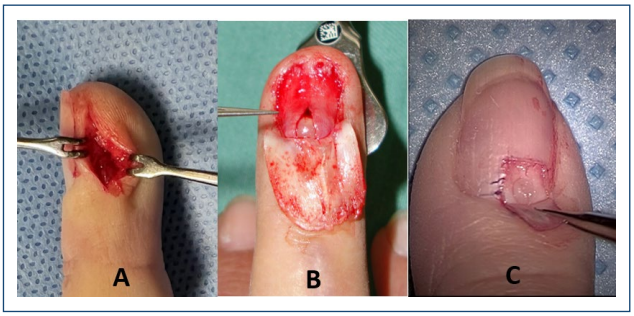

Figure 3. **(A)** Para-ungual access route. **(B)** Access with nail resection. **(C)** Access route through a window in the nail.

BENIGN BONE TUMORS

Enchondroma

Enchondroma is the bone tumor that most affects the hand, accounting for 90% of cases. It is a benign lesion of the cartilaginous matrix, with a predilection for the proximal phalanges, followed by the metacarpals, and middle phalanges[23]. The initial presentation is quite variable, ranging from a finding on a radiological examination (X-ray, computed tomography (CT), or magnetic resonance imaging) carried out for another reason (Figure 4A), such as complaints of pain and increased volume at the site of the lesions, to cases of pathological fractures[24]. The radiographic characteristic is similar to that of a lytic lesion, initially involving the metaphyseal area and then expanding to include diaphyseal and epiphyseal extensions, some internal calcifications, and mild to moderate degrees of expansion and thinning of the cortical bone (Figure 4B). Treatment depends on the appearance of the lesion. Small, asymptomatic lesions "accidentally" diagnosed by tests carried out for other reasons can be monitored only clinically. In symptomatic cases, those accidentally diagnosed with dimensions in which the risk of pathological fracture is high, or even in cases of pathological fracture, surgical treatment is recommended[23]. In the specific case of pathological fractures, there is some evidence that tumor treatment has better results after fracture consolidation. Considering the very characteristic appearance of the lesion, its high frequency in the hand region, and the very low degree of malignant transformation (<5%)[25], biopsy is generally unnecessary. Resection is performed by creating a bone window and intralesional curettage. There is no need for an adjuvant method. Filling the cavity with autologous bone graft is the most used

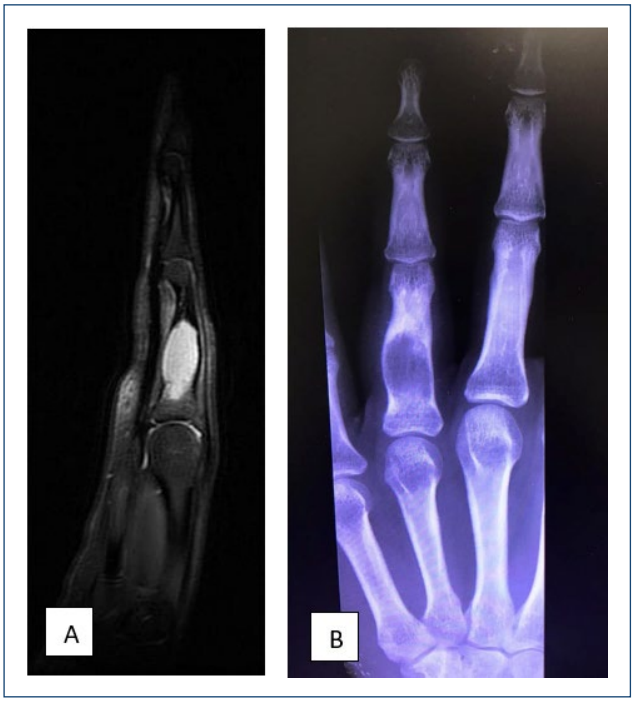

Figure 4. **(A)** T2-weighted magnetic resonance imaging, showing an enchondroma of the proximal phalanx of the left fourth digit, with high signal intensity of the lesion and cortical thinning. **(B)** X-ray AP view of the left hand showing a lytic, expanding lesion with cortical thinning in the proximal phalanx of the fourth finger, suggestive of enchondroma.

method, but the use of heterologous grafts, synthetic substitutes, or even no filling[26] is reported. The expected recurrence rate is low (2–15%)[25].

Osteochondroma

Although osteochondroma is relatively uncommon in its isolated form, it is one of the most common bone lesions of the skeleton and is more frequently found in the form of hereditary multiple osteochondromatosis. It generally appears between the second and third decades of life. According to histopathology, it is a bone growth with a layer of hyaline cartilage (Figure 5), generally originating from a herniation of the growth plate through the periosteum or the tendon insertion region and maintaining contact with the original innermost part of the bone. In the hand, the most common location is on the back of the proximal phalanges. Treatment for asymptomatic cases is observation only. For cases of angular or rotational deformity, pain, limitation of movement due to mechanical blockage, nerve compressions, prominence, irritation, and even tendon rupture, surgical treatment is recommended[23]. Malignant transformation in isolated chondrosarcomas is generally low (1%) and not reported in specific cases of the hand. In cases of multiple osteochondromatosis, it can be 2–5%[24].

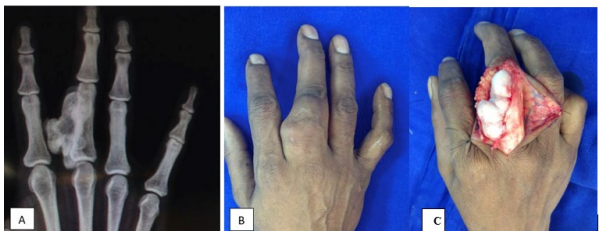

Figure 5. **(A)** X-ray AP view showing massive osteochondroma on the proximal phalanx of the third finger of the right hand. **(B)** Clinical image. **(C)** Exposure of the osteochondroma, with the hyaline cartilage layer being observed.

Osteoid osteoma

Skeletal bone tumors can be divided into benign, primary malignant, and metastatic. Osteoid osteoma (OO) is a benign neoplasm that rarely occurs in the hand bones and is often difficult to diagnose. It mainly affects males (61.5%), aged between 20 and 29 years (53%), and is most frequently found in the phalanges (52.9%), mainly in the proximal phalanx, followed by the metacarpals (14.5%) and distal phalanx (13%). The occurrence in the carpal bones is lower, with the scaphoid being the most affected (7.7%). The most frequently observed location is within the cortical bone (intracortical), followed by cancellous bone, subperiosteal, and juxta-articular regions[27].

The clinical picture is characterized mainly by nocturnal pain, which responds well to the use of acetylsalicylic acid and non-steroidal anti-inflammatory drugs. Edema, mobility restrictions, and nail deformities are also described. CT (Figure 6) is the exam with the highest sensitivity (93.1%), showing a central nidus with surrounding sclerosis, and is followed by magnetic resonance imaging (MRI) (81.6%). Plain radiography and scintigraphy are also of great value[27].

The surgical treatments described are en bloc resection or nidus open curettage, followed by bone grafting of the distal radius or iliac bone. Alternative treatments of CT-guided percutaneous ablation of the nidus using radiofrequency (RF), laser photocoagulation (LPC), and thermocoagulation (TCG) are described. In the latter, the main complications described are local recurrence, mainly in TCG, and osteonecrosis in RF[27].

Osteoblastoma

Osteoblastoma (OB) is a benign and aggressive primary bone tumor rarely found in the hand bones. It has a higher incidence in patients between 10 and 30 years old, with a predominance in males (3:1). Clinically, progression can vary from slow to rapid and aggressive, with exuberant symptoms such as pain, swelling, and local heat. Unlike OO, generally, it does not respond to the use of nonsteroidal anti-inflammatory drugs

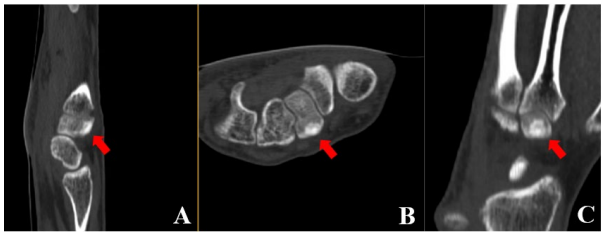

Figure 6. Computed tomography showing a central nidus with surrounding sclerosis in the trapezoid (arrow). **(A)** Sagittal. **(B)** Axial. **(C)** Coronal. Photos cordially provided by Dr. Fábio Augusto Caporrino from Escola Paulista de Medicina, Federal University of São Paulo.

(NSAIDs) and the pain does not worsen at night. Plain radiography can show irregularly shaped radio-transparent lesions surrounded by a thin shell of bone. However, these characteristics are not exclusive, being found in other infectious bone pathologies as well as benign and malignant neoplasms. OB is more frequently observed in the cortical bone and less in the innermost part and the juxtacortical regions. Histologically, it is considered benign, even when the lesion appears to be aggressive radiographically, and is similar to OO, although larger. Some authors consider lesions smaller than 1.5 cm as OO and larger than this arbitrary value as OB[28]. Regarding treatment, excision of the tumor, through intralesional curettage or en bloc resection, is the treatment of choice. Chemotherapy and radiotherapy, used in inoperable cases, have demonstrated high levels of recurrence. A recent initial study showed promising results with the use of denosumab in the clinical treatment of first metacarpal OB[29].

MALIGNANT BONE TUMORS

Osteosarcoma

Osteosarcoma is rare in the hand, representing between 0.18 and 0.9% of all osteosarcomas (0.3% of bone sarcomas) and having less than 50 cases reported in the literature[25,30]. Most of them are neoplasms secondary to radiotherapy, Paget's disease, or osteosarcoma metastasis from other regions[31]. In a retrospective series of 402 cases of hand tumors, only one case of osteosarcoma was observed[32]. The 10-year survival rate for osteosarcoma is 63% when located in the hand and wrist regions[30].

Surgical resection is recognized as an effective basic treatment and, recently, limb-salvage techniques have become standard for patients with osteosarcoma of the limbs, with success rates of 60–80% regions[33]. Classical treatments for osteosarcoma include neoadjuvant chemotherapy, limb-salvage surgery, and adjuvant chemotherapy. The purpose of neoadjuvant chemotherapy is to reduce the tumor and the reactive inflammatory edema to facilitate subsequent resection surgery, as well as to control the primary lesion and eliminate micrometastases early. When well applied, limb-salvage surgery tends to result in better functional scores and greater 5-year survival when compared with amputation[34].

Ewing sarcoma

Location in the hand is rare with few cases described in the literature, with the long bones being more affected than the carpal bones. The metacarpal and proximal phalanges are the most involved bones in the hand, with the thumb and middle finger being the most affected[35].

Typically, it manifests with insidious pain and edema. Radiography generally shows less bone destruction, often in the metaphysodiaphyseal region of a long bone, with ill-defined margins, and many times with a moth-eaten appearance associated with an onion skin periosteal reaction. Magnetic resonance imaging is requested to assess the extent of the disease, generally showing significant involvement of soft tissues.

The classic treatment of Ewing sarcoma is based on chemotherapy and local control, either surgically or with radiotherapy. In recent decades, the advancement of chemotherapy has greatly improved survival, although in cases where metastases are already present, it is not very effective. The use of chemotherapy and radiotherapy can also be useful to shrink the tumor preoperatively, improving the resection margin and often allowing the minimization of local sequelae.

Ewing sarcoma of the hand has a better prognosis in more proximal locations, probably because the primary tumor is also considerably smaller[36,37].

Chondrosarcoma

Primary chondrosarcoma is very rare in the hand, being more frequent in the secondary form. Classically, we divide it into primary chondrosarcoma when it originates from previous bone tissue without lesions, and secondary when it originates from an initially benign bone tumor, such as enchondroma or osteochondroma[38], especially in patients with multiple lesions such as Ollier's disease, Mafucci syndrome, or hereditary multiple osteochondromatosis[39].

These are tumors that do not respond well to chemotherapy and radiotherapy, with surgical resection being the treatment of choice. Depending on the histological analysis, they are classified as low, medium, or high grades. For high-medium and high-grade lesions, the recommended treatment is wide surgical resection. In low-grade lesions, some authors recommend

intralesional curettage with clearly less local sequelae compared with wide resection[40]. They justify the procedure arguing that the tumor rarely metastasizes, although it often presents with intense local aggressiveness.

AUTHORS' CONTRIBUTIONS

ATNF: Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **ACC:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing –review & editing. **RSMB:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **LRN:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **MPR:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **SCAS:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **RKO:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **SAMG:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **RGS:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing. **CKH:** Conceptualization, Formal Analysis, Supervision, Visualization, Writing – review & editing.

REFERENCES

1. Nahra ME, Bucchieri JS. Ganglion cysts and other tumor related conditions of the hand and wrist. Hand Clin. 2004;20(3):249-60. https://doi.org/10.1016/j.hcl.2004.03.015
2. Oliveira RK, Brunelli JPF, Bayer LR, Aita M, Mantovani G, Delgado PJ. Artrhoscopic resection of volar wrist ganglion: surgical technique and case series. Rev Bras Ortop (Sao Paulo). 2019;54(6):721-30. https://doi.org/10.1055/s-0039-1700811
3. Osterman AL, Raphael J. Arthroscopic resection of dorsal ganglion of the wrist. Hand Clin. 1995;11(1):7-12. PMID: 7751333
4. Mathoulin C, Hoyos A, Pelaez J. Arthroscopic resection of wrist ganglia. Hand Surg. 2004;9(2):159-64. https://doi.org/10.1142/s0218810404002169
5. Ho PC, Lo WN, Hung LK. Arthroscopic resection of volar ganglion of the wrist: a new technique. Arthroscopy. 2003;19(2):218-21. https://doi.org/10.1053/jars.2003.50035
6. Oliveira RK, Brunelli JPF, Carratalá V, Aita M, Mantovani G, Delgado PJ. Arthroscopic resection of wrist volar synovial cyst: technique description and case series. J Wrist Surg. 2021;10(4):350-8. https://doi.org/10.1055/s-0040-1721438
7. Kaempf OR, Gómez G, Brunelli JPF, Aita MA, Carratalà V, Delgado SPJ. Arthroscopic needling technique for the treatment of wrist ganglia. J Wrist Surg. 2022;12(4):377-82. https://doi.org/10.1055/s-0042-1751015
8. Galbiatti J, Milhomens G, Silva L, Santiago D, Neto JS, Belluci S. Estudo retrospectivo dos resultados do tratamento cirúrgico de 31 tumores de células gigantes da bainha do tendão da mão. Rev Bras Ortop. 2019;54(4):26-32. https://doi.org/10.1016/j.rbo.2017.11.005
9. Gouin F, Noailles T. Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented villonodular synovitis). Orthop Traumatol Surg Res. 2017;103(1S):S91-7. https://doi.org/10.1016/j.otsr.2016.11.002
10. Ganguly A, Chaudhary SR, Rai M, Kesavanarayanan V, Aniq H. Thenar lumps: a review of differentials. Clin Radiol. 2019;74(12):978.e15-27. https://doi.org/10.1016/j.crad.2019.08.025
11. Toft F. Surgical resection of a giant intramuscular lipoma of the biceps brachii: a case report and review of the literature. Arch Orthop Trauma Surg. 2022;142(3):373-9. https://doi.org/10.1007/s00402-020-03614-0
12. Velázquez-Rueda ML, Hernández-Méndez-Villamil E, Mendoza-Muñoz M, Rivas-Montero JA, Espinosa-Gutiérrez A. [Primary tumours and pseudotumors of the hand in adults. Epidemiological analysis of cases, management and evolution]. Acta Ortop Mex. 2019;33(2):81-7. PMID: 31480108
13. Chou T, Pan SC, Shieh SJ, Lee JW, Chiu HY, Ho CL. Glomus tumor: twenty-year experience and literature review. Ann Plast Surg. 2016;76(Suppl. 1):S35-40. https://doi.org/10.1097/SAP.0000000000000684
14. Bhaskaranand K, Navadgi BC. Glomus tumour of the hand. J Hand Surg Br. 2002;27(3):229-31. https://doi.org/10.1054/jhsb.2001.0746
15. Abidin MA, Kitta MI, Nong I, Rahmansyah N, Johan MP. Diagnosis and surgical approach in treating glomus tumor distal phalanx left middle finger: a case report. Int J Surg Case Rep. 2023;108(2):108426. https://doi.org/10.1016/j.ijscr.2023.108426
16. Karegowda LH, Shenoy PM, Maddukuri SB, Kyalakond H. Importance of radiological imaging in a case of subungual glomus tumour. BMJ Case Rep. 2014;2014:bcr2014205649. https://doi.org/10.1136/bcr-2014-205649
17. Woodward JF, Jones NF. Malignant glomus tumors of the hand. Hand (N Y). 2016;11(3):287-9. https://doi.org/10.1177/1558944715614874
18. Mason ML. Carcinoma of the hand. Arch Surg. 1929;18:2107-58. https://doi.org/10.1001/archsurg.1929.01140140063004
19. Edge SB, Byrd DR, Compton CC, Fritz AG, Green FL, Trotti A. AJCC cancer staging manual. 7th ed. New York (NY): Springer; 2010. p. 301-14.
20. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. J Am Acad Dermatol. 1992;27(2):241-8. https://doi.org/10.1016/0190-9622(92)70178-i
21. Ruffolo AM, Sampath AJ, Kozlow JH, Neumeister MW. Melanoma of the hands and feet (with reconstruction). Clin Plast Surg. 2021;48(4):687-98. https://doi.org/10.1016/j.cps.2021.05.009
22. Loh TY, Rubin AG, Brian Jiang SI. Basal cell carcinoma of the dorsal hand: an update and comprehensive review of the literature. Dermatol Surg. 2016;42(4):464-70. https://doi.org/10.1097/DSS.0000000000000695
23. Henderson M, Neumeister MW, Bueno RA. Hand tumors: II. Benign and malignant bone tumors of the hand. Plast Reconstr Surg. 2014;133(6):814e-21e. https://doi.org/10.1097/PRS.0000000000000178

24. Teodoreanu RN, Grosu-Bularda A, Liţă FF, Hodea FV, Enache V, Frunză A, et al. Benign cartilaginous tumors of the hand, a five-year retrospective study. Rom J Morphol Embryol. 2022;63(4):625-32. https://doi.org/10.47162/RJME.63.4.04
25. Mavrogenis AF, Panagopoulos GN, Angelini A, Lesenský J, Vottis C, Megaloikonomos PD, et al. Tumors of the hand. Eur J Orthop Surg Traumatol. 2017;27(6):747-62. https://doi.org/10.1007/s00590-017-1984-y
26. Lindfors N, Kukkonen E, Stenroos A, Nordback PH, Anttila T, Aspinen S. Enchondromas of the hand: curettage with autogenous bone vs. bioactive glass S53P4 for void augmentation. In Vivo. 2022;36(3):1267-73. https://doi.org/10.21873/invivo.12826
27. Meyer J, Rolvien T, Reiter A, Priemel M, Frosch KH, Krukenberg A, et al. Osteoid osteoma in the bones of the hand: a systematic literature review. Arch Orthop Trauma Surg. 2023;143(8):5437-44. https://doi.org/10.1007/s00402-023-04839-5
28. Goel A, Bhatia N, Dabas V, Mehndiratta A, Singh M. Osteoblastoma of the distal radius. J Hand Surg Am. 2022;47(4):392.e1-5. https://doi.org/10.1016/j.jhsa.2021.02.003
29. Kooner P, Ferguson P. The use of denosumab in osteoblastoma of the metacarpal. J Hand Surg Am. 2019;44(11):994.e1-6. https://doi.org/10.1016/j.jhsa.2019.02.001
30. Huayllani MT, Restrepo DJ, Boczar D, Sisti A, Spaulding AC, Parker AS, et al. Osteosarcoma of the upper extremities: a national analysis of the US population. Anticancer Res. 2019;39(10):5663-8. https://doi.org/10.21873/anticanres.13763
31. Woo T, Lalam R, Cassar-Pullicino V, Degrieck B, Verstraete K, Donati DM, et al. Imaging of upper limb tumors and tumorlike pathology. Radiol Clin North Am. 2019;57(5):1035-50. https://doi.org/10.1016/j.rcl.2019.03.008
32. Cavit A, Özcanli H, Sançmiş M, Ocak GA, Gürer Eİ. Tumorous conditions of the hand: a retrospective review of 402 cases. Turk Patoloji Derg. 2018;34(1):66-72. https://doi.org/10.5146/tjpath.2017.01413
33. Xu M, Wang Z, Yu XC, Lin JH, Hu YC. Guideline for limb-salvage treatment of osteosarcoma. Orthop Surg. 2020;12(4):1021-9. https://doi.org/10.1111/os.12702
34. Han G, Bi WZ, Xu M, Jia JP, Wang Y. Amputation versus limb-salvage surgery in patients with osteosarcoma: a meta-analysis. World J Surg. 2016;40(8):2016-27. https://doi.org/10.1007/s00268-016-3500-7
35. Skinner S, Conant S, Lansinger Y. Ewing sarcoma in an infant metacarpal. J Hand Surg Am. 2019;44(8):701.e1-5. https://doi.org/10.1016/j.jhsa.2018.09.001
36. Froeb D, Ranft A, Boelling T, Paulussen M, Klco-Brosius S, Jürgens H, et al. Ewing sarcoma of the hand or foot. Klin Padiatr. 2012;224(6):348-52. https://doi.org/10.1055/s-0032-1327607
37. Leavey PJ. Important principles in Ewing sarcoma treatment. Pediatr Blood Cancer. 2014;61(12):2149-50. https://doi.org/10.1002/pbc.25214
38. Patil S, Silva MV, Crossan J, Reid R. Chondrosarcoma of small bones of the hand. J Hand Surg Br. 2003;28(6):602-8. https://doi.org/10.1016/s0266-7681(03)00149-9
39. Jones HB, Murphree J, Suryavanshi JR, Osemwengie BO, Rosqvist S, Cox CT, et al. Multifocal chondrosarcoma of the hand: case report and review of the literature. Clin Case Rep. 2021;9(6):e04352. https://doi.org/10.1002/ccr3.4352
40. Dierselhuis EF, Goulding KA, Stevens M, Jutte PC. Intralesional treatment versus wide resection for central low-grade chondrosarcoma of the long bones. Cochrane Database Syst Rev. 2019;3(3):CD010778. https://doi.org/10.1002/14651858.CD010778.pub2

REVIEW ARTICLE

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The role of Pediatric Surgery in childhood cancer

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Brazilian Society of Pediatric Surgery

INTRODUCTION

Childhood cancer, a significant cause of morbidity and mortality among children worldwide, is the focal point of this article. With an estimated 8,460 cases diagnosed in Brazil in 2022, childhood cancer represents only 2% of all cancer cases but is a leading cause of death in children aged 1–14 years[1,2]. The incidence rate is 16.2 per 100,000 children aged below 15 years, featuring a bimodal distribution in pediatric tumors, peaking before the age of 2 years and again in adolescents and young adults. Survivors face increased risks of chronic health conditions, second malignancies, and reproductive health implications[2].

Pediatric cancer differs from adult cancer in common types and treatment approaches. Central nervous system malignancies, neuroblastoma, acute myeloid leukemia, Wilms tumor, and retinoblastoma are more prevalent in younger children, while acute lymphoblastic leukemia, Hodgkin lymphoma, osteosarcoma, and Ewing sarcoma are common in older children[1,2]. Advances in treatment, including clinical research integration and pediatric cooperative groups, have enhanced therapy effectiveness. The focus on minimizing therapy's late effects, like infertility, led to oncofertility options in pediatric cancer treatment[3].

Childhood cancer survival and prognosis have improved significantly. Collaborative efforts by pediatric oncology consortia and risk stratification algorithms have optimized therapy, increasing overall survival rates to 84%[4]. While the incidence remains flat, death rates have declined by 66%, with the 5-year relative survival rate improving from 58 to 83% for children and 68 to 84% for adolescents. However, certain pediatric solid tumors remain resistant to these improvements[5,6].

Pediatric surgery plays a pivotal role in diagnosing, staging, and treating childhood cancer. Surgical resection, often the primary treatment modality for solid tumors, affects outcomes and quality of life. Pediatric surgeons also manage complications and provide supportive care, including central venous catheter insertions and symptom palliation[7]. This field demands specialized training and close collaboration with other disciplines such as oncology and pathology. The role of pediatric surgeons extends beyond surgery for solid tumors; they follow up with oncology patients, perform biopsies and catheter implants, and manage complications from treatments like neutropenic colitis. Tailoring surgical approaches to each patient's needs, considering cancer type, stage, age, and health, is crucial for optimal outcomes. Research in pediatric surgical oncology is key to developing new techniques and improving survival rates and quality of life for children with cancer[7-12].

Pediatric surgeons are often the first point of contact for children diagnosed with tumors, building vital therapeutic relationships and guiding families through the treatment process[9,12]. Their expertise in performing biopsies, central line placements, and fertility preservation procedures is crucial for timely diagnosis and treatment[3,8,12]. As part of multidisciplinary teams, they bring anatomical knowledge and surgical expertise, performing a range of surgeries from tumor resections to complex reconstructive procedures[4]. Their understanding of children's unique needs helps in implementing appropriate treatments while minimizing complications. Despite their critical role, access to pediatric surgical oncology training is limited globally, especially in low- and middle-income countries. This highlights the need for further research and education to develop a global workforce capable of providing high-quality pediatric cancer care[7,13]. The role of pediatric surgery in childhood cancer outcomes is the focus of this article, which aims to provide an overview of the state-of-the-art and the future directions of this field.

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METHODS

We conducted a comprehensive, nonsystematic review of the literature to investigate the role of pediatric surgery in childhood cancer outcomes. Four major bibliographic databases were searched: PubMed, EMBASE, LILACS, and Web of Science. A combination of controlled vocabulary terms [Medical Subject Headings (MeSH) and Emtree terms] and keywords was employed, including "pediatric surgery" OR "surgical oncology" AND "childhood cancer" OR "pediatric cancer" AND "cancer outcome" OR "survival rate" OR "complication" OR "quality of life." Our search was restricted to articles published in English, Spanish, or Portuguese within the past 10 years, focusing on studies involving children aged 0–18 years diagnosed with childhood cancers. Initial screening involved reviewing titles and abstracts to identify relevant articles. Subsequently, full-text evaluation was conducted on selected articles, focusing on those that explicitly addressed the impact of pediatric surgery on outcome measures. Reference lists of retrieved articles were also scanned to identify additional relevant publications. Gray literature was excluded from the review.

RESULTS AND DISCUSSION

Over time, the role of the pediatric surgeon in childhood cancer treatment has evolved significantly, becoming crucial in modern oncology due to various factors[12,14,15]. This evolution is largely attributed to the specialization and continuous training of pediatric surgeons, as highlighted by Alaish et al.[10], who associated participation in specialized training programs with improvements in technical skills, operative time, and patient-centered performance. Moreover, the implementation of enhanced recovery programs in pediatric oncology surgery, as reported by Wells et al.[16], has been shown to improve patient outcomes, underscoring the importance of postoperative management training and specialization. Advancements in surgical approaches, such as the use of three-dimensional (3D) models and augmented reality over conventional imaging for preoperative assessment in Wilms tumor cases[17,18], also emphasize the impact of specialized training. Furthermore, fellowship in pediatric oncologic surgery has been linked to improved survival rates, indicating the positive effect of specialized training on optimizing therapy based on risk stratification algorithms[9]. The expertise and ongoing training of pediatric surgeons are also critical in managing surgical complications in pediatric oncology patients, requiring technical skills and a deep understanding of treatment guidelines and care specific to this population. Additionally, adapting standardized surgical approaches in resource-limited settings poses challenges, highlighting the importance of specialization and training in devising local control strategies to improve outcomes[13].

The field of pediatric surgical oncology is undergoing a transformative phase, marked by rapid advancements in technology and surgical methods. Robotic surgery has added a new dimension to pediatric oncology, providing enhanced precision, dexterity, and superior visualization. This minimally invasive approach facilitates complex procedures, leading to reduced blood loss, improved cosmetic outcomes, and potentially better surgical margins. The use of robotic surgery in the resection of pediatric solid tumors has shown promising results in terms of patient recovery and postoperative quality of life[19]. Despite its advantages, the integration of robotic surgery faces significant challenges, notably the high costs of equipment and the specialized training required for surgeons. These challenges are particularly acute in low- and middle-income countries (LMICs), where limited resources and access to training can impede the widespread adoption of robotic surgery. Additionally, the learning curve associated with these techniques necessitates ongoing education and skill development among surgical teams[13,15,19].

The advent of 3D modeling and augmented reality has revolutionized preoperative preparation in pediatric surgical oncology. These technologies offer an unparalleled depth of insight into complex anatomical structures, enabling surgeons to plan and execute surgical interventions with enhanced precision. 3D reconstructions, including cinematic rendering and volume rendering, provide a detailed visualization of pediatric tumors, significantly aiding in therapeutic decisions and prognostic assessments in various areas such as thoracic, brain, urology, and abdominal surgery[18]. The use of these technologies in the preoperative assessment of children, for instance, in cases like Wilms tumors, has demonstrated potential for guiding surgical decision-making[17]. These advanced imaging techniques enable surgeons to tailor diagnosis and treatment plans more accurately, thus improving surgical outcomes and patient care. However, the integration of these technologies in varied clinical settings, especially in low-resource environments, presents challenges, including the limited availability of advanced imaging equipment, the high costs involved, and the need for specialized training[17,18,20].

Enhanced recovery after surgery (ERAS) programs in pediatric oncology represent a significant stride toward improving surgical precision, enhancing patient safety, and reducing postoperative complications. By leveraging advanced techniques like 3D imaging and augmented reality, these programs provide detailed anatomical visualizations that aid in meticulous surgical planning. The multidisciplinary nature of ERAS, involving collaboration among surgeons, anesthesiologists, nurses, and other healthcare professionals, is crucial in

minimizing the physiological stress associated with surgery. Studies have indicated that ERAS protocols in pediatric oncology surgery lead to faster recovery, reduced hospital stays, and fewer complications, thereby improving the quality of life for pediatric patients[16]. Despite their benefits, the application of ERAS protocols, particularly in the surgical resection of solid tumors in children, requires further research, including randomized prospective studies. Moreover, implementing these protocols in resource-limited settings encounters hurdles such as limited resource availability, a lack of awareness, and resistance to change[21].

Looking ahead, pediatric surgical oncology faces several challenges that need to be addressed to continue advancing the field. First, the disparities in the availability of advanced surgical techniques and technologies between high-income countries and LMICs present a major challenge[5,6,7,22]. Addressing these disparities requires a concerted effort to improve educational infrastructure, training programs, and access to essential resources globally. Second, the implementation of innovative surgical approaches such as 3D modeling, augmented reality, and robotic surgery in LMICs is hindered by financial constraints, a lack of infrastructure, and the need for specialized training. Collaborations between healthcare institutions, governments, and international organizations are essential to provide the necessary support and infrastructure development. Third, the ethical considerations in conducting research involving pediatric patients, obtaining funding for research projects, and ensuring long-term follow-up and data collection are challenges that researchers in pediatric surgical oncology face. Fostering a research environment that emphasizes ethical practices and long-term patient care is vital. Finally, keeping pace with rapid technological advancements while ensuring equitable access to these innovations remains a significant challenge. The field must balance the excitement of new technologies with the practicalities of their implementation in diverse healthcare settings.

CONCLUSION

The landscape of pediatric surgical oncology is undergoing a transformative era, marked by remarkable technological advancements and strategic approaches that significantly impact the prognosis of childhood cancer. The integration of minimally invasive and robotic surgeries, alongside the innovative preoperative planning and recovery strategies embodied by ERAS programs, represents a leap forward in enhancing surgical precision, reducing patient morbidity, and accelerating recovery. However, the journey forward is not without challenges, particularly in harmonizing these advances across diverse global healthcare settings and ensuring equitable access to these cutting-edge technologies and methods.

As we look toward the future, the field of pediatric surgical oncology stands on the precipice of an exciting era of research and development. The continued collaboration, innovation, and commitment to overcoming the existing barriers will be pivotal in shaping a world where every child battling cancer has the best possible prognosis and quality of life, irrespective of their geographical or socioeconomic background. This journey, though complex, is filled with hope and potential, promising a brighter, healthier future for children worldwide facing the challenges of cancer.

AUTHORS' CONTRIBUTIONS

VK: Data curation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **WEOJ:** Data curation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

REFERENCES

1. Instituto Nacional de Câncer (INCA). Estimativa 2022: incidência de câncer no Brasil. Rio de Janeiro (RJ): INCA; 2021.
2. Ward E, Santis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):83-103. https://doi.org/10.3322/caac.21219
3. Lautz TB, Harris CJ, Laronda MM, Erickson LL, Rowell EE. A fertility preservation toolkit for pediatric surgeons caring for children with cancer. Semin Pediatr Surg. 2019;28(6):150861. https://doi.org/10.1016/j.sempedsurg.2019.150861
4. Ehrlich PF. The impact of cooperative group studies on childhood cancer: improving outcomes and quality and international collaboration. Semin Pediatr Surg. 2019;28(6):150857. https://doi.org/10.1016/j.sempedsurg.2019.150857
5. Pritchard-Jones K, Pieters R, Reaman GH, Hjorth L, Downie P, Calaminus G, et al. Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. Lancet Oncol. 2013;14(3):e95-103. https://doi.org/10.1016/S1470-2045(13)70010-X
6. Allmen D. Pediatric surgical oncology: a brief overview of where we have been and the challenges we face. Semin Pediatr Surg. 2019;28(6):150864. https://doi.org/10.1016/j.sempedsurg.2019.150864
7. Davidoff AM. Advocating for the surgical needs of children with cancer. J Pediatr Surg. 2022;57(6):959-66.https://doi.org/10.1016/j.jpedsurg.2022.01.050
8. Rich BS, Silverberg JT, Fishbein J, Raval MV, Gadepalli SK, Moriarty KP, et al. Subspecialization in pediatric surgery: results of a survey to the American pediatric surgical association. J

Pediatr Surg. 2020;55(10):2058-63. https://doi.org/10.1016/j.jpedsurg.2020.02.006

9. Fernandez-Pineda I, Sanders D, Rao BN, Shochat SJ, Davidoff AM. Outcomes of a pediatric surgical oncology fellowship in a pediatric cancer institution. Pediatr Blood Cancer. 2017;64(10):e26618. https://doi.org/10.1002/pbc.26618
10. Alaish SM, Powell DM, Waldhausen JHT, Dunn SP. The right child/right surgeon initiative: a position statement on pediatric surgical training, sub-specialization, and continuous certification from the American Pediatric Surgical Association. J Pediatr Surg. 2020;55(12):2566-74. https://doi.org/10.1016/j.jpedsurg.2020.08.001
11. Losty PD. Training in pediatric surgical oncology. Front Pediatr. 2022;10:848543. https://doi.org/10.3389/fped.2022.848543
12. Losty PD. Evidence-based paediatric surgical oncology. Semin Pediatr Surg. 2016;25(5):333-5. https://doi.org/10.1053/j.sempedsurg.2016.09.008
13. Abdelhafeez AH, Reljic T, Kumar A, Banu T, Cox S, Davidoff AM, et al. Evidence-based surgical guidelines for treating children with Wilms tumor in low-resource settings. Pediatr Blood Cancer. 2022;69(12):e29906. https://doi.org/10.1002/pbc.29906
14. Richardson WR. Progress in pediatric cancer surgery. Recent advances in the surgical management of neoplasms in infants and children. Arch Surg. 1961;82(5):641-55. https://doi.org/10.1001/archsurg.1961.01300110003001
15. Wijnen M. Innovations in pediatric surgical oncology. J Pediatr Surg. 2022;57(6):967-9. https://doi.org/10.1016/j.jpedsurg.2022.02.003
16. Wells SJ, Austin M, Gottumukkala V, Kruse B, Mayon L, Kapoor R, et al. Development of an enhanced recovery program in pediatric, adolescent, and young adult surgical oncology patients. Children (Basel). 2021;8(12):1154. https://doi.org/10.3390/children8121154
17. Wellens LM, Meulstee J, Ven CP, Terwisscha Scheltinga CEJ, Littooij AS, Heuvel-Eibrink MM, et al. Comparison of 3-dimensional and augmented reality kidney models with conventional imaging data in the preoperative assessment of children with Wilms tumors. JAMA Netw Open. 2019;2(4):e192633. https://doi.org/10.1001/jamanetworkopen.2019.2633
18. Valls-Esteve A, Adell-Gómez N, Pasten A, Barber I, Munuera J, Krauel L. Exploring the potential of three-dimensional imaging, printing, and modeling in pediatric surgical oncology: a new era of precision surgery. Children (Basel). 2023;10(5):832. https://doi.org/10.3390/children10050832
19. Chang S, Lin Y, Yang S, Yang W, Cheng H, Chang X, et al. Safety and feasibility of laparoscopic resection of abdominal neuroblastoma without image-defined risk factors: a single-center experience. World J Surg Oncol. 2023;21(1):113. https://doi.org/10.1186/s12957-023-02997-9
20. Urla C, Fuchs J, Grimm A, Schmidt A, Schäfer J, Schuhmann MU, et al. Interdisciplinary surgical approach enables complete tumor resection with preservation of neurological function in specific conditions of pediatric solid malignancies. J Cancer Res Clin Oncol. 2023;149(8):4497-507.https://doi.org/10.1007/s00432-022-04273-x
21. Zhu K, He J, Chen T, Yu X, He X, Su Y. Retroperitoneal localized neuroblastoma in children: a comparison of enhanced recovery after surgery versus traditional care. Pediatr Surg Int. 2023;39(1):208. https://doi.org/10.1007/s00383-023-05493-z
22. Hadley LG, Rouma BS, Saad-Eldin Y. Challenge of pediatric oncology in Africa. Semin Pediatr Surg. 2012;21(2):136-41. https://doi.org/10.1053/j.sempedsurg.2012.01.006

REVIEW ARTICLE

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Lung cancer screening: a mini review of the major trials and guidelines

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INTRODUCTION

Lung cancer remains a notable global health concern due to its high incidence and mortality rates. In 2020, there were an estimated 1.8 million lung cancer-related deaths and 2.2 million new lung cancer cases, making it the leading cause of cancer death (18% of all cancer deaths) and the second most frequently diagnosed cancer in the world (11.4% of all cancer diagnoses)[1].

Lung cancer often goes undetected until its advanced stages, with these late diagnoses contributing immensely to a poor prognosis. In most countries, the 5-year survival rate in patients with lung cancer is only 10–20%[1]. The presence of metastasis upon first diagnosis, indicating advanced disease, is the main cause of treatment failure, while patients diagnosed at an earlier stage, like stage IA, and adequately treated have significantly higher 5-year survival rates, exceeding 70%[2]. This underscores the importance of early diagnosis and appropriate treatment for better outcomes in lung cancer patients.

Exposure to risk factors is intimately linked to lung cancer etiology. The most important and prevalent risk factor is tobacco smoking, which accounts for 80–90% of lung cancer diagnoses, despite the fact that only about 15% of smokers develop this neoplasm. Tobacco smoke contains many carcinogens, causing the relative risk of lung cancer in a smoker to be around 20 times higher than the risk in a nonsmoker[3]. The global pattern of lung cancer incidence is related to the tobacco epidemic, and since the disease has poor survival and high fatality rates, its mortality is also associated with such an epidemic[1]. It is important to note that there are also other risk factors that can be associated with lung cancer, such as secondhand smoke, electronic cigarettes, pre-existing lung disease, occupational exposures, and oncogenic viruses[3].

In this context, it is evident the importance of primary prevention of lung cancer, which consists of reducing smoking initiation, particularly in the younger population, and increasing smoking cessation, to achieve a reduction in risk and mortality[1,3]. It is also important to implement secondary prevention in people who are at high risk (current and former heavy smokers) to detect lung cancer in its earliest stages, when treatment, mainly surgical, is most successful[3].

In this sense, significant effort was made to enhance early diagnosis and treatment for lung cancer in order to improve patient outcomes. Initially, in the 1970s, trials using chest radiography and sputum cytology to detect early lung cancer were performed, which proved to be ineffective in reducing its mortality. Later, in the 1990s, low-dose spiral chest computed tomography (LDCT) was shown to have potential usefulness in lung cancer screening (LCS)[2]. Since then, multiple international observational studies and randomized trials have been executed, confirming the efficacy of annual LDCT in reducing lung cancer mortality and thus serving as the basis for current guidelines concerning lung cancer prevention and screening[1,2]. In the present study, we aim to do a mini-review of the major trials and guidelines concerning lung cancer screening (LCS).

METHODS

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published until August 2023, with the following descriptors: lung cancer; screening; diagnosis; smoking cessation; treatment. Our team also reviewed reference lists of pertinent articles and studies suggested by the review writers.

The aim was to find the most pertinent randomized controlled trials regarding screening for lung cancer with LDCT and guidelines about the same topic, published by different respected entities with a broad spectrum of different countries.

Two reviewers selected the trials and/or guidelines, taking into consideration the relevance, methodology, impact in the scientific community, quality of the journals, and range and respect of the entities when it came to the guidelines.

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RESULTS AND DISCUSSION

The first double-blind randomized controlled trial regarding LCS with statistically relevant results was the National Lung Screening Trial (NLST), which was also the largest trial ever performed in that matter, as shown in Table 1. It opened the door for discussion and research on early diagnosis and screening for lung cancer, considering that most of the research regarding that disease targets treatment options.

Table 1. Major trials about lung cancer screening and their results.

Trial	Study design	Number of participants	Target group (age and smoking status)	Summary of findings	Additional points
NLST (National Lung Screening Trial)	Participants randomly assigned to one of two screening groups: one group underwent LDCT annually for 3 years, and the other group underwent chest X-ray annually for the same period.	>53,000	55–74 years old, with a history of smoking for at least 30 years or had quit smoking within the past 15 years.	The results of the study showed that LDCT reduced lung cancer mortality by 20% compared with chest X-ray.	X
NELSON ((NEderlands Leuvens Screening ONderzoek)	Participants were randomly assigned to either LDCT group or the control group. The LDCT group received screening with low-dose computed tomography scans at baseline and after 1, 2, and 4 years.	>15,000	40–74 years old, who were current or former smokers with a smoking history of at least 10 cigarettes per day for at least 30 years or 15 cigarettes per day for at least 25 years.	The primary endpoint of the study was lung cancer mortality. The LDCT group had a significantly lower cancer mortality (up to 20%) rate compared with the control group.	X
UKLS (UK Lung Screen Trial)	Participants were randomly assigned to LDCT screening (periodicity defined according to the Wald Single Screen Design) or no screening (usual care).	4,055	50–75 years old with the risk score Liverpool Lung Project (LLPv2)≥4.5%	While the UKLS showed benefits in early detection, the study was not sufficiently large or long term to determine a direct impact on lung cancer mortality reduction.	Screening with LDCT resulted in a high proportion of lung cancers being detected at early stages. In the screened group, 87.8% of diagnosed cancers were at stage I or II. The trial shows, however, a proportion of false-positive results of 18.5% (nodules that were initially suspicious but later confirmed as benign).
LUSI (Lung Screening Intervention Trial)	Participants were recruited from the general population and randomly assigned to LDCT screening or no screening during 5 years.	4,052	50–69 years old, with eligibility criteria being defined by at least 25 years smoking of at least 15 cigarettes per day or at least 30 years smoking of at least 10 cigarettes per day, including ex-smokers who had stopped smoking not more than 10 years before invitation to screening.	Modeling by sex showed a statistically significant reduction in lung cancer mortality among women (HR=0.31 [95%CI 0.10–0.96], p=0.04), but not among men (HR=0.94 [95%CI 0.54–1.61], p=0.81) screened by LDCT.	X
MILD (Multicentric Italian Lung Detection)	Participants were randomized to annual or biennial LDCT, with a median screening period of 6.2 years or no screening (usual care).	4,099	49–75 years old, current or formers smokers (<10 years of quitting) of ≥20 packs/year without history of cancer in ≤5 years.	LDCT screening was associated with a significant 39% reduction in lung cancer mortality at 10 years (HR 0.61; 95%CI 0.39–0.95; p=0.017), as well as a nonsignificant 20% decrease in all-cause mortality.	The biennial LDCT arm showed a similar overall mortality (HR 0.80, 95%CI 0.57–1.12) and LC specific mortality at 10 years (HR 1.10, 95%CI 0.59–2.05), as compared with annual LDCT arm.

Those trials have all come to similar findings, showing that LDCT is a great choice for LCS, and it has the capability of reducing up to 20%, in some trials even more, of lung cancer-related mortality. That comes up as extremely enthusiastic for the scientific community that had, and still has, witnessed the dramatic cases of advanced lung cancer.

The trials showed, however, some points that need to be analyzed carefully before implementing a screening program, such as the presence of false-positives, which lead to unnecessary surgical intervention and patient-family anxiety, and the detection of lesions that may never become cancer, leading to overdiagnosis and overtreatment. Smaller trials in low- to middle-income countries have shown that the rate of false-positives increases significantly in tuberculosis-endemic areas. Those outcomes were minimized, though, with the performance of the screening in specialized centers with highly defined protocols, the analysis of an experienced multidisciplinary team, and the presence of a thoracic radiologist.

Alongside that, much has been speculated about the cost-effectiveness of LCS with LDCT, considering the cost of that screening for large populations. A systematic review from the Lung Cancer Journal, published in 2022, evaluates that matter. The review looked at 45 studies, including trials and modeling studies. 86.7% of the studies found screening with LDCT to be cost-effective, being optimal between the ages of 55 and 75 years, with a history of at least 20 packs per year.

Another aspect shown in the trials was that, in patients who were current smokers during screening, the smoking cessation rate was extremely higher compared to those that didn't undergo screening.

Considering all that, important societies and entities started publishing guidelines based on those trials; they can be seen in Table 2. Most of the guidelines have similar recommendations, with annual LDCT screening for risk groups as the standard. Also, specialized centers are recommended, as described.

Those guidelines evaluated important aspects of LCS, such as the difference in all-cause mortality, lung cancer mortality, and quality of life; effectiveness in different subgroups; effectiveness associated with frequency of screening; accuracy of screening with LDCT; harms associated with that; and other practices that should be encouraged to diminish the incidence of lung cancer, being able to minimize, in the future, the number of people in the risk groups.

One of those practices, encouraged by most of the guidelines, takes place in smoking cessation programs that should have a broad range for all the population, with multidisciplinary teams involving mental health care professionals and multiple strategies for smokers to quit smoking, as well as educational programs for nonsmokers. That increases tremendously the cost-effectiveness of screening, considering that the risk groups would become smaller and smaller with time.

Table 2. Guidelines for screening for lung cancer.

Guideline	Recommendations
USPSTF (United States Prevention Taskforce), 2021	Screening with annual LDCT in individuals between the ages of 50 and 80 years with a history of smoking at least 20 packs/year. The screening must be done in specialized centers with highly defined protocols, to minimize the rate of false positives and overdiagnosis.
European Society of Radiology+European Respiratory Society, 2020	Screening with LDCT in individuals aged 50–75 years with a smoking history of at least 20 packs/year and a quit time of less than 10 years. Should be done yearly for at least 3 years. The results must be interpreted by radiologists with expertise in thoracic imaging.
Brazilian Society of Pneumology and Phthisiology+Brazilian Society of Thoracic Surgery+Brazilian College of Radiology and Imaging Diagnosis, 2023	LDCT annually in individuals between 50 and 80 years old, who are current smokers or quit smoking in the last 15 years, with a smoking history of at least 20 packs/year.
Canadian Task Force on Preventive Health Care, 2016	Screening with LDCT in individuals aged 55–74 years with at least a 30 packs/year smoking history, who currently smoke or quit less than 15 years ago. Annual screening with LDCT up to three consecutive years. Screening should only be carried out in health care settings with expertise in early diagnosis and treatment of lung cancer.
National Comprehensive Cancer Network, 2022	LCDT screening in individuals aged between 55 and 77 years, with a >30 packs/year smoking history, who are current smokers or quit in the past 15 years. Or individuals with more than 50 years old, with a smoking history of > 20 packs/year, with additional risk factors.
Royal Australian and New Zealand College of Radiologists (RANZCR), 2021	Age between 50 and 74 years; 20 or more packs/year history of smoking tobacco; and, if former smoker, have quit within 20 years should undergo helical LDCT. To be involved in the program, participants should also be willing to receive counseling and participate in shared decision-making before screening.

CONCLUSION

Even though the benefits of LDCT in LCS have been proven, the implementation of such programs still faces important challenges. The first one concerns continuing medical education programs, so all of the medical society becomes aware of the need for LCS, as it already happens in other neoplasms, such as breast cancer and colorectal cancer.

Another concern regards the stigma still present in the face of a lung cancer diagnosis, considering the intimate relationship with smoking and the consequent guilt and stress that the diagnosis may trigger in the patient and their family.

Also, understanding and developing culture-sensitive screening approaches is essential, especially when it comes to low- and middle-income countries, where infrastructure and access to healthcare may be a problem, and that must be faced with strategies such as public-private partnerships and the employment of mobile CT scanners.

At last, the results shown here must be seen with extreme hope that, in the future, hopefully in the short term, our community will be able to see fewer advanced lung cancer cases, with more early diagnosis, and an exponential reduction in smoking levels.

AUTHORS' CONTRIBUTIONS

WWSA: Conceptualization, Supervision, Writing – review & editing. **DOB:** Methodology, Writing – review & editing. **FMN:** Methodology, Writing – review & editing. **CAPP:** Data curation, Writing – review & editing. **ASS:** Data curation, Writing – original draft, Writing – review & editing.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
2. Pastorino U. Lung cancer screening. Br J Cancer. 2010;102(12):1681-6. https://doi.org/10.1038/sj.bjc.6605660
3. Schabath MB, Cote ML. Cancer progress and priorities: lung cancer. Cancer Epidemiol Biomarkers Prev. 2019;28(10):1563-79. https://doi.org/10.1158/1055-9965.EPI-19-0221
4. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409. https://doi.org/10.1056/NEJMoa1102873
5. Manser R, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ, et al. Screening for lung cancer. Cochrane Database Syst Rev. 2013;2013(6):CD001991. https://doi.org/10.1002/14651858.CD001991.pub3
6. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, et al. Screening for lung cancer: US preventive services task force recommendation statement. JAMA. 2021;325(10):962-70. https://doi.org/10.1001/jama.2021.1117
7. Koning HJ, Aalst CM, Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med. 2020;382(6):503-13. https://doi.org/10.1056/NEJMoa1911793
8. Kauczor HU, Baird AM, Blum TG, Bonomo L, Bostantzoglou C, Burghuber O, et al. ESR/ERS statement paper on lung cancer screening. Eur Respir J. 2020;55(2):1900506. https://doi.org/10.1183/13993003.00506-2019
9. Grover H, King W, Bhattarai N, Moloney E, Sharp L, Fuller L. Systematic review of the cost-effectiveness of screening for lung cancer with low dose computed tomography. Lung Cancer. 2022;170:20-33. https://doi.org/10.1016/j.lungcan.2022.05.005
10. Patz EF, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemägi MC, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med. 2014;174(2):269-74. https://doi.org/10.1001/jamainternmed.2013.12738
11. Brazilian Consensus on Lung Cancer Screening. Brazilian Society of Pneumology and Phthisiology, Brazilian Society of Thoracic Surgery and Brazilian College of Radiology and Imaging Diagnosis. 2023.
12. Canadian Task Force on Preventive Health Care. Recommendations on screening for lung cancer. CMAJ. 2016;188(6):425-32. https://doi.org/10.1503/cmaj.151421
13. Wood DE, Kazerooni EA, Aberle D, Berman A, Brown LM, Eapen GA, et al. NCCN guidelines® insights: lung cancer screening, version 1.2022. J Natl Compr Canc Netw. 2022;20(7):754-64. https://doi.org/10.6004/jnccn.2022.0036
14. Field JK, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess. 2016;20(40):1-46. https://doi.org/10.3310/hta20400
15. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, et al. Lung cancer mortality reduction by LDCT screening-results from the randomized German LUSI trial. Int J Cancer. 2020;146(6):1503-13. https://doi.org/10.1002/ijc.32486
16. Pastorino U, Silva M, Sestini S, Sabia F, Boeri M, Cantarutti A, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: new confirmation of lung cancer screening efficacy. Ann Oncol. 2019;30(7):1162-9. https://doi.org/10.1093/annonc/mdz117

REVIEW ARTICLE

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Current guidelines for the management of rectal cancer patients: a review of recent advances and strategies

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INTRODUCTION

Colorectal cancer (CRC) is a common and lethal disease, the third most common cancer diagnosed in both men and women in the United States[1]. The American Cancer Society's estimates are 106,970 new cases of colon cancer and 46,050 new cases of rectal cancer (RC) for 2023[2].

Despite this, general rates dropped by about 1% each year from 2011 to 2019, probably due to the use of screening colonoscopy[3-5]. However, this decrease occurred in the older population, as in the population under 50 years, the rates increased by 1–2% a year since mid-1990s[1]. In Brazil, the National Cancer Institute (INCA) estimates 45,630 new CRC cases will be diagnosed annually in 2023–2025[4].

Colorectal cancer results from the interaction of genetic predisposition and environmental risk factors, but increasing age remains the most important risk factor. In this setting, CRC familial history, personal history of adenomas or inflammatory bowel disease, and inherited syndromes should always be evaluated[5,6]. Simultaneously, tobacco, alcohol use, obesity, lack of physical activity, and unhealthy lifestyle choices, such as a diet high in processed meats and low in fruits and vegetables, sedentary behavior, obesity, smoking, and excessive alcohol consumption, have been associated with increased risk[6].

Colorectal cancer development occurs from genetic defects (mutations), inherited or acquired[7,8]. Also, chemical, physical, or biological agents in the intestinal lumen may cause colonocyte DNA damage and form cell clones with neoplastic cell attributes. A better understanding of the mechanisms by which a normal epithelium of the colon transforms into an adenoma and, subsequently, into an invasive carcinoma has become possible with the clarification of the adenoma-carcinoma sequence[7,8].

At the molecular level, CRC is a heterogeneous disease due to at least three major molecular tumorigenesis pathways. The most common (85%) is classical chromosomal instability (CIN). These mechanisms are typically associated with mutations in oncogenes or tumor suppressor genes such as adenomatous polyposis coli (APC) and others that regulate cell proliferation[8].

The microsatellite instability (MSI) pathway is caused by a deficiency of the DNA mismatch repair gene[9,10]. And the serrated pathway is responsible for approximately 20–30% CRC cases. There may be some overlap between these mechanisms, which explains the different molecular features existing in CCR[9,10].

In 2012, the Cancer Genome Atlas Network (CGAN) classified CRC into four subtypes with distinct molecular, biological, and clinical characteristics: CMS1 (microsatellite instability immune), CMS2 (canonical), CMS3 (metabolic), and CMS4 (mesenchymal)[11].

CLINICAL PRESENTATION AND INITIAL EVALUATION

Rectal cancer represents around 30% of all CRC tumors. Symptoms like hematochezia, tenesmus, and mucous discharge always suggest a rectal location. Other complaints are anemia, abdominal pain, changes in bowel habits, and weight loss[12,13].

Initial evaluation is made by detailed anamnesis, digital rectal examination, endoscopic assessment, tissue biopsy, and serum carcinoembryonic antigen (CEA). Colonoscopy may identify polyps or synchronous tumors upstream of the primary lesion located in the rectum.

Preliminary information from proctological and gynecological examinations is crucial, such as distance from the anal verge and vaginal infiltration. The finding of ascites, hepatomegaly, inguinal nodes, and severe malnutrition may raise the possibility of metastatic disease.

Local and distant staging is achieved with chest and abdominal computed tomography and pelvic magnetic resonance

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imaging (MRI). Depending on specific findings, a transrectal ultrasound or a positron emission tomography-computed tomography (PET-CT) scan may add some information.

Extracted information from an MRI may help to evaluate the possibility of achieving free radial and distal margins after surgery, the tumor's relation to the mesorectal fascia, peritoneal reflection, and anorectal muscular ring. Other data include invasion of the rectal wall, mesorectum, and adjacent organs or structures (T status). Likewise, the number and appearance of lymph nodes, the presence of tumor deposits in the mesorectum (N status), the presence or absence of vascular invasion, and the enlargement of the lymph nodes of the lateral pelvic wall must be described.

After neoadjuvant treatment, a re-evaluation with MRI, digital rectal examination, and endoscopy in accessible lesions will select bad and good responders (Figure 1)[14]. The selection of complete responders may allow organ preservation with a watch and wait (W&W) strategy and long-term surveillance. All other patients should deserve surgical treatment.

More recently, the colorectal community in Western Europe has driven attention to the importance of lateral pelvic lymph node involvement, mainly in distal rectal tumors[15]. Patients with locally advanced rectal cancers (LARC) who present enlarged lateral pelvic lymph nodes (>5 mm in their shortest axis) after neoadjuvant chemoradiotherapy should undergo lateral pelvic lymphadenectomy.

THE ROLE OF MULTIMODALITY MANAGEMENT

Before the 1980s, surgical resection was considered the best option for all tumor stages. However, high recurrence rates led to the evaluation of neoadjuvant chemoradiation as an integral part of RC treatment before total mesorectal excision (TME)[16]. Neoadjuvant chemotherapy in stages II (T3 or T4 node-negative) and III (node-positive) patients aims to reduce local and distant recurrence rates, besides having no survival benefits.

Nowadays, a multidisciplinary team (the tumor board) composed of a radiotherapist, oncologist, and colorectal surgeon should discuss together the best combination of chemoradiation protocol and surgery. Attempts to design new therapeutic strategies included different drug combinations, modifications in the sequence and duration of chemotherapy protocols, dose and radiotherapy duration, and the time interval between neoadjuvancy and surgery. Simultaneously, it was possible to gradually increase the number of patients treated with nonoperative management (NOM), an option that was introduced by Habr-Gama et al.[17] in Brazil. In this setting, patients are not referred for immediate surgery and are put under close surveillance[17]. Published results from the International W&W Database (IWWD) have corroborated the safety of the NOM strategy, and the number of patients undergoing NOM has progressively increased[18].

Another strategy called total neoadjuvant therapy (TNT) was designed to offer all chemotherapy before surgery, aiming to ensure that a greater fraction of patients would complete all chemotherapy regimens (induction or consolidation chemotherapy) before chemotherapy. A series of phase III randomized multicentric studies have evaluated different TNT regimens in LARC patients, the so-called RAPIDO, PRODIGE-23, and OPRA trials[19-21].

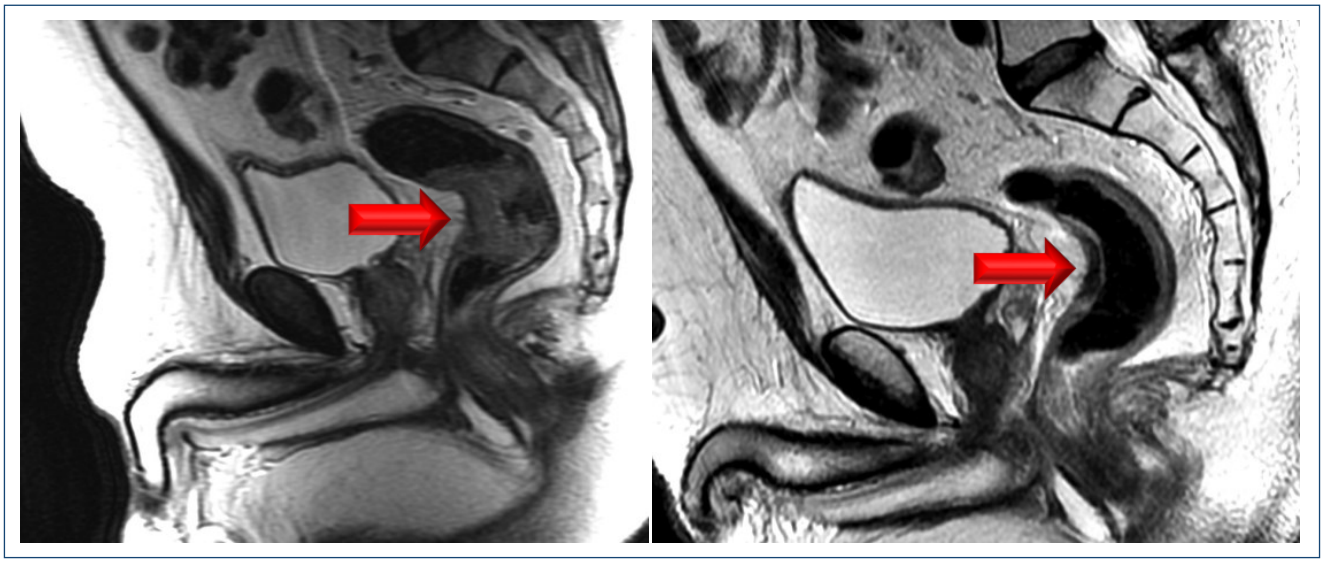

Figure 1. (A) Middle rectal tumor before neoadjuvant chemoradiotherapy (red arrow). (B) Good response after neoadjuvant chemoradiotherapy (red arrow). Courtesy of the Department of Radiology at UNICAMP (Prof. Daniel Lahan).

In the first two, it was demonstrated that patients undergoing the TNT protocol had lower rates of distant recurrence, despite no gain in overall survival (OS)[19,20]. In the OPRA study, a prospective randomized phase II trial assessed the outcomes of patients with stage II or III LARC treated with two different protocols[21]. The study concluded that the introduction of different TNT protocols allowed organ preservation in half of them without an apparent detriment to survival[21].

THE BASIS FOR MODERN SURGICAL TREATMENT

Rectal resection was historically studied and designed by the famous English surgeon William Ernest Miles (Figure 2), who published his seminal paper in 1908 and initiated the era of radical resections to treat RC[16,22].

Surgery for RC involves complex decisions and great challenges for colorectal surgeons. Primary lesions are managed with variable endoscopic, endoanal, or surgical procedures depending on the surgeon's experience, patients', and tumor features. Treatment may be performed with endoscopic or surgical techniques.

MANAGEMENT OF LOCALIZED RECTAL CANCER

Local resection of RC performed by endoscopic or surgical approaches may be offered to selected tumors and well-informed patients agreeing with close surveillance. Patients with T0-1N0 lesions smaller than 3 cm and clinically mobile will benefit from this approach, although recurrence rates (7–21%) may be higher than radical resection. The presence of favorable histologic features in a pedunculated polyp will not require further surgery.

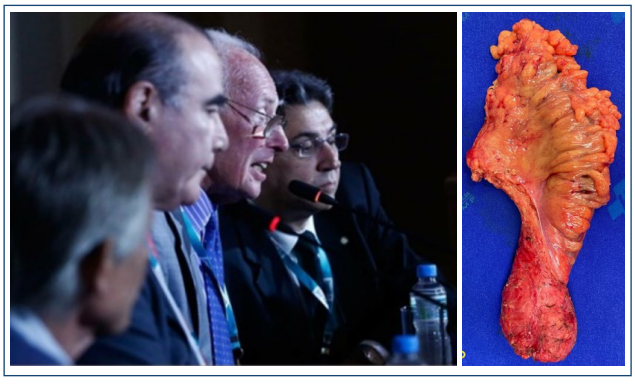

Figure 2. Dr. Richard Heald between the authors Campos FG (right) and Martinez CA (left) during a visit to Brazil some years ago. On the right, a surgical specimen of rectal cancer with total mesorectal excision. Right: Courtesy: CARM, Left: Courtesy: Department of Surgery at UNICAMP.

As well, those considered unfit for surgical radical resection may also be candidates. Features such as muscularis propria invasion (T2 tumors), poor histological grade, lymph nodes, vascular or perineal invasion, and flat or depressed morphology are deemed high-risk factors for this type of procedure.

Submucosal invasion greater than 1000 micrometers may lead to a 12% nodal involvement rate. Similarly, surgical resection may be indicated if patients treated with endoscopic resection exhibit fragmented or not assessable margins. The same idea is not applied to T2 lesions, where recurrence rates may achieve 26–47% in patients[23]. In those presenting an almost complete response after neoadjuvant treatment, endoanal local excision may also be recommended, despite wound complications in a rectum previously irradiated[24].

TRANSABDOMINAL RESECTION

A transabdominal resection may be required to treat LARC in the upper, middle, or low rectum. Surgery must remove the tumor-bearing bowel with adequate margins while preserving functions.

The introduction of TME represented a great technical advance that significantly reduced local recurrence rates. Technical details were designed and disseminated among colorectal surgeons by Dr. Richard Heald (Figure 2).

A 1-cm distal margin is generally adequate for well- or moderately differentiated tumors. After TME, a temporary deviation with an ileostomy is advisable to protect the anastomosis. In cases with direct involvement of the anal sphincters or levator muscles, an abdominoperineal excision of the rectum (APR) with a definitive colostomy will be necessary. Prophylactic dissection of lateral pelvic lymph nodes is not advisable, but this approach is recommended when lateral lymph node enlargement is detected in restaging MRI.

MINIMALLY INVASIVE TECHNIQUES

In recent decades, the introduction of minimally invasive surgery (MIS) in RC surgery has provided excellent outcomes[25]. Both laparoscopic and robotic approaches seem to have excellent short- and long-term results when compared to conventional access. Evidence suggests numerous MIS advantages, besides greater costs[26]. A meta-analysis of randomized clinical trials comparing laparoscopic and open rectal resection for cancer was performed by analyzing a total of 26 end points[27]. They demonstrated that laparoscopic surgery for RC was associated with a

statistically significant reduction in intraoperative blood loss and the number of blood transfusions, an earlier resuming of a solid diet, a return of bowel function, and a shorter duration of hospital stay. Laparoscopy also reduced post-operative abdominal bleeding, late adhesion obstruction, and morbidity. No differences were found in terms of intraoperative and late oncological outcomes.

A recent meta-analysis compared the long-term oncologic outcomes of laparoscopic and open surgery[28]. The 5-year estimated disease-free survival (DFS) rates were 72.2% for the laparoscopic group and 70.1% for the open surgery group, with 5-year estimated OS rates of 76.2 and 72.7%, respectively. The OS was significantly better in the laparoscopic group. The authors concluded that a similar DFS but a significantly better OS were found for patients who had undergone laparoscopic surgery.

Robot-assisted colorectal surgery is an evolving field suitable for transabdominal, trans-anal, and endoluminal approaches and encompasses many surgical techniques, including dissection, resection, and anastomosis. It is particularly advantageous in confined spaces such as the low rectum and endoluminal areas. While robotic surgery has great potential for improving outcomes, its' possible disadvantages over traditional laparoscopy and open surgery are still being debated[29]. Due to the advantages of greater freedom of movement, increased three-dimensional (3D) vision, better ergonomics, and a static camera, robotic surgery has provided greater surgical quality in difficult situations, such as inferior rectal tumors.

The ability to expose and separate fine tissues provides better dissection of embryological planes and drastically reduces damage to pelvic nerves and blood vessels by providing a clear view and identification of small nerves, thus protecting urinary and sexual functions. The robotic access allows for easier access to the lower rectum, particularly in obese men and those with a narrow pelvis. Studies confirm that the robotic approach in obese patients resulted in a shorter length of stay and a lower 30-day readmission rate, but longer operative time when compared to laparoscopic surgery. Robotic rectal surgery in the obese may be associated with a quicker postoperative recovery and a reduced morbidity profile[30].

In conclusion, robotic surgery is a rapidly evolving field that offers many benefits over traditional surgical methods. Robotic platforms have enabled surgeons to perform procedures with greater precision, dexterity, and flexibility. Additionally, robotic surgery has reduced pain and recovery time, leading to shorter hospital stays and improved clinical outcomes. Despite its advantages, robotic surgery still has limitations, such as undefined long-term oncologic outcomes, the need for specialized training, incompatible instruments, higher costs, and the lack of haptic feedback. However, ongoing technological advancements and studies are addressing these limitations and opening up new possibilities for the future of surgical robotics.

CONCLUSION

Rectal cancer is a complex and challenging disease in which oncological outcomes depend on accurate diagnosis, multidisciplinary management, and specialized surgery. Treatment should typically incorporate a tumor board discussion to define the best therapeutic option to achieve good results, and therefore it should be preferably planned in specialized centers.

AUTHORS' CONTRIBUTIONS

CARM: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **FGC:** Conceptualization, Data curation, Supervision, Writing – review & editing.

REFERENCES

1. American Cancer Society. Key statistics for colorectal cancer. 2023. [cited on 2023 Aug 19]. Available from: https://www.cancer.org/cancer/types/colon-rectal-cancer/about/key-statistics.html
2. World Health Organization. Colorectal cancer. 2023. [cited on 2023 Aug 21]. Available from: https://www.who.int/news-room/fact-sheets/detail/colorectal-cancer#:~:text=In%202020%2C%20more%20than%201.9,and%20mortality%20rates%20were%20observed
3. Phillips KA, Liang SY, Ladabaum U, Haas J, Kerlikowske K, Lieberman D, et al. Trends in colonoscopy for colorectal cancer screening. Med Care. 2007;45(2):160-7. https://doi.org/10.1097/01.mlr.0000246612.35245.21
4. Instituto Nacional de Câncer. Câncer de cólon e reto. 2023. [cited on 2023 Oct 09]. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document/estimativa-2023.pdf
5. Campos FG, Logullo Waitzberg AG, Kiss DR, Waitzberg DL, Habr-Gama A, Gama-Rodrigues J. Diet and colorectal cancer: current evidence for etiology and prevention. Nutr Hosp. 2005;20(1):18-25. PMID: 15762416
6. Campos FG, Figueiredo MN, Martinez CA. Colorectal cancer risk in hamartomatous polyposis syndromes. World J Gastrointest Surg. 2015;7(3):25-32. https://doi.org/10.4240/wjgs.v7.i3.25
7. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319(9):525-32. https://doi.org/10.1056/NEJM198809013190901

8. Huang Z, Yang M. Molecular network of colorectal cancer and current therapeutic options. Front Oncol. 2022;12:852927. https://doi.org/10.3389/fonc.2022.852927
9. Schmitt M, Greten FR. The inflammatory pathogenesis of colorectal cancer. Nat Rev Immunol. 2021;21(10):653-67. https://doi.org/10.1038/s41577-021-00534-x
10. Currais P, Rosa I, Claro I. Colorectal cancer carcinogenesis: from bench to bedside. World J Gastrointest Oncol. 2022;14(3):654-63. https://doi.org/10.4251/wjgo.v14.i3.654
11. The Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330-7. https://doi.org/10.1038/nature11252
12. Campos FG. Colorectal cancer in young adults: a difficult challenge. World J Gastroenterol. 2017;23(28):5041-4. https://doi.org/10.3748/wjg.v23.i28.5041
13. You YN, Hardiman KM, Bafford A, Poylin V, Francone TD, Davis K, et al. The American society of colon and rectal surgeons clinical practice guidelines for the management of rectal cancer. Dis Colon Rectum. 2020;63(9):1191-222. https://doi.org/10.1097/DCR.0000000000001762
14. São Julião GP, Habr-Gama A, Vailati BB, Perez RO. The good, the bad and the ugly: rectal cancers in the twenty-first century. Tech Coloproctol. 2017;21(7):573-5. https://doi.org/10.1007/s10151-017-1651-7
15. Chang G, Halabi WJ, Ali F. Management of lateral pelvic lymph nodes in rectal cancer. J Surg Oncol. 2023;127(8):1264-70. https://doi.org/10.1002/jso.27317
16. Campos FG, Habr-Gama A, Nahas SC, Perez RO. Abdominoperineal excision: evolution of a centenary operation. Dis Colon Rectum. 2012;55(8):844-53. https://doi.org/10.1097/DCR.0b013e31825ab0f7
17. Habr-Gama A, Souza PM, Ribeiro U, Nadalin W, Gansl R, Sousa AH, et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. Dis Colon Rectum. 1998;41(9):1087-96. https://doi.org/10.1007/BF02239429
18. Fernandez LM, São Julião GP, Figueiredo NL, Beets GL, Valk MJM, Bahadoer RR, et al. Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the international watch & wait database: a retrospective, international, multicentre registry study. Lancet Oncol. 2021;22(1):43-50. https://doi.org/10.1016/S1470-2045(20)30557-X
19. Valk MJM, Marijnen CAM, Etten B, Dijkstra EA, Hilling DE, Kranenbarg EM, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - results of the international randomized RAPIDO-trial. Radiother Oncol. 2020;147:75-83. https://doi.org/10.1016/j.radonc.2020.03.011
20. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(5):702-15. https://doi.org/10.1016/S1470-2045(21)00079-6
21. Garcia-Aguilar J, Patil S, Gollub MJ, Kim JK, Yuval JB, Thompson HM, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol. 2022;40(23):2546-56. https://doi.org/10.1200/JCO.22.00032
22. Campos FG. The life and legacy of William Ernest Miles (1869-1947): a tribute to an admirable surgeon. Rev Assoc Med Bras (1992). 2013;59(2):181-5. https://doi.org/10.1016/j.ramb.2012.09.001
23. You YN, Hardiman KM, Bafford A, Poylin V, Francone TD, Davis K, et al. The American society of colon and rectal surgeons clinical practice guidelines for the management of rectal cancer. Dis Colon Rectum. 2020;63(9):1191-222. https://doi.org/10.1097/DCR.0000000000001762
24. Teste B, Rouanet P, Tuech JJ, Valverde A, Lelong B, Rivoire M, et al. Early and late morbidity of local excision after chemoradiotherapy for rectal cancer. BJS Open. 2021;5(3):zrab043. https://doi.org/10.1093/bjsopen/zrab043
25. Araújo SE, Seid VE, Bertoncini A, Campos FG, Sousa A, Nahas SC, et al. Laparoscopic total mesorectal excision for rectal cancer after neoadjuvant treatment: targeting sphincter-preserving surgery. Hepatogastroenterology. 2011;58(110-1):1545-54. https://doi.org/10.5754/hge11114
26. Campos FG, Valarini R. Evolution of laparoscopic colorectal surgery in Brazil: results of 4744 patients from the national registry. Surg Laparosc Endosc Percutan Tech. 2009;19(3):249-54. https://doi.org/10.1097/SLE.0b013e3181a1193b
27. Trastulli S, Cirocchi R, Listorti C, Cavaliere D, Avenia N, Gullà N, et al. Laparoscopic vs open resection for rectal cancer: a meta-analysis of randomized clinical trials. Colorectal Dis. 2012;14(6):e277-96. https://doi.org/10.1111/j.1463-1318.2012.02985.x
28. Kong M, Chen H, Shan K, Sheng H, Li L. Comparison of survival among adults with rectal cancer who have undergone laparoscopic vs open surgery: a meta-analysis. JAMA Netw Open. 2022;5(5):e2210861. https://doi.org/10.1001/jamanetworkopen.2022.10861
29. Huang YJ, Kang YN, Huang YM, Wu AT, Wang W, Wei PL. Effects of laparoscopic vs robotic-assisted mesorectal excision for rectal cancer: an update systematic review and meta-analysis of randomized controlled trials. Asian J Surg. 2019;42(6):657-66. https://doi.org/10.1016/j.asjsur.2018.11.007
30. Panteleimonitis S, Pickering O, Abbas H, Harper M, Kandala N, Figueiredo N, et al. Robotic rectal cancer surgery in obese patients may lead to better short-term outcomes when compared to laparoscopy: a comparative propensity scored match study. Int J Colorectal Dis. 2018;33(8):1079-86. https://doi.org/10.1007/s00384-018-3030-x

REVIEW ARTICLE

https://doi.org/10.1590/1806-9282.2024S113

Field cancerization in dermatology

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INTRODUCTION

The concept of the cancerization field was described in 1953 when a group of pathologists, studying malignant neoplasms of the mouth, detected atypical cells far from the main malignant lesion. It could be assumed that there was a carcinogenic stimulus, with modifications already existing in the nucleus of the cells, in apparently normal skin.

This change became evident where areas intensely exposed to the sun showed a frequent and progressive appearance of malignant and pre-malignant lesions[1,2].

The definition of a field cancerization (CC) in dermatology is not yet fully established and is based on the visible identification of signs of sun damage associated with the finding of actinic keratoses and malignant epithelial tumors[3].

The field cancerization by photo exposure is the most studied in dermatology.

The observation of this occurrence made it important to plan and approach patients with this alteration, as there was the potential for the condition to progress.

On the skin, in areas exposed to an aggressive factor such as sun exposure or radiation therapy, xerosis, atrophy, scaling, actinic melanosis, leukoderma, actinic keratosis, and tumors such as epidermoid carcinoma[1,4,5].

In medical practice, highlighting this risk area is important for treatment, periodic and ongoing follow-up, and attention to the eventual appearance of more serious injuries.

There is still disagreement in the literature as to the exact field of cancerization, but some findings are considered highlights, such as actinic keratosis[1,4] (Figure 1).

ASSOCIATED FACTORS

Several factors may be associated with the development of a field cancerization, the most notable being chronic sun exposure. Sun exposure from childhood is considered and, even if the patient does not give correct information about the intensity and time of exposure, indirect data such as sports practices, free leisure activities, and rural work should be considered (Figure 2).

There is a greater risk in fair-skinned individuals, older patients, and immunosuppressed patients such as transplant patients.

A history of a lesion treated with a diagnosis of squamous cell carcinoma puts the region at greater risk of developing others[4,5].

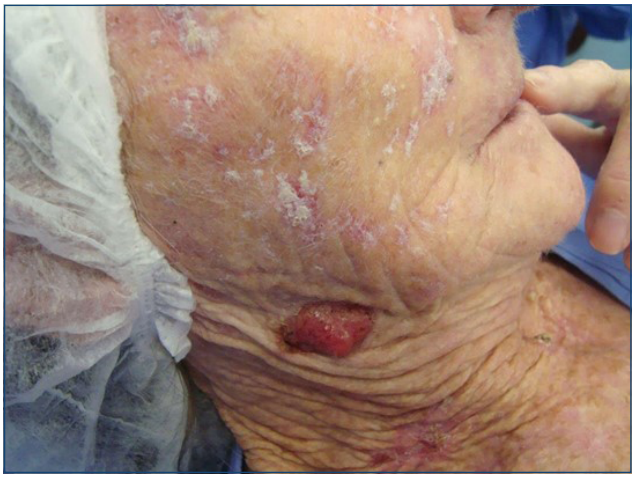

Figure 1. Multiple actinic keratoses on the face and squamous cell carcinoma on the neck.

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CLINICAL MANIFESTATIONS

The lesion that stands out on examination is actinic keratosis. It can be a precursor to squamous cell carcinoma or show histopathological atypia in the process of developing into carcinoma.

Actinic keratosis can be single or multiple, as papular lesions with hyperkeratosis and erythema.

They may be painful, have a burning sensation, or feel like a "thorn in the skin." They may be more palpable than visible, giving a feeling of local roughness.

Hyperkeratosis, which can be pronounced, suggests the shape of a cutaneous horn.

There are agglomerated, confluent actinic keratoses, forming extensive hyperkeratotic plaques[5-7].

The presence of actinic keratosis in a region of the skin requires careful observation as other manifestations suggestive of a field cancerization can be found such as xerosis, desquamation, actinic melanosis, and tumoral lesions of epidermoid carcinoma.

This can present as a nodule, tumor, vegetating lesion, and infiltration in varying sizes.

The areas most affected are those exposed to the sun, such as the bald head, face, upper limbs, and neckline.

There are attempts in the literature to grade actinic keratoses and to establish a relationship between higher keratosis rates and a higher risk of developing epidermoid carcinoma[1,8].

HISTOPATHOLOGICAL ASPECTS

The histopathological study of the field cancerization refers to the clinical lesions studied, such as actinic keratoses or carcinomas (Figure 3).

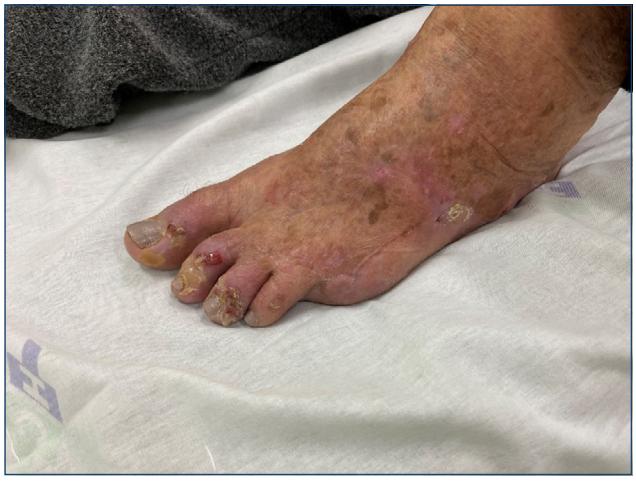


Figure 2. Foot intensely exposed to the sun, actinic keratoses, and carcinomas. Loss of finger due to a tumor.

It is possible to observe epidermal changes of atypia and architectural irregularities along the path of clinically normal areas in a large field.

Histopathological view of actinic keratosis showing epidermal nuclear atypia, hyperkeratosis, and structural disarray (Figures 4 and 5).

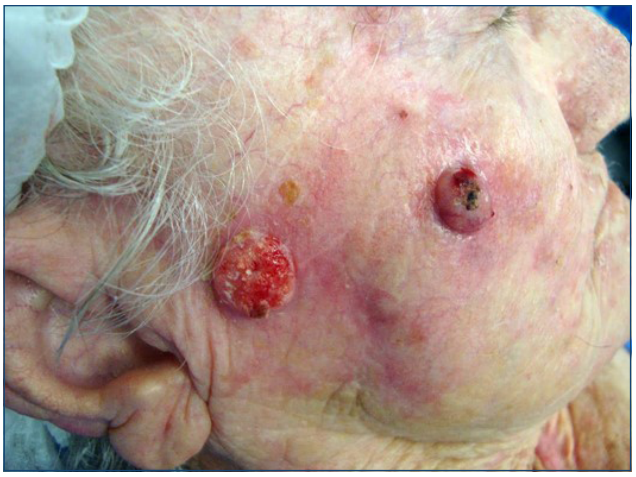
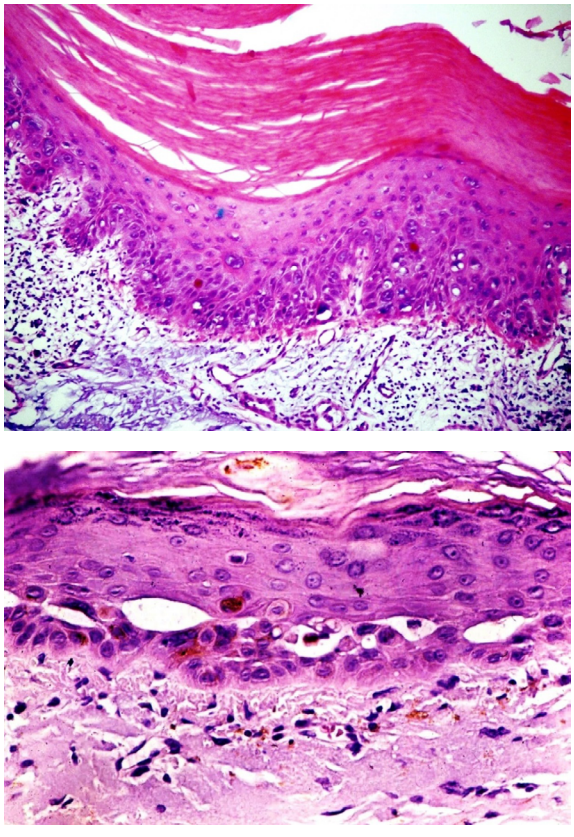


Figure 3. On the face, squamous cell carcinomas at different stages of development.



Figures 4 and 5. Histopathological view of actinic keratosis showing epidermal nuclear atypia, hyperkeratosis, and structural disarray.

TREATMENTS

Treatments for the field cancerization have evolved a lot in recent years, given the demand for the number and diversity of new cases.

Treatments can be single or combined, starting with one approach and extending to others depending on the presentation, number of lesions, and severity.

The following steps are suggested in the treatment of the field cancerization:

a. Define the area of involvement and the number of lesions;
b. Collect samples from lesions with the clinical appearance of carcinomas, hypertrophic actinic keratoses, or lesions clustered in plaques;
c. If epidermoid carcinoma is confirmed, prioritize its treatment, preferably surgical;
d. Establish an ablative treatment program for multiple, hypertrophic actinic keratosis lesions;
e. Propose treatment of the field with non-ablative methods;
f. Establish regular treatments, at least annually;
g. Propose preventive treatments (Table 1).

Ablative treatments

Ablative treatments include conventional surgery, cryosurgery, and laser therapy.

Conventional surgery is indicated for the excision of clinically and histologically diagnosed carcinomas. It is recommended to excise all carcinoma lesions with a safety margin of at least 0.4 cm beyond the safety margin[11,12].

It is well known that the safest method for excising these tumors is Mohs micrographic surgery, which is performed with microscopic control of the margins. The cure rate with this method is known to be higher than with conventional surgery.

According to clinical and histopathological criteria, epidermoid carcinoma is currently classified into low and high risk[11-13]. Both can be found in a field cancerization and will be treated according to risk. In the case of established carcinoma lesions, these are considered a priority for treatment.

Table 1. Principal treatments[4,8-10].

Ablative treatments	Topical treatments
Conventional surgery and MMS	5-Fluorouracil
Curettage and electrocoagulation	Imiquimod
Cryosurgery	Diclofenac sodium
Laser	Retinoic acid
Photodynamic therapy	Ingenol mebutate
Dermabrasion	

For low-risk carcinomas and actinic keratoses, cryosurgery with liquid nitrogen is recommended.

Cryosurgery is performed by applying a jet of liquid nitrogen to the lesion, freezing it, and resulting in coagulation necrosis. The lesion will be eliminated once the necrosis and crust have been removed[8,14] (Figure 6).

Curettage and electrocoagulation are also described. This method involves curettage of the lesion, which is more suitable for actinic keratoses, ulcer formation, and subsequent electrocoagulation of the wound. In addition to hemostasis, the electric current promotes coagulation necrosis, which helps to eliminate the atypical cells located there[3,5] (Figure 7).

In recent years, the use of photodynamic therapy for cancerizable areas has been well described.

This involves applying a photosensitive substance, for example, methyl 8-aminolevulinate, to the affected area. The affected area should be prepared by light curettage of the most prominent

Figure 6. Cryosurgery with liquid nitrogen in actinic keratoses of the field cancerization.

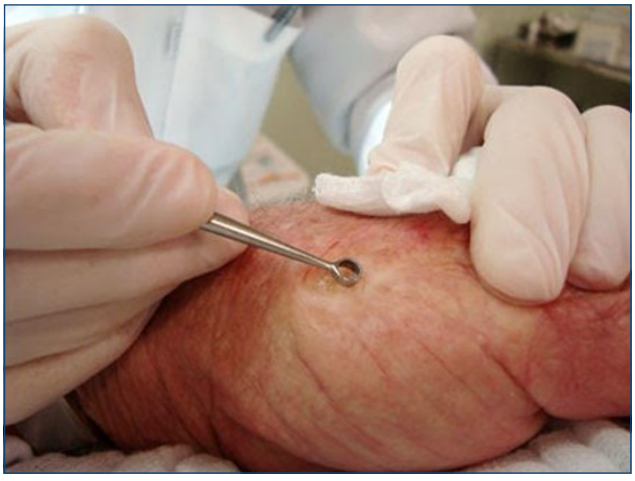


Figure 7. Actinic keratoses curettage.

keratoses and the photosensitive material is incubated under occlusion for 1 h. Afterward, a red light source can be applied or the patient is instructed to take mild sun exposure (daylight method). The affected area will be sensitized by the reaction of the drug with the light and the lesions that absorb the product will react more intensely at the most impregnated points. The result will be an erythematous area, followed by peeling and the elimination of actinic keratoses.

This method has been advocated for field cancerization areas and superficial epithelial tumors, squamous cell, and basal cell carcinomas. It is recognized that possible clinically unnoticeable lesions will be eliminated with this method[3,5,15].

There are references to the use of ablative laser therapy, such as CO_2 laser and dermabrasion, in the treatment of keratoses and fields cancerization. These resources are considered when treating heavily affected areas and hypertrophic lesions.

The knowledge and availability of different therapeutic methods increase the resolutions in different presentations of the disease[4].

Topical treatments

There are various topical treatments available, recommended mainly for superficial actinic keratosis lesions and basal cell and squamous cell carcinomas. For the drugs described below, prior curettage of the hypertrophic lesions is recommended to improve penetration of the active products.

The following therapies are mainly described.

5-Fluorouracil

An antimetabolite that inhibits DNA synthesis, presented in 0.5–5% cream, promotes deposition in epithelial cells in accelerated turnover and their consequent apoptosis. The area of application becomes erythematous and edematous with visible scaling in the most active lesions. Daily applications are recommended for 4 weeks[3,8,16].

Imiquimod

Imiquimod is a 3.75–5% cream, non-specific immunomodulatory agent. Applications are recommended three times a week for 6–16 weeks (Figure 8).

Both of the above drugs promote an intense inflammatory reaction with erythema, edema, exudation, and crust formation. The continuity of applications depends on the patient's tolerance[8].

Diclofenac sodium

It is presented in 3% aqueous gel formulations associated with 3% hyaluronic acid; it inhibits prostaglandin synthesis, elevated in lesions due to actinic damage; and its use should be prolonged and recommended twice a day for 3 months. Improvement of actinic keratosis lesions is slow and is estimated to be relevant in preventing new ones[6,7,17].

Ingenol mebutate

It is prepared as a gel at 0.05 and 0.1% and applied to the face or body for 2–3 days. It induces necrosis of abnormal keratinocytes, an inflammatory reaction, and stimulates the production of anti-tumor antibodies. The advantage of this treatment is its short course, which does not lead to the patient discontinuing it. It also produces an intense inflammatory reaction and its correlative signs on the skin[8-10].

Systemic treatments

Although it is not the scope of this text, it should be emphasized that when squamous cell carcinomas are found that are clearly developed or with the possibility of distant metastases, they should be evaluated for systemic therapy.

Treatment includes chemotherapy and immunotherapy drugs such as cemiplimab[12].

PREVENTION

The constant search for preventive treatments for multiple actinic lesions has been intense worldwide, considering the limitations and costs that this condition produces in populations, especially those with fair skin and those who frequent environments with high sun exposure[17,18].

The prevention of cancerizable skin lies mainly in protection from solar ultraviolet radiation. Early protection, from childhood onwards, is recognized as a major factor against the development of the field[18,19].

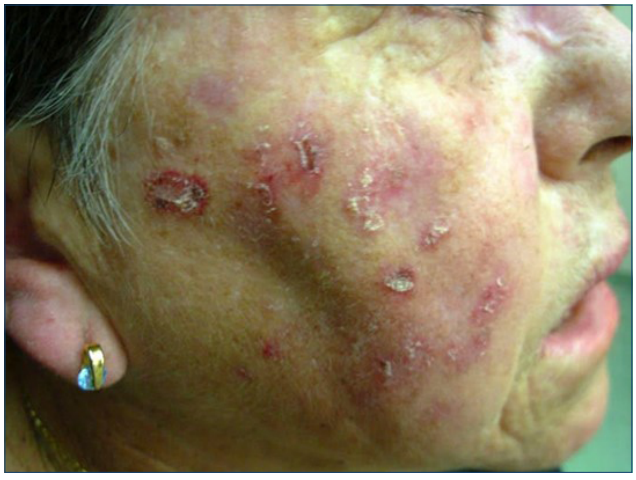


Figure 8. Patient using imiquimod on the seventh day.

The use of appropriate clothing and sunscreen in its different presentations and sports and work habits during periods of lower radiation are recognized as important to avoid the development of the field cancerization and its skin lesions.

Current studies have indicated nicotinamide in the chemoprevention of skin cancer. It is the amide form of vitamin B3. It has been implicated in maintaining genomic stability and may have beneficial effects on skin aging and tumor development[20-22].

The authors described a reduction in the appearance of malignant epithelial tumors in patients who used nicotinamide 500 mg twice a day compared with placebo[5,20,21].

Periodic follow-up of patients who have treated a field cancerization is necessary, at least annually and, if new lesions appear, this period should be brought forward.

It is recognized that actinic keratoses are recurrent.

Periodic courses of topical treatments are indicated for the chemoprevention of squamous cell carcinoma, as described by Weinstock et al.[16].

Recent research has pointed to the maintenance of the cutaneous microbiome in the chemoprevention of cutaneous carcinomas and suggests studies to be carried out on the involvement of diets, vitamin D, and microbial therapies[23].

AUTHORS' CONTRIBUTIONS

RFM: Writing – review & editing. **THB**: Writing – review & editing. **HSG**: Writing – review & editing. **CBB**: Writing – review & editing. **AMM**: Writing – review & editing.

REFERENCES

1. Willenbrink TJ, Ruiz ES, Cornejo CM, Schmults CD, Arron ST, Jambusaria-Pahlajani A. Field cancerization: definition, epidemiology, risk factors, and outcomes. J Am Acad Dermatol. 2020;83(3):709-17. https://doi.org/10.1016/j.jaad.2020.03.126
2. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res. 2003;63(8):1727-30. PMID: 12702551
3. Figueras Nart I, Cerio R, Dirschka T, Dréno B, Lear JT, Pellacani G, et al. Defining the actinic keratosis field: a literature review and discussion. J Eur Acad Dermatol Venereol. 2018;32(4):544-63. https://doi.org/10.1111/jdv.14652
4. Gutzmer R, Wiegand S, Kölbl O, Wermker K, Heppt M, Berking C. Actinic keratosis and cutaneous squamous cell carcinoma. Dtsch Arztebl Int. 2019;116(37):616-26. https://doi.org/10.3238/arztebl.2019.0616
5. Cornejo CM, Jambusaria-Pahlajani A, Willenbrink TJ, Schmults CD, Arron ST, Ruiz ES. Field cancerization: treatment. J Am Acad Dermatol. 2020;83(3):719-30. https://doi.org/10.1016/j.jaad.2020.03.127
6. Berman B, Cohen DE, Amini S. Qual o papel da terapia de campo no tratamento da queratose actínica? Parte 1. 241-50.
7. Berman B, Cohen DE, Amini S. Qual o papel da terapia de campo no tratamento da queratose actínica? Parte 2: tratamentos de campo e de lesão comumente usados. Cutis. 2012;9:294-301.
8. Dianzani C, Conforti C, Giuffrida R, Corneli P, Meo N, Farinazzo E, et al. Current therapies for actinic keratosis. Int J Dermatol. 2020;59(6):677-84. https://doi.org/10.1111/ijd.14767
9. Goldenberg G. Treatment considerations in actinic keratosis. J Eur Acad Dermatol Venereol. 2017;31(Suppl. 2):12-6. https://doi.org/10.1111/jdv.14152
10. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012;366(11):1010-9. https://doi.org/10.1056/NEJMoa1111170
11. Caudill J, Thomas JE, Burkhart CG. The risk of metastases from squamous cell carcinoma of the skin. Int J Dermatol. 2023;62(4):483-6. https://doi.org/10.1111/ijd.16164
12. Nehal KS, Bichakjian CK. Update on Keratinocyte Carcinomas. N Engl J Med. 2018;379(4):363-74. https://doi.org/10.1056/NEJMra1708701
13. Bander TS, Nehal KS, Lee EH. Cutaneous squamous cell carcinoma: updates in staging and management. Dermatol Clin. 2019;37(3):241-51. https://doi.org/10.1016/j.det.2019.03.009
14. Heppt MV, Steeb T, Ruzicka T, Berking C. Cryosurgery combined with topical interventions for actinic keratosis: a systematic review and meta-analysis. Br J Dermatol. 2019;180(4):740-8. https://doi.org/10.1111/bjd.17435
15. Torino ABB. Comparative analysis between photodynamic therapy versus cryosurgery in treating low risk basocellular carcinoma – randomized and prospective study [thesis]. Campinas (SP): Faculdade de Ciências Médicas - Universidade Estadual de Campinas; 2022.
16. Weinstock MA, Thwin SS, Siegel JA, Marcolivio K, Means AD, Leader NF, et al. Chemoprevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream: a randomized clinical trial. JAMA Dermatol. 2018;154(2):167-74. https://doi.org/10.1001/jamadermatol.2017.3631
17. Jarvis B, Figgitt DP. Topical 3% diclofenac in 2.5% hyaluronic acid gel: a review of its use in patients with actinic keratoses. Am J Clin Dermatol. 2003;4(3):203-13. https://doi.org/10.2165/00128071-200304030-00007
18. Watson M, Holman DM, Maguire-Eisen M. Ultraviolet radiation exposure and its impact on skin cancer risk. Semin Oncol Nurs. 2016;32(3):241-54. https://doi.org/10.1016/j.soncn.2016.05.005
19. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. JAMA Dermatol. 2016;152(4):419-28. https://doi.org/10.1001/jamadermatol.2015.4994

20. Fania L, Mazzanti C, Campione E, Candi E, Abeni D, Dellambra E. Role of nicotinamide in genomic stability and skin cancer chemoprevention. Int J Mol Sci. 2019;20(23):5946. https://doi.org/10.3390/ijms20235946

21. Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziell RA, McKenzie CA, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med. 2015;373(17):1618-26. https://doi.org/10.1056/NEJMoa1506197

22. Young AR, Narbutt J, Harrison GI, Lawrence KP, Bell M, O'Connor C, et al. Optimal sunscreen use, during a sun holiday with a very high ultraviolet index, allows vitamin D synthesis without sunburn. Br J Dermatol. 2019;181(5):1052-62. https://doi.org/10.1111/bjd.17888

23. Sherwani MA, Tufail S, Muzaffar AF, Yusuf N. The skin microbiome and immune system: Potential target does chemoprevention? Photodermatol Photoimmunol Photome. 2018;34:25-34. https://doi.org/10.1111/phpp.12334

REVIEW ARTICLE

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Cardiology and oncology: a meeting of giants

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INTRODUCTION

The oncology field has experienced a revolution in recent decades. The ability for early diagnosis, associated with the emergence of various life-extending treatments, has reduced mortality rates for several neoplasms[1]. As a result, cancer often needs to be treated as a chronic disease that coexists with cardiovascular conditions. This advancement, coupled with the significant increase in cancer survivors, redefines the interdisciplinary relationship between oncology and other medical specialties. Given the need to enhance cardiovascular care for individuals who have or have had cancer, cardio-oncology has emerged as an exemplary area of this synergistic collaboration with oncology[2].

Cardio-oncology is not limited solely to the study of the adverse effects of oncologic treatments. Instead, it encompasses a broader perspective on all possible interactions between cardiology and oncology[3]. In this context, we can highlight reverse cardio-oncology, which studies the intricate relationships between cardiovascular diseases and cancer[4]. In addition to aging, a range of modifiable risk factors, such as high blood pressure, diabetes, smoking, obesity, and a sedentary lifestyle, have a bidirectional relationship with the onset of cardiovascular and oncological diseases[5]. It is observed that oncology patients, following the oncological diagnosis across various primary sites, are more likely to die from cardiovascular diseases than the general population throughout follow-up[6]. Particularly in the older population and across multiple types of cancer, cardiovascular mortality can surpass cancer-related mortality over the follow-up period for these individuals[7]. In the postmenopausal women with hormone receptor-positive breast cancer subgroup, cardiovascular mortality is reported as the primary cause of death 8 years after diagnosis[8]. Furthermore, in surviving patients, cardiovascular events are associated with a higher likelihood of oncological disease recurrence[9]. On the other hand, individuals with cardiovascular disease are considered at higher risk of developing cancer, even when excluding conventional factors associated with atherosclerosis and cancer simultaneously[10]. Evidence from observational studies has shown an association between heart failure and an increased risk of cancer, highlighting the importance of prevention measures and early oncological diagnosis in this population[11].

It is important to note that individuals with significant cardiovascular diseases are generally excluded from oncological clinical trials, and similarly, individuals with cancer are excluded from cardiology-related trials[12]. Thus, although there is significant overlap between these two specialties, there are many gaps regarding the optimal management of individuals with overlapping cancer and cardiovascular diseases, and we still lack robust evidence in this population. Therefore, it becomes essential to foster collaboration between these two

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fields, focusing on scientific research to elucidate the intersections between these areas, enhance cooperation, and improve communication among the involved professionals to provide better patient care.

CARDIOLOGY: AN OLD GIANT

The history of cardiology is marked by significant developments throughout the 20th century. Examples include the development of the electrocardiogram, coronary care units, cardiac surgery, thrombolysis, cardiac catheterization, and coronary angioplasty, all of which drastically transformed the treatment of cardiovascular diseases. The Framingham study in the late 1950s was a milestone in cardiology research as it demonstrated the association between risk factors such as high blood pressure, dyslipidemia, and smoking and the development of atherosclerosis and major cardiovascular events. In modern times, it is known that these same factors are also related to the onset of cancer[13,14].

With the advancement of knowledge in cardiology, whether in understanding common risk factors and overlap with various diseases, a significant interaction with other medical specialties has been observed. This interaction led to new subspecialties, such as cardiometabolism and cardio-oncology[15].

ONCOLOGY: AN EXPANDING GIANT

Oncology is a rapidly expanding field of medicine. The history of its development demonstrates a significant evolution in understanding the mechanisms related to the onset of cancer, coupled with the continuous development of new therapies[16-18]. Despite advancements in new cancer treatments and diagnostic methods, the number of individuals affected by oncological diseases worldwide remains enormous.

After the epidemiological transition, particularly in the second half of the 20th century, cardiovascular diseases and cancer emerged as the leading causes of mortality. Based on current trends, it is considered that cancer will surpass cardiovascular diseases as the primary cause of mortality in most countries in the following years[19].

Over time, the mainstays of cancer treatment have been surgery, chemotherapy, and radiation therapy. However, in recent years, targeted therapies have played a prominent role in research in the pursuit of greater precision regarding the action of drugs against specific proteins and genes related to cancer[20]. These interventions targeted at specific sites have altered the course of numerous oncological diseases, with imatinib emerging as a pioneering example[21]. Furthermore, a better understanding of the immune system and its interactions with cancer has also positioned immunotherapy as a critical player in many oncological treatments[22]. Therefore, molecular therapy, cellular therapy, immunotherapy, metabolomics, proteomics, and various genetic markers have been the cornerstones of precision medicine in the oncology field. These personalized approaches support guided medical decisions, allowing treatments to be more effective and with fewer adverse events[23]. One of the current challenges is the implementation of and increased access to precision medicine[24].

ONCOLOGY AND THE PANDORA'S BOX

Oncological treatments can cause toxicities in various forms. The discovery and application of innovative therapies are associated with growing concerns about new side effects. Advancing the field with novel and particular treatments is always challenging because one needs to learn how to manage unknown and unexpected adverse clinical outcomes in real time.

The ideal scenario where targeted therapies can affect only cancer cells has not yet been achieved. To illustrate, we can mention the adverse effects of tyrosine kinase inhibitors (TKIs), which can occur in two models: 1. "on-target" toxicity, where the inhibited molecular target plays a crucial role in tumor proliferation and normal cell survival pathways and 2. "off-target" toxicity, that results from the action of TKIs on other targets that are unrelated to their antitumor activity, more familiar with multitarget inhibitors, such as sunitinib[25].

Regarding cardiovascular adverse effects, there is a spectrum regarding the severity of toxicities. For example, the new immunotherapy drugs (immune checkpoint inhibitors, or ICIs), which have rapidly expanded their indications in various oncological treatment scenarios (curative, palliative, and adjuvant), present situations like immune-mediated myocarditis. Although the incidence of this condition is very low, it carries a high mortality rate[26,27]. Therefore, with the emergence of numerous oncological therapies, it becomes crucial to learn, identify, and manage the specific complications of each drug, ensuring that these events do not hinder the continuation of such promising oncological treatments[28].

CARDIO-ONCOLOGY AND THE MYTH OF SISYPHUS

Cardio-oncology emerged in the 1970s when cardiac damage related to chemotherapy drugs, specifically anthracyclines, was observed[29]. The findings were based on myocardial biopsy analysis, considering today's imaging methods are not yet accessible[30].

However, cardio-oncology regained attention following the introduction of trastuzumab treatment for breast cancer. In the first study that combined anthracycline with this anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody, high rates of cardiotoxicity were observed, leading to the understanding that these medications cannot be used concurrently due to their synergistic mechanisms of cardiotoxicity[31]. Since then, numerous treatments and possible cardiovascular complications have emerged in recent years. With this demand, we have seen the expansion of cardio-oncology and the requirement for professionals involved in this field to understand the cardiovascular management of oncological patients[3].

An illustration of the interaction between cardiology and oncology is the association between cancer and its treatments and coronary artery disease, a significant cause of mortality in cancer survivors[32]. In this context, it is noteworthy that some individuals may have coronary artery disease even without the four standard modifiable risk factors (high blood pressure, diabetes, dyslipidemia, and smoking). Global data mention that it can account for up to 11.6% of cases of acute coronary syndrome where no conventional risk factors are found[33]. Oncological treatments associated with the possibility of coronary artery disease as an adverse event should be included in this population's list of items to be evaluated[34].

There is also a hypothesis that individuals with advanced cancer may exhibit a syndrome associated with heart failure related to various cancer-related factors, which would result in something called cardiac wasting, a degenerative form of cardiomyopathy linked to structural and electrical changes in the heart, leading, for example, to a higher risk of arrhythmias in these individuals[35]. This condition, independent of the adverse effects of oncological therapies, must be considered to identify patients with "cancer cardiomyopathy" so they can be promptly treated[36]. Therefore, the bidirectional relationship between cancer and heart failure motivates the study of the role of specific biomarkers in identifying individuals at higher risk of having existing cardiac alterations and a greater likelihood of cardiotoxicity with oncological treatments[37].

To illustrate the complexity related to cardio-oncology, especially in cancer types where survival has significantly increased in recent years, such as breast and prostate cancer, we can draw parallels with the myth of Sisyphus. This king tried to cheat death and was condemned by Zeus to roll a stone uphill, only to watch it fall back down for eternity. Similar to this mythological story, physicians and healthcare providers who treat patients with oncology and cardiology complications often face a heavy burden and continuous challenges related to cancer and cardiovascular diseases[38].

CARDIOTOXICITY AND ITS CHALLENGES

Cardiotoxicity is defined as any cardiovascular impairment during or after oncological treatment, whether symptomatic or detected in complementary tests, after excluding other causes[39]. Therefore, we should understand that cardio-oncology deals with all cardiovascular diseases in the context of individuals with cancer. A point that poses difficulty in understanding cardiotoxicity is the need for more agreement among various medical societies regarding the definition of each specific cardiovascular condition. For example, there is significant variability in the left ventricular ejection fraction criteria that characterize an individual as having cancer therapeutics-related cardiac dysfunction (CTRCD) (Table 1)[3,40]. One of the initiatives that tried to unify different definitions systematically was the publication of the European Cardio-Oncology Guidelines in 2022, a comprehensive document serving as a guide for study and practice in the field[3].

As mentioned earlier, a challenging aspect is the rapid emergence of many new oncology drugs in recent years. Pivotal oncological studies responsible for approving new therapies are typically done with a small number of patients, which limits the ability to determine possible adverse effects. Often, adverse effects are properly assessed after large-scale, real-world use of these therapies. Moreover, with the same speed at which treatments emerge, they can also become obsolete from an oncological standpoint. Therefore, if cardiologists take too long to determine the best way to deal with the cardiotoxicity of these drugs, this knowledge may become out of date. Thus, although basic and translational research has defined many pathophysiological mechanisms related to various forms of cardiotoxicity, best practices regarding monitoring and management are still to be studied in large-scale clinical trials[41].

It is important to note that cardio-oncology generally bases its approaches on knowledge derived from general cardiology. This is the case of the management of cardiovascular conditions overlapping with oncological diseases, which are handled in the same way one would take patients without cancer. However, it is crucial to emphasize that there are many circumstances where these generalist approaches are insufficient[42]. To contextualize these situations, we should mention the concept of permissive cardiotoxicity—allowing the continuation of oncological treatment in a scenario of tolerable cardiovascular changes, establishing optimized clinical management, and frequent cardiac follow-up in conjunction with oncology. Thus, continuing oncological therapy is associated with increased survival and improved quality of life[43].

Another example of an unexpected cardiac complication following cancer treatment is the appearance of atrial fibrillation

Table 1. Differences in published definitions of cardiotoxicity.

	Cutoff for left ventricular ejection fraction (LVEF)	Change in EF (ejection fraction) (absolute reduction)	Global longitudinal strain (GLS)
ESC 2022	Severe—new LVEF to <40% Moderate—new LVEF reduction by ≥10% to an LVEF of 40–49% Mild—LVEF o an LVEF of 40y ≥r ejection fracGLS by 15% from baseline	–	Moderate—new LVEF reduction by 10% to an LVEF of 40–49% and either new relative decline in GLS by 15% from baseline Mild—LVEF ≥50% and new relative decline in GLS by >15% from baseline
EACVI/ASE	<53%	>10% decline from baseline	Relative reduction in GLS >15% from baseline
ESMO	<55%	Decline ≥5% to less than 55% with symptoms or decline ne ≥5% to less thawithout symptoms	–
ASCO	<55%	–	Relative reduction in GLS >15% from baseline
CTCAE	<50%	Grade 2 (resting EF 40–50%; 10–19% drop from baseline); Grade 3 (resting LVEF 20–39%; >20% drop from baseline) Grade 4 (resting LVFE <20%)	–
FDA	–	>20% decrease if LVEF remained normal, or >10% decrease if LVEF is less than normal	–

ASCO: American Society of Clinical Oncology; ASE: American Society of Echocardiography; CTCAE: Common Terminology Criteria for Adverse Events; EACVI: European Association of Cardiovascular Imaging; ESC: Cardio-Oncology Council of the European Society of Cardiology; ESMO: European Society for Medical Oncology; FDA: US Food and Drug Administration; HFA: Heart Failure Association.

related to using Bruton's TKIs, which are primarily manageable and do not necessarily require suspending oncological therapy[44]. Alternatively, in cases of hypertension related to vascular endothelial growth factor (VEGF) inhibitors, elevated blood pressure can occur rapidly after initiating these medications and reflect effective inhibition of VEGF signaling, which has been considered a biomarker related to tumor responsiveness. Therefore, in these situations, it is necessary to be vigilant for this joint adverse event and control hypertension to allow patients to continue treatment with VEGF inhibitors[45,46].

It is crucial to go into the details of each therapy and the various conditions related to cardiotoxicity. The primary goal is to recognize that not all cardiovascular changes require treatment interruption. Permissive cardiotoxicity opposes the concept of prohibitive cardiotoxicity, where, due to a lack of knowledge related to cardio-oncology, there might be hasty recommendations to discontinue oncological therapies that could be essential for the survival of some individuals[43]. In HER2-positive breast cancer, for example, discontinuing treatment due to cardiotoxicity is associated with worse oncological outcomes[47,48].

Additionally, we should emphasize the importance of imaging methods in the interaction between cardiology and oncology. Advanced imaging technology enables the early detection of cardiac changes in oncology patients, allowing for timely and personalized interventions[49]. The ability to critically interpret and understand the benefits and limitations of each exam, such as the details related to intra- and inter-observer variability in the analysis of left ventricular ejection fraction on echocardiograms, is essential[50]. Ultimately, the main goal is to avoid the erroneous interruption of oncological treatments. In cardio-oncology, attention should be paid to preventing overscreening and overdiagnosis, which are related to the unnecessary use of complementary tests. Cardio-oncology guidelines present extensive recommendations guiding the frequency of biomarkers and imaging testing that seem excessive and challenging to implement in clinical practice[51].

CARDIO-ONCOLOGY SERVICES AND THE LESSONS OF HERMES

The primary goal in treating cardio-oncology patients is to provide comprehensive, multidisciplinary, and integrated care so they can receive the best available oncological treatment with the highest possible safety (Figure 1). Therefore, the aim is to identify and treat pre-existing cardiovascular conditions and assist in risk assessment and monitoring to mitigate the potential adverse effects of oncological therapies[52]. There are several documents worldwide about the establishment and

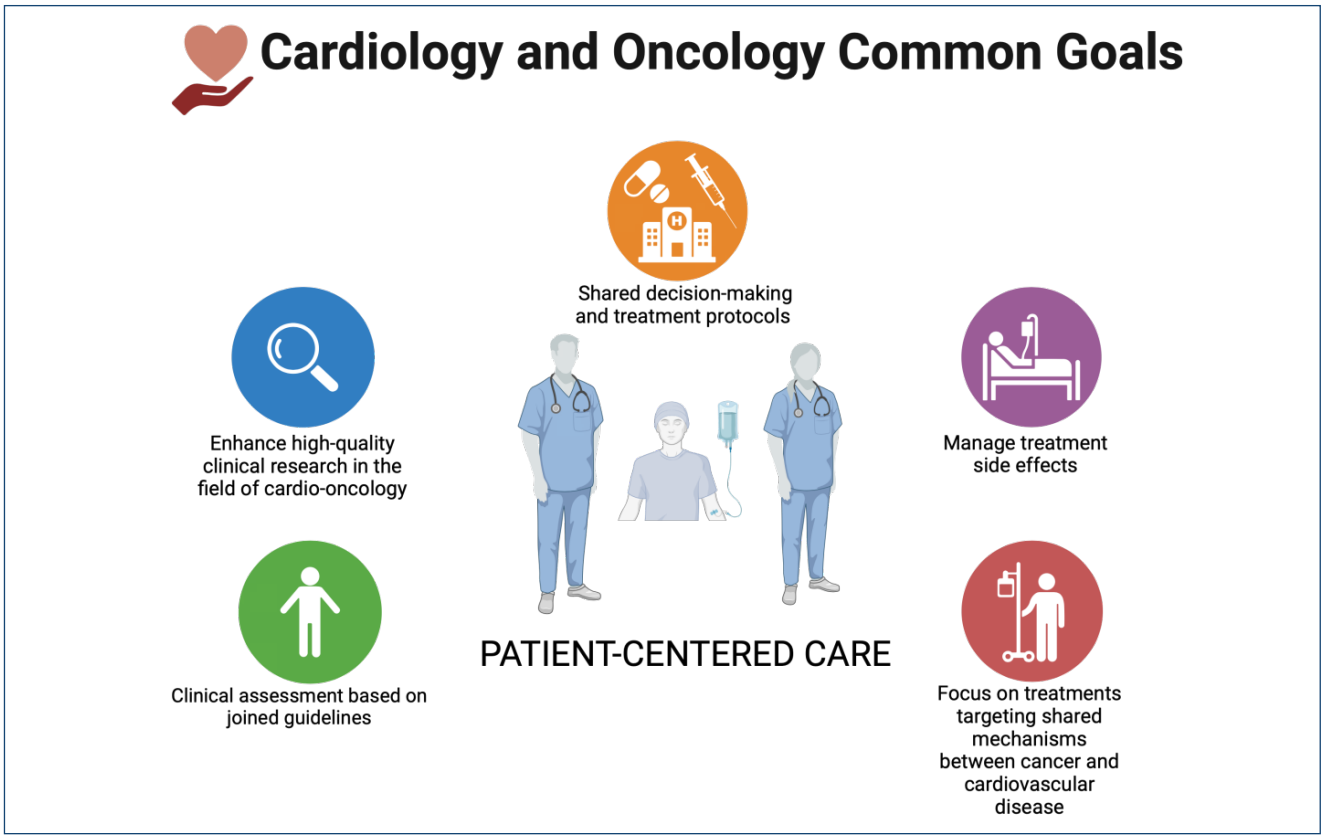

Figure 1. Cardiology and oncology—common goals.

structuring of cardio-oncology services. In most of them, particular emphasis is given to strengthening communication[53-55]. To illustrate, we draw a parallel here with the lessons we can learn from the mythological god Hermes, an intelligent and clever entity responsible for communication between gods and mortals. Therefore, fostering better communication is crucial in various aspects and among all stakeholders involved with cardio-oncology.

The care of oncology patients is a complex endeavor that emerges from collaboration among various medical specialties and all healthcare providers. The intersection between cardiology and oncology also highlights the need for a patient-centered, multidisciplinary approach and the individualization of decisions. Another point is to encourage patients to be active participants in their care by adopting habits associated with preventing cardiovascular diseases and assisting in oncological treatment[56]. Furthermore, allowing patients the space to express their viewpoints in medical conferences, for example, it is important to note that oncology patients, especially those with overlapping cardiovascular diseases, can experience significant psychological impact. Therefore, we should have a broad perspective regarding the approach to this population, placing patient support and understanding their needs at the center of care. Thus, we emphasize that empathy, effective communication, and emotional support play a vital role in this process[57]. It is worth highlighting that these skills, known as soft skills, can and should be trained to improve the connections between physicians and patients[58]. Some points that can be mentioned in this regard are (a) prepare with intention: review the patient's history; (b) listen intently and thoroughly: listen without interruption; (c) agree on what matters most: determine the patient's concerns and priorities; (d) connect with the patient's story: empathize; and (e) explore emotional cues: be attentive, elicit, reflect, and validate the patient's signals[59].

The current need for more research in cardio-oncology and the generation of better evidence related to the management and monitoring of oncology patients is evident. Many decisions in cardio-oncology are based on limited evidence. It is worth noting that in the 2022 European cardio-oncology guideline, only 2.6% of the 272 recommendations were classified as level of evidence A, with more than 75% earning the lowest level of evidence C. Although this is frustrating, it also makes cardio-oncology an exciting and dynamic field with significant opportunities for the development of clinical studies. One way

to enhance collaboration between the fields would be the partnership between cardiologists and oncologists in participating in and designing clinical trials to establish and analyze cardiovascular outcomes in an adjudicated manner, for example, as occurred in the Pronounce study[60]. Furthermore, for cardio-oncology to strengthen, more studies demonstrating the beneficial impact of specialized cardio-oncology care are needed[61].

Academic training for healthcare professionals is another crucial aspect to consider. In Brazil, cardio-oncology still needs to have the status of a regulated subspecialty, but there are postgraduate courses recognized by the Ministry of Education (MEC). We should emphasize the importance of the International Cardio-oncology Society (IC-OS), an organization that, in addition to various educational activities, organizes the international certification exam for professionals dedicated to cardio-oncology.

The expansion and relevance of cardio-oncology in recent years are undeniable, both due to epidemiological issues and the complexity of cardiovascular care for oncology patients. Therefore, we should consider expanding the discussion with society and healthcare providers about the availability of more structured cardio-oncology services. In this debate, the focus should be on appreciating and integrating professionals with expertise in the field into the oncology patient's journey. Encouraging oncology clinics to consider excellent cardiovascular safety inpatient treatment as a mandatory point of service excellence is crucial. Additionally, for the development of cardio-oncology clinics, it is critical to observe the particularities of each center. This approach identifies structural possibilities and the main areas needing improvement in various oncology-related aspects.

CONCLUSION

Cardio-oncology is still a new field in medical knowledge, with a growing number of publications and increasing recognition due to the significant interaction between cancer and cardiovascular diseases in a bidirectional relationship. Through collaboration and a profound understanding of the complexities of these conditions, we can offer patients a better quality of life and improve outcomes related to cancer and cardiovascular diseases. Everyone involved in cardio-oncology is responsible for seeking a better understanding of the balance between cardiovascular risk and the optimal management of cancer, aiming to minimize unnecessary interruptions in oncological treatments and mitigate effects related to cardiotoxicity. Advances in research, a dedicated focus on comprehensive educational programs, the promotion of better communication among healthcare professionals, and humanizing care are essential to pave the way for more precise and evidence-based approaches to treating oncology patients.

AUTHORS' CONTRIBUTIONS

RDL: Conceptualization. **JPPD:** Conceptualization, Writing – original draft. **AVSM:** Conceptualization. **TFLFP:** Supervision, Writing – review & editing. **JDSG:** Supervision, Writing – review & editing. **BCB:** Supervision, Writing – review & editing. **PM:** Supervision, Writing – review & editing. **AMV:** Supervision, Writing – review & editing. **BJAM:** Supervision, Writing – review & editing. **CMPDCS:** Supervision, Writing – review & editing.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
2. Lenihan DJ, Cardinale D, Cipolla CM. The compelling need for a cardiology and oncology partnership and the birth of the international cardioncology society. Prog Cardiovasc Dis. 2010;53(2):88-93. https://doi.org/10.1016/j.pcad.2010.06.002
3. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European hematology association (EHA), the European society for therapeutic radiology and oncology (ESTRO) and the international cardio-oncology society (IC-OS). Eur Heart J. 2022;43(41):4229-361. https://doi.org/10.1093/eurheartj/ehac244
4. Aboumsallem JP, Moslehi J, Boer RA. Reverse cardio-oncology: cancer development in patients with cardiovascular disease. J Am Heart Assoc. 2020;9(2):e013754. https://doi.org/10.1161/JAHA.119.013754
5. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation. 2016;133(11):1104-14. https://doi.org/10.1161/CIRCULATIONAHA.115.020406
6. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J. 2019;40(48):3889-97. https://doi.org/10.1093/eurheartj/ehz766
7. Strongman H, Gadd S, Matthews AA, Mansfield KE, Stanway S, Lyon AR, et al. Does cardiovascular mortality overtake cancer mortality during cancer survivorship?: an English retrospective cohort study. JACC CardioOncol. 2022;4(1):113-23. https://doi.org/10.1016/j.jaccao.2022.01.102
8. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res. 2011;13(3):R64. https://doi.org/10.1186/bcr2901
9. Koelwyn GJ, Newman AAC, Afonso MS, Solingen C, Corr EM, Brown EJ, et al. Myocardial infarction accelerates breast cancer via innate immune reprogramming. Nat Med. 2020;26(9):1452-8. https://doi.org/10.1038/s41591-020-0964-7

10. Bell CF, Lei X, Haas A, Baylis RA, Gao H, Luo L, et al. Risk of cancer after diagnosis of cardiovascular disease. JACC CardioOncol. 2023;5(4):431-40. https://doi.org/10.1016/j.jaccao.2023.01.010
11. Roderburg C, Loosen SH, Jahn JK, Gänsbacher J, Luedde T, Kostev K, et al. Heart failure is associated with an increased incidence of cancer diagnoses. ESC Heart Fail. 2021;8(5):3628-33. https://doi.org/10.1002/ehf2.13421
12. Morgans AK, Shore N, Cope D, McNatty A, Moslehi J, Gomella L, et al. Androgen receptor inhibitor treatments: cardiovascular adverse events and comorbidity considerations in patients with non-metastatic prostate cancer. Urol Oncol. 2021;39(1):52-62. https://doi.org/10.1016/j.urolonc.2020.08.003
13. Mehta NJ, Khan IA. Cardiology's 10 greatest discoveries of the 20th century. Tex Heart Inst J. 2002;29(3):164-71. PMID: 12224718
14. Nicolas J, Pivato CA, Chiarito M, Beerkens F, Cao D, Mehran R. Evolution of drug-eluting coronary stents: a back-and-forth journey from the bench to bedside. Cardiovasc Res. 2023;119(3):631-46. https://doi.org/10.1093/cvr/cvac105
15. Zullig LL, Sung AD, Khouri MG, Jazowski S, Shah NP, Sitlinger A, et al. Cardiometabolic comorbidities in cancer survivors: JACC: cardiooncology state-of-the-art review. JACC CardioOncol. 2022;4(2):149-65. https://doi.org/10.1016/j.jaccao.2022.03.005
16. Vita VT, Rosenberg SA. Two hundred years of cancer research. N Engl J Med. 2012;366(23):2207-14. https://doi.org/10.1056/NEJMra1204479
17. Weinstein IB, Case K. The history of cancer research: introducing an AACR Centennial series. Cancer Res. 2008;68(17):6861-2. https://doi.org/10.1158/0008-5472.CAN-08-2827
18. Jassim A, Rahrmann EP, Simons BD, Gilbertson RJ. Cancers make their own luck: theories of cancer origins. Nat Rev Cancer. 2023;23(10):710-24. https://doi.org/10.1038/s41568-023-00602-5
19. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. Cancer. 2021;127(16):3029-30. https://doi.org/10.1002/cncr.33587
20. Choi HY, Chang JE. Targeted therapy for cancers: from ongoing clinical trials to FDA-approved drugs. Int J Mol Sci. 2023;24(17):13618. https://doi.org/10.3390/ijms241713618
21. Iqbal N, Iqbal N. Imatinib: a breakthrough of targeted therapy in cancer. Chemother Res Pract. 2014;2014(2):357027. https://doi.org/10.1155/2014/357027
22. Liu C, Yang M, Zhang D, Chen M, Zhu D. Clinical cancer immunotherapy: current progress and prospects. Front Immunol. 2022;13:961805. https://doi.org/10.3389/fimmu.2022.961805
23. Beger RD, Schmidt MA, Kaddurah-Daouk R. Current concepts in pharmacometabolomics, biomarker discovery, and precision medicine. Metabolites. 2020;10(4):129. https://doi.org/10.3390/metabo10040129
24. Prasad V, Fojo T, Brada M. Precision oncology: origins, optimism, and potential. Lancet Oncol. 2016;17(2):e81-6. https://doi.org/10.1016/S1470-2045(15)00620-8
25. Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. N Engl J Med. 2016;375(15):1457-67. https://doi.org/10.1056/NEJMra1100265
26. Tan S, Day D, Nicholls SJ, Segelov E. Immune checkpoint inhibitor therapy in oncology: current uses and future directions: JACC: cardiooncology state-of-the-art review. JACC CardioOncol. 2022;4(5):579-97. https://doi.org/10.1016/j.jaccao.2022.09.004
27. Ball S, Ghosh RK, Wongsaengsak S, Bandyopadhyay D, Ghosh GC, Aronow WS, et al. Cardiovascular toxicities of immune checkpoint inhibitors: JACC review topic of the week. J Am Coll Cardiol. 2019;74(13):1714-27. https://doi.org/10.1016/j.jacc.2019.07.079
28. Rao VU, Reeves DJ, Chugh AR, O'Quinn R, Fradley MG, Raghavendra M, et al. Clinical approach to cardiovascular toxicity of oral antineoplastic agents: JACC state-of-the-art review. J Am Coll Cardiol. 2021;77(21):2693-716. https://doi.org/10.1016/j.jacc.2021.04.009
29. Saleh Y, Abdelkarim O, Herzallah K, Abela GS. Anthracycline-induced cardiotoxicity: mechanisms of action, incidence, risk factors, prevention, and treatment. Heart Fail Rev. 2021;26(5):1159-73. https://doi.org/10.1007/s10741-020-09968-2
30. Hoff DD, Layard MW, Basa P, Davis HL, Hoff AL, Rozencweig M, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710-7. https://doi.org/10.7326/0003-4819-91-5-710
31. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-92. https://doi.org/10.1056/NEJM200103153441101
32. Costa IBSDS, Andrade FTA, Carter D, Seleme VB, Costa MS, Campos CM, et al. Challenges and management of acute coronary syndrome in cancer patients. Front Cardiovasc Med. 2021;8:590016. https://doi.org/10.3389/fcvm.2021.590016
33. Kong G, Chin YH, Chong B, Goh RSJ, Lim OZH, Ng CH, et al. Higher mortality in acute coronary syndrome patients without standard modifiable risk factors: results from a global meta-analysis of 1,285,722 patients. Int J Cardiol. 2023;371:432-40. https://doi.org/10.1016/j.ijcard.2022.09.062
34. Figtree GA, Vernon ST, Harmer JA, Gray MP, Arnott C, Bachour E, et al. Clinical pathway for coronary atherosclerosis in patients without conventional modifiable risk factors: JACC state-of-the-art review. J Am Coll Cardiol. 2023;82(13):1343-59. https://doi.org/10.1016/j.jacc.2023.06.045
35. Anker MS, Sanz AP, Zamorano JL, Mehra MR, Butler J, Riess H, et al. Advanced cancer is also a heart failure syndrome: a hypothesis. J Cachexia Sarcopenia Muscle. 2021;12(3):533-7. https://doi.org/10.1002/jcsm.12694
36. Fabiani I, Panichella G, Aimo A, Grigoratos C, Vergaro G, Pugliese NR, et al. Subclinical cardiac damage in cancer patients before chemotherapy. Heart Fail Rev. 2022;27(4):1091-104. https://doi.org/10.1007/s10741-021-10151-4
37. Chianca M, Panichella G, Fabiani I, Giannoni A, L'Abbate S, Aimo A, et al. Bidirectional relationship between cancer and heart failure: insights on circulating biomarkers. Front Cardiovasc Med. 2022;9:936654. https://doi.org/10.3389/fcvm.2022.936654
38. Mavrogeni SI, Sfendouraki E, Markousis-Mavrogenis G, Rigopoulos A, Noutsias M, Kolovou G, et al. Cardio-oncology, the myth of sisyphus, and cardiovascular disease in breast cancer survivors. Heart Fail Rev. 2019;24(6):977-87. https://doi.org/10.1007/s10741-019-09805-1
39. Hajjar LA, Costa IBSS, Lopes MACQ, Hoff PMG, Diz MDPE, Fonseca SMR, et al. Brazilian cardio-oncology guideline - 2020. Arq Bras Cardiol. 2020;115(5):1006-43. https://doi.org/10.36660/abc.20201006
40. Čelutkienė J, Pudil R, López-Fernández T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the heart failure association (HFA), the European association of cardiovascular imaging (EACVI) and the cardio-oncology council of the European society of cardiology (ESC). Eur J Heart Fail. 2020;22(9):1504-24. https://doi.org/10.1002/ejhf.1957

41. Abe JI, Yusuf SW, Deswal A, Herrmann J. Cardio-oncology: learning from the old, applying to the new. Front Cardiovasc Med. 2020;7:601893. https://doi.org/10.3389/fcvm.2020.601893
42. Herrmann J. From trends to transformation: where cardio-oncology is to make a difference. Eur Heart J. 2019;40(48):3898-900. https://doi.org/10.1093/eurheartj/ehz781
43. Porter C, Azam TU, Mohananey D, Kumar R, Chu J, Lenihan D, et al. Permissive cardiotoxicity: the clinical crucible of cardio-oncology. JACC CardioOncol. 2022;4(3):302-12. https://doi.org/10.1016/j.jaccao.2022.07.005
44. Essa H, Lodhi T, Dobson R, Wright D, Lip GYH. How to manage atrial fibrillation secondary to ibrutinib. JACC CardioOncol. 2021;3(1):140-4. https://doi.org/10.1016/j.jaccao.2020.11.016
45. Humphreys BD, Atkins MB. Rapid development of hypertension by sorafenib: toxicity or target? Clin Cancer Res. 2009;15(19):5947-9. https://doi.org/10.1158/1078-0432.CCR-09-1717
46. Touyz RM, Lang NN. Hypertension and antiangiogenesis: the Janus face of VEGF inhibitors. JACC CardioOncol. 2019;1(1):37-40. https://doi.org/10.1016/j.jaccao.2019.08.010
47. Sardesai S, Sukumar J, Kassem M, Palettas M, Stephens J, Morgan E, et al. Clinical impact of interruption in adjuvant Trastuzumab therapy in patients with operable HER-2 positive breast cancer. Cardiooncology. 2020;6(1):26. https://doi.org/10.1186/s40959-020-00081-9
48. Gong IY, Verma S, Yan AT, Ko DT, Earle CC, Tomlinson GA, et al. Long-term cardiovascular outcomes and overall survival of early-stage breast cancer patients with early discontinuation of trastuzumab: a population-based study. Breast Cancer Res Treat. 2016;157(3):535-44. https://doi.org/10.1007/s10549-016-3823-y
49. Melo MDT, Paiva MG, Santos MVC, Rochitte CE, Moreira VM, Saleh MH, et al. Brazilian position statement on the use of multimodality imaging in cardio-oncology - 2021. Arq Bras Cardiol. 2021;117(4):845-909. https://doi.org/10.36660/abc.20200266
50. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013;61(1):77-84. https://doi.org/10.1016/j.jacc.2012.09.035
51. Witteles RM, Reddy SA. ESC cardio-oncology guidelines: a triumph-but are we overscreening? JACC CardioOncol. 2022;5(1):133-6. https://doi.org/10.1016/j.jaccao.2022.10.008
52. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the cardio-oncology study group of the heart failure association of the European society of cardiology in collaboration with the international cardio-oncology society. Eur J Heart Fail. 2020;22(11):1945-60. https://doi.org/10.1002/ejhf.1920
53. Fradley MG, Wilcox N, Frain I, Rao VU, Carver J, Guha A, et al. Developing a clinical cardio-oncology program and the building blocks for success: JACC: CardioOncology how to. JACC CardioOncol. 2023;5(5):707-10. https://doi.org/10.1016/j.jaccao.2023.06.002
54. Adusumalli S, Alvarez-Cardona J, Khatana SM, Mitchell JD, Blaes AH, Casselli SJ, et al. Clinical practice and research in cardio-oncology: finding the "Rosetta Stone" for establishing program excellence in cardio-oncology. J Cardiovasc Transl Res. 2020;13(3):495-505. https://doi.org/10.1007/s12265-020-10010-x
55. Lancellotti P, Suter TM, López-Fernández T, Galderisi M, Lyon AR, Meer P, et al. Cardio-oncology services: rationale, organization, and implementation. Eur Heart J. 2019;40(22):1756-63. https://doi.org/10.1093/eurheartj/ehy453
56. Brown SA. Preventive cardio-oncology: the time has come. Front Cardiovasc Med. 2020;6:187. https://doi.org/10.3389/fcvm.2019.00187
57. Ky B. Cardio-oncology and the patient-physician relationship. JACC CardioOncol. 2020;2(1):146-8. https://doi.org/10.1016/j.jaccao.2020.02.014
58. Gilligan T, Coyle N, Frankel RM, Berry DL, Bohlke K, Epstein RM, et al. Patient-clinician communication: American society of clinical oncology consensus guideline. J Clin Oncol. 2017;35(31):3618-32. https://doi.org/10.1200/JCO.2017.75.2311
59. Zulman DM, Haverfield MC, Shaw JG, Brown-Johnson CG, Schwartz R, Tierney AA, et al. Practices to foster physician presence and connection with patients in the clinical encounter. JAMA. 2020;323(1):70-81. https://doi.org/10.1001/jama.2019.19003
60. Lopes RD, Higano CS, Slovin SF, Nelson AJ, Bigelow R, Sørensen PS, et al. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: the primary results of the PRONOUNCE randomized trial. Circulation. 2021;144(16):1295-307. https://doi.org/10.1161/CIRCULATIONAHA.121.056810
61. White J, Byles J, Williams T, Untaru R, Ngo DTM, Sverdlov AL. Early access to a cardio-oncology clinic in an Australian context: a qualitative exploration of patient experiences. Cardiooncology. 2022;8(1):14. https://doi.org/10.1186/s40959-022-00140-3

REVIEW ARTICLE

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Beyond the diagnosis: gender disparities in the social and emotional impact of cancer

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FEBRASGO

INTRODUCTION

A diagnosis of cancer not only triggers physical challenges and profound emotional distress but also creates an increased demand for healthcare resources. The surge in psychological symptoms, particularly anxiety and depression, not only worsens morbidity but also correlates with suboptimal clinical outcomes and diminished quality of life for survivors. This emotional burden and the subsequent need for social adjustment often diverge along gender lines, revealing a complex interplay between gender-specific social roles and stress and adjustment processes[1].

Navigating the unexplored landscapes of their new reality, cancer patients derive substantial benefits from questioning traditional societal expectations, particularly in the realm of caregiving. This essential shift calls for a more extensive embrace, notably from male partners, as it confronts ingrained gender norms. Fostering a more inclusive approach to caregiving not only fortifies emotional support during trying times but also possesses the potential to instigate transformative changes in social identity, contesting deeply rooted gender roles[2].

As the global rise in cancer survivor numbers continues, driven by an aging population, enhanced early detection, and groundbreaking treatments, the aftereffects of cancer therapies cast long shadows over survivors' lives. Understanding gender disparities and their social repercussions, including financial consequences impacting health-related quality of life, becomes crucial for developing strategies attuned to gender nuances[3,4].

Cancer ranks among the leading causes of premature mortality in women globally, featuring prominently in the top three in nearly all countries. Despite this, the global focus on women's health often centers around reproductive and maternal aspects, reflecting a patriarchal framework that aligns with narrow, anti-feminist views of women's worth and societal roles[5].

The aftermath of cancer therapies extends far beyond the cessation of treatments, leaving a lasting impact on the lives of survivors. These lingering effects cast long shadows over their well-being, underscoring the importance of recognizing and addressing the distinct challenges faced by individuals of different genders. This recognition becomes a cornerstone for developing more targeted and supportive interventions that cater to the diverse needs of cancer patients and survivors[6].

This article delves into the intricacies of gender differences in the social impact of cancer, exploring psychological adjustment, sexual intimacy challenges, marital dynamics, and the enduring disparities in healthcare access. Additionally, it highlights the complexities of life beyond cancer treatment, emphasizing the need for a holistic approach to care that considers emotional, behavioral, and social factors. The implications for clinical practice and avenues for future research underscore the importance of continuous efforts to improve healthcare equity and outcomes for all individuals affected by cancer.

UNRAVELING GENDER DIFFERENCES IN THE SOCIAL IMPACT OF CANCER

Gender is not merely a biological distinction; it encompasses a broad spectrum of socially constructed roles, relationships, and individual characteristics such as personality traits, attitudes, behaviors, and values. These aspects, which are differentially applied to and internalized by men and women, are deeply entrenched within our societal fabric[7]. Such constructs invariably shape the psychological and social responses to health challenges, particularly in the context of a life-altering illness like cancer.

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The literature has consistently illuminated the influence of gender roles and societal expectations on the health behaviors of men and women, especially in the coping mechanisms employed when faced with chronic diseases[8]. It is commonly posited that women, whose societal roles often resonate with acceptance and nurturing, may navigate the vicissitudes of chronic illness with a certain grace, perhaps due to a closer alignment with the conventional feminine archetype[9].

Typically, women are perceived to adopt emotional coping strategies, expressing, and processing their emotions more openly. Conversely, men are often inclined toward a problem-solving approach, seeking solutions, and occasionally resorting to avoidance as a coping mechanism. The expected patient role, necessitating emotional expression and reliance on others, poses a greater challenge for men, who are socially conditioned to value rationality and independence. Traditionally seen as more relational and interdependent, women might find a semblance of comfort in the socio-emotional patient role.

Notably, these gender-driven differences in psychological adjustment seem to converge when patients face the rigors of treatments such as chemotherapy or confront advanced disease stages. At this juncture, both genders report a marked increase in psychological distress, a testament to the leveling nature of severe health adversity[9].

The ripple effects of a cancer diagnosis extend beyond the individual to the family unit, impacting the relational dynamics and well-being of caregivers and other family members. Cancer's reach spares none, challenging the resilience and adaptive capacities of all involved[10,11].

In the intimate dance of managing cancer within a partnership, gender emerges as a significant determinant of distress levels, transcending the roles of patient or caregiver. Strikingly, women report higher levels of distress than men, a difference that is consistent across various research methodologies and unaffected by variables such as time since diagnosis or sample demographics[12].

Considering these insights, supportive care must be envisioned as an all-encompassing strategy. It should provide support to individuals with cancer and their families throughout the entire cancer journey, from the shock of the initial diagnosis to the uncertainties of treatment, the ups and downs of recovery, the trials of chronic management, and the finality of end-of-life care, extending into the bereavement process[13].

INFLUENCE OF RACE AND BIOLOGICAL FACTORS.

The etiology of disparities in cancer treatment and outcomes can be attributed to a complex interplay of factors, including race, ethnicity, cultural differences, socioeconomic status, and educational background. Geographic variations in healthcare provider and hospital standards, as well as biological distinctions among different ethnic groups, must also be considered. Additionally, non-adherence to evidence-based treatment guidelines has been identified as a modifiable factor that can lead to worse survival outcomes[14].

Due to variations in survival outcomes among minority patients, there has been a growing emphasis on recruiting them for clinical trials. This focus aims to uncover inherent differences in tumor biology, treatment responses, and survival, particularly in controlled treatment regimens between different patient groups. There is a lack of minority enrollment in gynecologic cancer clinical trials. A paper examining 170 Gynecologic Oncology Group (GOG) trials conducted between 1994 and 2013 reported that out of the 45,259 patients involved in these trials, 83% were White, 8% were Black, and 9% were classified as "other" ($p<0.01$)[15]. The Center for Disease Control (CDC) age-adjusted incidence data found that the enrollment of Black patients was significantly lower than expected for various types of gynecologic cancer trials. For example, it was 15 times lower than expected for ovarian cancer trials, 10 times lower for endometrial cancer trials, 4.5 times lower for cervical cancer trials, and 5.2 times lower for sarcoma trials ($p<0.001$), regardless of the type of study or the publication year[14].

The natural history of cancer has several critical junctures: prevention [human papillomavirus (HPV) vaccination], risk factor acquisition (obesity), screening (cervical cytology), diagnosis (endometrial biopsy for postmenopausal bleeding), and treatment (appropriate surgery by appropriate provider). Racial variation at any point along this course might contribute to minor disparate outcomes, while even subtle inequities at multiple nodes might accumulate to create more glaring gaps in outcomes[16].

The cause of existing disparities is multifaceted, and so will be the solution. As the World Health Organization clearly states, cervical cancer can be eradicated through addressing several main pillars: ensuring equal access and ready availability of the HPV vaccine to vulnerable populations, stressing the importance of cervical cancer screening, facilitating follow-up of abnormal cytology results, and employing guideline-concurrent therapies in the treatment of cervical cancer. Similarly, adherence whenever possible to evidence-based guidelines would likely diminish disparities in survival among ovarian cancer patients[16].

While endometrial cancer presents unique challenges, there are clear opportunities for improved practice. Physicians must be vigilant about counseling patients on the importance of reporting postmenopausal bleeding to their physicians. Physicians should

in turn have a high level of suspicion when evaluating Black women, particularly of an older age, with abnormal uterine bleeding, knowing current evaluation algorithms may offer significantly lower sensitivity for cancer in this population[16].

COMPLEXITIES OF SEXUAL INTIMACY AFTER CANCER

Cancer's assault on the body extends beyond the physiological, delving deeply into the personal realm of sexual intimacy. The metamorphosis in physical appearance and function, which is a result of aggressive cancer treatments, carries significant emotional and psychological weight. Body image dissatisfaction and sexual dysfunction rank among the most profound challenges faced by those on the cancer journey[17].

The overall prevalence of sexual dysfunction among female cancer survivors ranged from 16.7 to 67%. Patients and their intimate partners often find themselves in a maelstrom of sexuality-related issues, which is a struggle that persists through the illness and often into the recovery phase. Regrettably, a substantial number of patients are left unprepared for the sexual alterations that may arise and lack the essential information and support to navigate these changes effectively.

Sexual issues are frequently overlooked and inadequately addressed in routine healthcare practice, representing an unmet need that significantly impacts the overall health and quality of life of cancer survivors. Proactive engagement by healthcare professionals in couple's communication and strategic interventions is crucial. Such initiatives are foundational in fostering a mutual understanding of the sexual modifications following cancer, potentially safeguarding the quality of the relationship[18].

Gynecologic cancer survivors are susceptible to a heightened risk of sexual dysfunction and body image concerns due to the direct impact of treatment on genital anatomy and hormonal milieu. This vulnerability can surface immediately post-treatment or linger into the long-term survivorship phase. Recent endeavors in the medical community have pivoted toward recognizing and ameliorating these quality-of-life concerns for these survivors[19].

The prevalence and severity of psychosexual dysfunction following radical interventions, such as vulvectomy, are stark, with nearly half of the patients reporting a decline in the quality of their sexual relationships[20]. Pelvic radiotherapy, while lifesaving, is not without its drawbacks, often leading to complications such as vaginal stenosis, dryness, and vulvodynia, which can drive patients toward psychological avoidance of sexual contact to elude pain and discomfort[20].

Surgical treatments, especially those involving the pelvis, can severely disrupt a patient's self-perception. Procedures that result in anatomical alterations, such as vaginal shortening and vulva deformities, can instigate fears surrounding pain during intercourse, impacting the patient's sexual health even in the absence of physical sequelae[21].

The hormonal repercussions of oophorectomy, particularly when bilateral, are profound, inducing immediate surgical menopause with all its attendant symptoms—hot flashes, vaginal dryness, and sleep disturbances. These physical manifestations are mirrored by a decline in sexual satisfaction for a significant portion of those who undergo the procedure[22,23].

Furthermore, the impact on fertility and the sense of femininity is acutely felt by younger women, instilling fears, and insecurities about resuming sexual activity. These anxieties, coupled with the emotional weight of fertility loss, can erode self-confidence and dampen sexual desire[20].

Chemotherapy introduces its own set of challenges, with common side effects such as nausea and hair loss. For women, in particular, hair is a pillar of self-identity, and its loss can have a disproportionately negative impact on self-esteem and body image[21,24].

MARITAL TIES IN THE SHADOW OF CANCER: DIVORCE RATES AND RELATIONSHIP DYNAMICS

The crucible of cancer diagnosis exerts a profound influence on couples, reshaping the dynamics of their relationship in fundamental ways. Even when the prognosis is not dire, the ramifications of cancer diagnosis and subsequent treatment phases can be transformative for both the patient and their partner. They become mutual pillars of support, intertwining their coping mechanisms, and providing both emotional and practical support on this arduous journey[25].

Marriage can be a fortress of social and emotional support for those battling cancer, offering vital resources during treatment and convalescence, such as financial stability through a spouse's income and health insurance benefits. Yet, the tremors of a cancer diagnosis can precipitate marital discord, as couples grapple with the evolving health landscape, emotional upheaval, and financial strain. The specter of long-term sequelae and chronic conditions stemming from cancer treatment, especially for younger survivors, can impinge on their general well-being, sexual health, and reproductive potential[26].

Statistical analysis, adjusted for demographic factors, reveals that young cancer survivors bear a 77% heightened risk of divorce or separation compared with their healthy counterparts. This risk

is particularly acute among young female survivors, who are 80% more likely to experience marital dissolution than their non-cancer-afflicted peers[27]. Conversely, among older adults, evidence suggests that cancer does not significantly impact the likelihood of divorce[26].

In the daily rhythm of family life, responsibilities such as childcare and housework frequently fall disproportionately on women. A cancer diagnosis has the potential to intensify this imbalance, especially in younger families where the female partner is the one facing the illness. Such a situation strains the fabric of the family, disrupting the traditional caregiver role and adding complexity to the already demanding dynamics[28].

Infertility can stem from the cancer itself, surgical procedures, or as a consequence of gonadotoxic treatments such as chemotherapy and radiotherapy[29]. Fertility concerns and sexual dysfunction can be pivotal in destabilizing marriages, especially among younger couples who are navigating the complexities of conception. These issues can exert additional emotional and psychological pressure on the relationship, underscoring the intricate nexus between health, intimacy, and marital stability in the shadow of cancer[30]. Whether fertility is permanently compromised or temporarily impaired, the associated concerns contribute to heightened levels of anxiety, depression, grief, and stress, ultimately decreasing the overall quality of life[29].

There is emerging evidence suggesting that individuals, particularly those dealing with cancer-related fertility concerns, may harbor fears of abandonment or rejection by current or future partners. Additionally, they may experience a reduction in sexual satisfaction and encounter difficulties or even breakdowns in their relationships. This highlights the need for more focused research and support to address the unique challenges that cancer-related fertility concerns pose to the dynamics of couple relationships.

Approximately 21% of diagnosed cases of gynecological cancer involve women of childbearing age. As survival rates rise, preserving fertility in reproductive-age women becomes crucial for enhancing quality of life. Fertility-sparing surgical approaches and assisted reproductive technologies (ARTs), including ovarian transposition and cryopreservation of oocytes or embryos, are preferred strategies. Emerging techniques, such as antiapoptotic/cell-preserving agents and stem cell technologies, are advancing the field of fertility preservation[31].

A binational study from Denmark and Sweden highlights an increased prevalence of mental health disorders among spouses of cancer patients, with a 30% surge in the risk of first-onset mental health conditions, predominantly within the initial year post-diagnosis. This increase is particularly notable for depressive and stress-related disorders, illustrating the substantial psychological burden borne by partners of cancer patients[32].

PSYCHOLOGICAL AND EMOTIONAL RESILIENCE

Approximately 9.2 million new cases of cancer and 4.4 million cancer-related deaths were estimated among women of all ages in 2020[5]. The psychological impact of a cancer diagnosis reverberates profoundly, spanning from the turbulent treatment phase into the uncertain aftermath, presenting unique challenges for women at various stages. Patients grapple with a spectrum of emotions, including stress, anxiety, depression, sexual dysfunction, and sleep deprivation[32].

Fear of cancer recurrence emerges as a pervasive emotion, casting its shadow across all patients, irrespective of prognosis. Those with a severe fear report constant, intrusive thoughts about cancer, a steadfast belief in its inevitable return regardless of the current prognosis, and an inability to plan for the future. Elevated levels of this fear can significantly compromise quality of life, alter health service utilization, and prevent adherence to follow-up protocols.

In the face of these challenges, individual resilience becomes a beacon of hope. It means an individual's ability to adapt positively to adversity, trauma, and various pressures. Cultures worldwide have recognized resilience as a powerful personal resource to navigate stressful situations, offering potentially positive effects on quality of life and overall adjustment, particularly when coping with cancer.

Looking ahead, as the number of cancer survivors is projected to soar to 26.1 million by 2040, this resilient community confronts enduring challenges. The repercussions—physical, emotional, and financial—persist throughout survivorship. Notably, 60% contend with persistent distress and an unsettling fear of recurrence. Additionally, around 36.5% find themselves unable to return to work, while between 15 and 75% navigate the intricate terrain of cancer-related cognitive impairment. Gender assumes significance in the broader context of the psychological and social adjustment process for cancer patients[6].

Understanding the nuanced impact of gender on the social adjustment and psychological distress experienced by cancer patients and their spouses enriches our understanding of the multifaceted challenges individuals and couples encounter in the aftermath of cancer[33].

DISPARITIES IN HEALTHCARE ACCESS

Inequality profoundly impacts access to healthcare across various societal levels, affecting both resource availability and information accessibility, especially for women facing cancers undergoing complex, multimodal therapy, and frequent interactions with the healthcare system. Vulnerable populations with

basic social resource needs may not receive optimal care, even when recommended by their healthcare provider. Recognizing and incorporating these factors into the formulation of public policies is vital for achieving a more effective and cost-efficient healthcare approach.

Across the globe, a woman's geographical location (including the country, region, or local environment concerning the proximity of healthcare services) and her socioeconomic status significantly influence the likelihood of developing any cancers. Factors such as poverty and social disenfranchisement play a pivotal role in determining the timing of her presentation to healthcare services and the accessibility of affordable, high-quality diagnostic and treatment options. Addressing these disparities is crucial, and one powerful strategy lies in the widespread implementation of preventive measures, like HPV vaccination.

Unfortunately, many women face limited opportunities to benefit from these life-saving interventions. In numerous resource-poor regions within countries, the availability and accessibility of early detection programs, cancer surgery, essential cancer treatment, palliative care, and support for cancer survivors, often termed as survivorship care, are inadequate. These discrepancies contribute to a scenario where disability and premature death resulting from preventable diseases such as breast or cervical cancer become tragically inevitable[34].

Furthermore, within the domain of women's health, disparities disproportionately impact sexual and racial minorities. A study in the United States revealed that women from sexual minority backgrounds faced a higher likelihood of experiencing adverse health outcomes, surpassing even their sexual minority male counterparts. Among the demographic groups scrutinized, Hispanic women from sexual minority backgrounds exhibited the highest prevalence of negative outcomes, with alarming rates reaching 59% for depression, 41% for poor mental health, and 41% for poor physical health[35].

This inequality extends beyond health outcomes and permeates socio-cultural and political dimensions. Historical instances, such as the apartheid era, underscore the absence of public policies for cervical cancer screening, exacerbating disparities. During that period, screening efforts were confined to family planning clinics, conducted in an unorganized manner, and lacking a defined age group, thereby perpetuating a cycle of inequality in healthcare access. Addressing these multifaceted disparities is essential to ensuring equitable health outcomes for all women, regardless of their sexual orientation or racial background[36].

Numerous studies have explored issues related to cancer information access. One study revealed that men reported higher satisfaction with the information they received, suggesting a potential disparity in the quality of information received by men and women. The importance of this observation lies in acknowledging information as a fundamental tool for enhancing healthcare quality. Successful information dissemination is correlated with improved diagnoses and greater efficacy of screening programs.

In numerous countries worldwide, irrespective of their geographic location or economic resources, women often find themselves at a disadvantage compared with men, lacking both the knowledge and the authority to make informed decisions regarding their healthcare. The choice of language in addressing this issue is of utmost importance. Adopting gender-transformative approaches can shift the narrative from assigning blame to women for "late presentation," "neglected cancer," or "treatment abandonment." Instead, it emphasizes the value of women, recognizing their diverse experiences, as equal counterparts to men. This approach acknowledges women as individuals with agency and knowledge, empowering them to make evidence-based, informed decisions about their own healthcare[5].

Raising public awareness about breast cancer can lead to earlier diagnoses. Further supporting this, in Thailand, where 97% of the population has access to cervical cancer screening, individuals with higher education levels demonstrate two to four times greater engagement. This highlights the crucial role of information in enhancing the quality of healthcare[37].

To institutionalize this transformative perspective, an intersectional gender-transformative competency framework can be integrated into the education and training of the global cancer workforce. This ensures that healthcare professionals are equipped with the skills necessary to provide high-quality and respectful care that acknowledges the diverse needs of all individuals. By fostering a culture of equality and empowerment, we can strive to create an environment where women are actively engaged in their healthcare decisions, contributing to improved overall health outcomes and a more equitable healthcare landscape globally[5].

One of the first steps of any cancer control effort is to define the cancer burden. Regrettably, less than 20% of cancer patients reside in areas equipped with a cancer registry. In low- and middle-income countries, evidence indicates a deficiency in cancer registries, which compromises the development of public policies relying on biased and unrepresentative data. Compounding this challenge, patients in these regions face the additional burden of inadequate treatment, with an estimated 70% of breast cancer patients grappling with this issue[38].

SURVIVAL AND BEYOND

Recovery from cancer encompasses more than just physical healing; it is also shaped by emotional, behavioral, and social factors.

The stigmas do not cease after the end of treatment, even people with clinical cure criteria present sequelae from the disease and the treatments undergone. A Chinese systematic review identified the main unmet care needs, among them social support (74%), difficulty with daily activities (54%), worsening of sexual/intimate function (52%), fear of recurrence/spread (50%), and information support (45%)[39]. Furthermore, survivors deal with chronic pain, sleep problems, substance abuse, sexual issues, and loss of physical abilities/functions[40,41].

One study indicated that one of the main unmet demands of oncology patients is emotional support, which highlights the importance of including psychological care in post-treatment follow-up. Moreover, many patients experience chronic physical sequelae even after being cured, such as lymphedema, chronic treatment-related pain, insomnia, and even metabolic syndrome. It is necessary to consider the particularities of post-cancer patients and value their complaints, always remembering that they are patients with a chronically weakened psychological state, and in large part, they have repressed demands that should be addressed in a welcoming and humanized environment[40,41].

Considering that the economic cost of cancer accounts for up to 4% of the global gross domestic product (GDP), governments should view addressing the global burden of women's cancers as a wise investment. This investment is particularly crucial considering the significant impact of these cancers on premature death and disability, leading to enduring social, financial, and economic consequences for affected women, their immediate families, and broader communities[34].

The macroeconomic consequences of women's cancers are noteworthy, extending their influence on the national economy and society. This impact manifests through heightened health expenditures, losses in labor and productivity, and diminished investments in human and physical capital formation[34].

At the microeconomic level, cancer profoundly affects women, their families, individual firms, and governments. Notably, a substantial portion of women's work goes beyond monetary transactions and is thus unlikely to be reflected in conventional macroeconomic indicators. Any calculations seeking to evaluate the economic burden associated with women's cancer should encompass non-income-generating activities, such as gathering water and firewood, preparing food, tending to livestock, and caring for children[5,34].

When it comes to social support, it is important to consider the financial aspect of the patient's life. A study pointed out that cancer survivors have a 37% higher relative risk of not returning to work activities compared with people without a cancer diagnosis.

Looking beyond the individual effects on women and incorporating their families, the probability of catastrophic expenditures is alarmingly high in low-resource settings. Frequently, families faced with substantial direct and indirect costs linked to cancer and its treatment find themselves compelled to sell assets and accumulate debts. This already challenging situation is often exacerbated by employment-related complications, including decreased productivity, job loss, dismissal, and a reduction in work-related benefits. Addressing the economic impact of women's cancers is not only a health imperative but also an economic necessity for sustainable development[5].

It is necessary for healthcare professionals to be aware of the main challenges that oncology patients face even after treatment so that they can provide appropriate support. Furthermore, it is essential to understand that cancer treatment itself, including radiotherapy, chemotherapy, surgeries, hormonal therapies, and monoclonal antibodies, is only part of the process, and there should be a holistic view of the cancer patient, considering both the treatment and disease-related sequelae.

IMPLICATIONS FOR CLINICAL PRACTICE

Considering the points discussed thus far, it is possible to propose practical recommendations for the care of women undergoing cancer treatment. Considering the informational aspect, it is essential to provide space for patients to ask questions and express their needs. Especially for patients from racial and social minorities, higher rates of mental and physical disorders persist even after cancer treatment. Therefore, demonstrating concern for their needs can have a positive impact on recognizing these situations, allowing them to be addressed in the therapeutic plan once identified.

Furthermore, in a globalized world, it is important to consider socio-cultural aspects when approaching patients. For example, in Asia, the peak incidence of breast cancer occurs at an earlier age, typically between 45 and 55 years, while in the Western world, the incidence tends to rise post-menopause. Additionally, Indigenous and African American patients, as well as individuals of African descent, have a higher incidence of aggressive tumors such as triple-negative breast cancer[36].

Moreover, in this regard when it comes to nutrition, the Western traditional diet is rich in salt and fat, high glycemic index carbohydrates, and red meat as the most used protein, these aspects are highly correlated with increased rates of endometrial, breast, and colorectal cancer. It is estimated that dietary improvements can reduce the incidence of colorectal cancer by up to 70%.

FUTURE DIRECTIONS FOR RESEARCH

The future of cancer patient care is intricately linked to continuous research, leading to increasingly effective treatments with more manageable side effects. Despite this progress, substantial research gaps persist. Notably, it is crucial to highlight that only 5% of cancer research investment is directed toward developing and underdeveloped countries, despite these nations bearing 65% of all cancer-related deaths[42].

Gender inequality is apparent in the populations studied for oncology trials. Among the 5,157 patients in trials leading to FDA approval of 17 new drugs in 2018, only 38% were women[42]. In clinical trials conducted from 2003 to 2016 (excluding prostate and breast cancer trials), women were underrepresented in studies on lung cancer, melanoma, and pancreatic cancer, despite the significant prevalence of these cancers in the female population[43].

Furthermore, when it comes to gynecological cancers, it is evident that minorities and elderly women have been underrepresented in studies. Between 1985 and 2012, elderly individuals accounted for only 17% of participants in breast cancer studies, even though 42% of all breast neoplasms diagnosed annually are in this population[36].

It is essential to continue advocating for this issue because research outcomes are influenced by the population involved in the study. Studies need to accurately represent the real-world profile of the population that will receive the medications under investigation. This ensures that treatments are effective and safe for all individuals, regardless of gender, age, or minority status. Closing the research gap and achieving better representation in clinical trials are crucial steps toward improving healthcare equity and outcomes for all.

CONCLUSION

The individual impacts of cancer on the female population are crucial to examine, as a comprehensive understanding of these intricacies can significantly enhance our approach to addressing the unique challenges faced by women. This article contributes to ongoing efforts by delving into the gender-specific ramifications of cancer on social impact, sexuality, divorce rates, and other dimensions. By doing so, it supports the goal of providing comprehensive and gender-sensitive care to individuals navigating the complexities of cancer diagnosis, treatment, and survival.

Looking ahead, it is imperative to work toward mitigating social inequality in access to treatments and the conduct of clinical trials. This proactive approach can ensure that study populations more accurately reflect the diversity of real populations, ultimately advancing the effectiveness and inclusivity of cancer research and care.

AUTHORS' CONTRIBUTIONS

MSLP: Data curation, Formal Analysis, Methodology, Resources, Writing – original draft. **FTRS:** Data curation, Methodology, Resources, Writing – original draft. **EBC:** Data curation, Methodology, Resources, Writing – original draft. **RML:** Data curation, Methodology, Resources, Writing – original draft. **ALSF:** Data curation, Formal Analysis, Methodology, Resources, Supervision, Writing – original draft. **MCOW:** Data curation, Methodology, Resources, Writing – original draft.

REFERENCES

1. Rondanina G, Siri G, Marra D, Censi A. Effect of sex on psychological distress and fatigue over time in a prospective cohort of cancer survivors. J Cancer Surviv. 2022. https://doi.org/10.1007/s11764-022-01291-z
2. Peleg-Oren N, Sherer M. Cancer patients and their spouses: gender and its effect on psychological and social adjustment. J Health Psychol. 2001;6(3):329-38. https://doi.org/10.1177/135910530100600306
3. Hashim D, Boffetta P, Vecchia C, Rota M, Bertuccio P, Malvezzi M, et al. The global decrease in cancer mortality: trends and disparities. Ann Oncol. 2016;27(5):926-33. https://doi.org/10.1093/annonc/mdw027
4. Yi JC, Syrjala KL. Anxiety and depression in cancer survivors. Med Clin North Am. 2017;101(6):1099-113. https://doi.org/10.1016/j.mcna.2017.06.005
5. Ginsburg O, Vanderpuye V, Beddoe AM, Bhoo-Pathy N, Bray F, Caduff C, et al. Women, power, and cancer: a lancet commission. Lancet. 2023;402(10417):2113-66. https://doi.org/10.1016/S0140-6736(23)01701-4
6. Acquati C, Miller-Sonet E, Zhang A, Ionescu E. Social wellbeing in cancer survivorship: a cross-sectional analysis of self-reported relationship closeness and ambivalence from a community sample. Curr Oncol. 2023;30(2):1720-32. https://doi.org/10.3390/curroncol30020133
7. Canada Government. Health portfolio sex- and gender-based analysis plus policy: advancing equity, diversity and inclusion. In: H.C.H. Canada, editor. 2023. Available from: https://www.canada.ca/en/health-canada/corporate/transparency/heath-portfolio-sex-gender-based-analysis-policy.html
8. Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. Neuroimage. 2009;47(3):864-71. https://doi.org/10.1016/j.neuroimage.2009.05.074
9. Peleg-Oren N, Sherer M, Soskolne V. Effect of gender on the social and psychological adjustment of cancer patients. Soc Work Health Care. 2003;37(3):17-34. https://doi.org/10.1300/J010v37n03_02
10. Rolland JS. Cancer and the family: an integrative model. Cancer. 2005;104(11):2584-95. https://doi.org/10.1002/cncr.21489
11. Chen JJ, Wang QL, Li HP, Zhang T, Zhang SS, Zhou MK. Family resilience, perceived social support, and individual resilience in cancer couples: analysis using the actor-partner interdependence mediation model. Eur J Oncol Nurs. 2021;52:101932. https://doi.org/10.1016/j.ejon.2021.101932
12. Matud MP, Díaz A, Bethencourt JM, Ibáñez I. Stress and psychological distress in emerging adulthood: a gender analysis. J Clin Med. 2020;9(9):2859. https://doi.org/10.3390/jcm9092859

13. Yadav S, Turner K, Xie Z, Chen G, Islam JY, Suk R, et al. Utilization of inpatient palliative care services among adolescents and young adults with cancer: evidence from National Inpatient Sample 2016-2019. Palliat Support Care. 2023;1-8. https://doi.org/10.1017/S1478951523000354
14. Chatterjee S, Gupta D, Caputo TA, Holcomb K. Disparities in gynecological malignancies. Front Oncol. 2016;6:36. https://doi.org/10.3389/fonc.2016.00036
15. Scalici J, Finan MA, Black J, Harmon MD, Nicolson W, Lankes HA, et al. Minority participation in gynecologic oncology group (GOG) studies. Gynecol Oncol. 2015;138(2):441-4. https://doi.org/10.1016/j.ygyno.2015.05.014
16. Towner M, Kim JJ, Simon MA, Matei D, Roque D. Disparities in gynecologic cancer incidence, treatment, and survival: a narrative review of outcomes among black and white women in the United States. Int J Gynecol Cancer. 2022;32(7):931-8. https://doi.org/10.1136/ijgc-2022-003476
17. Wang Y, Feng W. Cancer-related psychosocial challenges. Gen Psychiatr. 2022;35(5):e100871. https://doi.org/10.1136/gpsych-2022-100871
18. Jonsdottir JI, Vilhjalmsson R, Svavarsdottir EK. Effectiveness of a couple-based intervention on sexuality and intimacy among women in active cancer treatment: a quasi-experimental study. Eur J Oncol Nurs. 2021;52:101975. https://doi.org/10.1016/j.ejon.2021.101975
19. Lin H, Fu HC, Wu CH, Tsai YJ, Chou YJ, Shih CM, et al. Evaluation of sexual dysfunction in gynecologic cancer survivors using DSM-5 diagnostic criteria. BMC Womens Health. 2022;22(1):1. https://doi.org/10.1186/s12905-021-01559-z
20. Juraskova I, Butow P, Robertson R, Sharpe L, McLeod C, Hacker N. Post-treatment sexual adjustment following cervical and endometrial cancer: a qualitative insight. Psychooncology. 2003;12(3):267-79. https://doi.org/10.1002/pon.639
21. Pizetta LM, Reis ADC, Méxas MP, Guimarães VA, Paula CL. Management strategies for sexuality complaints after gynecologic cancer: a systematic review. Rev Bras Ginecol Obstet. 2022;44(10):962-71. https://doi.org/10.1055/s-0042-1756312
22. Nathorst-Böös J, Schoultz B, Carlström K. Elective ovarian removal and estrogen replacement therapy--effects on sexual life, psychological well-being and androgen status. J Psychosom Obstet Gynaecol. 1993;14(4):283-93. https://doi.org/10.3109/01674829309084451
23. Elit L, Esplen MJ, Butler K, Narod S. Quality of life and psychosexual adjustment after prophylactic oophorectomy for a family history of ovarian cancer. Fam Cancer. 2001;1(3-4):149-56. https://doi.org/10.1023/a:1021119405814
24. Trusson D, Pilnick A. The role of hair loss in cancer identity: perceptions of chemotherapy-induced alopecia among women treated for early-stage breast cancer or ductal carcinoma in situ. Cancer Nurs. 2017;40(2):E9-16. https://doi.org/10.1097/NCC.0000000000000373
25. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC. Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects. Psychol Bull. 2008;134(1):1-30. https://doi.org/10.1037/0033-2909.134.1.1
26. Kirchhoff AC, Yi J, Wright J, Warner EL, Smith KR. Marriage and divorce among young adult cancer survivors. J Cancer Surviv. 2012;6(4):441-50. https://doi.org/10.1007/s11764-012-0238-6
27. Glantz MJ, Chamberlain MC, Liu Q, Hsieh CC, Edwards KR, Horn A, et al. Gender disparity in the rate of partner abandonment in patients with serious medical illness. Cancer. 2009;115(22):5237-42. https://doi.org/10.1002/cncr.24577
28. Baucom DH, Porter LS, Kirby JS, Gremore TM, Keefe FJ. Psychosocial issues confronting young women with breast cancer. Breast Dis. 2005;23:103-13. https://doi.org/10.3233/bd-2006-23114
29. Hawkey AJ, Ussher JM, Perz J, Parton C, Patterson P, Bateson D, et al. The impact of cancer-related fertility concerns on current and future couple relationships: people with cancer and partner perspectives. Eur J Cancer Care (Engl). 2021;30(1):e13348. https://doi.org/10.1111/ecc.13348
30. Levin AO, Carpenter KM, Fowler JM, Brothers BM, Andersen BL, Maxwell GL. Sexual morbidity associated with poorer psychological adjustment among gynecological cancer survivors. Int J Gynecol Cancer. 2010;20(3):461-70. https://doi.org/10.1111/IGC.0b013e3181d24ce0
31. Zhao J, Kong Y, Xiang Y, Yang J. The research landscape of the quality of life or psychological impact on gynecological cancer patients: a bibliometric analysis. Front Oncol. 2023;13:1115852. https://doi.org/10.3389/fonc.2023.1115852
32. Mehnert-Theuerkauf A, Hufeld JM, Esser P, Goerling U, Hermann M, Zimmermann T, et al. Prevalence of mental disorders, psychosocial distress, and perceived need for psychosocial support in cancer patients and their relatives stratified by biopsychosocial factors: rationale, study design, and methods of a prospective multi-center observational cohort study (LUPE study). Front Psychol. 2023;14:1125545. https://doi.org/10.3389/fpsyg.2023.1125545
33. Spagnoletti BRM, Bennett LR, Keenan C, Shetty SS, Manderson L, McPake B, et al. What factors shape quality of life for women affected by gynaecological cancer in South, South East and East Asian countries? A critical review. Reprod Health. 2022;19(1):70. https://doi.org/10.1186/s12978-022-01369-y
34. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, et al. The global burden of women's cancers: a grand challenge in global health. Lancet. 2017;389(10071):847-60. https://doi.org/10.1016/S0140-6736(16)31392-7
35. Boehmer U, Jesdale BM, Streed CG, Agénor M. Intersectionality and cancer survivorship: sexual orientation and racial/ethnic differences in physical and mental health outcomes among female and male cancer survivors. Cancer. 2022;128(2):284-91. https://doi.org/10.1002/cncr.33915
36. Gompel A, Baber RJ, Villiers TJ, Huang KE, Santen RJ, Shah D, et al. Oncology in midlife and beyond. Climacteric. 2013;16(5):522-35. https://doi.org/10.3109/13697137.2013.823539
37. Harris E. How to reduce worldwide cancer inequities for women. JAMA. 2023;330(16):1516. https://doi.org/10.1001/jama.2023.19206
38. Shah SC, Kayamba V, Peek RM, Heimburger D. Cancer control in low- and middle-income countries: is it time to consider screening? J Glob Oncol. 2019;5:1-8. https://doi.org/10.1200/JGO.18.00200
39. Fan R, Wang L, Bu X, Wang W, Zhu J. Unmet supportive care needs of breast cancer survivors: a systematic scoping review. BMC Cancer. 2023;23(1):587. https://doi.org/10.1186/s12885-023-11087-8
40. Emery J, Butow P, Lai-Kwon J, Nekhlyudov L, Rynderman M, Jefford M. Management of common clinical problems experienced by survivors of cancer. Lancet. 2022;399(10334):1537-50. https://doi.org/10.1016/S0140-6736(22)00242-2
41. Leeuwen M, Husson O, Alberti P, Arraras JI, Chinot OL, Costantini A, et al. Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire. Health Qual Life Outcomes. 2018;16(1):114. https://doi.org/10.1186/s12955-018-0920-0
42. Nazha B, Mishra M, Pentz R, Owonikoko TK. Enrollment of racial minorities in clinical trials: old problem assumes new urgency in the age of immunotherapy. Am Soc Clin Oncol Educ Book. 2019;39:3-10. https://doi.org/10.1200/EDBK_100021
43. Freedman RA, Foster JC, Seisler DK, Lafky JM, Muss HB, Cohen HJ, et al. Accrual of older patients with breast cancer to alliance systemic therapy trials over time: protocol A151527. J Clin Oncol. 2017;35(4):421-31. https://doi.org/10.1200/JCO.2016.69.4182

REVIEW ARTICLE

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Gastric cancer: an overview

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Brazilian Federation of Gastroenterology

INTRODUCTION

Gastric cancer (GC) represents an important global health problem since it is the fifth leading cancer in the world and the third leading cause of cancer-related death[1], although the overall incidence is declining. This decline has been mainly attributed to the decreased prevalence of *Helicobacter pylori* (*Hp*) infection, but also to the progress in food storage and preservation, probably by allowing the reduction of salty and smoked food consumption[2]. There is great geographic variation in GC incidence, with the majority of new diagnoses per year of GC occurring mainly in Asian and South American countries[3]. In Brazil, it is the third most common type among men and the fifth among women[4]. GC occurs approximately twice as frequently in men as in women, with most cases occurring after the age of 60 years[1]. Adenocarcinoma is the most common histological type, accountable for about 90–95% of cases[5].

There are two main topographic subsites of GC: esophagogastric junction (EGJ) and nonjunctional. The descriptive epidemiology and risk factor profiles of each are different. In contrast to the pattern seen with nonjunctional GC, the incidence rates of adenocarcinomas at the EGJ are rising[6], probably due to an increased rate of obesity and gastroesophageal reflux disease (GERD), which are considered the major risk factors for the latter[7]. Furthermore, current data suggests an increase in the incidence of nonjunctional GC in a group of young individuals, especially women under the age of 50 years[8].

ETIOLOGY AND PATHOGENESIS

Numerous dietary, environmental, and genetic risk factors have been related to gastric adenocarcinoma. The dominant risk factor remains, however, *Hp* infection and the associated chronic-active inflammation of the gastric mucosa. Up to 10% of GCs can be attributed to less common causes, including infection with the Epstein-Barr virus (EBV), autoimmune gastritis, and Menetrier's disease. Other factors associated with increased risk include tobacco smoking, low socioeconomic status, low level of physical activity, and radiation exposure; obesity and GERD are only associated with increased risk of EGJ GC[6]. Although most GC are sporadic, familial clustering is observed in up to 10% of patients[9].

Gastric cancer can be subdivided using the Laurén classification into distinct histologic subtypes with different epidemiologic and prognostic features. Well-differentiated (intestinal) GC is predominately found in individuals of an older age, >70 years, who are mostly male and patients present with larger tumor sizes. This subtype has overall better prognoses than the poorly differentiated (diffuse) subtype. The diffuse subtype has poor survival statistics and is commonly found in younger women[10]. Extensive involvement of the stomach by that subtype can result in a rigid and thickened stomach, a condition referred to as linitis plastic. Another key feature of diffuse subtype cancers are signet-ring cells, special mucin-filled cells that are not present in intestinal subtype adenocarcinomas. There are also mixed phenotypes that contain heterogeneous areas that feature predominantly either intestinal or diffuse characteristics. The mixed subtype is present within a much smaller subset of patients, usually male, and it is known to be highly invasive and metastatic[6].

It is accepted that the development of intestinal subtype GC occurs through a multistep process in which the normal mucosa is sequentially transformed into a hyperproliferative epithelium, followed by metaplastic processes leading to preneoplastic conditions (glandular atrophy, intestinal metaplasia), dysplasia, and then carcinoma[11]. Correa et al., postulates that there is a temporal sequence of preneoplastic changes that eventually lead to the development of GC. A common feature of the initiation and progression to intestinal subtype GC is chronic inflammation of the gastric mucosa by *Hp* infection[12]. Eradication of *Hp* has the potential to prevent GC as shown in recent meta-analyses, particularly if there are no preneoplastic conditions of the gastric mucosa at the time of intervention[13].

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SCREENING

An important question is whether there is room for a population-based screening for GC. While it is justified and already adopted in several Asian countries where the GC incidence is high, it is much more debatable in the countries with low incidence. Guidelines from high-risk areas recommend biennial GC screening via upper endoscopy or upper gastrointestinal series for men and women aged ≥40 years[14].

Patients with atrophic gastritis (AG) and gastric intestinal metaplasia (GIM) should be tested for *Hp* infection and, if positive, should be eradicated. Guidelines recommend endoscopic surveillance every 3 years in patients in whom extensive AG and/or extensive incomplete GIM has been diagnosed[15,16].

CLINICAL MANIFESTATIONS

The diagnosis of GC is generally made when the patient undergoes an endoscopy due to dyspeptic or reflux complaints. In more advanced cases, the individual may experience anemia, gastrointestinal bleeding, vomiting, weight loss or dysphagia[17]. The most common symptom related to the worst outcome is cachexia[18].

Paraneoplastic syndromes are a rare manifestation of GCs. These include dermatological findings such as acanthosis nigricans, membranous nephropathy, microangiopathic hemolytic anemia, and trousseau syndrome (hypercoagulable state)[19]. Although a strong relationship between GC and SIADH (syndrome of inappropriate antidiuretic hormone) secretion has not yet been established, it is suggested that it can be included as a differential diagnosis associated with SIADH[20]. Hypercalcemia is extremely rare in metastatic gastric adenocarcinoma[21].

EXAMS FOR DIAGNOSIS AND STAGING

Upper digestive endoscopy with biopsy

Fundamental exam for diagnosis, staging, treatment, and palliative resection[22] enables the identification of preneoplastic and early lesions, which are suspected in the presence of surface irregularities or mucosal color[23]. Good representation of the material can be guaranteed by collecting 5–8 fragments[24]. A good exam must contain information about location, size, extension, infiltration, distance from the esophagogastric transition, and the pylorus, detailing the biopsies' locations. In cases of high suspicion and repeated negative biopsies, including macrobiopsies, endoscopic or surgical resection should be considered[5].

Computed tomography of the chest and abdomen with oral and intravenous contrast

It must be performed after diagnosis for staging. Pelvis imaging can be performed only if there is clinical suspicion of involvement. When tomography is not possible, magnetic resonance imaging can be performed[22].

Echoendoscopy

Patients who do not present distant metastases or have lymph node (LN) involvement on initial tomography may undergo endoscopic ultrasound[22]. This examination will evaluate the extent of tumor invasion and determine the presence of abnormal or enlarged regional LN and the presence of ascites and metastases in nearby organs. It can also be used when there is doubt about the early appearance of the neoplasia[5].

Laparoscopy

It is an option for those who are not candidates for neoadjuvant therapy. This is a highly sensitive procedure for detecting peritoneal metastases or involvement of the gastric serosa, in addition to allowing cytology studies of the peritoneal fluid. If this is positive, the disease is considered metastatic even in the absence of visible implants[22].

Positron emission tomography/computed tomography

Positron emission tomography/computed tomography is not routinely recommended, but can be used to exclude metastatic disease when other diagnostic methods fail[22]. It has a limited role in the assessment of T stage, due to its low level of spatial resolution, but it could help in the detection of distant LN and bone metastasis[5].

Tumor markers

Analysis of tumor markers CA 19.9, CEA, CA 72.4 must be performed in all cases. Such markers have good sensitivity for recurrence, especially if elevated at the time of diagnosis. Your analysis must be carried out in a combined manner. Only CA 72.4 positivity should be considered as a specific indicator of cancer recurrence throughout the follow-up[5].

HISTOPATHOLOGICAL CLASSIFICATION AND STAGING

In addition to the previously mentioned Laurén histological classification, the tumor can be classified as grades I, II, and III, based on well, moderately, and poorly differentiated cells, respectively[22].

According to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM (tumor-node-metastasis) 8th edition staging manual, tumors involving the EGJ that have an epicenter within 2 cm proximal to the gastric cardia or proximal stomach should be classified as esophageal cancer. Tumors with an epicenter located more than 2 cm distal from the EGJ, regardless of its involvement, should be classified as GC according to TNM parameters[25-27].

The TNM classification correlates with 5-year survival and its clinical staging is shown in Table 1[25,26]. Regardless of the histological variant, the degree of invasion into the gastric wall determines the primary stage of the tumor. Early GC is defined as a lesion confined to the mucosa and submucosa (T1), regardless of LN involvement[23]. When it involves the muscularis propria, it is classified as T2, and T3 if the subserosa is affected. It is denominated as T4a in case that the tumor perforates the serosa and T4b if it invades adjacent structures[25,26].

It is recommended that a minimum number of 16 LNs is evaluated by the pathologist to improve the N staging accuracy. The number of regional LN with metastasis determines the N stage (N1: 1-2; N2: 3-6; and N3: 7 or more). The presence of distant metastasis is classified as M1[25-27].

TREATMENT

Multidisciplinary treatment is required, and the team must include gastroenterologists, surgeons, oncologists, radiologists, pathologists, nutritionists, endoscopists, and several other specialists. Combined modality therapy is generally used and more effective for patients with GC[17].

Regular follow-up is recommended, tailored to each patient and stage of disease, for investigation and treatment of symptoms, provision of psychological support, and early detection of recurrence. Special attention must be paid to vitamin and mineral deficiencies, providing dietary support to the patient[24].

Table 1. Tumor-node-metastasis clinical staging of gastric cancer according to the American Joint Committee on Cancer/Union for International Cancer Control 8th edition.

Clinical stages			
Stage I	T1, T2	N0	M0
Stage IIA	T1, T2	N1, N2, N3	M0
Stage IIB	T3, T4a	N0	M0
Stage III	T3, T4a	N1, N2, N3	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

A treatment flowchart for localized (stages I–III) and advanced (stage IV) GC is shown on Figure 1.

Endoscopic treatment

Most early gastric tumors (neoplasms limited to the mucosa or submucosa) do not present LN metastasis, making the curative treatment of these lesions possible by endoscopy[22].

Mucosectomy or endoscopic submucosal dissection (ESD) is indicated if: well to moderately differentiated tumor histology, size ≤2 cm, without invasion of the deep submucosa, non-ulcerated, and without lymphovascular invasion. Clear negative lateral and deep margins must be obtained[17].

Gastric echoendoscopy can be performed before the procedure in order to assess the depth of tumor invasion[22].

Surgical resection

Patients with the absence of distant metastases should be considered for surgery with curative intent unless candidates present criteria for endoscopic resection. Gastrectomy (subtotal or total) with D2 lymphadenectomy is generally the surgery of choice[22].

In advanced or metastatic cases, palliative surgery remains an alternative to cases of obstruction, perforation, or bleeding. Resection of metastases might be considered an individual approach in highly selected patients[22].

Chemotherapy

The preferential regimen depends on individual patient factors (using parameters such as performance status, age, comorbidities, and clinical contraindications), as well as clinical and surgical staging. Schemes like FLOT (5-fluorouracil–leucovorin–oxaliplatin–docetaxel), FOLFOX (5-fluorouracil–leucovorin– oxaliplatin), and CAPOX (capecitabine–oxaliplatin) can be prescribed[22].

Perioperative chemotherapy (before and after surgery) or postoperative chemotherapy plus chemoradiation is listed as a

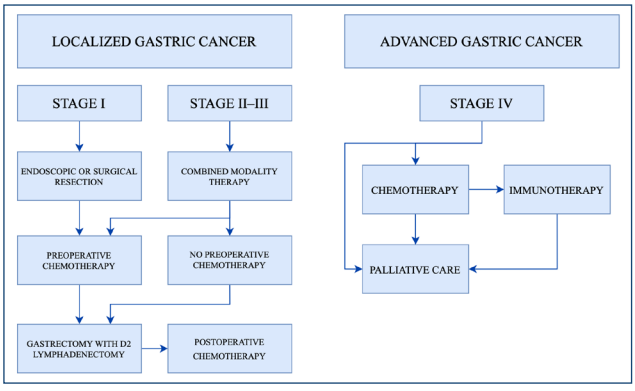

Figure 1. Treatment flowchart for gastric cancer.

preferred approach in current guidelines, although postoperative chemotherapy alone is an option after an adequate LN dissection[22].

Patients in good clinical condition with metastatic disease have an indication for palliative chemotherapy[5].

Immunotherapy

Molecular targeted drugs are also present in the treatment of GC. Trastuzumab, a monoclonal antibody anti-human epidermal growth factor 2 (HER2) receptor, can be used for patients with HER2 overexpression[22]. Ramucirumab is another type of monoclonal antibody that binds to a different protein, i.e., vascular endothelial growth factor receptor 2 (VEGFR2), blocking receptor activation[17].

Immune checkpoint blockade includes monoclonal antibodies that inhibit programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4). This kind of therapy can be used in patients with advanced or metastatic GC[17].

Radiotherapy

Radiotherapy is recommended in some cases, such as those with an indication for adjuvant chemotherapy who did not have an adequate LN dissection during surgery[5].

Palliative care

Best supportive care must be offered for those patients with metastatic GC who have not responded to palliative chemotherapy or in poor clinical condition[5].

AUTHORS' CONTRIBUTIONS

GCC: Conceptualization, Supervision, Visualization, Writing – original draft, Writing – review & editing. **RMC:** Visualization, Writing – original draft, Writing – review & editing. **TMFA:** Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492
2. Howson CP, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. Epidemiol Rev. 1986;8(1):1-27. https://doi.org/10.1093/oxfordjournals.epirev.a036288
3. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol. 2019;14(1):26-38. https://doi.org/10.5114/pg.2018.80001
4. Amorim CA, Moreira JP, Rial L, Carneiro AJ, Fogaça HS, Elia C, et al. Ecological study of gastric cancer in Brazil: geographic and time trend analysis. World J Gastroenterol. 2014;20(17):5036-44. https://doi.org/10.3748/wjg.v20.i17.5036
5. Barchi LC, Ramos MFKP, Dias AR, Andreollo NA, Weston AC, LourenÇo LG, et al. II Brazilian consensus on gastric cancer by the Brazilian gastric cancer association. Arq Bras Cir Dig. 2020;33(2):e1514. https://doi.org/10.1590/0102-672020190001e1514
6. Thrift AP, El-Serag HB. Burden of gastric cancer. Clin Gastroenterol Hepatol. 2020;18(3):534-42. https://doi.org/10.1016/j.cgh.2019.07.045
7. Petryszyn P, Chapelle N, Matysiak-Budnik T. Gastric cancer: where are we heading? Dig Dis. 2020;38(4):280-5. https://doi.org/10.1159/000506509
8. Anderson WF, Rabkin CS, Turner N, Fraumeni JF, Rosenberg PS, Camargo MC. The changing face of noncardia gastric cancer incidence among US non-hispanic whites. J Natl Cancer Inst. 2018;110(6):608-15. https://doi.org/10.1093/jnci/djx262
9. Spoto CPE, Gullo I, Carneiro F, Montgomery EA, Brosens LAA. Hereditary gastrointestinal carcinomas and their precursors: an algorithm for genetic testing. Semin Diagn Pathol. 2018;35(3):170-83. https://doi.org/10.1053/j.semdp.2018.01.004
10. Sexton RE, Hallak MN, Diab M, Azmi AS. Gastric cancer: a comprehensive review of current and future treatment strategies. Cancer Metastasis Rev. 2020;39(4):1179-203. https://doi.org/10.1007/s10555-020-09925-3
11. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--first American cancer society award lecture on cancer epidemiology and prevention. Cancer Res. 1992;52(24):6735-40. PMID: 1458460
12. Correa P, Haenszel W, Cuello C, Zavala D, Fontham E, Zarama G, et al. Gastric precancerous process in a high risk population: cohort follow-up. Cancer Res. 1990;50(15):4737-40. PMID: 2369748
13. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? Ann Intern Med. 2009;151(2):121-8. https://doi.org/10.7326/0003-4819-151-2-200907210-00009
14. Choi KS, Suh M. Screening for gastric cancer: the usefulness of endoscopy. Clin Endosc. 2014;47(6):490-6. https://doi.org/10.5946/ce.2014.47.6.490
15. Gupta S, Li D, Serag HB, Davitkov P, Altayar O, Sultan S, et al. AGA clinical practice guidelines on management of gastric intestinal metaplasia. Gastroenterology. 2020;158(3):693-702. https://doi.org/10.1053/j.gastro.2019.12.003
16. Shah SC, Piazuelo MB, Kuipers EJ, Li D. AGA clinical practice update on the diagnosis and management of atrophic gastritis: expert review. Gastroenterology. 2021;161(4):1325-32.e7. https://doi.org/10.1053/j.gastro.2021.06.078
17. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. CA Cancer J Clin. 2021;71(3):264-79. https://doi.org/10.3322/caac.21657
18. Poonyam P, Aumpan N, Vilaichone RK. Prognostic factors for survival in patients with gastric adenocarcinoma. Cancer Rep (Hoboken). 2021;4(1):e1305. https://doi.org/10.1002/cnr2.1305
19. Pai A, Pervin S. Unusual paraneoplastic syndrome of inappropriate antidiuretic hormone secretion with gastric cancer. Int J Res Med Sci. 2019;7:3192-4. https://doi.org/10.18203/2320-6012.ijrms20193418
20. Hwang K, Jeon DH, Jang HN, Bae EJ, Lee JS, Cho HS, et al. Inappropriate antidiuretic hormone syndrome presenting as ectopic antidiuretic hormone-secreting gastric adenocarcinoma: a case

report. J Med Case Rep. 2014;8:185. https://doi.org/10.1186/1752-1947-8-185

21. Kumar M, Kumar A, Kumar V, Kaur S, Maroules M. Hypercalcemia as initial presentation of metastatic adenocarcinoma of gastric origin: a case report and review of the literature. J Gastric Cancer. 2016;16(3):191-4. https://doi.org/10.5230/jgc.2016.16.3.191
22. Peixoto RD, Rocha-Filho DR, Weschenfelder RF, Rego JFM, Riechelmann R, Coutinho AK, et al. Brazilian group of gastrointestinal tumours' consensus guidelines for the management of gastric cancer. Ecancermedicalscience. 2020;14:1126. https://doi.org/10.3332/ecancer.2020.1126
23. Martins BC, Moura RN, Kum AST, Matsubayashi CO, Marques SB, Safatle-Ribeiro AV. Endoscopic imaging for the diagnosis of neoplastic and pre-neoplastic conditions of the stomach. Cancers (Basel). 2023;15(9):2445. https://doi.org/10.3390/cancers15092445
24. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(10):1005-20. https://doi.org/10.1016/j.annonc.2022.07.004
25. Brierley JD, Gospodarowicz MK, Wittekind C, editors. UICC TNM classification of malignant tumours. 8th ed. Oxford: Wiley-Blackwell; 2017.
26. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., editors. AJCC cancer staging manual. 8th ed. New York (NY): Springer; 2017. p. 203-20.
27. Mranda GM, Xue Y, Zhou XG, Yu W, Wei T, Xiang ZP, et al. Revisiting the 8th AJCC system for gastric cancer: a review on validations, nomograms, lymph nodes impact, and proposed modifications. Ann Med Surg (Lond). 2022;75:103411. https://doi.org/10.1016/j.amsu.2022.103411

REVIEW ARTICLE

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Importance of genetic cancer risk assessment as a strategy to stratify risk and provide precision prevention in high-risk patients and families

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Brazilian Society of Medical Genetics and Genomics

CANCER STATISTICS, HEREDITARY CANCER IN BRAZIL, AND THE CREATION OF THE BRAZILIAN NETWORK OF HEREDITARY CANCER (REBRACH)

Approximately 704,000 new cases of cancer are expected to occur per year in Brazil between 2023 and 2025, corresponding to an incidence of 222 per 100,000 in men and 186 per 100,000 in women. Data from the last decades show that an epidemiological transition is occurring and cancer will soon be the first cause of death by disease in Brazil[1,2], overtaking cardiovascular diseases. Consequently, it is estimated that the annual cost of cancer treatment in the Brazilian public health system (SUS) will practically double until 2040, reaching R$ 7.8 billion[3]. Therefore, cancer prevention and early detection are key strategies to lower incidence, mortality growth, and costs of cancer care in the public health system. Although most cancers are associated with environmental causes, approximately 5–10% are mainly due to hereditary predisposition, characterized by multiple cases in a family, early age of onset, and frequently, diagnosis of multiple primary cancers in one person. Hereditary syndromes have been well-established for the most common solid tumors such as breast and colorectal cancers. However, recent expansion of genetic testing has identified hereditary versions of practically all types of cancers, associated or not with specific phenotypic criteria. In Brazil, several studies carried out in the last decades characterized the prevalence of germline pathogenic genetic variants associated with distinct cancer types including breast, colorectal, retinoblastoma, adrenocortical carcinoma, and ovarian cancers[4-8]. These studies showed a high prevalence of specific mutations also found in other populations as well as variants mostly or only observed in the Brazilian population[9] and contributed to the growth of scientific knowledge in the field. They also helped insert oncogenetics and genetic cancer risk assessment (GCRA) in public and private health services and established in 2009 a network funded by the Brazilian National Council for Scientific and Technological Development (CNPq) and coordinated by the Brazilian National Cancer Institute (INCA) (Rede Nacional de Cancer Familial)[10,11]. This network is now an autonomous organization (www.rebrach.org.br) intended to promote actions to optimize access, health care assistance, training of health care professionals, and scientific investigations in hereditary cancer.

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IMPORTANCE OF IDENTIFYING INDIVIDUALS WITH INHERITED PREDISPOSITION TO CANCER

Inherited predisposition to cancer may be suspected by the presence of clinical features ("phenotype"), but nowadays, it may also be identified by genomic testing for other diseases (i.e., exome testing for pediatric disorders unrelated to cancer). Even when there is a phenotype suggesting hereditary cancer, germline genetic testing (molecular diagnosis) should be done to confirm the presence of a pathogenic variant in one or more of the hereditary cancer predisposition genes. Although these variants occur mostly in people with a suggestive phenotype, they may also be present in up to 26–56% of individuals who do not meet any clinical criteria. Several factors may explain this situation including: (1) individual from a small family, with few relatives, also known as limited family structure; (2) incomplete penetrance of most genes related to hereditary syndromes; (3) diagnosis of late-onset cancer; or (4) lack of knowledge about family history. The presence of a germline pathogenic or likely pathogenic variant in a cancer predisposition gene increases, often more than five times the lifetime risk of one or multiple cancers. Once a pathogenic or likely pathogenic variant is identified, regardless of the presence or absence of a characteristic phenotype, the carrier must be closely assessed for lifetime cancer risk and genetic counseling as well as cascade testing of other at-risk relatives is warranted.

WHAT IS GENETIC CANCER RISK ASSESSMENT AND HOW IS IT DONE?

Genetic cancer risk assessment is the process of evaluating risk, identifying appropriate patients for genetic testing, reviewing the limitations, and determining the risks, benefits, and scope of testing. It is recommended before any genetic testing and should ideally also be performed after the test, especially if a positive result is found. It should be performed by a trained clinical geneticist or other health care professional who is experienced in cancer genetics. The most commonly used genetic testing approach nowadays is multi-gene panel testing (MGPT), which usually includes analysis of high and moderate penetrance genes and, in many cases, genes that are considered preliminary evidence, for which limited information is available about association with and/or causality for disease. MGPT increases the likelihood of identifying variants of unknown significance (VUS), and it also allows the identification of patients with more than one pathogenic variant. Despite the improved clinical utility of an expanded hereditary cancer gene panel, a higher rate of VUS is also expected which constitutes a challenge for counseling. Post-test counseling is an important part of the process, enabling discussions with the patient about the result itself, rationale for additional genetic testing in the patient or relatives (when appropriate), definition of cancer risks, and referrals (if necessary) for ongoing management. It is important to emphasize that counseling after genetic testing is key to discuss cancer risk for other family members and to provide clear recommendations about cascade testing of relatives.

In circumstances where genetic tests are not available, it is possible to use mathematical models to predict risks. Risk assessment tools often use models that combine personal health history information, family history, non-disease indicators of risk, and genetic/genomic data. However, the final confirmation of hereditary predisposition to cancer depends on the molecular diagnosis. The empiric risk models may help in the management of cases with a phenotype but no identifiable genetic variant after comprehensive genetic testing, a situation also known as "missing heritability."

IMPORTANCE OF HIGH-QUALITY GENETIC TESTS IN THE IDENTIFICATION OF INDIVIDUALS WITH HEREDITARY CANCER

Germline genetic testing is offered by various laboratories, employing distinct approaches to assess sequence variants and large gene rearrangements. In recent years, laboratory practices have been rapidly evolving as a result of advancements in DNA and RNA analysis technologies, increased demand for genetic testing, and developments in the field of personalized medicine, where treatments are guided by test results. Therefore, when developing a molecular test for clinical diagnosis, it should meet certain minimum quality requirements, such as precision, accuracy, detection limits, and coverage. Furthermore, after designing and developing the test, validation studies must be conducted to ensure that the predefined performance has been achieved. In the report, identified variants need to be classified for their pathogenicity in accordance with internationally validated and updated guidelines, ensuring reproducibility in variant classification among different laboratories. Furthermore, the continuous deposition of detected variants in public databases by diagnostic laboratories will be essential for advancing the correct classification of potential pathogenicity and, consequently, the most appropriate clinical management for affected patients. Finally, other investigative avenues must often be pursued to assess potential pathogenicity or benignity, including functional assays in cellular and animal models and cosegregation analysis of variants in affected and unaffected family members, which is a process that may take several years until a final definition on pathogenicity is reached.

WHAT CHANGES IN TERMS OF CANCER MANAGEMENT AND PREVENTION WITH GENETIC CANCER RISK ASSESSMENT?

The identification of hereditary cancer predisposition impacts various aspects of care, from risk reduction and screening recommendations to the planning of oncological treatment. It also enables genetic counseling tailored to reproductive issues, including preimplantation genetic diagnosis. This clinical utility, based on an increasingly robust literature, has positioned Oncogenetics as an integral part of the comprehensive medical care of oncologic patients. In addition to recommendations for a protective lifestyle (i.e., healthy diet, weight control, regular physical activity, and avoidance of alcohol and tobacco), high-risk management is based on differentiated recommendations for screening, chemoprophylaxis, and risk-reducing surgeries. Intensified screening is defined as screening beyond the level recommended for individuals at average risk. It includes adjustments to the recommended age of screening onset, the recommended screening intervals, and the methods involved in screening[12]. The screening protocol is defined taking into account individual-specific aspects, the diagnosed cancer predisposition syndrome, and the familial phenotype. For cancer risk reduction, evidence for chemoprophylaxis is still preliminary. Literature data suggest a protective role of tamoxifen or aromatase inhibitors for breast cancer[13] and a potential role for aspirin in reducing the risk of colorectal cancer in patients with Lynch syndrome[14]. The role of other medications is still under development. In some scenarios, risk-reducing surgery may be the most appropriate approach. For example, in women with a hereditary predisposition to ovarian cancer associated with high-penetrance genes such as BRCA1 and BRCA2, the role of bilateral risk-reducing salpingo-oophorectomy (RRSO) is well established and reduces mortality[15]. In recent years, germline alterations have also gained value as predictive biomarkers for response to targeted systemic treatments. The best example of this is the use of poly(ADP-ribose) polymerase (PARP) inhibitors in patients with homologous recombination-deficient tumors, notably those with mutated BRCA1 and BRCA2. The success of this approach has so far led to the approval of four different PARP inhibitors for the treatment of several types of cancers, such as breast, ovarian, prostate, and pancreatic cancer[16].

COST-EFFECTIVENESS OF GENETIC TESTING AND PREVENTIVE STRATEGIES

Currently, the most studied cost-effectiveness models are conducted through analyses of hereditary breast/ovarian cancer panels, where the cost per quality-adjusted life-year (QALY) and the incremental cost-effectiveness ratio (ICER) are calculated, serving as a cost-effective screening measure in European countries and the United States, preventing cases of breast and ovarian cancer and avoiding deaths[17,18]. In Brazil, there are two studies of economic modeling of screen-and-treat strategies for women at risk of HBOC evaluating the implementation of BRCA1 and BRCA2 testing[19,20]. In both studies, Markov models with a lifelong time horizon were developed for a cohort of healthy women aged 30 years who fulfilled the criteria for testing according to the guidelines. Women who tested positive had several alternatives, including increased surveillance and the option of risk-reducing bilateral mastectomy and bilateral salpingo-oophorectomy. The BRCA1/BRCA2 genetic test and preventive strategies result in more QALYs and costs with an ICER of R$ 11,900–R$ 24,263/QALY. This ICER determined for BRCA1/BRCA2 genetic testing provision closely aligns with the cost-effectiveness threshold set forth by the World Health Organization (WHO) for low- and middle-income countries. Despite the absence of a stringent cost-effectiveness threshold in Brazil, the outcomes of this analysis advocate in favor of the implementation of BRCA1/BRCA2 testing among high-risk women in SUS.

ACCESS TO GENETIC CANCER RISK ASSESSMENT IN THE BRAZILIAN HEALTH CARE SYSTEM (PUBLIC AND PRIVATE SECTORS)

The 2019 National Health Survey[21] shows that around 71.5% of the Brazilian population has, as the only health care resource, the free, state-owned, and universal SUS. This proportion increases in the north and northeast of Brazil, reflecting historical inequities in the country's development. Additional private health insurance plan coverage was 26.0%, with the same great inequity between the Large Regions and Federation Units. The Southeast and South Regions emerged with the highest coverage proportional to their populations (34.9 and 30.5%, respectively). In Brazil, the clinical and laboratory assessment of hereditary cancer risk is under construction and reflects the challenges of health care for the Brazilian population. Within the scope of SUS, some public services, most linked to universities, philanthropic hospitals, or linked to foundations, established outpatient clinics for this purpose from the 1990s onward. Diagnostic resources, specifically molecular biology tests to investigate the presence of causative variants, are offered through research projects and other proprietary sources, as to date, they are not available in the public health system. In 2016, Ashton-Prolla and Seuanez[11] highlighted that these resources covered less than 5% of the

Brazilian population. This scenario has changed little since then. Supplementary Health has addressed this issue a little better, through its regulatory agency, the National Supplementary Health Agency (ANS). In 2013, the ANS published the first version of its list of procedures, accompanied by use guidelines for coverage of procedures in supplementary health care that includes, for the first time, cancer predisposition syndromes investigation. Currently, there are guidelines[22] for Hereditary Breast and Ovarian Cancer Syndrome (HBOC), Lynch, and several other cancer predisposition syndromes. However, the guidelines adopted by ANS are restrictive and do not accommodate cancer-unaffected individuals, with a family history, except those who already have a relative with a detected mutation. Another restriction of these guidelines is the limitation on the use of multigene panel sequencing, favoring single-gene, sequential testing. Because of these restrictions, the ANS guidelines have become progressively more distant from the current approaches to testing proposed by several international medical societies.

IMPORTANCE OF CAPACITY BUILDING AMONG HEALTH CARE PROFESSIONALS TO ENABLE GENETIC CANCER RISK ASSESSMENT AND ACCURATE IDENTIFICATION AND MANAGEMENT OF HIGH HIGH-RISK PATIENTS

Identification and management of hereditary cancer play an important role in identifying high-risk individuals and ensuring access to interventions that can prevent disease. However, to enable the benefits of the effective incorporation of genetic or genomic information into health care, a significant barrier to more equitable access to this technology is proper training of health care professionals at different levels[23]. In this sense, the limited availability of providers of GCRA is an important issue in most countries worldwide. Several professional societies have developed specific curricula and a few multidisciplinary short- and long-term training programs have been established[12,24]. Despite existing initiatives, there is an urgent need to invest in the education of health care providers to expand the number of providers available, reduce variability in knowledge regarding hereditary cancer, and qualify genetic service provision. The knowledge needed to provide accurate and comprehensive GCRA is complex and constantly changing. It requires training in several important domains: state of cancer genetics, state of genetic counseling and risk communication, state of technology of genetic testing and variant interpretation, and state of the art in terms of risk management including knowledge of the constantly changing treatment recommendations based on actionable inherited genetic variants. These professionals must also be equipped to handle the complex and rapidly evolving medical, technological, and ethical issues involved in the care of hereditary cancer patients and their relatives[25]. Therefore, capacity building should include training at different levels, from basic knowledge about the importance of identifying at-risk patients, need for referral and promoting this practice among peers (i.e., capacity-building interventions in primary care teams), to disease-specific training (i.e., in a specific tumor of a subset of tumors) to comprehensive training in all aspects of GCRA. Once training is complete, continuous education through periodic participation in multidisciplinary case discussions and tumor boards is also relevant to address the issue of rapidly evolving knowledge in the field. In Brazil, no formal qualification in GCRA, as proposed by international accreditation programs, exists to date for physicians or other health care professionals. For physicians, formal training in genetic counseling is offered only in medical genetics residency programs, but even among some of these, there is a lack of comprehensive and dedicated supervised training experience in cancer genetics. To approach this gap, two important initiatives are being developed by several professional societies led by the Brazilian Society of Medical Genetics and Genomics (SBGM). The first is the development of a 2000-h Theoretical and Practical Course in cancer genetics for physicians already approved by the Brazilian Medical Association (AMB) and currently under review by the Federal Council of Medicine (CFM). The second is the creation of a comprehensive genetic counseling training program for non-MD health care professionals sponsored by the Ministry of Health. Such initiatives are key to enhance adherence to and effectiveness of GCRA. They will also reduce the increasing harms related to lack of access to adequate genetic testing, inaccurate result interpretation, or failure to tailor cancer risk-reducing interventions appropriately.

AUTHORS' CONTRIBUTIONS

PAP: Conceptualization, Data curation, Formal Analysis, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MIWA:** Conceptualization, Data curation, Formal Analysis, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MAMM:** Data curation, Formal Analysis, Validation, Visualization, Writing – original draft. **EIP:** Data curation, Formal Analysis, Validation, Visualization, Writing – original draft. **DCQS:** Data curation, Formal Analysis, Validation, Visualization, Writing – original draft. **VEFF:** Data curation, Formal Analysis, Validation,

Visualization, Writing – original draft. **IQSC:** Data curation, Formal Analysis, Validation, Visualization, Writing – original draft. **RSCG:** Data curation, Formal Analysis, Validation, Visualization, Writing – original draft. **ACLVCG:** Data curation, Formal Analysis, Validation, Visualization, Writing – original draft.

REFERENCES

1. Instituto Nacional de Câncer (INCA). Estimativa 2023: incidência de câncer no Brasil / Instituto Nacional de Câncer. Rio de Janeiro (RJ): INCA; 2022a. p. 160.
2. Instituto Nacional de Câncer (INCA). A situação do câncer no Brasil/Ministério da Saúde, Secretaria de Atenção à Saúde, Instituto Nacional de Câncer, Coordenação de Prevenção e Vigilância. Rio de Janeiro (RJ): INCA; 2006. p. 120.
3. Instituto Nacional de Câncer (INCA). Gastos federais atuais e futuros com os cânceres atribuíveis aos fatores de risco relacionados à alimentação, nutrição e atividade física no Brasil. Rio de Janeiro (RJ): INCA; 2022b. p. 50.
4. Ribeiro RC, Sandrini F, Figueiredo B, Zambetti GP, Michalkiewicz E, Lafferty AR, et al. An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. Proc Natl Acad Sci USA. 2001;98(16):9330-5. https://doi.org/10.1073/pnas.161479898
5. Giacomazzi J, Graudenz MS, Osorio CA, Koehler-Santos P, Palmero EI, Zagonel-Oliveira M, et al. Prevalence of the TP53 p.R337H mutation in breast cancer patients in Brazil. PLoS One. 2014;9(6):e99893. https://doi.org/10.1371/journal.pone.0099893
6. Palmero EI, Carraro DM, Alemar B, Moreira MAM, Ribeiro-Dos-Santos Â, Abe-Sandes K, et al. The germline mutational landscape of BRCA1 and BRCA2 in Brazil. Sci Rep. 2018;8(1):9188. https://doi.org/10.1038/s41598-018-27315-2
7. Paula AE, Galvão HCR, Bonatelli M, Sabato C, Fernandes GC, Berardinelli GN, et al. Clinicopathological and molecular characterization of Brazilian families at risk for lynch syndrome. Cancer Genet. 2021;254-5:82-91. https://doi.org/10.1016/j.cancergen.2021.02.003
8. Guindalini RSC, Viana DV, Kitajima JPFW, Rocha VM, López RVM, Zheng Y, et al. Detection of germline variants in Brazilian breast cancer patients using multigene panel testing. Sci Rep. 2022;12(1):4190. https://doi.org/10.1038/s41598-022-07383-1
9. Achatz MI, Zambetti GP. The inherited p53 mutation in the Brazilian population. Cold Spring Harb Perspect Med. 2016;6(12):a026195. https://doi.org/10.1101/cshperspect.a026195
10. Instituto Nacional de Câncer (INCA). Rede nacional de câncer familial: manual operacional / Instituto Nacional de Câncer – Rio de Janeiro (RJ): INCA; 2009. p. 229.
11. Ashton-Prolla P, Seuanez HN. The Brazilian hereditary cancer network: historical aspects and challenges for clinical cancer genetics in the public health care system in Brazil. Genet Mol Biol. 2016;39(2):163-5. https://doi.org/10.1590/1678-4685-GMB-2014-0373
12. Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO clinical practice guideline. Ann Oncol. 2023;34(1):33-47. https://doi.org/10.1016/j.annonc.2022.10.004
13. King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: national surgical adjuvant breast and bowel project (NSABP-P1) breast cancer prevention trial. JAMA. 2001;286(18):2251-6. https://doi.org/10.1001/jama.286.18.2251
14. Burn J, Bishop DT, Mecklin JP, Macrae F, Möslein G, Olschwang S, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the lynch syndrome. N Engl J Med. 2008;359(24):2567-78. https://doi.org/10.1056/NEJMoa0801297
15. Liu YL, Breen K, Catchings A, Ranganathan M, Latham A, Goldfrank DJ, et al. Risk-reducing bilateral salpingo-oophorectomy for ovarian cancer: a review and clinical guide for hereditary predisposition genes. JCO Oncol Pract. 2022;18(3):201-9. https://doi.org/10.1200/OP.21.00382
16. O'Malley DM, Krivak TC, Kabil N, Munley J, Moore KN. PARP inhibitors in ovarian cancer: a review. Target Oncol. 2023;18(4):471-503. https://doi.org/10.1007/s11523-023-00970-w
17. Asphaug L, Melberg HO. The cost-effectiveness of multigene panel testing for hereditary breast and ovarian cancer in Norway. MDM Policy Pract. 2019;4(1):2381468318821103. https://doi.org/10.1177/2381468318821103
18. Sun L, Brentnall A, Patel S, Buist DSM, Bowles EJA, Evans DGR, et al. A cost-effectiveness analysis of multigene testing for all patients with breast cancer. JAMA Oncol. 2019;5(12):1718-30. https://doi.org/10.1001/jamaoncol.2019.3323
19. Simoes Correa-Galendi J, Pilar Estevez Diz M, Stock S, Müller D. Economic modelling of screen-and-treat strategies for Brazilian women at risk of hereditary breast and ovarian cancer. Appl Health Econ Health Policy. 2021;19(1):97-109. https://doi.org/10.1007/s40258-020-00599-0
20. Lourenção M, Simões Correa Galendi J, Galvão HCR, Antoniazzi AP, Grasel RS, Carvalho AL, et al. Cost-effectiveness of BRCA 1/2 genetic test and preventive strategies: using real-world data from an upper-middle income country. Front Oncol. 2022;12:951310. https://doi.org/10.3389/fonc.2022.951310
21. Instituto Brasileiro de Geografia e Estatística (IBGE). Pesquisa nacional de saúde: 2019: informações sobre domicílios, acesso e utilização dos serviços de saúde: Brasil e grandes regiões. IBGE, Coordenação de Trabalho e Rendimento. Rio de Janeiro (RJ): IBGE; 2020. p. 96.
22. Agência Nacional de Saúde Suplementar (ANS). Diretrizes da utilização para cobertura de procedimentos de saúde suplementar 2021. Brasília. 2021. [cited on 2023 Nov 11]. Available from: https://www.gov.br/ans/pt-br/arquivos/assuntos/consumidor/o-que-seu-plano-deve-cobrir/Anexo_II_DUT_2021_RN_465.2021_TEA.AL.pdf
23. Ashton-Prolla P, Goldim JR, Vairo FP, Silveira Matte U, Sequeiros J. Genomic analysis in the clinic: benefits and challenges for health care professionals and patients in Brazil. J Community Genet. 2015;6(3):275-83. https://doi.org/10.1007/s12687-015-0238-0
24. Blazer KR, Macdonald DJ, Culver JO, Huizenga CR, Morgan RJ, Uman GC, et al. Personalized cancer genetics training for personalized medicine: improving community-based healthcare through a genetically literate workforce. Genet Med. 2011;13(9):832-40. https://doi.org/10.1097/GIM.0b013e31821882b7
25. Ginsburg O, Ashton-Prolla P, Cantor A, Mariosa D, Brennan P. The role of genomics in global cancer prevention. Nat Rev Clin Oncol. 2021;18(2):116-28. https://doi.org/10.1038/s41571-020-0428-5.

REVIEW ARTICLE

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The role of geriatric oncology in the care of older people with cancer: some evidence from Brazil and the world

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EPIDEMIOLOGY OF CANCER AND AGING

According to the World Health Organization (WHO), cancer is defined as a large group of malignant diseases that have the common characteristic of disordered and abnormal cell growth, which can invade adjacent structures or spread through metastases. According to WHO data, in 2018, 17 million new cases and 9.6 million deaths from cancer were recorded worldwide, generating a great impact not only physically but also emotionally and financially on individuals, families, communities, and health systems[1]. In Brazil, 704,000 new cases of cancer are expected for each year of the 2023–2025 triennium, with emphasis on the South and Southeast regions, which account for around 70% of cases. Among the most common malignant neoplasms in Brazil, non-melanoma skin neoplasms are the most common (31.3% of total cases), followed by breast neoplasms (10.5%), prostate (10.2%), colon and rectum (6.5%), lung (4.6%), and stomach (3.1%)[1,2].

Cancer is considered a public health problem because it is the second leading cause of mortality in the world and, consequently, one of the main barriers to increasing the population's life expectancy. Furthermore, the impact of its incidence and mortality is increasing rapidly on the global stage due to the demographic and epidemiological transition that the world is going through, with the increase in population aging, especially in developing countries such as Brazil[2,3].

Age is known to be an important risk factor for the development of cancer. It is known that 56% of cancer diagnoses and 70% of all deaths from oncological diseases occur in older people[4]. Furthermore, cancer is the second leading cause of death in women and men aged 60–79 years. The average age of cancer diagnosis is 68 years, and the incidence of cancer increases with age, with an 11 times greater risk of developing cancer in people over 65 years of age. It is estimated that, by 2040, the incidence of cancer will double in the older population over 65 years of age, with an even greater increase in incidence among octogenarians[5].

Faced with this increase in the incidence of cancer in the older, geriatric oncology has become a field in full expansion, nationally and internationally. Guidelines for acting in geriatric oncology have been recommended by the main international oncology societies, bringing the importance of discussing the topic between geriatrics and oncology societies in Brazil and health professionals who assist the older population with cancer[6,7].

HISTORY OF GERIATRIC ONCOLOGY AND ITS CHALLENGES

The history of geriatric oncology is evident in the first conference focused on Cancer in the older, in 1983, organized by Rosemary Yancik (PhD) and Paul Carbone (MD) at the National Institutes of Health[4,8]. Subsequently, in 1990, a group of seven medical oncologists from Guy's Hospital in London published the paper "Cancer in the older: Why So Badly Treated?" in The Lancet journal[9]. The article detailed the enormity of the

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problem and inspired many young investigators and clinicians to join the field of geriatric oncology. In 2000, the International Society of Geriatric Oncology (SIOG) was founded.

International Society of Geriatric Oncology is a multidisciplinary membership-based society with members engaged in more than 80 countries around the world. Their network includes geriatricians, medical oncologists, surgical oncologists, radiation oncologists, anesthesiologists, nurses, and allied health professionals. Ever since, SIOG has established a long-standing history of implementing programmatic activities in the field of geriatric oncology in four strategic directions: education, clinical practice, research, and collaborations and partnerships[10]. Since 2010, the Journal of Geriatric Oncology is the official journal of SIOG. It is an international multidisciplinary journal that is focused on advancing research in the pathogenesis, biology, treatment, and survivorship issues of older adults with cancer. The journal covers all aspects of geriatric oncology, from basic scientific research through to clinical research, as well as research that is relevant to education and policy development, and it has a high impact factor of 3.9[10].

The literature raises many challenges in covering the care of older people with cancer. Globally, the geriatric training of healthcare personnel is regulated by diverse organizations, leading to high variability in curriculum and certificates[11]. In order to solve this, efforts to put together a homogeneous core curriculum in geriatric medicine and to include geriatric oncology in training programs have been undertaken by several medical societies around the world. The American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) included recommendations for core geriatric oncology training as a part of the global curriculum in medical oncology[11,12]. Likewise, the European Oncology Nursing Society has also published recommendations for the creation of a homogeneous curriculum for cancer in older people[13].

In Brazil, many initiatives in geriatric oncology began to appear in the last two decades. Most of them have been undertaken in the southeast of the country and in the last 5 years expanding to the center and northeast of the country. In 2012, the Cancer Institute of the State of São Paulo (ICESP) established a geriatric oncology program that employs four geriatricians full-time and provides training for medical residents and fellows in both geriatrics and oncology[7,14]. In 2013, the geriatric oncology outpatient service was also created at the Clinics Hospital of the Faculty of Medicine of Ribeirão Preto to care for older people with cancer and support medical oncologists in therapeutic decision-making. Both services are linked to the University of São Paulo and the public health system and develop assistance, teaching, and research activities. There are other geriatric oncology clinics that are located at private hospitals in São Paulo, such as Sírio-Libanês Hospital, Israelita Albert Einstein Hospital, A.C. Camargo Cancer Center, and Prevent Senior Health System, or in public hospitals as Institute of Integral Medicine Professor Fernando Figueira (IMIP) that is located in Recife, in the northeast of the country. Most of these clinics follow an interconsultation model, in which specialized geriatricians perform geriatric assessment-based recommendations to referring oncologists[14]. Recently, a national survey aimed at understanding the geriatric knowledge of oncology professionals in the country was designed and administered using a web-based platform. Notably, 60% of respondents reported having a population of older patients in their clinics between 26 and 50%, and 65% of them believed that chronological age should not be the single factor determining treatment initiation in an older patient. However, most participants (70%) didn't have a geriatrics program at their institution[15].

In 2011, with the support of the Brazilian Society of Clinical Oncology (SBOC) and the Brazilian Society of Geriatrics and Gerontology (SBGG), the first international symposium of geriatric oncology took place in São Paulo. In 2012, the first national book on geriatric oncology was published. However, just in 2020, a commission of geriatricians who work caring the older people with cancer across the country was formed by SBGG with the main objective of developing a competency matrix that determines the skills required for geriatricians regarding the care of older with cancer, especially geriatricians in training, to be used in various geriatrician training centers across the country. The objective of this matrix would be to guarantee the quality of care and safety of older patients with cancer. The secondary objectives of this commission were disseminating basic scientific knowledge in geriatric oncology to health professionals who treat the older population, promoting educational actions on prevention, diagnosis, and treatment of oncological diseases in this population, and promoting the integration between the different societies involved in the care of older people with cancer in the country.

The implementation of a geriatric oncology service is challenging in both high-income countries and low-income countries, as there is a significant demand for economic and human resources needed for structure and training[14]. A recent publication by the geriatric oncology service of the ICESP raises the importance of initiatives for better interdisciplinary integration between the specialties of geriatrics, oncology, radiology, and surgery in the treatment of older people with cancer[16].

THE ROLE OF THE GERIATRICIAN IN THE CARE OF THE OLDER WITH CANCER

Management of older patients with cancer is often complex. As the aging process is multifactorial and does not occur in the same way in all individuals, the older population is quite heterogeneous in several aspects. Thus, chronological age does not reflect biological or functional age and should not be the only factor to be considered when making decisions about cancer treatment for older people[6].

The impact of cancer and its treatment on the older can be significant, depending on factors such as functionality, cognition, emotional profile, socioeconomic status, nutritional status, presence of comorbidities, and drug use profile, in addition to individual values and preferences[17].

Some studies have shown that traditional functional assessments in oncology, such as Karnofsky performance status (KPS) or Eastern Cooperative Oncology Group (ECOG) performance status scores, are not accurate enough to predict outcomes in older adults with cancer[18,19]. Thus, the Comprehensive Geriatric Assessment (CGA), a systematized process well known to geriatrics and gerontology professionals for the multidimensional assessment of the older, has come to be widely studied in the scenario of cancer treatment and in aid to decision-making in geriatric oncology, with detailed evaluation of domains such as functionality, cognition, comorbidities, medications in use, nutritional status, psychological status and social support, as well as estimates of life expectancy and risk of toxicity to chemotherapy[17,20,21]. The main instruments used in the implementation of the AGA are listed in Table 1.

The use of CGA in oncology has been shown to be beneficial in several studies, allowing better identification of areas of greater vulnerability or fragility and helping to predict the

Table 1. Domains in a comprehensive geriatric assessment.

Domain	Geriatric assessment tool	Intervention for positive finding
Functional status	Self-reported: - Activities of daily living (ADLs) - Instrumental activities of daily living (IADLs) - Falls Objective tests: - Timed up and go test (TUG) - Gait speed - Short physical performance battery (SPPB)	- Mobility and health aids - Home safety equipment - Promote physical activity - Physical therapy and rehab
Comorbidity	- Charlson Comorbidity Index (CCI) - Cumulative index rating scale (CIRS) - Adult comorbidity evaluation-27 (ACE-27)	- Comorbidity management - Referral to geriatrician - Clarify goals of care
Social functioning and support	- Medical outcomes study (MOS) survey - RAND health survey	- Consult social work - Consult financial services
Cognition	- Mini-cog - Mini-mental state examination (MMSE) - Blessed orientation memory concentration (BOMC) test - Montreal Cognitive Assessment (MoCA)	- Counseling - Assess inappropriate medications - Evaluate capacity - Referral to geriatric neuropsychologist
Psychological	- Mental health inventory distress thermometer - Geriatric Depression Scale-4 (GDS-4) - Patient health questionnaire-2 (PHQ-2)	- Cognitive behavioral therapy - Non-pharmacologic approaches (meditation) - Antidepressants - Referral to a geriatric psychiatrist
Nutrition	- Body mass index (BMI) - Mini nutritional assessment (MNA) - Malnutrition universal screening tool (MUST)	- Address factors contributing to malnutrition - Address chemotherapy-induced adverse effects such as nausea/vomiting - Oral care - Supplemental nutrition - Refer to a dietician
Polypharmacy	- Beers criteria - Medication - Appropriateness Index (MAI) - STOPP/START criteria	- Medication reconciliation - Evaluate adherence - Evaluate drug interactions - Deprescribing - Home health for medication management

Adapted from Kapoor and Arora[20].

risk of negative outcomes, toxicity to cancer treatment, functional impairment, and mortality[18,20].

Functional dependence on instrumental activities of daily living is associated with worse outcomes throughout treatment and reduced overall survival in several types of cancers. Among the negative outcomes found are a higher risk of additional functional loss and toxicity to treatment, as well as a higher rate of treatment interruption. Reduction in gait speed is associated with a higher risk of mortality, unplanned hospitalizations, and visits to urgent and emergency departments. Decreased handgrip strength is associated with worse survival[18,20,22]. In an important study that aimed to evaluate the main risk factors for chemotherapy toxicity, the measures of functional capacity were predictors of high risk for falls in the last 6 months, limitations to walk one block, need for assistance to take medications, and decrease in social activities[19].

Cognitive decline in older adults is associated with a higher risk of all-cause mortality, including cancer mortality, and is associated with poor medication adherence in any health setting. Low scores on cognitive assessment tests, such as the Mini-Mental State Examination (MMSE), have been shown to be an independent risk factor for unplanned hospitalization and discontinuation of cancer treatment in several types of cancer[18,20,22].

Malnutrition and increased risk of nutritional impairment identified by the Mini Nutritional Assessment (MNA) scale, especially reduced food intake in the last 3 months, are associated with a higher risk of toxicity and low tolerance to chemotherapy, early discontinuation of cancer treatment, loss of functionality, prolonged hospitalizations, impaired quality of life, and lower survival[18,20,22].

In older cancer patients, comorbidities can complicate the diagnosis and treatment of cancer. The presence of comorbidities is associated with worst survival in older cancer patients, a higher risk of toxicity to chemotherapy, a higher rate of hospitalization, and early discontinuation of cancer treatment[18,20,23].

Depression is quite prevalent in older people with cancer and can affect up to 30% of patients. It may be associated with a higher risk of functional and cognitive impairment during cancer treatment[18,20,22,23].

The presence of polypharmacy in older adults with cancer is associated with a higher risk of falls, frailty, postoperative complications, chemotherapy toxicity, increased healthcare costs, and mortality. The absence of social support or insufficient support was identified as a predictor of mortality in older adults with cancer[18,20,22].

Recent randomized controlled trials evaluating the impact of CGA-guided geriatric interventions have demonstrated important benefits such as reduced severe toxicity to chemotherapy, reduced rates of treatment interruption due to toxicity, reduced unplanned hospitalization, and higher rates of advance directives. Thus, the results of the AGA help not only to inform patients and families about the risks and benefits of cancer treatment, aiding in shared decision-making processes, but also to promote appropriate interventions, counseling, and referrals, improving the journey of older patients throughout their cancer treatment[21,23,24].

GERIATRIC ONCOLOGY PERSPECTIVES

Despite the evidence about the benefits of using the CGA in the care of patients with cancer, there are points to explore and challenges to overcome. Most studies include patients with solid tumors and lymphoma who received cytotoxic treatment and there is evidence about the role of the CGA in the context of immunotherapy, targeted therapy, bone marrow transplant, and cell therapy. Furthermore, the CGA is important in the beginning of the cancer treatment. However, no data indicate what is the best interval time to reassess the patient during the cancer treatment[21].

In addition to the complexity of older patients and the peculiarities of cancer treatment in this population, oncologists and geriatricians still need to deal with the challenge of little scientific evidence related to the treatment of older people with cancer, especially those over 75 years of age. There is still a significant underrepresentation of older people in clinical trials that establish standards for oncological care, making it difficult to extrapolate results to the older population[25]. In the coming years, it is expected that more older people will be included in clinical trials and that functional and quality of life outcomes will also be evaluated, in addition to survival[26].

From a practical point of view, there are barriers to implementing geriatric oncology services such as the lack of qualified geriatricians and the lack of oncologist's knowledge about the role of geriatricians in the care of older patients with cancer. According to the National Council of Medicine, as of 2014, there were 1405 geriatricians practicing throughout Brazil, which translates to an average of 0.7 geriatricians per 100,000 inhabitants. At the same time, the number of certified oncologists was 3409, translating into an average of 1.7 oncologists per 100,000 inhabitants[27].

Because there are multiple tools, geriatric scales, and recommendations, it is mandatory to develop a standard objective language to avoid ambiguous interpretations that may hinder information integration and patient care[28].

CONCLUSION

As life expectancy increases, the number of older patients with cancer will certainly continue to rise in Brazil and healthcare systems throughout the country will be forced to respond to this situation in a timely manner. Although, in Brazil, geriatric oncology is still at a very early stage, there is a great opportunity to develop resources and research for the creation and implementation of novel models of care that meet the needs of the older population with cancer in the country.

Given the above, geriatric oncology emerged as an area of activity for oncologists and geriatricians to provide better care for older people with cancer and has been growing exponentially in recent years. This is an area of activity that aims to develop more integrated therapeutic strategies that allow the creation of an individualized geriatric care plan. This integration allows for a more careful and comprehensive assessment of older people with cancer and ensures that age is not a factor of discrimination in access to oncological treatment, in addition to improving clinical outcomes and quality of life through geriatric interventions that, many sometimes, they would not be performed or would go unnoticed in the usual oncological evaluation.

AUTHORS' CONTRIBUTIONS

TK: Conceptualization, Writing – original draft, Writing – review & editing. **PMRS:** Writing – original draft. **ALK:** Writing – original draft. **LC:** Writing – original draft. **MRB:** Writing – original draft. **OLSA:** Methodology, Writing – original draft, Writing – review & editing.

REFERENCES

1. World Health Organization (WHO). Cancer. What is cancer? Geneva: WHO; 2023. [cited on 2023 Oct 15]. Available from: https://www.who.int/health-topics/cancer#tab=tab_1
2. Instituto Nacional de Câncer (Brasil). Estimativa 2023: incidência de câncer no Brasil / Instituto Nacional de Câncer. Rio de Janeiro (RJ): INCA; 2022.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
4. Yancik R. Population aging and cancer: a cross-national concern. Cancer J. 2005;11(6):437-41. https://doi.org/10.1097/00130404-200511000-00002
5. International Agency for Research on Cancer, World Health Organization. Cancer today. Geneva: WHO; 2023. [cited on 2023 Oct 15]. Available from: https://gco.iarc.fr/today/home
6. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32(24):2595-603. https://doi.org/10.1200/JCO.2013.54.8347
7. Karnakis T, Gattás-Vernaglia IF, Saraiva MD, Gil-Junior LA, Kanaji AL, Jacob-Filho W. The geriatrician's perspective on practical aspects of the multidisciplinary care of older adults with cancer. J Geriatr Oncol. 2016;7(5):341-5. https://doi.org/10.1016/j.jgo.2016.07.001
8. Yancik R, Ries LA. Cancer in older persons: an international issue in an aging world. Semin Oncol. 2004;31(2):128-36. https://doi.org/10.1053/j.seminoncol.2003.12.024
9. Fentiman IS, Tirelli U, Monfardini S, Schneider M, Festen J, Cognetti F, et al. Cancer in the elderly: why so badly treated? Lancet. 1990;335(8696):1020-2. https://doi.org/10.1016/0140-6736(90)91075-I
10. Monfardini S, Balducci L, Overcash J, Aapro M. Landmarks in geriatric oncology. J Geriatr Oncol. 2021;12(7):991-4. https://doi.org/10.1016/j.jgo.2021.02.015
11. Reiter R, Diraoui S, Noortgate N, Cruz-Jentoft AJ. How to become a geriatrician in different European countries. Eur Geriatr Med. 2014;5:347-51. https://doi.org/10.1016/j.eurger.2014.07.008
12. Dittrich C, Kosty M, Jezdic S, Pyle D, Berardi R, Bergh J, et al. ESMO / ASCO recommendations for a global curriculum in medical oncology edition 2016. ESMO Open. 2016;1(5):e000097. https://doi.org/10.1136/esmoopen-2016-000097
13. Foubert J, Faithfull S. Education in Europe: are cancer nurses ready for the future? J BUON. 2006;11(3):281-4. PMID: 17309150
14. Soto-Perez-de-Celis E, Cordoba R, Gironés R, Karnakis T, Paredero I, Chavarri-Guerra Y, et al. Cancer and aging in Ibero-America. Clin Transl Oncol. 2018;20(9):1117-26. https://doi.org/10.1007/s12094-018-1844-1
15. Karnakis T. How is geriatric oncology perceived in Brazil? A national survey. 1st Brazilian oncology week. Rio de Janeiro (RJ); 2017.
16. Karnakis T, Kanaji AL, Gattás-Vernaglia IF, Adriazola IO, Ramos PT, Lima MEPLS, et al. Ten years of a geriatric oncology service at a public university cancer centre in Brazil. Ecancermedicalscience. 2023;17:1596. https://doi.org/10.3332/ecancer.2023.1596
17. Chapman AE, Elias R, Plotkin E, Lowenstein LM, Swartz K. Models of care in geriatric oncology. J Clin Oncol. 2021;39(19):2195-204. https://doi.org/10.1200/JCO.21.00118
18. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol. 2018;36(22):2326-47. https://doi.org/10.1200/JCO.2018.78.8687
19. Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. J Clin Oncol. 2016;34(20):2366-71. https://doi.org/10.1200/JCO.2015.65.4327
20. Kapoor V, Arora SP. Geriatric assessments tools for every oncologist to stage the aging when caring for older adults with cancer. Adv Oncol. 2022;2:81-97.
21. Dale W, Klepin HD, Williams GR, Alibhai SMH, Bergerot C, Brintzenhofeszoc K, et al. Practical assessment and management of vulnerabilities in older patients receiving systemic cancer therapy: ASCO guideline update. J Clin Oncol. 2023;41(26):4293-312. https://doi.org/10.1200/JCO.23.00933

22. Mohile SG, Velarde C, Hurria A, Magnuson A, Lowenstein L, Pandya C, et al. Geriatric assessment-guided care processes for older adults: a Delphi consensus of geriatric oncology experts. J Natl Compr Canc Netw. 2015;13(9):1120-30. https://doi.org/10.6004/jnccn.2015.0137

23. Mohile SG, Mohamed MR, Xu H, Culakova E, Loh KP, Magnuson A, et al. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. Lancet. 2021;398(10314):1894-904. https://doi.org/10.1016/S0140-6736(21)01789-X

24. Li D, Sun CL, Kim H, Soto-Perez-de-Celis E, Chung V, Koczywas M, et al. Geriatric assessment-driven intervention (GAIN) on chemotherapy-related toxic effects in older adults with cancer: a randomized clinical trial. JAMA Oncol. 2021;7(11):e214158. https://doi.org/10.1001/jamaoncol.2021.4158

25. Hurria A, Balducci L. Geriatric oncology: treatment, assessment and management. New York (NY): Springer Science & Business Media; 2009.

26. Hurria A, Dale W, Mooney M, Rowland JH, Ballman KV, Cohen HJ, et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J Clin Oncol. 2014;32(24):2587-94. https://doi.org/10.1200/JCO.2013.55.0418

27. Conselho Federal de Medicina. Medical demographics 2015 (in Portuguese). 2023. [cited on 2023 Oct 24]. Available from: https://portal.cfm.org.br/index.php?option=com_content&view=article&id=25874

28. Monfardini S, Perrone F, Balducci L. Pitfalls in oncogeriatrics. Cancers (Basel). 2023;15(11):2910. https://doi.org/10.3390/cancers15112910

REVIEW ARTICLE

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Kidney care in patients with cancer: perspectives from the onconephrology committee of the Brazilian Society of Nephrology

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Brazilian Society of Nephrology

INTRODUCTION

The number of new cases of cancer is expanding worldwide, with a projection of 28.4 million cases in 2040, an increase of 47% compared to 2020[1]. Conversely, global 5-year relative cancer survival has increased from 50% in 1975 to approximately 70% in 2014 due to early cancer diagnosis[2]. In consequence, there is an unprecedented population of cancer patients under treatment and follow-up in high-, middle-, and low-income regions.

Cancer incidence has been increasing in Latin American countries, such as Brazil. The Brazilian National Cancer Institute (INCA) estimates 704,000 new cancer cases per year for the period 2023–2025[3]. In Brazil, cancer diagnosis and treatment are usually concentrated in tertiary centers located in large metropolitan areas, which are able to provide access to essential cancer treatments such as surgery, standard chemotherapy, radiotherapy, and palliative care. For instance, the south and southeast regions, which have better socioeconomic status, account for about 70% of cancer incidence due to greater access to cancer screening exams and more robust cancer registries compared to lower-income areas of the country[3]. Despite local disparities, Brazil has shown a significant improvement in the quality and availability of data about cancer, an expansion in the number of cancer centers, and a substantial improvement in anticancer treatment.

INTERPLAY BETWEEN CANCER AND KIDNEY CARE: MAIN ASPECTS OF KIDNEY CARE IN PATIENTS WITH CANCER

The rapid advancement of new therapies in recent years has substantially enhanced the survival prospects of cancer patients, prompting a multifaceted intersection between nephrology and oncology. Nephrologists are increasingly encountering different aspects of this interrelation, such as patients with chronic

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Members of the Onconephrology Committee of the Brazilian Society of Nephrology

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kidney disease (CKD), kidney transplant recipients who are diagnosed with cancer, and patients who may also experience acute kidney injury (AKI), electrolyte imbalances, and proteinuria. These manifestations can arise from the cancer itself or the therapies employed (Table 1)[4].

Acute kidney injury in patients with cancer

Acute kidney injury is a common complication in cancer patients, and its incidence is dependent on the type of cancer, ongoing treatment, and patient's comorbidities or clinical events, ranging from 11 to 22%. Patients in intensive care units (ICUs) are at a higher risk of AKI, as are those undergoing hematopoietic stem cell transplantation (HSCT). Some specific points in the evaluation of patients with AKI and cancer include:

1. Diagnosis of high-risk neoplasms for AKI such as symptomatic multiple myeloma, bladder cancer, and leukemia[5].
2. Evaluate the risk of obstructive uropathy or local complications associated with the cancer.
3. Assess the risk of tumor lysis syndrome, an urgent medical situation due to the potential for life-threatening arrhythmias, respiratory failure, and AKI[6].
4. Consider any prior medical procedures that might have reduced renal mass, such as nephrectomies or other ablative treatments.
5. Review the patient's history of exposure to chemotherapy agents and other therapies. Conventional chemotherapies still play a central role in the treatment of many cancer types and are known to promote vascular, glomerular, and tubular injuries[6]. Cisplatin is associated with a significant incidence of AKI, reported in 32% of adults receiving a single dose[7]. Immune checkpoint inhibitors (ICPis) enhance the activity and proliferation of cytotoxic T cells, leading to acute tubulointerstitial nephritis in most AKI cases[8]. AKI occurs in 19–24% of patients treated by CAR-T cell therapies[9].
6. Check for the use of nononcologic medications with nephrotoxic potential, like nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and proton pump inhibitors (PPIs)[10].

Electrolyte disorders in patients with cancer

Among patients diagnosed with cancer, hyponatremia stands out as the most prevalent electrolyte disturbance, and there is a clear relationship between serum sodium levels, hospital stay, and mortality[11]. Syndrome of inappropriate antidiuretic hormone (SIADH) secretion is the leading cause of hyponatremia in this population, and when directly linked to cancer, it often results from increased ADH production

Table 1. Clinical issues related to kidney care in cancer patients.

Acute kidney injury
Volume depletion: vomiting, diarrhea
Sepsis and septic shock
Surgery-related kidney injury
Severe electrolyte disorders
Hyponatremia
Hypercalcemia
Hypo/hyperkalemia
Renal toxicity of non-chemotherapeutic drug treatments
Analgesics
Opioids
Antibiotics
Biphosphonates
Pump proton inhibitors
Onco-urology
Obstructive uropathy
Post-nephrectomy AKI and CKD
Radiofrequency and cryoablation of kidney mass
Post-cystectomy kidney dysfunction
Post-TURP syndrome
Management of CKD patients
Use of ESA
Management of hypertension
GFR estimation: equations based on SCr vs. measured GFR through exogenous markers
Modifications of dosing of chemotherapy in patients with CKD and ESRD
Issues related to kidney transplantation
Assessment of cancer risk and cancer screening strategies in transplanted patients
Management of immunosuppression in transplanted patients with cancer
Transplantation in cancer patients after cancer treatment
Management of proteinuria
Kidney infiltration by cancer disease
Tumor or tumor treatment-related microangiopathies and GN
Radiotherapy-induced kidney injury
Management of radiotherapy in ESRD patients
Tumor lysis syndrome
Myeloma-related kidney injury

AKI: acute kidney injury; CKD: chronic kidney disease; TURP: transurethral resection of the prostate; ESA: erythropoiesis stimulating agents; GFR: glomerular filtration rate; SCr: serum creatinine level; ESRD: end-stage renal disease; GN: glomerulonephritis.

due to primary or metastatic neoplasms affecting the lungs or brain. Decreased oral intake and gastrointestinal losses in those patients can also contribute to hyponatremia, hypernatremia, hypomagnesemia, hypokalemia, and hypophosphatemia[12]. Hypercalcemia is also a common electrolyte complication seen in cancer patients, occurring in up to 30% of cases. It is essential to emphasize that successful treatment of these conditions hinges on addressing the cancer itself[13]. The renal effects of chemotherapy and targeted therapies, including their direct tubular effects, can induce losses of potassium, magnesium, and phosphate in the kidneys. Therefore, it is imperative to monitor these ions during therapy[14].

Chronic kidney disease and cancer

Chronic kidney disease is common in patients with cancer, with more than half of patients with solid tumors reportedly having an estimated glomerular filtration rate (GFR) (eGFR) of less than 90 mL/min/1.73 m^2. Most of these patients have stage 2 (eGFR, 60–89 mL/min) or 3 (eGFR, 30–59 mL/min) (40–50% and 15–20%, respectively) CKD[15].

Chemotherapy medications are often metabolized by the kidneys, making the accurate estimation of GFR one of the primary challenges in the kidney care of these patients. It is essential to determine the proper dosage of medications, including chemotherapy, in order to avoid excessive kidney and systemic toxicity or underdosing and compromise of cancer outcomes[14].

Other clinically relevant aspects of routine care for CKD patients, such as the management of anemia, treatment of hypertension, diabetes, and mineral bone disease, should be tailored to the cancer scenario (Table 1). Patients considered to be cured, without active cancer disease, and with expected survival long enough to benefit from specific interventions should be treated in a similar manner as CKD patients without cancer. These patients are suitable for more intensive blood pressure control, glycemic levels, and strategies to prevent CKD progression. Conversely, patients with reduced survival should be managed, prioritizing control of symptoms and prevention of acute complications such as hyperkalemia, acidosis, and congestion.

Transplantation and oncology

Kidney transplantation offers a new lease on life for individuals with end-stage renal disease. However, it also introduces unique challenges, particularly concerning cancer risk. Transplant recipients are at an increased risk of developing certain cancers due to long-term immunosuppressive therapy. As a result, regular screenings to detect cancer at an early, treatable stage and vigilant monitoring for post-transplant lymphoproliferative disorder (PTLD) and other hematologic malignancies are part of the interplay between nephrologists and oncologists[16].

The timing of transplantation in patients with a prior history of malignancy remains another topic of considerable debate. With the ongoing rapid advancements in cancer treatments, transplant centers should revisit their existing protocols for establishing pretransplant waiting periods for cancer-free status[17].

On the other hand, when cancer is diagnosed in kidney transplant recipients, the challenge lies in finding a balance between managing cancer effectively and preserving the transplanted kidney. Additionally, immunosuppressive regimens may need to be modified or temporarily withdrawn during cancer treatment[16].

ONCONEPHROLOGY GLOBALLY

Thanks to a worldwide effort, led mainly by centers in North America and Europe, a considerable amount of information has been accumulated in the last few years in the onconephrology scenario. Several initiatives in assistance, education, and research areas have been developed worldwide, which are crucial to moving this field forward.

Onconephrology fellowships

One of the most critical initiatives in the field was the development of training programs. Currently, there are six onconephrology fellowship programs in North America—five in the United States (US) and one in Canada[18]. The programs include outpatient clinics and inpatient rotations in the hematology, oncology, palliative care, and oncopharmacology groups, as well as research activities, highlighting the close working relationship between oncologists, hematologists, and nephrologists as part of a multidisciplinary team[19]. Although onconephrology fellowships are still lacking in South America and other regions of the globe, the inclusion of onconephrology rotations and a dedicated education program have been included as core curriculum in general nephrology fellowships, such as the Nephrology Fellowship Program from the University of São Paulo School of Medicine in Brazil.

Onconephrology centers

One crucial step in this field was the development of well-designed onconephrology centers and clinics, such as the one led by M. Gallieni and collaborators in Milan[20]. The working team includes nephrologists, hematologists, oncologists, a dedicated data manager, and a nursing care coordinator with specialized training in onconephrology. The assistance is grounded in multidisciplinary meetings incorporating urologists, radiation

therapists, pathologists, radiologists, palliative care providers, and others for case management and guided by dedicated protocols and a set of performance indicators. Since onconephrology is presently more experience-based than evidence-based, these centers are successful models of addressing onconephrological issues in a dedicated setting with a tight interspecialty collaboration, able to provide better kidney care for patients with cancer.

Onconephrology societies and working groups

In the onconephrology field, a number of medical societies and working groups have been created in recent years. The most robust was the American Society of Onconephrology (ASON), launched in the US in 2021, including nephrologists from multiple countries worldwide. Since its creation, ASON has established a partnership with the International Society of Nephrology, leading to active collaborations with nephrology societies across the globe, including Asia, Africa, and South America. ASON has created several research groups aiming to enhance scientific collaboration among its members and developed an agenda of research topics, apart from a relevant role in spreading scientific content (papers, talks, and podcasts) through its communication channels (website, Twitter account, and Instagram) to educate the nephrology community on onconephrology topics. Scientific discussions, webinars, and scientific meetings are freely advertised. ASON is also working on position statement documents to offer guidance to health professionals on critical aspects related to the kidney care of patients with cancer and has developed an initiative to support cataloging the renal toxicities of anticancer therapies[21].

The increase in onconephrology research and education initiatives is also observed in Europe. The Onconephrology Research Group of French Speaking Language has developed several activities and published many papers[22]. In Spain, a working group called "onconephrology" has been created by the Spanish Society of Nephrology. The working group holds regular meetings, and multicenter collaborative projects are proposed in different hospitals with onconephrology units, combined with training courses for nephrologists[23]. The Portuguese Society of Nephrology has created a similar working group[24]. As mentioned earlier, Galliani's group has been a leading team in onconephrology research and assistance in Italy.

Journals, meetings, and other initiatives

The number of papers published in high-impact journals addressing topics in the onconephrology field has dramatically increased, with some special editions in a few over the years. In 2017, the Journal of Onconephrology, the first peer-reviewed periodic exclusively devoted to the topic, was released and is now a major reference for onconephrologists[25]. Every year, an international symposium on onconephrology, now organized by the ASON leadership, takes place in academic institutions in the US, gathering the foremost researchers at a global level. In parallel, symposiums, premeetings, and scientific and poster sections are now routine at the American Society of Nephrology meetings, the World Congress of Nephrology, and other top nephrology congresses worldwide.

Despite these exciting and unprecedented steps on a global level, onconephrology is still an incipient field in Latin American countries such as Brazil, which face local challenges in the kidney care of patients with cancer.

CHALLENGES AND PRIORITY INITIATIVES FROM THE ONCONEPHROLOGY COMMITTEE OF THE BRAZILIAN SOCIETY OF NEPHROLOGY TO IMPROVE KIDNEY CARE IN FOR PATIENTS WITH CANCER IN BRAZIL

Brazil is a country of continental dimension, with a population of 220 million people, in which 90% of cancer treatment relies on the public health system, struggling with financial limitations to fund appropriate care and research. Additionally, cancer treatment is concentrated in large cancer centers located in major cities, especially in the south and southeast regions, where nephrology training usually occurs, contributing to geographic disparities in kidney care.

The increasing number of cancer patients under treatment in the country is leading to an unprecedented and unmet demand for nephrologists with experience and training in onconephrology in order to appropriately treat patients with cancer and kidney diseases. Unfortunately, the opportunities available for onconephrology education and research in Brazil are scarce. There are only a few onconephrology groups working in cancer centers; there are no onconephrology fellowship programs; rotations in onconephrology during nephrology fellowships are rare; and research projects in the field are still incipient. To face these challenges, the Brazilian Society of Nephrology (SBN) officially created an onconephrology committee with the mission of developing initiatives to promote onconephrology education and research in the country. The committee gathers nephrologists with expertise in the care of cancer patients. This is the first working group devoted to the onconephrology field attached to a medical or nephrology association in Latin America, and the committee is currently organizing the first onconephrology

premeeting within an SBN Congress in 2024 and is working in partnership with the ASON to collaborate in scientific activities.

The committee has identified six main education initiatives to improve the background and training of nephrologists in the onconephrology field (Figure 1): (1) Create onconephrology fellowships in large academic cancer centers grounded in a multidisciplinary collaboration with oncology, hematology, and urology services. These specialized doctors could work in sequence in smaller cities and rural areas in order to replicate their experience and educate doctors working locally. (2) Create onconephrology rotations in cancer services during nephrology and internal medicine fellowships across the country, which could be an effective entry for young doctors into the field. (3) Organize podcasts and online webinars to promote the discussion of clinical cases led by members of the committee with young nephrologists. These discussions will be advertised and supported by the SBN, available free of charge to the medical community, and may count on the collaboration of hematologists, oncologists, urologists, and nephrologists from cancer centers across the country and from the ASON. (4) Promote onconephrology courses that cover the most frequent topics in clinical practice, such as multiple myeloma, obstructive uropathy, the toxicity of new anticancer treatments, palliative care, and kidney transplant patients with cancer, on the SBN platform. Talks and audiovisual material should be free of charge and remain available online for consultation. (5) Develop onconephrology workshops in cancer centers and nephrology fellowship programs nationwide to discuss common topics in onconephrology clinical practice, participate in clinical rounds, and debate cases in clinical meetings. (6) Develop protocols that can guide clinicians and nephrologists on the most common questions and conditions related to the nephrology practice during the patient's journey with cancer in order to standardize routine practices.

The committee also elected six actions to stimulate research (Figure 2): (1) Create national and regional registries of common conditions leading to kidney impairment, such as multiple myeloma and obstructive uropathy, which suffer from a paucity of data. Accurate information on the incidence and prognosis of these diseases could provide valuable information to plan better management and tailored treatment strategies that could improve patients' prognosis. These data could also inform health policies by government agencies. (2) Develop clinical studies on relevant topics to our population, such as the nephrotoxicity of anticancer drugs and the assessment of kidney function. Most of the studies in the onconephrology field are developed in high-income countries, including North American and European patients, assessing interventions (e.g., expensive chemotherapy drugs) that are frequently unavailable in Brazil. Consequently, there is a paucity of clinical data to respond to local needs that can be applied to our distinct population profile. National clinical studies are fundamental

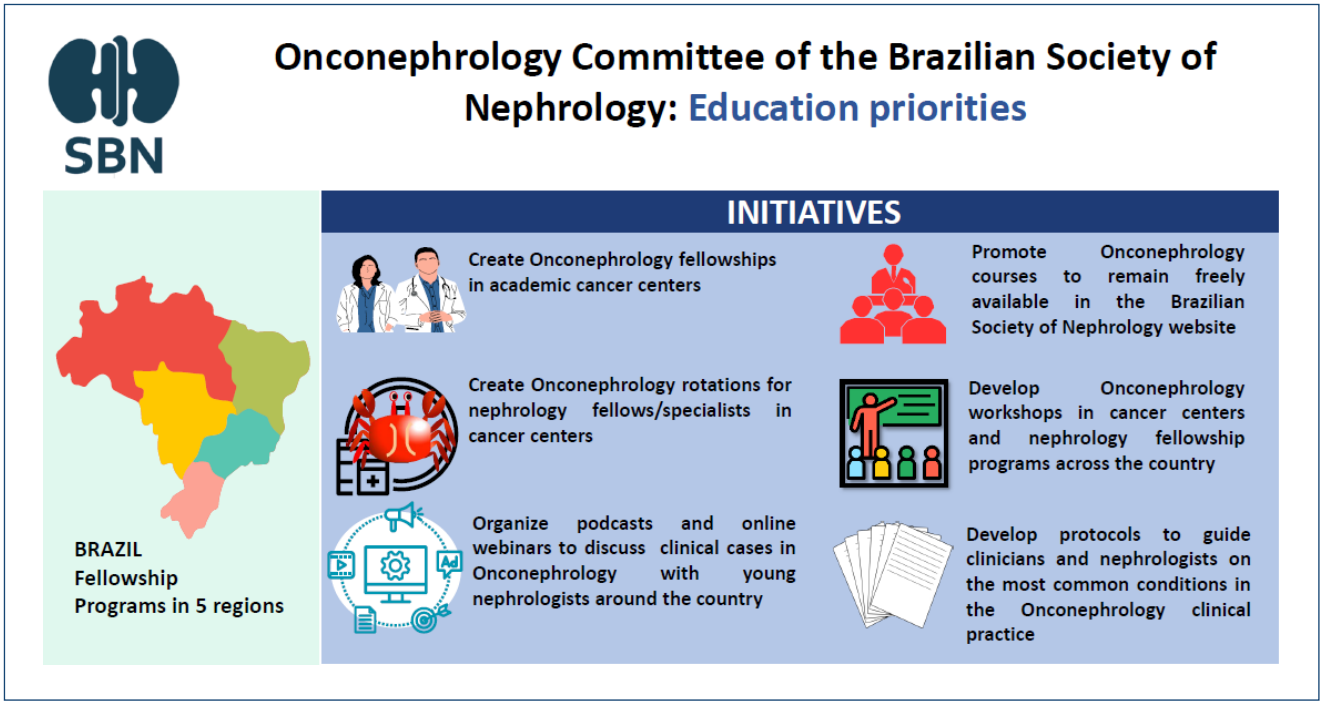

Figure 1. Education initiatives undertaken by the onconephrology committee of the Brazilian Society of Nephrology.

Figure 2. Research initiatives suggested by the onconephrology committee of the Brazilian Society of Nephrology.

to mitigating this drawback. (3) Implement research teams in Brazilian academic centers with onconephrology groups aiming to fund, train, and organize research teams capable of conducting well-designed projects. Research structure is still immature in a subspecialty as incipient as onconephrology. Well-established scientific groups can take the lead, gather graduate students from different geographic areas, educate junior investigators, consolidate expertise areas, and allow for increased funding. (4) Secure funds from national and international research institutions to support local projects that can provide funds to overcome local budget constraints. There is a shortage of funds for studies not sponsored by the pharmaceutical industry. Therefore, local research largely depends on public funding from government agencies. Partnerships with national and international private, nonprofit, or public research institutions can fill this gap. (5) Develop research partnerships with oncology and hematology societies inside and outside the country in order to share the same research and logistics structure, optimizing resources and enabling a multidisciplinary approach. (6) Guarantee the engagement of Brazilian leadership in international research guidelines, increasing the representation of these leaders in global discussions and guidelines.

The committee's main objectives are to minimize inequalities, train young nephrologists, and contribute to the improvement of onconephrology research in Brazil. Our efforts aim to involve onconephrology groups throughout the country to meet local needs and promote the establishment and growth of onconephrology as the new subspecialty in the war against kidney diseases. We hope these initiatives will improve kidney care, leading to better quality of life and the survival of cancer patients in Brazil.

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AUTHORS' CONTRIBUTIONS

GAB: Conceptualization, Writing – review & editing. **RAC:** Conceptualization, Writing – review & editing. **FOC:** Conceptualization, Writing – review & editing. **FLG:** Conceptualization, Writing – review & editing. **MFTC:** Writing – review & editing. **DFC:** Writing – review & editing. **ECC:** Writing – review & editing. **BJP:** Writing – review & editing. **MSDJ:** Writing – review & editing. **FA:** Writing – review & editing. **AMES:** Writing – review & editing. **VTCS:** Conceptualization, Supervision, Writing – review & editing.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
2. National Cancer Institute. Surveillance, epidemiology, and end results program. n.d. Available from: https://seer.cancer.gov/registries/terms.html
3. Instituto Nacional do Câncer (Brasil). Estimativa 2023: incidência de câncer no Brasil. 2023. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2023
4. Gupta S, Murakami N. Introduction: clinical innovations in onconephrology: what's new in 2023. Semin Nephrol. 2022;42(6):151350. https://doi.org/10.1016/j.semnephrol.2023.151350
5. Rosner MH, Perazella MA. Acute kidney injury in patients with cancer. N Engl J Med. 2017;376(18):1770-81. https://doi.org/10.1056/NEJMra1613984
6. Gupta S, Gudsoorkar P, Jhaveri KD. Acute kidney injury in critically Ill patients with cancer. Clin J Am Soc Nephrol. 2022;17(9):1385-98. https://doi.org/10.2215/CJN.15681221
7. Tang C, Livingston MJ, Safirstein R, Dong Z. Cisplatin nephrotoxicity: new insights and therapeutic implications. Nat Rev Nephrol. 2023;19(1):53-72. https://doi.org/10.1038/s41581-022-00631-7
8. Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int. 2016;90(3):638-47. https://doi.org/10.1016/j.kint.2016.04.008
9. Kanduri SR, Cheungpasitporn W, Thongprayoon C, Petnak T, Lin Y, Kovvuru K, et al. Systematic review of risk factors and incidence of acute kidney injury among patients treated with CAR-T cell therapies. Kidney Int Rep. 2021;6(5):1416-22. https://doi.org/10.1016/j.ekir.2021.02.013
10. Seethapathy H, Zhao S, Chute DF, Zubiri L, Oppong Y, Strohbehn I, et al. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. Clin J Am Soc Nephrol. 2019;14(12):1692-700. https://doi.org/10.2215/CJN.00990119
11. Workeneh BT, Jhaveri KD, Rondon-Berrios H. Hyponatremia in the cancer patient. Kidney Int. 2020;98(4):870-82. https://doi.org/10.1016/j.kint.2020.05.015
12. Rosner MH, Dalkin AC. Electrolyte disorders associated with cancer. Adv Chronic Kidney Dis. 2014;21(1):7-17. https://doi.org/10.1053/j.ackd.2013.05.005
13. Guise TA, Wysolmerski JJ. Cancer-associated hypercalcemia. N Engl J Med. 2022;386(15):1443-51. https://doi.org/10.1056/NEJMcp2113128
14. Yarandi N, Shirali AC. Onconephrology: core curriculum 2023. Am J Kidney Dis. 2023;82(6):743-61. https://doi.org/10.1053/j.ajkd.2023.04.014
15. Rosner MH, Sprangers B, Sandhu G, Malyszko J. Glomerular filtration rate measurement and chemotherapy dosing. Semin Nephrol. 2022;42(6):151340. https://doi.org/10.1016/j.semnephrol.2023.151340
16. Al-Adra D, Al-Qaoud T, Fowler K, Wong G. De novo malignancies after kidney transplantation. Clin J Am Soc Nephrol. 2022;17(3):434-43. https://doi.org/10.2215/CJN.14570920
17. Murakami N, Webber AB, Nair V. Transplant onconephrology in patients with kidney transplants. Adv Chronic Kidney Dis. 2022;29(2):188-200.e1. https://doi.org/10.1053/j.ackd.2021.09.002
18. American Society of Onconephrology. Onconephrology fellowship training. 2022. Available from: https://www.ason-online.org/team-3
19. Latcha S, Kala J, Leung N. An extra year of onco-nephrology fellowship training is required for the subspecialty: PRO. J Onco-Nephrol. 2020;5(1):31-4. https://doi.org/10.1177/2399369320965578
20. Cosmai L, Porta C, Perazella MA, Launay-Vacher V, Rosner MH, Jhaveri KD, et al. Opening an onconephrology clinic: recommendations and basic requirements. Nephrol Dial Transplant. 2018;33(9):1503-10. https://doi.org/10.1093/ndt/gfy188
21. Onconephrotoxins Library Collaboration. 2022. Available from: https://www.olic-app.info/about-1
22. GRIFON. Groupe de recherche interdisciplinaire francophone em onco-néphrologie. 2021. Available from: https://assogrifon.webnode.fr/
23. Alonso F, Auñón P, Cavero T, Salgueira M, Praga M, Quiroga B, et al. Monographic consultation of onconephrology. Rationale and implementation. Nefrologia (Engl Ed). 2021;41(2):154-64. https://doi.org/10.1016/j.nefroe.2021.04.006
24. Grupo de trabalho de Onconefrologia. n.d. Available from: https://spnefro.pt/sociedade/grupo-de-trabalho-de-onconefrologia
25. Journal of Onco-nephrology. 2024. Available from: https://journals.sagepub.com/home/jnp

REVIEW ARTICLE

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Palliative care in glioblastoma patients: a systematic review

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INTRODUCTION

Glioblastoma (GBM) is a type of brain tumor that belongs to the subgroup of gliomas. It is the most common malignant primary brain tumor in adults[1,2]. The average age at diagnosis is around 65 years, and the incidence rate is approximately 3.23 cases per 100,000 people[3]. The average life expectancy is 10–15 months, and the survival rate is estimated at 2 years in 25% of patients[3].

The standard treatment for newly diagnosed GBM became the Stupp protocol after its publication in 2005, leading to significant improvements in survival rates[4]. However, it's important to note that GBM remains incurable despite multimodal treatment approaches involving surgery, radiotherapy (RT), and chemotherapy (CT). This aggressive form of brain cancer can have a profound impact on various aspects of a person's life, resulting in a range of progressive and often concurrent symptoms such as headaches, hemiparesis, cognitive disorders, personality changes, and language difficulties. The complexity of these symptoms and problems can negatively affect the health-related quality of life (HRQoL) not only of patients but also of their relatives[3].

The fact that GBM patients have a progressive brain disease can seriously interfere with their ability to make their own treatment decisions. It is worth noting that soon after diagnosis, approximately half of glioma patients already encounter challenges in making treatment decisions, and this percentage tends to increase as the disease progresses toward its terminal stages[1]. Therefore, the importance of initiating advance care planning (ACP) and introducing GBM patients to palliative care (PC) early in the treatment process cannot be overstated[5-9]. There is evidence to suggest that early PC, coupled with structured ACP, with a focus on topics such as timely identification and treatment of disease-specific symptoms, can enhance the HRQoL for GBM patients and improve symptom management[7].

The purpose of this systematic review is to evaluate the quality of life of GBM patients, regardless of the treatment performed, with a specific focus on PC and end-of-life care.

This review will assess various dimensions of quality of life, including physical, psychological, and social well-being.

METHODS

We conducted a literature search encompassing the past 10 years, from October 2012 to October 2022, using terms such as "glioblastoma," "palliative care," "terminal care," "end-of-life care," "hospice," and "quality of life." The search was performed in multiple databases, including Cochrane, PubMed, LILACS, the Virtual Health Library, and EMBASE, resulting in the identification of 4,985 articles. From this pool, we selected only complete works published in the English language that were freely accessible, including completed clinical trials, literature reviews, systematic literature reviews, case-control studies, cross-sectional studies, and cohorts. No meta-analysis was found. We excluded case reports, case series, letters, and published abstracts. Duplicate titles were removed, leaving a total of 24 articles that met all the inclusion criteria.

The primary objective of this review is to evaluate the quality of life of GBM patients, focusing on PC and end-of-life care. As secondary objectives, we evaluated the communication of prognosis to patients and family members/caregivers, ACP, and care for patients, family members, and caregivers at the end of life.

RESULTS

Quality of life

The vast majority of studies do not use objective tools to assess HRQoL in GBM patients. Studies generally consider the following aspects to assess quality of life: performance status,

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pain, dyspnea, headache, swallowing disturbances, dysarthria, drowsiness, behavioral changes, depression, anxiety, spirituality, motor changes, seizures, visual changes, incoordination, language changes, sphincter changes, and being independent, among others. The heterogeneity of the studies becomes an important limitation for quality-of-life assessment[10-12].

Prognosis communication

Prognosis communication should start early in the trajectory of serious illnesses and be embedded in broader conversations about patients' priorities. However, it is observed that these conversations and PC occur near the end of life. Clear and frank conversations regarding the prognosis of GBM patients are associated with more goal-consistent care, a better quality of life, and better family coping[13].

In all cancer types, discussions about prognosis are difficult for patients, caregivers, and oncologists, but are particularly challenging in the GBM setting due to cognitive and functional decline. In a prospective study of patients with malignant glioma and their caregivers, only 40% of patients had a full understanding of their prognosis, while 69% of caregivers had full knowledge of the patient's prognosis[14]. Physicians need to communicate more clearly about aspects of prognosis to help patients and caregivers understand the importance of ACP. Studies have not yet clarified the ideal time to communicate the prognosis to GBM patients[14].

Advance care planning

Progressive cognitive decline in GBM patients can seriously interfere with the patients' ability to make treatment or care decisions. It is important to involve patients with glioma early in the disease trajectory in making decisions about future care, including treatment and end-of-life care. One way to achieve this is with ACP. Just as the optimal time for communicating the prognosis to GBM patients is not yet defined, there is also no universally agreed-upon timing for introducing ACP[7].

Healthcare professionals unanimously decided that the ideal time to offer ACP to patients would be after chemoradiation[7]. The main reason for this decision is that patients are still competent, have no cognitive decline early in the disease trajectory, and are therefore usually able to communicate their desires. However, family members believe that the best time is once the diagnosis is made. For patients, the best moment is divided mainly between the time of diagnosis, after chemoradiation and after six cycles of adjuvant CT (Figure 1)[7].

In patients with malignancies, advanced and systematic care planning has been associated with numerous benefits, including less aggressive end-of-life care, improved quality of life for both patients and caregivers, earlier involvement in PC, reduced psychological distress, care alignment with patient preferences, cost-effective care, and potentially improved survival. However, research in the context of GBM is limited. Much of the existing data encompass a broader population of malignant brain

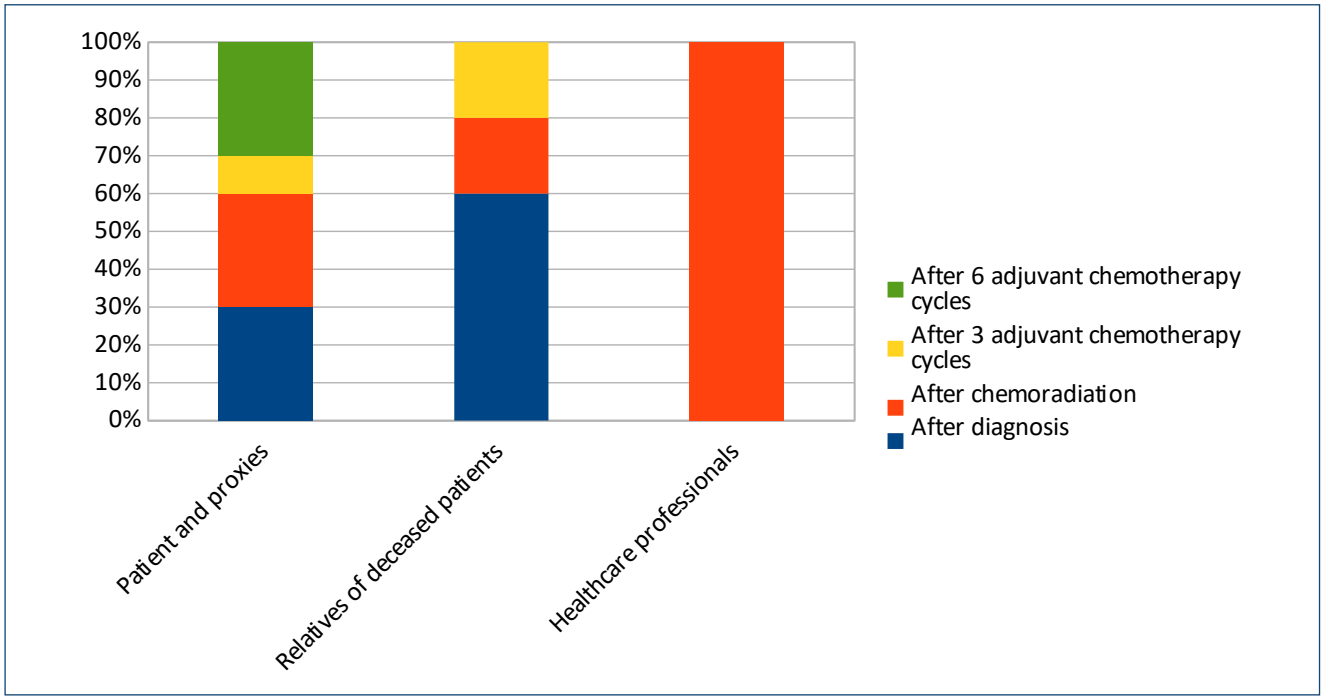

Figure 1. Preference for the moment of the disease trajectory in which the advance care planning program should be implemented (adapted from "Fritz et al.[7]").

tumors, making interpretation challenging due to variations in prognosis among different tumor types[15].

End-of-life care

For patients with incurable cancer, it is critical to provide end-of-life medical and psychosocial care that minimizes symptom burden and optimizes quality of life. At the end of life, GBM patients suffer a wide variety of neurological symptoms, including headaches, incontinence, and seizures, as well as non-neurological symptoms such as acute infection or pulmonary embolism. In one study, 20% of patients with malignant brain tumors were referred to PC 1 week before death, and 59% were referred within 30 days before death[16]. There is still no consensus on when the final stage of life begins in patients with glioma.

Fatigue was the most common symptom in GBM patients during the end of life, followed by a decreased level of consciousness and aphasia (Figure 2). Only 20% of patients remained fully independent in their mobility, reflecting the high need for care for GBM patients during the final stage of life[17].

A study demonstrated that CT frequently used among GBM patients close to death does not benefit survival and may even worsen these patients' quality of life[18]. It is reported that a quarter of patients do not die with dignity, which may be due to several factors, including inadequate training of the physicians and caregivers providing end-of-life care, inadequate healthcare environments in the terminal phase, and the patient's inability to communicate effectively[19].

One study confirmed that HRQoL and emotional well-being are affected not only in patients but also in family members.[20] In fact, relatives are more vulnerable before surgery in terms of mental health and emotional well-being than the patients themselves. Family members scored worse on items covering mental HRQoL and reported more frequent symptoms of anxiety and depression than GBM patients themselves (Figure 3)[20,21].

DISCUSSION

Quality of life is a complex entity that originates from the interaction between a person's values and expectations and their actual experience. It is defined as a multidimensional concept consisting of social, psychological, and physical phenomena. Fatigue, poor sleep quality, inability to concentrate, depression, financial burden, and impaired personal and social relationships significantly impact the quality of life for GBM survivors. Moreover, various domains of cognition, including sustained attention, long-term memory, mental flexibility, and executive functions, are notably impaired, thereby affecting these patients' personal, social, and professional lives. These impairments in cognitive functions are multifactorial, resulting from the tumor itself, the surgery, radiation therapy, and the effects of CT[22]. Cognitive deterioration is considered the main indicator of poor disease progression after treatment[23].

There was also an apparent correlation between tumor progression and the deterioration of HRQoL scores. This indicates that progression-free survival is not only a surrogate marker for survival but also for quality of life. Patients with persistent and progressive decline in HRQoL shortly after surgery may represent a subgroup with a worse prognosis, despite active

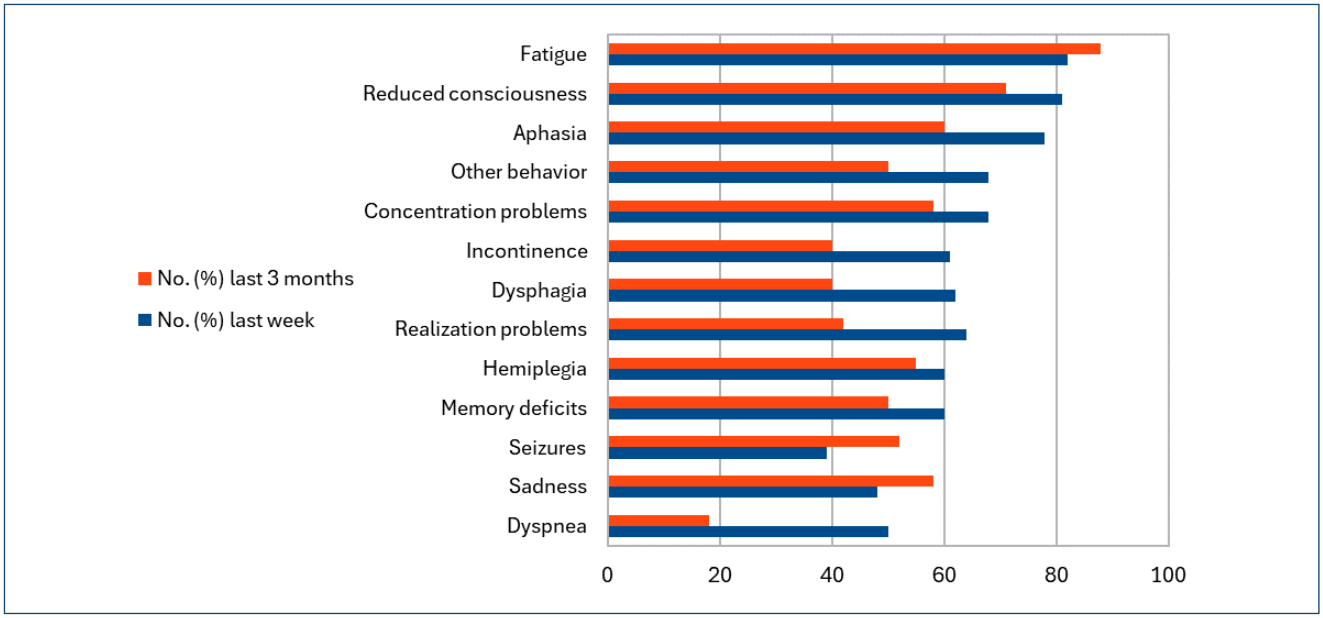

Figure 2. Symptoms reported during the last three months of life and the last week of life (adapted from "Flechl et al.[17]").

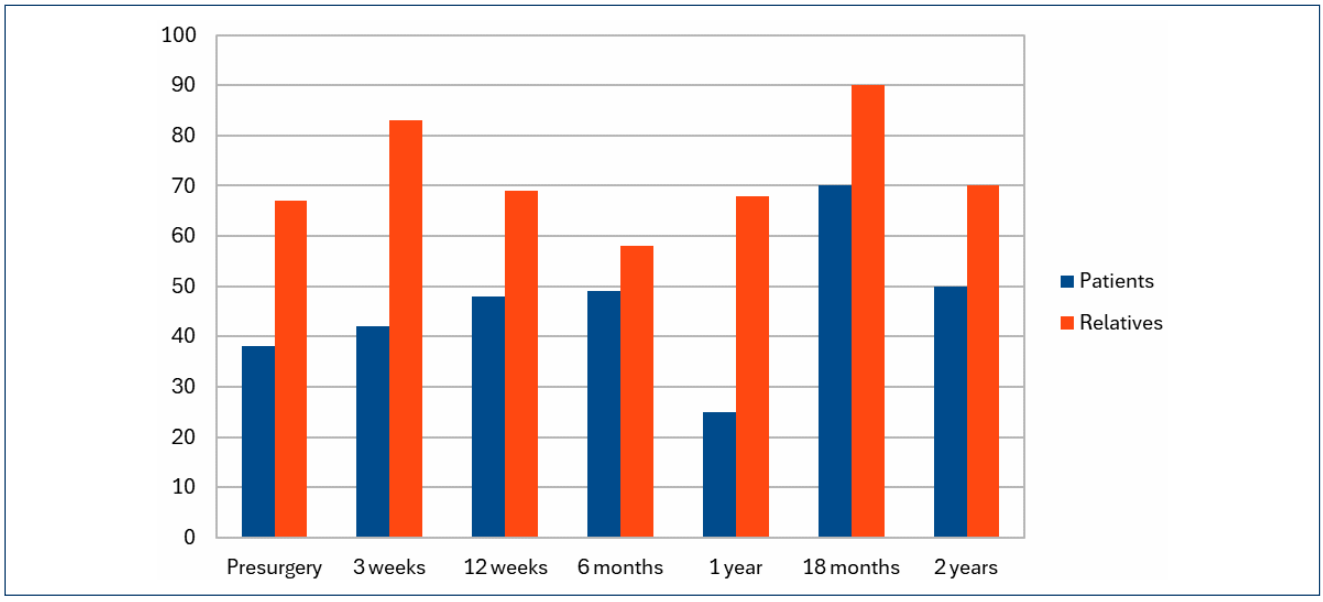

Figure 3. Percentage of patients and family members experiencing anxiety symptoms (hospital anxiety and depression scale ≥8) at different time periods (adapted from "Ståhl et al.[20]").

treatment. Independent predictors of better quality of survival at 1 year after diagnosis were high preoperative Karnofsky score and gross total resection, while preoperative cognitive symptoms were predictive of poorer quality of survival[24].

Many patients with high-grade glioma receive less PC than other cancer patients, despite the high symptom burden. An optimal model for integrating early PC into the treatment of gliomas has not been established. Patient screening to initiate PC is variable. The use of a PC screening tool can facilitate early referral to PC and improve patient outcomes in symptom management and quality of life[25].

Standard PC assessments have identified the primary burdens faced by GBM patients as psychosocial issues and increased dependence on care. These assessments should be supplemented with specific questions about neuropsychiatric symptoms and family caregiver burden, as both factors are of utmost importance and significantly influence the well-being of patients and their caregivers[26]. There is a pressing need to enhance the quality of life for both patients and caregivers, as they often have multiple supportive care needs. To address these needs effectively, a multidisciplinary approach focusing on ACP should be initiated as soon as the GBM diagnosis is established. This approach is considered the most suitable way to provide comprehensive treatment along with PC, which can improve the long-term quality of life for these patients and prevent unnecessary suffering at the end of life[26].

CONCLUSION

There are still relatively few studies that specifically address the quality of life in GBM patients, and most of these studies tend to assess quality of life subjectively. This underscores the importance of developing a standardized scale for assessing the quality of life in future studies involving these patients. Early PC is crucial for GBM patients and their families, as it helps preserve quality of life despite aggressive tumor progression even with current therapies.

AUTHORS' CONTRIBUTIONS

LHC: Conceptualization, Formal Analysis, Methodology, Project administration, Writing – original draft. **CF:** Conceptualization, Methodology, Supervision, Writing – review & editing.

REFERENCES

1. Fritz L, Dirven L, Reijneveld JC, Koekkoek JA, Stiggelbout AM, Pasman HR, et al. Advance care planning in glioblastoma patients. Cancers (Basel). 2016;8(11):102. https://doi.org/10.3390/cancers8110102
2. Ståhl P, Henoch I, Smits A, Rydenhag B, Ozanne A. Quality of life in patients with glioblastoma and their relatives. Acta Neurol Scand. 2022;146(1):82-91. https://doi.org/10.1111/ane.13625
3. Stupp R, Mason WP, Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-96. https://doi.org/10.1056/NEJMoa043330
4. Wu A, Ruiz Colón G, Aslakson R, Pollom E, Patel CB. Palliative care service utilization and advance care planning for adult glioblastoma patients: a systematic review. Cancers (Basel). 2021;13(12):2867. https://doi.org/10.3390/cancers13122867

5. Berthold D, Carrasco AP, Uhl E, Müller H, Dumitrascu R, Sibelius U, et al. Palliative care of older glioblastoma patients in neurosurgery. J Neurooncol. 2022;157(2):297-305. https://doi.org/10.1007/s11060-022-03985-x
6. Fritz L, Zwinkels H, Koekkoek JAF, Reijneveld JC, Vos MJ, Dirven L, et al. Advance care planning in glioblastoma patients: development of a disease-specific ACP program. Support Care Cancer. 2020;28(3):1315-24. https://doi.org/10.1007/s00520-019-04916-9
7. Pompili A, Telera S, Villani V, Pace A. Home palliative care and end of life issues in glioblastoma multiforme: results and comments from a homogeneous cohort of patients. Neurosurg Focus. 2014;37(6):E5. https://doi.org/10.3171/2014.9.FOCUS14493
8. Gomes ALZ, Othero MB. Palliative care. Adv Stud. 2016;30(88):155-66. https://doi.org/10.1590/S0103-40142016.30880011
9. Travers S, Litofsky NS. Daily lifestyle modifications to improve quality of life and survival in glioblastoma: a review. Brain Sci. 2021;11(5):533. https://doi.org/10.3390/brainsci11050533
10. Kuchinad KE, Strowd R, Evans A, Riley WA, Smith TJ. End of life care for glioblastoma patients at a large academic cancer center. J Neurooncol. 2017;134(1):75-81. https://doi.org/10.1007/s11060-017-2487-8
11. Gately L, McLachlan SA, Dowling A, Philip J. Life beyond a diagnosis of glioblastoma: a systematic review of the literature. J Cancer Surviv. 2017;11(4):447-52. https://doi.org/10.1007/s11764-017-0602-7
12. Miranda SP, Bernacki RE, Paladino JM, Norden AD, Kavanagh JE, Palmor MC, et al. A descriptive analysis of end-of-life conversations with long-term glioblastoma survivors. Am J Hosp Palliat Care. 2018;35(5):804-11. https://doi.org/10.1177/1049909117738996
13. Walsh LE, Polacek LC, Panageas K, Reiner A, Walbert T, Thomas AA, et al. Coping with glioblastoma: prognostic communication and prognostic understanding among patients with recurrent glioblastoma, caregivers, and oncologists. J Neurooncol. 2022;158(1):69-79. https://doi.org/10.1007/s11060-022-04010-x
14. Hemminger LE, Pittman CA, Korones DN, Serventi JN, Ladwig S, Holloway RG, et al. Palliative and end-of-life care in glioblastoma: defining and measuring opportunities to improve care. Neurooncol Pract. 2017;4(3):182-8. https://doi.org/10.1093/nop/npw022
15. Diamond EL, Panageas KS, Dallara A, Pollock A, Applebaum AJ, Carver AC, et al. Frequency and predictors of acute hospitalization before death in patients with glioblastoma. J Pain Symptom Manage. 2017;53(2):257-64. https://doi.org/10.1016/j.jpainsymman.2016.09.008
16. Flechl B, Ackerl M, Sax C, Oberndorfer S, Calabek B, Sizoo E, et al. The caregivers' perspective on the end-of-life phase of glioblastoma patients. J Neurooncol. 2013;112(3):403-11. https://doi.org/10.1007/s11060-013-1069-7
17. Rivoirard R, Vallard A, Boutet C, Falk AT, Garin C, Adjabi A, et al. A retrospective survey of the last 3 months of life in patients carrying glioblastoma: clinical treatments and profiles. Mol Clin Oncol. 2018;8(1):115-20. https://doi.org/10.3892/mco.2017.1479
18. Thier K, Calabek B, Tinchon A, Grisold W, Oberndorfer S. The last 10 days of patients with glioblastoma: assessment of clinical signs and symptoms as well as treatment. Am J Hosp Palliat Care. 2016;33(10):985-8. https://doi.org/10.1177/1049909115609295
19. Ståhl P, Fekete B, Henoch I, Smits A, Jakola AS, Rydenhag B, et al. Health-related quality of life and emotional well-being in patients with glioblastoma and their relatives. J Neurooncol. 2020;149(2):347-56. https://doi.org/10.1007/s11060-020-03614-5
20. Seibl-Leven M, Reeken C, Goldbrunner R, Grau S, Ruge MI, Galldiks N, et al. Clinical routine assessment of palliative care symptoms and concerns and caregiver burden in glioblastoma patients: an explorative field study. J Neurooncol. 2018;138(2):321-33. https://doi.org/10.1007/s11060-018-2800-1
21. Solanki C, Sadana D, Arimappamagan A, Rao KVLN, Rajeswaran J, Subbakrishna DK, et al. Impairments in quality of life and cognitive functions in long-term survivors of glioblastoma. J Neurosci Rural Pract. 2017;8(2):228-35. https://doi.org/10.4103/0976-3147.203829
22. Baba MA, Adali N. Neurocognitive state and quality of life of patients with glioblastoma in mediterranean countries: a systematic review. Ann Palliat Med. 2021;10(11):11980-93. https://doi.org/10.21037/apm-21-1900
23. Sagberg LM, Solheim O, Jakola AS. Quality of survival the 1st year with glioblastoma: a longitudinal study of patient-reported quality of life. J Neurosurg. 2016;124(4):989-97. https://doi.org/10.3171/2015.4.JNS15194
24. Kim JY, Peters KB, Herndon JE, Affronti ML. Utilizing a palliative care screening tool in patients with glioblastoma. J Adv Pract Oncol. 2020;11(7):684-92. https://doi.org/10.6004/jadpro.2020.11.7.3
25. Golla H, Ale Ahmad M, Galushko M, Hampl J, Maarouf M, Schroeter M, et al. Glioblastoma multiforme from diagnosis to death: a prospective, hospital-based, cohort, pilot feasibility study of patient reported symptoms and needs. Support Care Cancer. 2014;22(12):3341-52. https://doi.org/10.1007/s00520-014-2384-z
26. Celis MÁ, Alegría-Loyola MA, González-Aguilar A, Martínez-Tlahuel J, Green-Renner D, Reyes-Soto G, et al. [First Mexican consensus on recommendations of the multidisciplinary care of patients with glioblastoma multiforme (GBM): Mexican interdisciplinary group on neuro-oncology research (GIMINO)]. Gac Med Mex. 2015;151(3):403-15. PMID: 26089278

REVIEW ARTICLE

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Nutrological therapy in oncology: from prevention to nutritional support during treatment

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INTRODUCTION

Protein-calorie malnutrition is highly prevalent in oncology patients, particularly in the advanced stages of the disease, with an estimated 20–30% of patient deaths attributed to this nutritional state[1]. Loss of lean body mass, muscle strength, and performance, along with increased morbidity and mortality, reduced quality of life, and lower tolerance to treatment toxicity leading to more frequent treatment interruptions, are characteristic features of malnutrition[1,2]. Its causes may stem from the cancer itself and/or its treatment and encompass factors such as reduced food intake, increased energy expenditure, metabolic disturbances related to the tumor, and, in some cases, malabsorption. Hyporexia can occur in 40–80% of cases and is multifactorial, potentially arising from issues like nausea, dysgeusia, dysphagia, pain, and depression, among others.

Given the high prevalence of malnutrition, all patients should be assessed to detect nutritional risk and be reassessed throughout their treatment journey[3]. Nutritional care ranges from prevention to nutritional therapy for cachexia and the follow-up of survivors. Furthermore, it is of paramount importance in newly diagnosed cases. Unfortunately, it is estimated that only 30–70% of oncology patients at risk of malnutrition are evaluated, and only about half of them receive appropriate intervention[4].

SCREENING AND DIAGNOSIS

Every patient should be evaluated to determine their nutritional risk and status at the time of oncology diagnosis and periodically reassessed during each stage of treatment[3]. To screen for nutritional risk, a validated tool called Nutritional Risk Screening–2002 (NRS-2002), developed by Kondrup et al.[3] and certified by the European Society for Parenteral and Enteral Nutrition (ESPEN), is utilized.

The patient's nutritional status correlates with the severity of the disease and its prognosis. Patients at nutritional risk benefit more from nutritional therapy[3]. Nutritional screening and diagnostic tools correlate the cause and consequence effects of malnutrition. The causes include reduced food intake, poor absorption, or increased energy expenditure, while the consequences encompass weight loss, low body mass index (BMI), and loss of body compartments.

In NRS-2002, all cause and consequence variables are scored according to their severity. The sum of these scores, if greater than 3, indicates nutritional risk. Elderly patients receive an additional point in NRS-2002 due to their inherent age-related risk[3]. The initial stage involves asking four questions (Stage 1), and if the answer is "yes" to any of them, one should proceed to the subsequent stage (Stage 2).

NUTRITIONAL DIAGNOSES IN ONCOLOGY

Possible nutritional diagnoses in oncology include adequate nutritional status, sarcopenia, malnutrition, and cachexia[5]. Sarcopenia is a skeletal muscle disorder that correlates with the risk of falls, fractures, physical disability, and mortality[6]. It is also described as a geriatric syndrome, and its diagnosis relies on the assessment of muscle strength, mass, and performance[7]. Cachexia is associated with a catabolic state, loss of lean mass, and often a decrease in fat mass. It affects the

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majority of advanced cancer patients, reducing treatment tolerance, efficacy, quality of life, and survival. It can also occur in other conditions besides cancer, such as cardiac cachexia in heart failure or pulmonary cachexia in patients with chronic obstructive pulmonary disease[5].

DIAGNOSIS OF CACHEXIA[5]

Malnutrition can occur in any medical condition, with unintentional weight loss being one of its key criteria (Table 1).

For the diagnosis of malnutrition, the Global Leadership Initiative on Malnutrition (GLIM; Table 2)[8] has proven to be an excellent tool with good specificity and sensitivity. It is based on phenotypic and etiological criteria encompassing various mechanisms and causes of malnutrition. In GLIM, different instruments for assessing body composition can be used to evaluate muscle mass, such as dual-energy X-ray absorptiometry (DEXA), bioimpedance, or computed tomography.

LABORATORY TESTS

In addition to the previously mentioned diagnostic tools, some biochemical and imaging tests can be added to support the nutritional diagnosis of oncology patients, using them as prognostic indicators. The preoperative serum albumin level is inversely related to a higher incidence of fistulas and postoperative infectious complications[9]. Some studies use the perioperative total serum protein value as part of the risk calculation for anastomotic fistulas[10]. The Glasgow Prognostic Score is another example of a prognostic calculation where the serum albumin level associated with the C-reactive protein value reflects the nutritional status and degree of inflammation in patients with various types of cancer[11].

NUTRITIONAL MANAGEMENT AT THE TIME OF DIAGNOSIS

Nutritional management is essential for preventing losses, providing support, or facilitating recovery. It is a non-pharmacological and essential adjuvant approach for chemotherapy (CT), radiotherapy (RT), immunotherapy, and/or surgery. Approximately 80% of solid tumor patients will undergo some form of surgical treatment. According to ESPEN Guidelines[1], oncology patients diagnosed with malnutrition should be nutritionally prepared for surgery. The optimization of daily calorie intake should be calculated at around 25–30 kcal/kg and above 1.0 g of protein/kg, reaching 1.5 g/kg[1].

Table 1. Cachexia diagnosis criteria.

Pre-cachexia	Cachexia	Refractory cachexia
All of the criteria	One or more criteria	One criterion
Weight loss	Weight loss >5% over past 6 months	Limited self-care
Clinical Symptoms (i.e., anorexia)	Weight loss >2% and BMI <20	Complete disability on WHO performance status and life expectancy less than 3 months
Metabolic symptoms (i.e., glucose intolerance)	Weight loss >2% and sarcopenia as detected by MUMA or ASMI by DXA, or LSMI by CT, or FFMI by BIA*	

*MUMA: mid upper-arm muscle area – reference values: men <32 cm^2, women <18 cm^2; ASMI: appendicular skeletal muscle index – reference values: men <7·26 kg/m^2; women <5·45 kg/m^2; DXA: dual energy x-ray absorptiometry; LSMI: lumbar skeletal muscle index – reference values: men <55 cm^2/m^2; women <39 cm^2/m^2; CT: computed tomography; FFMI: fat-free mass index without bone – reference values: men <14·6 kg/m^2; women <11·4 kg/m^2; BIA: bioelectrical impedance; WHO: World Health Organization.

Table 2. Global leadership initiative on malnutrition[8].

Phenotypic criteria			Etiologic criteria	
Weight loss (%) in 6 months	Low body index	Reduced muscle mass	Reduced food intake or assimilation	Inflammation
>5%: moderate malnutrition or >10%: severe malnutrition	<20 kg/m^2 if <70 yo; <22 kg/m^2 if >70 yo; Asiatic population: <18.5 kg/m^2 if <70 yo; <20 kg/m^2 if > 70 yo;	Diagnosed by validated body composition measuring techniques	≤50% of RER for 1 week or any reduction for >2 weeks or any chronic GI condition that adversely impacts food assimilation or absorption	Acute disease/ injury or chronic disease-related

RER: resting energy requirements; GI: gastrointestinal.

Nutritional therapy to achieve this goal includes hyperprotein and high-calorie oral supplements when the patient can consume more than 60% of their caloric needs orally. Nasoenteral feeding should be indicated when intake is less than 60% of requirements. In cases where gastrointestinal (GI) function is partially compromised or intestinal failure occurs, supplemental or total parenteral nutrition, respectively, is recommended[1]. For patients with a surgical perspective, a minimum prehabilitation of 7–14 days before surgery should be performed, and it may be delayed for this purpose[1,12]. This approach has also been studied for other oncological treatments, including CT and RT, with benefits in terms of morbidity, mortality, and hospitalization time[12]. Currently, studies have suggested that the use of probiotics for 3–8 days in the preoperative period of colorectal cancer patients could reduce postoperative infectious complications and improve intestinal permeability with a reduction in bacterial translocation[13]. For malnourished patients with upper GI neoplasms, there is moderate evidence for the use of supplements enriched with omega-3, arginine, and nucleotides[1,12].

The systematic multimodal approach of Enhanced Recovery After Surgery (ERAS[14]) and the ACERTO project[12] place nutritional therapy in a prominent position as a measure that can modify surgical outcomes.

Prehabilitation is now recommended as a preparation for CT, RT, and immunotherapy as well. Special attention should be given to patients with head and neck cancers undergoing RT. These patients often experience a drastic deterioration in their nutritional and hydration status, leading to treatment interruptions and frequent hospitalizations. Prehabilitation protocols include clinical, psychological, nutritional, and physiotherapeutic preparation to ensure that the patient is in the best possible clinical condition for the proposed therapy, whether surgical, CT, or RT[12]. Managing depression is of paramount importance, as it can impact food intake, the ability to engage in physical therapy, and the patient's prognosis. Physiotherapeutic intervention aims to stimulate protein synthesis and prepare the patient both physically and respiratory-wise for the postoperative period. Prehabilitation should begin at the time of oncology diagnosis and last between 2 and 6 weeks when surgery allows for this waiting period[15]. Attention should be paid to patients with a high body mass index and neoplasia, as there is a high incidence of sarcopenic obesity, which can affect prognosis and treatment outcomes[16].

NUTRITIONAL MANAGEMENT DURING TREATMENT

The tumor has various effects on the GI tract. Up to 50% of patients experience taste changes at the time of diagnosis, directly affecting food intake[1]. In addition to this factor, CT and RT cause side effects such as oral mucositis, nausea, vomiting, diarrhea, and sarcopenic dysphagia. About 35% of patients experience GI symptoms during CT and RT, and more than 60% experience late-onset symptoms[17]. GI symptoms should be prevented and treated, and menu adjustments and consistency modifications can help improve oral diet acceptance[18]. Another important approach is to assess hedonic changes of taste and provide diets adapted to that change focusing at increasing ingestion.[19] Recurrent fasting for tests and procedures can also compromise intake. Malnutrition is a key determinant of worse outcomes in cancer treatments[18]. One significant challenge in managing these patients is how to prevent or delay the onset of refractory cachexia. Due to the inflammatory process triggered by the tumor and its resulting metabolic changes, medication interventions are necessary to improve anorexia. Some options include the use of omega-3, preferably eicosapentaenoic acid (EPA), at a dose of 600 mg to 2.2 g/day. However, there are varying doses in the literature, ranging from 1 g to 3 g/day of a combination of EPA and docosahexaenoic acid (DHA) in a ratio of 1.5:2.0. There is evidence for the use of mirtazapine at 15–45 mg/day or olanzapine at 5 mg/day in the treatment of anorexia. Although some evidence suggests the use of megestrol acetate and corticosteroids, these are not considered first-line options due to their side effects: 1 in 4 patients experiences increased appetite, 1 in 12 experiences weight gain, but 1 in 6 develops thromboembolic events, and 1 in 23 dies as a result of the medication[20].

NUTRITIONAL MANAGEMENT IN PREVENTION

Among the various factors related to cancer are chronic inflammation, oxidative stress, cell cycle changes, and the activation of pro-oncogenes. The quality of nutrition significantly influences the risk of developing cancer. Preventive measures based on lifestyle changes, including physical activity and a healthy diet, can impact around 3–4 million new cases worldwide[21]. The Mediterranean diet (MD) is the most studied in oncological prevention.

The Mediterranean diet

The potential for reducing the risk of cancer through the MD has been extensively studied due to its profile of anti-inflammatory foods, including antioxidants, polyphenols, and omega-3 fatty acids (FAs). Its antioxidants and polyphenols are associated with an antineoplastic effect[22].

This diet is primarily based on plant-based foods such as fresh fruits, unrefined grains, nuts, whole grains, seafood, olive oil, and low-fat dairy products such as cow's milk and low-fat cheeses. The consumption of wine is permitted, while the consumption of red meat and sugar should be occasional[22].

The MD is rich in fruits, vegetables, and legumes, which are abundant sources of antioxidants such as vitamin C and E, as well as phytochemicals like flavonoids and carotenoids[23]. These components neutralize the harmful effects of free radicals in the body, which can cause DNA damage and increase the risk of cancer[24].

The MD includes healthy fats from sources like olive oil, nuts, and fish. This provides an adequate intake of polyunsaturated omega-3 fatty acids (PUFAs) and monounsaturated omega-9 FAs. This profile of FAs can reduce inflammation, a factor correlated with oncological diseases.

The variety of grains, legumes, and pulses in the MD ensures an adequate intake of fiber. Fiber aids in digestion, maintains a healthy microbiota, and has the potential to reduce the risk of colorectal cancer.

The consumption of red meat in the MD is reduced, with a preference for lean meats such as poultry and fish. High consumption of red and processed meat is associated with the risk of certain cancers, including colorectal cancer[25].

Moderate wine consumption in the MD may protect against certain neoplasms, although it is known that there is no safe minimum dose of ethanol intake[26]. The Mediterranean lifestyle also includes regular physical activities and group activities, which contribute to well-being and can reduce the risk of cancer.

Weight control can be achieved even with normocaloric diets, as there is better appetite control through diets with higher nutritional density. Maintaining a healthy weight is essential to reduce the risk of various types of cancer, including breast, colorectal, and endometrial cancers[27].

Some nutrients in the MD can act protectively through epigenetics, inhibiting tumor development. The MD can protect against metabolic and oxidative DNA damage[28].

In addition to the Mediterranean lifestyle, smoking should be ceased, and exposure to environmental carcinogens should be reduced.

Diets rich in vegetables

The diets that are rich in vegetables include paleolithic (PD) and vegetarian (VD). The PD consists of consuming foods that our ancestors would have used during the Paleolithic era. It includes the consumption of lean meats, fish, fruits, vegetables, nuts, and seeds while avoiding processed foods, grains, dairy, and legumes. There are theories that the PD may bring health benefits and prevent cancer[29], but caution should be exercised in drawing conclusions for this purpose.

When well balanced, the VD can also have benefits in reducing the risk of cancer. This is partly due to the benefits of plant-based foods with their antioxidant components, but also due to the restriction of animal product consumption[30]. Additionally, in the VD, there is a reduction in exposure to hormones and antibiotics, which are common in dairy and meat products[31]. The consumption of fruits and vegetables, as well as the restriction of meat consumption, show benefits, as previously mentioned in the MD[31]. However, attention should be paid to the adequate intake of vitamin B12, iron, calcium, and protein.

Both diets are rich in vitamins, minerals, and antioxidants, which can prevent DNA damage and reduce the risk of cancer[32]. Nevertheless, well-designed studies that can recommend these diets for cancer prevention are still needed.

Ketogenic diet

Diets based on fasting have been extensively studied, including the ketogenic diet (KD), fasting itself, and the fasting mimicking diet. The KD is a high-fat, low-carbohydrate diet that can assist in cancer prevention and treatment and may have anticancer effects.

The theoretical premise is that neoplastic cells use glucose as an energy substrate through the Warburg effect, which involves aerobic fermentation (or aerobic glycolysis). By depriving the oncological cell of carbohydrates, its development and survival can be compromised. The KD could reduce chronic inflammation, which is correlated with oncogenesis, tumor growth, invasion, and insulin resistance[33].

It is important to note that despite the benefits demonstrated in vitro, we currently lack sufficient clinical studies, and there is no scientific evidence supporting the use of this diet during cancer treatment[34]. Additionally, the KD, like other restrictive diets, is difficult to sustain in the long term. It can also lead to nutritional deficiencies, constipation, and cardiovascular risk if not closely monitored by a nutrologist or healthcare professional[35].

Foods to be avoided

For the prevention of cancer, reducing the consumption of saturated and trans fats is recommended to lower the risk of breast and colorectal cancer. This includes avoiding processed meats such as bacon and sausages, which are associated with colorectal cancer[36].

According to the World Health Organization and the International Agency for Research on Cancer, dietary patterns based on the regular consumption of fruits, vegetables, and foods rich in selenium, folic acid, vitamins (B12 or D), and antioxidants (such as carotenoids and lycopene) play a protective role in cancer prevention[37] and should be prioritized in a healthy diet. Omega-3, abundant in fish, especially sardines and mackerel, can help slow down the development of cancer[38].

A high intake of fiber-rich products (e.g., whole grains) and moderate consumption of milk and dairy products can reduce the incidence of various types of cancer, including colorectal, lung, stomach, breast, esophageal, and oral cancer[39,40].

CONCLUSION

Cancer is one of the leading causes of mortality and disability in today's world. Antineoplastic treatments are advancing gradually; however, from a nutritional standpoint, early diagnosis of malnutrition and the introduction of nutritional therapy as soon as necessary remain crucial. Prevention focuses on a healthy lifestyle with a diet rich in vegetables, unsaturated fats, and complex carbohydrates, coupled with regular physical activity.

AUTHORS' CONTRIBUTIONS

ANM: Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review and editing. **SCMS:** Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review and editing. **NIJ:** Conceptualization, Data curation, Supervision, Writing – original draft. **SLF:** Writing – original draft. **AAP:** Writing – original draft. **RFWP:** Writing – original draft. **MCR:** Writing – original draft. **LCA:** Writing – original draft.

REFERENCES

1. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: clinical nutrition in cancer. Clin Nutr. 2021;40(5):2898-913. https://doi.org/10.1016/j.clnu.2021.02.005
2. Bossi P, Delrio P, Mascheroni A, Zanetti M. The spectrum of malnutrition/cachexia/sarcopenia in oncology according to different cancer types and settings: a narrative review. Nutrients. 2021;13(6):1980. https://doi.org/10.3390/nu13061980
3. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321-36. https://doi.org/10.1016/s0261-5614(02)00214-5
4. Aprile G, Basile D, Giaretta R, Schiavo G, Verde N, Corradi E, et al. The clinical value of nutritional care before and during active cancer treatment. Nutrients. 2021;13(4):1196. https://doi.org/10.3390/nu13041196
5. Meza-Valderrama D, Marco E, Dávalos-Yerovi V, Muns MD, Tejero-Sánchez M, Duarte E, et al. Sarcopenia, malnutrition, and cachexia: adapting definitions and terminology of nutritional disorders in older people with cancer. Nutrients. 2021;13(3):761. https://doi.org/10.3390/nu13030761
6. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31. https://doi.org/10.1093/ageing/afy169
7. Horie LM, Barrére APN, Castro MG, Liviera AMB, Carvalho AMB, Pereira A, et al. Diretriz braspen de terapia nutricional no paciente com câncer. Braspen J. 2019;34(Suppl. 1):2-32.
8. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - a consensus report from the global clinical nutrition community. Clin Nutr. 2019;38(1):1-9. https://doi.org/10.1016/j.clnu.2018.08.002
9. Truong A, Hanna MH, Moghadamyeghaneh Z, Stamos MJ. Implications of preoperative hypoalbuminemia in colorectal surgery. World J Gastrointest Surg. 2016;8(5):353-62. https://doi.org/10.4240/wjgs.v8.i5.353
10. Sammour T, Lewis M, Thomas ML, Lawrence MJ, Hunter A, Moore JW. A simple web-based risk calculator (www.anastomoticleak.com) is superior to the surgeon's estimate of anastomotic leak after colon cancer resection. Tech Coloproctol. 2017;21(1):35-41. https://doi.org/10.1007/s10151-016-1567-7
11. Wang DS, Ren C, Qiu MZ, Luo HY, Wang ZQ, Zhang DS, et al. Comparison of the prognostic value of various preoperative inflammation-based factors in patients with stage III gastric cancer. Tumour Biol. 2012;33(3):749-56. https://doi.org/10.1007/s13277-011-0285-z
12. Sampaio MAF, Sampaio SLP, Leal PDC, Moura ECR, Alvares LGGS, Oliveira CMB, et al. Acerto project: impact on assistance of a public emergency hospital. Arq Bras Cir Dig. 2021;33(3):e1544. https://doi.org/10.1590/0102-672020200003e1544
13. Chen Y, Qi A, Teng D, Li S, Yan Y, Hu S, et al. Probiotics and synbiotics for preventing postoperative infectious complications in colorectal cancer patients: a systematic review and meta-analysis. Tech Coloproctol. 2022;26(6):425-36. https://doi.org/10.1007/s10151-022-02585-1
14. Scott MJ, Baldini G, Fearon KC, Feldheiser A, Feldman LS, Gan TJ, et al. Enhanced recovery after surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations. Acta Anaesthesiol Scand. 2015;59(10):1212-31. https://doi.org/10.1111/aas.12601
15. Bargetzi L, Brack C, Herrmann J, Bargetzi A, Hersberger L, Bargetzi M, et al. Nutritional support during the hospital stay reduces mortality in patients with different types of cancers: secondary analysis of a prospective randomized trial. Ann Oncol. 2021;32(8):1025-33. https://doi.org/10.1016/j.annonc.2021.05.793
16. Torres Stone RA, Waring ME, Cutrona SL, Kiefe CI, Allison J, Doubeni CA. The association of dietary quality with colorectal cancer among normal weight, overweight and obese men and women: a prospective longitudinal study in the USA. BMJ Open. 2017;7(6):e015619. https://doi.org/10.1136/bmjopen-2016-015619
17. Sommariva S, Pongiglione B, Tarricone R. Impact of chemotherapy-induced nausea and vomiting on health-related quality of life and

resource utilization: a systematic review. Crit Rev Oncol Hematol. 2016;99:13-36. https://doi.org/10.1016/j.critrevonc.2015.12.001

18. Pan H, Cai S, Ji J, Jiang Z, Liang H, Lin F, et al. The impact of nutritional status, nutritional risk, and nutritional treatment on clinical outcome of 2248 hospitalized cancer patients: a multi-center, prospective cohort study in Chinese teaching hospitals. Nutr Cancer. 2013;65(1):62-70. https://doi.org/10.1080/01635581.2013.741752
19. Kiss N, Loeliger J, Findlay M, Isenring E, Baguley BJ, Boltong A, et al. Clinical oncology society of Australia: position statement on cancer-related malnutrition and sarcopenia. Nutr Diet. 2020;77(4):416-25. https://doi.org/10.1111/1747-0080.12631
20. Lim YL, Teoh SE, Yaow CYL, Lin DJ, Masuda Y, Han MX, et al. A systematic review and meta-analysis of the clinical use of megestrol acetate for cancer-related anorexia/cachexia. J Clin Med. 2022;11(13):3756. https://doi.org/10.3390/jcm11133756
21. Costanzo R, Simonetta I, Musso S, Benigno UE, Cusimano LM, Giovannini EA, et al. Role of mediterranean diet in the development and recurrence of meningiomas: a narrative review. Neurosurg Rev. 2023;46(1):255. https://doi.org/10.1007/s10143-023-02128-8
22. Almanza-Aguilera E, Cano A, Gil-Lespinard M, Burguera N, Zamora-Ros R, Agudo A, et al. Mediterranean diet and olive oil, microbiota, and obesity-related cancers. From mechanisms to prevention. Semin Cancer Biol. 2023;95:103-19. https://doi.org/10.1016/j.semcancer.2023.08.001
23. Saka-Herrán C, Pereira-Riveros T, Jané-Salas E, López-López J. Association between the mediterranean diet and vitamin C and the risk of head and neck cancer. Nutrients. 2023;15(13):2846. https://doi.org/10.3390/nu15132846
24. Daniele A, Divella R, Pilato B, Tommasi S, Pasanisi P, Patruno M, et al. Can harmful lifestyle, obesity and weight changes increase the risk of breast cancer in BRCA 1 and BRCA 2 mutation carriers? A mini review. Hered Cancer Clin Pract. 2021;19(1):45. https://doi.org/10.1186/s13053-021-00199-6
25. Acevedo-León D, Gómez-Abril SÁ, Sanz-García P, Estañ-Capell N, Bañuls C, Sáez G. The role of oxidative stress, tumor and inflammatory markers in colorectal cancer patients: a one-year follow-up study. Redox Biol. 2023;62:102662. https://doi.org/10.1016/j.redox.2023.102662
26. Rehm J, Shield KD, Weiderpass E. Alcohol consumption. A leading risk factor for cancer. Chem Biol Interact. 2020;331:109280. https://doi.org/10.1016/j.cbi.2020.109280
27. Ubago-Guisado E, Rodríguez-Barranco M, Ching-López A, Petrova D, Molina-Montes E, Amiano P, et al. Evidence update on the relationship between diet and the most common cancers from the European prospective investigation into cancer and nutrition (EPIC) study: a systematic review. Nutrients. 2021;13(10):3582. https://doi.org/10.3390/nu13103582
28. Polo A, Labbé DP. Diet-dependent metabolic regulation of DNA double-strand break repair in cancer: more choices on the menu. Cancer Prev Res (Phila). 2021;14(4):403-14. https://doi.org/10.1158/1940-6207.CAPR-20-0470
29. Sohouli MH, Baniasadi M, Hernández-Ruiz Á, Magalhães EIDS, Santos HO, Akbari A, et al. Associations of the paleolithic diet pattern scores and the risk of breast cancer among adults: a case-control study. Nutr Cancer. 2023;75(1):256-64. https://doi.org/10.1080/01635581.2022.2108466
30. Long J, Liu Z, Liang S, Chen B. Cruciferous vegetable intake and risk of prostate cancer: a systematic review and meta-analysis. Urol Int. 2023;107(7):723-33. https://doi.org/10.1159/000530435
31. Yan H, Cui X, Zhang P, Li R. Fruit and vegetable consumption and the risk of prostate cancer: a systematic review and meta-analysis. Nutr Cancer. 2022;74(4):1235-42. https://doi.org/10.1080/01635581.2021.1952445
32. Shah S, Mahamat-Saleh Y, Hajji-Louati M, Correia E, Oulhote Y, Boutron-Ruault MC, et al. Palaeolithic diet score and risk of breast cancer among postmenopausal women overall and by hormone receptor and histologic subtypes. Eur J Clin Nutr. 2023;77(5):596-602. https://doi.org/10.1038/s41430-023-01267-x
33. Talib WH, Mahmod AI, Kamal A, Rashid HM, Alashqar AMD, Khater S, et al. Ketogenic diet in cancer prevention and therapy: molecular targets and therapeutic opportunities. Curr Issues Mol Biol. 2021;43(2):558-89. https://doi.org/10.3390/cimb43020042
34. Mundi MS, Mohamed Elfadil O, Patel I, Patel J, Hurt RT. Ketogenic diet and cancer: fad or fabulous? JPEN J Parenter Enteral Nutr. 2021;45(S2):26-32. https://doi.org/10.1002/jpen.2226
35. Batch JT, Lamsal SP, Adkins M, Sultan S, Ramirez MN. Advantages and disadvantages of the ketogenic diet: a review article. Cureus. 2020;12(8):e9639. https://doi.org/10.7759/cureus.9639
36. Huang Y, Cao D, Chen Z, Chen B, Li J, Guo J, et al. Red and processed meat consumption and cancer outcomes: umbrella review. Food Chem. 2021;356:129697. https://doi.org/10.1016/j.foodchem.2021.129697
37. Vineis P, Wild CP. Global cancer patterns: causes and prevention. Lancet. 2014;383(9916):549-57. https://doi.org/10.1016/S0140-6736(13)62224-2
38. Castelló A, Boldo E, Pérez-Gómez B, Lope V, Altzibar JM, Martín V, et al. Adherence to the western, prudent and mediterranean dietary patterns and breast cancer risk: MCC-Spain study. Maturitas. 2017;103:8-15. https://doi.org/10.1016/j.maturitas.2017.06.020
39. World Cancer Research Fund. Worldwide cancer data. 2023. Available from: https://www.wcfr.org/dietandcancer/cancer trend/worldwide-cancer-data
40. Solans M, Castelló A, Benavente Y, Marcos-Gragera R, Amiano P, Gracia-Lavedan E, et al. Adherence to the western, prudent, and mediterranean dietary patterns and chronic lymphocytic leukemia in the MCC-Spain study. Haematologica. 2018;103(11):1881-8. https://doi.org/10.3324/haematol.2018.192526

REVIEW ARTICLE

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Update in ocular surface squamous neoplasia

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INTRODUCTION

Ocular surface squamous neoplasia (OSSN) is an entity that comprises the spectrum of squamous neoplasia of the conjunctiva and cornea, which includes conjunctival intraepithelial neoplasia (CIN), corneal epithelial dysplasia, squamous cell carcinoma (SCC), and mucoepidermoid carcinoma[1]. It mimics common conjunctival and corneal surface pathologies, for instance, pinguecula, pterygium, conjunctival granulomas, and cysts. In addition, OSSN has a high potential to cause ocular damage and systemic morbidity[2]. For this reason, it is important to raise awareness among the population regarding adequate eye protection and early diagnosis by ophthalmologists of suspicious lesions.

EPIDEMIOLOGY

The prevalence of ocular surface squamous neoplasia (OSSN) demonstrates global variations due to differences in risk factors[1]. In the United States, its incidence rate has been documented in the range of 0.03–1.9 cases per 100,000 individuals per year, predominantly affecting Caucasian men between the sixth and seventh decades of life[1]. On the other hand, on the African continent, a notably high incidence was observed in younger patients, varying between 3 and 3.4 cases per 100,000 individuals per year, with a distribution that does not demonstrate gender preference[3].

ETIOLOGY, RISK FACTORS, AND PATHOPHYSIOLOGY

The etiology of OSSN proves to be multifactorial in nature and encompasses a diversity of elements, with the patient's immunological status possibly being the most crucial factor[3]. The risk factors most associated with the emergence of OSSN include exposure to ultraviolet B (UVB) radiation, human papillomavirus (HPV) infection, immunosuppression, and xeroderma pigmentosum[1]. The increased incidence of OSSN in individuals living in geographic regions close to the Equator is widely documented, due to greater exposure to UVB radiation[1]. Additional evidence corroborating this association is the finding that the majority of lesions occur in the interpalpebral fissure, nasal, and temporal limbus, regions that are most exposed to sunlight[3]. Limbal epithelial crypts are concentrated in the nasal region and contain epithelial stem cell niches in the basal layer[4]. It is possible that these are the progenitor cells in the OSSN that, after being altered, spread toward the surface before later invading the basement membrane[4]. UVB radiation acts by directly damaging DNA through the production of pyrimidine dimers in addition to other specific mutations in the p53 tumor suppressor gene, allowing cells with damaged DNA to surpass the cell cycle control point[4]. HPV is recognized as causing intraepithelial damage that culminates in the development of squamous neoplasms, and its subtypes 16 and 18 are specifically associated with the genesis of neoplastic lesions on the ocular surface[5]. UV radiation has also been described as causing local and systemic photoimmunosuppression and being capable of reactivating latent viruses, such as HPV[4]. Patients with some degree of immunodeficiency, especially those infected with the human immunodeficiency virus (HIV), have a substantially increased risk, approximately 10 times greater, for the development of OSSN and often exhibit more unfavorable clinical outcomes after treatment[5]. An additional etiological factor relevant to the development of OSSN is the failure of the DNA repair mechanism, as observed in xeroderma pigmentosum[3]. Other risk elements include advanced age, male sex, hypopigmented features of hair and eyes, xerophthalmia, trauma to the

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ocular surface, smoking, and chronic exposure to petroleum products[1]. Vitamin A deficiency interferes with the integrity of the ocular surface, creating microabrasions through which HPV can invade the basement membrane and conjunctival epithelial cells, initiating a cycle of local cellular changes[4].

GENERAL PATHOLOGY AND HISTOPATHOLOGY

The current classification for OSSN encompasses all dysplastic and carcinomatous lesions that affect the ocular surface[3]. Benign OSSN comprises conditions such as pseudotheliomatous hyperplasia, benign hereditary intraepithelial dyskeratosis, and papillomas[2]. Preinvasive OSSN, also known as intraepithelial neoplasias (CIN), are subdivided into three categories: CIN I (mild dysplasia restricted to the lower third of the conjunctival epithelium), CIN II (moderate dysplasia extending to the middle third), and CIN III (severe dysplasia affecting up to the upper third of the conjunctival epithelium)[2]. Dysplasia that involves the entire thickening of the epithelium is called carcinoma in situ (CIS)[2]. Finally, invasive OSSNs have the ability to cross the epithelial basement membrane, invading the conjunctival stroma and adjacent structures, and include SCC and mucoepidermoid carcinoma, which are more aggressive and recurrent than SCC[3].

HISTORY

Many patients affected by OSSN may remain asymptomatic, and the diagnosis is often suspected during routine ophthalmological examinations[3]. However, some may report the presence of a raised mass in the conjunctiva, accompanied by symptoms such as ocular irritation, itching, and ocular hyperemia[3].

CLINICAL PRESENTATION

The typical clinical presentation of OSSN involves the identification of elevated and nodular lesions in the interpalpebral region[1]. These lesions may vary in color from grayish white to reddish, have irregular margins, and are often accompanied by visible blood vessels[2]. Benign OSSN generally presents a papillomatous appearance[3]. On the other hand, intraepithelial neoplasias (CIN) can take on a leukoplastic and/or gelatinous macroscopic appearance[3]. Lesions with leukoplastic characteristics demonstrate superficial hyperkeratinization, while gelatinous lesions tend to be reddish and well defined, and may be nodular or diffuse[3]. When OSSN affects the cornea, resulting from the spread of abnormal epithelial cells from the limbus, it appears as an avascular, translucent, opalescent lesion with a ground-glass appearance, usually with defined margins[3]. Conjunctival SCC shares similarities with CIN; however, the conjunctival lesion tends to be higher, has a plaque shape, and presents less mobility[3]. In such cases, the identification of feeding vessels suggests rupture and invasion of the epithelial basement membrane[3]. Finally, mucoepidermoid carcinoma, a more aggressive and recurrent variant, clinically mimics SCC and can develop anywhere on the ocular surface[3].

DIAGNOSIS

The diagnosis of OSSN is generally established based on a combination of clinical data, ophthalmological examination, macroscopic characteristics, complementary noninvasive tests, and histopathological analysis[6]. Diagnostic suspicion based on an ophthalmological examination with the identification of a lesion is the fundamental step towards an adequate investigation of the case[3]. Although it is considered an invasive procedure, the gold standard for diagnosing OSSN is histopathological analysis after performing a biopsy, which is the only approach that makes it possible to detect the level of tissue invasion of the lesion[7]. It is evident that interest in conservative diagnostic approaches has grown significantly, and noninvasive methods, such as the use of vital dyes, cytology, confocal microscopy, and anterior segment optical coherence tomography (OCT-SA), have been applied with remarkable precision in the characterization of these lesions[3].

The application of vital dyes, such as rose bengal, methylene blue, and toluidine blue, provides support for the diagnosis of OSSN in a practical and efficient way[6]. Rose Bengal has the ability to highlight degenerated epithelial cells, while methylene blue is useful in identifying malignant lesions, although both lack specificity directed exclusively to OSSN[6]. Toluidine blue, an acidophilic dye, has the property of staining cells with a high mitotic rate and of accumulating between them, especially in tissues with limited cell adhesion. Although this test reveals high sensitivity (92% in diagnosing OSSN), its specificity is considerably lower (31%)[6,8,9].

Cytology represents an additional diagnostic method for OSSN and can be exfoliative or by impression[6]. Impression cytology involves obtaining superficial cells using filter paper made of cellulose acetate, which is applied directly to the target lesion[6]. Although this technique offers notable benefits, such as its minimally invasive nature and a correlation of results that reaches up to 80% agreement with histopathological analysis samples, it has limitations, including the superficial capture of cells and the requirement for an experienced cytologist to analyze the results[6].

Studies involving the application of in vivo confocal microscopy (IVCM) in the context of OSSN have demonstrated diverse results, with a notable overlap of features observed in benign and malignant lesions[6]. Although IVCM can occasionally play a useful and complementary role to histology, it should not be considered a reliable substitute for biopsy due to the inconsistency of its results[6].

Anterior Segment Optical Coherence Tomography has emerged as an extremely relevant diagnostic tool, allowing the acquisition of high-resolution images of the superficial ocular layers in a noninvasive manner and without the need for direct contact with the globe[7]. Its distinctive characteristics in the assessment of OSSN include the identification of an abrupt transition between the healthy epithelium and the abnormal epithelium, in addition to revealing the anomalous thickening of this epithelium and the presence of hyper-reflectivity in the tumor region[7]. OCT-SA currently plays a prominent and unquestionably effective role in the precise differentiation between OSSN and benign conditions, as well as in the identification of other tumor entities[7]. This discrimination capacity has provided significant contributions to the diagnosis and clinical management of various ocular surface pathologies[7].

DIFFERENTIAL DIAGNOSIS

Due to the sharing of risk factors and because they are considered synchronous lesions, pterygia and pingueculae should be considered and remembered as important differential diagnoses of OSSN[10]. Other conditions that should be considered as potential differential diagnoses include amelanotic melanoma, corneal pannus, nodular corneal degeneration, pyogenic granuloma, sebaceous cell carcinoma, actinic keratosis, conjunctival cysts, and Bitot's spots, among other possible entities[6]. Due to overlapping clinical features, the differential diagnosis of OSSN can be challenging, and in many cases, additional evaluations may be necessary to confirm the diagnosis[6].

TREATMENT

Treatment aims to eliminate the lesion, prevent recurrences, and preserve vision when possible[3]. Therefore, early detection and smaller tumors will have a better prognosis. Although surgical excision is still the gold standard of treatment, conservative medical approaches have been more commonly used in recent years[3,11-13].

Surgical excision of conjunctival lesions is performed following Shields "no touch" technique with the aim of avoiding the potential risk of seeding[14]. This technique involves wide tumor-free margins[3,15], associated with cryotherapy on the remaining conjunctiva in a "double freeze, slow thaw." The limbal application is avoided to prevent damage to limbal stem cell deficiency. The recommended duration of the contact is 3 s in one single application. Corneal lesions are removed through alcohol keratoepitheliectomy, while the scleral component is addressed with a partial lamellar sclerotomy. The residual conjunctival defect can be closed, primarily if the defect is less than 3 clock hours. In large defects (more than 3 clock hours), conjunctival autografts or amniotic membrane grafts may be used.

A biopsy, whether incisional (extensive lesions) or excisional, allows histopathological analysis and diagnosis. Enucleation or exenteration is reserved for cases with intraocular or periocular invasion, respectively.

The nonsurgical therapies include topical chemotherapy [mitomycin C (MMC) and 5-fluorouracil (5-FU)], injection/topical immunotherapy (interferon alpha-2b), topical antiviral medication (cidofovir), anti-vascular endothelial growth factor (anti-VEGF), or photodynamic therapy (PDT)[11,12].

Topical therapy has some advantages that include treatment of the entire ocular surface (areas of subclinical disease) as well as a lower risk of conjunctival scarring. Besides, these therapies can be used as adjuvants both preoperatively (chemoreduction) and postoperatively (to complement the treatment when margins are positive for tumor).

Mitomycin C (MMC) is an alkylating agent with antineoplastic properties. It is toxic to proliferating and non-proliferating cells by inducing apoptosis and inhibiting the migration of fibroblasts. Both the regimens of 1 drop of MMC 0.02% three times daily for two 1-week courses[16] and 1 drop of MMC 0.04% four times daily for two 1-week courses[17] have been demonstrated to be effective. Some side effects include dry eye, punctal stenosis, persistent epithelial defects, and allergic reactions. Therefore, MMC is often reserved for more recalcitrant cases that have failed prior therapy with alternative agents.

It is known that 5-fluorouracil (5-FU) is a pyrimidine analog that blocks thymidine synthase, which inhibits DNA formation. It acts on the S phase of the cell cycle and has been delivered topically as a 1% 5-FU formulation four times daily for four weeks[18] or for 1 week followed by a drug holiday of 3 weeks[19]. Primary therapy has shown an efficacy of 85–100%[18-20] and a recurrence rate ranging from 1.1 to 43%[21]. The side effects of topical 5-FU are, mainly, pain and redness at the instillation side; however, these side effects are fewer than those of MMC. The 5-FU is used in conjunction with topical corticosteroids and preservative-free artificial tears to reduce the symptoms[12].

Interferon-alpha 2b (IFN-α2b) is the immunotherapeutic agent used in the treatment of OSSN. Interferons correspond to natural glycoproteins with antimicrobial and antiviral properties[12]. Their role as an antineoplastic agent is due to their

antiproliferative, antiangiogenic, and cytotoxic effects, as well as their property of being a potential inducer of the host antitumor immunosurveillance[22]. IFN-α2b can be used as the primary agent for small lesions, as a neoadjuvant agent for diffuse tumors with the aim of assisting in surgical resection, and as adjuvant therapy when the margins after resection were positive for the presence of tumors[11,23]. It may be prescribed in two ways: topically as drops or locally as perilesional subconjunctival injections. The dosage of topical IFN-α2b is 1 million IU/mL, one drop four times per day without interruption until one or two more months after clinical resolution of the lesion[12,24]. There is no consensus on the dosage of local IFN-α2b to be injected. Subconjunctival injections (3 million IU/0.5 mL) are administered weekly until OSSN resolution (generally, 4 or 5 injections are necessary for adequate treatment). The injections have more side effects than the drops (e.g., flu-like symptoms)[12,25].

Cidofovir is an antiviral agent with activity against double-stranded DNA viruses, including HPV. The dose of 2.5 mg/mL topical cidofovir has shown good efficacy as a secondary treatment in multi-refractory OSSN[26].

Anti-VEGF agents are monoclonal antibodies that block the interaction of VEGF and its receptor, interfering with the growth of blood vessels[27]. There have been a few case reports on the use of these agents as primary therapy in OSSN or as adjuvants after surgical excision; therefore, their role remains uncertain[28,29].

PROGNOSIS

The recurrence rate of OSSN after treatment is variable, and the excision margin at the time of surgery is cited as the most important factor in predicting recurrence[3]. In general, the prognosis of CIN with free surgical margins is favorable, associated with low rates of local recurrence[3]. However, when excision margins are inadequate, especially in large lesions (greater than 2 mm), in elderly patients, or when deep tissue or cornea involvement occurs, the tendency for recurrence increases, reaching up to one-third of cases[3]. It is important to note that invasive carcinoma and mucoepidermoid carcinoma, more aggressive variants of OSSN, have less favorable prognoses and higher rates of local recurrence, even when undergoing surgical treatment with free margins[3]. Furthermore, due to the possibility of late recurrences that can occur even after years of treatment, it is recommended that patients undergo regular and permanent monitoring, with annual consultations, in order to monitor possible recurrences of the disease[30].

AUTHORS' CONTRIBUTIONS

AN: Methodology, Writing – original draft. **ILRK**: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **MAMF**: Supervision, Writing – review & editing.

REFERENCES

1. Shields CL, Chien JL, Surakiatchanukul T, Sioufi K, Lally SE, Shields JA. Conjunctival tumors: review of clinical features, risks, biomarkers, and outcomes—the 2017 J. Donald M. Gass lecture. Asia Pac J Ophthalmol (Phila). 2017;6(2):109-20. https://doi.org/10.22608/APO.201710
2. Hossain RR, McKelvie J. Ocular surface squamous neoplasia in New Zealand: a ten-year review of incidence in the Waikato region. Eye (Lond). 2022;36(8):1567-70. https://doi.org/10.1038/s41433-021-01662-3
3. Gurnani B, Kaur K. Ocular surface squamous neoplasia. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK573082/
4. Gichuhi S, Ohnuma S, Sagoo MS, Burton MJ. Pathophysiology of ocular surface squamous neoplasia. Exp Eye Res. 2014;129:172-82. https://doi.org/10.1016/j.exer.2014.10.015
5. Chalkia AK, Bontzos G, Spandidos DA, Detorakis ET. Human papillomavirus infection and ocular surface disease (review). Int J Oncol. 2019;54(5):1503-10. https://doi.org/10.3892/ijo.2019.4755
6. Nanji AA, Mercado C, Galor A, Dubovy S, Karp CL. Updates in ocular surface tumor diagnostics. Int Ophthalmol Clin. 2017;57(3):47-62. https://doi.org/10.1097/IIO.0000000000000174
7. Thomas BJ, Galor A, Nanji AA, Sayyad F, Wang J, Dubovy SR, Joag MG, Karp CL. Ultra high-resolution anterior segment optical coherence tomography in the diagnosis and management of ocular surface squamous neoplasia. Ocul Surf. 2014;12(1):46-58. https://doi.org/10.1016/j.jtos.2013.11.001
8. Romero IL, Barros JN, Martins MC, Ballalai PL. The use of 1% toluidine blue eye drops in the diagnosis of ocular surface squamous neoplasia. Cornea. 2013;32(1):36-9. https://doi.org/10.1097/ICO.0b013e318243f61f
9. Gichuhi S, Macharia E, Kabiru J, Zindamoyen AM, Rono H, Ollando E, et al. Toluidine blue 0.05% vital staining for the diagnosis of ocular surface squamous neoplasia in Kenya. JAMA Ophthalmol. 2015;133(11):1314-21. https://doi.org/10.1001/jamaophthalmol.2015.3345
10. Hirst LW, Axelsen RA, Schwab I. Pterygium and associated ocular surface squamous neoplasia. Arch Ophthalmol. 2009;127(1):31-2. https://doi.org/10.1001/archophthalmol.2008.531
11. Cicinelli MV, Marchese A, Bandello F, Modorati G. Clinical management of ocular surface squamous neoplasia: a review of the current evidence. Ophthalmol Ther. 2018;7(2):247-62. https://doi.org/10.1007/s40123-018-0140-z
12. Bayyat G, Arreaza-Kaufman D, Venkateswaran N, Galor A, Karp CL. Update on pharmacotherapy for ocular surface squamous neoplasia. Eye Vis (Lond). 2019;6:24. https://doi.org/10.1186/s40662-019-0150-5

13. Monroy D, Serrano A, Galor A, Karp CL. Medical treatment for ocular surface squamous neoplasia. Eye (Lond). 2023;37(5):885-93. https://doi.org/10.1038/s41433-023-02434-x
14. Shields JA, Shields CL, Potter P. Surgical management of conjunctival tumors. The 1994 Lynn B. McMahan lecture. Arch Ophthalmol. 1997;115(6):808-15. https://doi.org/10.1001/archopht.1997.01100150810025
15. Bowen RC, Soto H, Raval V, Bellerive C, Yeaney G, Singh AD. Ocular surface squamous neoplasia: outcomes following primary excision with 2 mm margin and cryotherapy. Eye (Lond). 2021;35(11):3102-9. https://doi.org/10.1038/s41433-020-01353-5
16. Birkholz ES, Goins KM, Sutphin JE, Kitzmann AS, Wagoner MD. Treatment of ocular surface squamous cell intraepithelial neoplasia with and without mitomycin C. Cornea. 2011;30(1):37-41. https://doi.org/10.1097/ICO.0b013e3181dee560
17. Wilson MW, Hungerford JL, George SM, Madreperla SA. Topical mitomycin C for the treatment of conjunctival and corneal epithelial dysplasia and neoplasia. Am J Ophthalmol. 1997;124(3):303-11. https://doi.org/10.1016/s0002-9394(14)70822-0
18. Parrozzani R, Lazzarini D, Alemany-Rubio E, Urban F, Midena E. Topical 1% 5-fluorouracil in ocular surface squamous neoplasia: a long-term safety study. Br J Ophthalmol. 2011;95(3):355-9. https://doi.org/10.1136/bjo.2010.183244
19. Joag MG, Sise A, Murillo JC, Sayed-Ahmed IO, Wong JR, Mercado C, et al. Topical 5-fluorouracil 1% as primary treatment for ocular surface squamous neoplasia. Ophthalmology. 2016;123(7):1442-8. https://doi.org/10.1016/j.ophtha.2016.02.034
20. Parrozzani R, Frizziero L, Trainiti S, Testi I, Miglionico G, Pilotto E, et al. Topical 1% 5-fluoruracil as a sole treatment of corneoconjunctival ocular surface squamous neoplasia: long-term study. Br J Ophthalmol. 2017;101(8):1094-9. https://doi.org/10.1136/bjophthalmol-2016-309219
21. Bahrami B, Greenwell T, Muecke JS. Long-term outcomes after adjunctive topical 5-flurouracil or mitomycin C for the treatment of surgically excised, localized ocular surface squamous neoplasia. Clin Exp Ophthalmol. 2014;42(4):317-22. https://doi.org/10.1111/ceo.12184
22. Bracarda S, Eggermont AM, Samuelsson J. Redefining the role of interferon in the treatment of malignant diseases. Eur J Cancer. 2010;46(2):284-97. https://doi.org/10.1016/j.ejca.2009.10.013
23. Meel R, Dhiman R, Vanathi M, Sen S, Gupta N, Tandon R. Treatment outcome with interferon alpha 2b in ocular surface squamous neoplasia: recommendation as primary treatment by peripheral ophthalmologists. Oman J Ophthalmol. 2021;14(1):27-32. https://doi.org/10.4103/ojo.OJO_201_2018
24. Zarei-Ghanavati M, Mousavi E, Nabavi A, Latifi G, Mehrjardi HZ, Mohebbi M, et al. Changes in in vivo confocal microscopic findings of ocular surface squamous neoplasia during treatment with topical interferon alfa-2b. Ocul Surf. 2018;16(2):235-41. https://doi.org/10.1016/j.jtos.2017.12.003
25. Sun Y, Hua R. Long-term efficacy and safety of subconjunctival/perilesional 5-fluorouracil injections for ocular surface squamous neoplasia. Drug Des Devel Ther. 2020;14:5659-65. https://doi.org/10.2147/DDDT.S285752
26. Ip MH, Coroneo MT. Treatment of previously refractory ocular surface squamous neoplasia with topical cidofovir. JAMA Ophthalmol. 2017;135(5):500-2. https://doi.org/10.1001/jamaophthalmol.2017.0365
27. Höllhumer R, Williams S, Michelow P. Ocular surface squamous neoplasia: management and outcomes. Eye (Lond). 2021;35(6):1562-73. https://doi.org/10.1038/s41433-021-01422-3
28. Finger PT, Chin KJ. Refractory squamous cell carcinoma of the conjunctiva treated with subconjunctival ranibizumab (Lucentis): a two-year study. Ophthalmic Plast Reconstr Surg. 2012;28(2):85-9. https://doi.org/10.1097/IOP.0b013e3182392f29
29. Faramarzi A, Feizi S. Subconjunctival bevacizumab injection for ocular surface squamous neoplasia. Cornea. 2013;32(7):998-1001. https://doi.org/10.1097/ICO.0b013e318289ddd8
30. Tabin G, Levin S, Snibson G, Loughnan M, Taylor H. Late recurrences and the necessity for long-term follow-up in corneal and conjunctival intraepithelial neoplasia. Ophthalmology. 1997;104(3):485-92. https://doi.org/10.1016/s0161-6420(97)30287-5

REVIEW ARTICLE

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A pilot study of quantitative real-time polymerase chain reaction metastases detection on sentinel lymph nodes of oral cancer and literature review

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INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) has a feature of lymphatic dissemination[1,2]. It represents a major prognostic factor[1,3-13]. However, the correct identification of metastatic deposits in lymph nodes (LNs) lacks effectiveness in the early stages of the disease[1]. Physical examination and imaging have proven unreliable, with false-positive and false-negative rates reaching 30%[14,15].

Inaccurate diagnosis of LN metastases can lead to unnecessary up-front neck dissection and increased morbidity in cN0 patients. Conversely, intraoperative frozen section analysis misses small metastatic lesions and could jeopardize permanent sections[1]. A recent approach suggests limiting surgery to nodal staging using sentinel lymph node (SLN) biopsy[16]. This strategy aims to select only pN+ necks in patients for subsequent neck dissection[16]. If the SLN biopsy is negative, neck dissection can be avoided[9].

Currently, there are different methods to analyze SLNs. A significant advantage of the frozen section is its intraoperative applicability, but sensitivity and negative predictive values range from 50 to 93%[16-20] and 85.7 to 99%[18-20], respectively. The method is subject to sampling errors, accuracy depends on the experience of the pathologist[21,22], and material loss can lead to false-negative results[16]. Trivedi et al.[20] demonstrated that the intraoperative analysis of SLNs failed to identify micrometastases and isolated tumor cells (ITC) in most patients. Although the clinical significance of ITC detection is controversial[20,23], the presence of these smaller foci of metastasis is considered to be pathologic and led to neck dissection in the Sentinel European Node Trial[23].

Even under microscopy, small tumor foci may not be detected, suggesting that 7–10% of pN0 patients have nodal recurrence even after elective neck dissection[22,24]. The current reference method is immunohistochemistry and step serial section[16,25]. Approximately 8–20% of patients with HNSCC have LN micrometastases on immunohistochemistry that are not detected by routine histopathological examination[7,26]. If immunohistochemistry confirms metastases not detected by hematoxylin-eosin, the patient may need a second surgical procedure[9]. However, the long time required prevents the use of this method for intraoperative diagnosis[16,26,27].

The accuracy of the intraoperative diagnosis of neck involvement is the gap to be filled in evaluating SLNs. In this respect, molecular techniques for detecting LN metastases have been investigated. A promising alternative is reverse transcription-polymerase chain reaction (RT-PCR). This study aimed to observe our results in a pilot study of RT-PCR in SLN biopsy in our institution, to review the literature on molecular techniques using RT-PCR with a focus on the tumor markers for neck metastases from HNSCC and to estimate the time required in SLN biopsy with quantitative RT-PCR (qRT-PCR).

METHODS

Three patients with cT1N0 of the lateral border of the tongue were consecutively enrolled in this study according to AJCC Eighth Edition for staging the primary lesions and neck. All were submitted to intraoral resection of the primary tumor with sentinel node biopsy. All participants were radiologically negative for lymphatic metastases by multi-slice computerized tomography

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(CT) scan with 128 detectors. All were submitted to two peri-tumorous injections of 0.2 MCI of fitato99m-TC 2 h before the surgery and lymphoscintigraphy 2 h after the injection. The activity of 25.6 MBq was injected along the submucosa of the normal mucous membrane surrounding the tumor in a volume of approximately 0.2 mL. Static images were accomplished in lateral and anteroposterior projections, and the radioactive LNs were marked in the skin. Lymphoscintigraphy and SPEC-CT were performed in all cases. The neck skin was marked accordingly, and a gamma probe was used to identify the sentinel LN intraoperatively. The handheld GP Neoprobe-1500 (Neoprobe Corp, Dublin, OH) identified the SLN in vivo and dissected and confirmed it ex vivo. Afterward, the remaining neck was re-evaluated for the absence of radioactivity. All LNs with radioactivity were dissected and considered SLN up to 10% of the first count. We obtained step serial sections at each 150 µm of the sentinel LN stained with hematoxylin-eosin and immunohistochemistry for cytokeratin AE-1/AE-3 in negative SLNB on HE.

Each SLN RNA was extracted from SLN biopsy samples to estimate the time required for molecular marker analysis in SLN biopsy by standard RT-PCR.

The Aurum™ Total RNA Mini Kit (Bio-Rad #732-6820) was used to extract three samples from different patients' peripheral blood from three lymphocyte samples used as controls. The entire purification process of the samples, including DNase I digestion, was completed in 35 min.

The TaqMan MicroRNA Reverse Transcription kit (Life Technologies, New York, USA) synthesized complementary DNA from total RNA extracted from biological samples. The reactions were carried out at 16°C for 10 min, 42°C for 30 min, and 85°C for 5 min in an Eppendorf 22331 thermal cycler (Eppendorf, Hamburg, Germany).

Real-time qRT-PCR was performed using *EpCAM* gene expression reagent kit—amplicon length of 95 (Thermo Fisher number 4331182), *DSG3* gene expression reagent kit—amplicon length of 69 (Thermo Fisher number 4331182), and *HMBS* gene expression reagent kit—amplicon length of 125 (Thermo Fisher number 4331182). All kits use FAM™ (6-carboxyfluorescein) as the fluorophore.

Reactions were performed in triplicate in a 7500 real-time PCR system (Applied Biosystems, Thermo Fisher Scientific, Waltham, USA) with an initial incubation of 50°C for 2 min and 95°C for 10 min, and then 40 cycles of 95°C for 15 s and 60°C for 60 s. Relative quantification values were obtained by analyzing the results in the 7500 System SDS software (Applied Biosystems, Thermo Fisher Scientific, Waltham, USA) using the comparative CT method (ΔΔCT)[28], considering the *HMBS* gene (former *PBGD*) as a reference.

We reviewed PubMed, Google Scholar, and UniGene (http://www.ncbi.nlm.nih.gov/) databases to identify the most relevant molecular markers for HNSCC metastasis in SLN biopsy.

The study was approved by the Research Ethics Committee of our institution (protocol number 24763919.9.0000.5404, approval number 4.070.277).

RESULTS

The samples were assayed in triplicate to estimate the time spent on molecular analysis by RT-PCR, and the relative expression values are summarized in Table 1.

Each assay step took 35 min for RNA extraction, 45 min for conversion of RNA to DNA, and 62 min for qPCR. The total laboratory procedure time was 2 h and 22 min, withholding the time spent on pipetting and transporting samples. SLN 2 was negative for metastasis, while SLN 1 and 3 were positive for metastases because they expressed proteins above normal. SLN 1 and 3 were also histopathological positive for SCC metastasis in hematoxylin-eosin, step serial sectioning analysis. This sample's relative gene expression values observed a difference between biopsies and relative to lymphocyte controls expression too but with a minimal expression of these last ones (Figures 1 and 2 and Table 2).

Table 1. Expression of *PVA* and *TACSTD1* genes related to squamous cell carcinoma metastases in sentinel lymph node biopsy samples relative to the *PBGD* control gene in lymphocytes from controls.

Samples	Mean expression — *PVA (DSG3)*	Repetition A	Repetition B	Repetition C	Mean expression —*TACSTD1/EpCAM*	Repetition A	Repetition B	Repetition C
SLN 1	37.666796	43.097121	32.116560	37.786709	45.751501	47.457656	41.453422	48.343427
SLN 2	0.0000036	0.000001	0.000003	0.000007	0.006088	0.005421	0.003211	0.009632
SLN 3	12.700829	12.544412	10.342264	15.215812	22.378324	22.580421	23.786763	20.767790
C 1	-2.168592	-2.167878	-2.169900	-2.167998	-3.184274	-2.191000	-3.145231	-4.216591
C 2	-2.174203	-2.171666	-2.180988	-2.169955	-3.965620	-3.345600	-3.548941	-5.002321
C 3	-2.168125	-2.166499	-2.166999	-2.170877	-2.322124	-2.456452	-2.183421	-2.326501

SLN: sentinel lymph node; C: control.

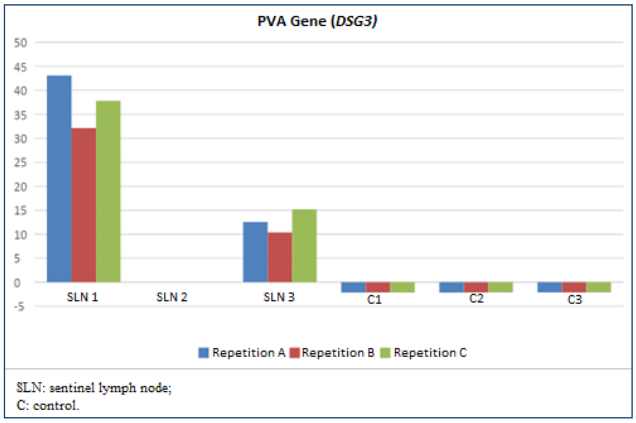

Figure 1. Gene expression detected by real-time polymerase chain reaction of the *PVA* gene (also called *DSG3*) in three sentinel lymph node biopsies and normalization as controls was performed with the expression of the *PBGD* gene (also called *HMBS*) in three lymphocyte samples from the controls. All models were made in triplicates (blue, red, and green).

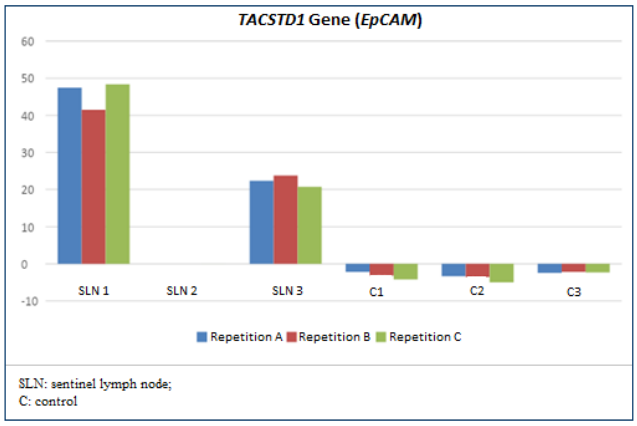

Figure 2. Gene expression detected by real-time polymerase chain reaction of the *TACSTD1* gene (also called *EpCAM*) in three sentinel lymph node biopsies and normalization as controls was performed with the expression of the *PBGD* gene (also called *HMBS*) in three lymphocyte samples from the control. All models were made in triplicates (blue, red, and green).

Our review identified 10 potential molecular markers in the search for cervical metastases from HNSCC: pemphigus vulgaris antigen (*PVA*), *TACSTD1*, squamous cell carcinoma antigen (*SCCA*), *E48*, parathyroid hormone-related protein (*PTHrP*), and cytokeratins (*CK13*, *CK14*, *CK17*, *CK19*, and *CK20*).

Using real-time qRT-PCR, Solassol et al.[27] found no significant difference in the *PVA*, *SCCA*, and *CK17*. However, there was a significant substantial difference in the levels of the three markers between positive and negative LNs (Table 2). Cutoff values were calculated to maximize sensitivity. For a 27.3% prevalence of SLN invasion, the positive predictive values of *CK17*, *SCCA*, and *PVA* were 79.3, 91.2, and 100%, respectively[27].

Table 2. Analysis of molecular markers by real-time polymerase chain reaction.

References	Marker	Sensitivity	Specificity	Accuracy
Ferris et al.[29]	PVA	100%	100%	100%
	TACSTD1	98.3%	94.4%	96.2%
	PTHrP	93.8%	98.8%	96.3%
	SCCA 1/2	99.8%	98.5%	99.1%
Ferris et al.[17]	PVA	92%	98%	98%
	TACSTD1	70%	99%	95%
	PTHrP	60%	98%	95%
Solassol et al.[27]	PVA	100%	100%	100%
	SCCA	100%	93.7%	95.4%
	CK17	100%	81.2%	86.3%
Garrel et al.[16]	CK17	100%	100%	100%
Shores et al.[25]	CK14	100%	96%	**

**Data not available in the study. *PVA:* pemphigus vulgaris antigen; *TACSTD1:* tumor-associated calcium signal transducer 1; *SCCA:* squamous cell carcinoma antigen; *E48:* squamous cell carcinoma specific antigen E48 (Ly-6D); *PTHrP:* parathyroid hormone-related protein; CK: cytokeratin.

Among 40 potential molecular markers, Ferris et al.[29] identified *PVA*, *TACSTD1*, *PTHrP*, and *SCCA 1* and *2* as possible detectors of LN metastases from HNSCC. In a later study, the authors compared the results obtained by qRT-PCR for *PVA*, *PTHrP*, and *TACSTD1* with pathological analysis performed in 35 min[17].

Using RT-PCR, Nieuwenhuis et al.[8] showed *E48*-positive signals in LNs in 22% of pN0 patients and 56% of pN+ patients. In the same study, of 15 patients with *E48*-positive LNs, seven were upstaged regarding N-stage (N0 to N1 or N1/2a to N2b)[8].

Garrel et al.[16] assessed the accuracy of qRT-PCR targeting *CK5*, *CK14*, and *CK17* in HNSCC SLNs. The mean duration of qRT-PCR was 180 min. The area under the curve was 87.1% for *CK5*, 82.8% for *CK14*, and 100% for *CK17*, but *CK17* performed better based on the cutoff value determined by the authors (Table 1)[16]. Shores et al.[25] showed 100% sensitivity and 96% specificity for *CK14* by qRT-PCR, with five possible false positives of a total of 138 negative LNs.

Hamakawa et al.[30] investigated *CK13*, *CK19*, and *CK20* by RT-PCR in primary tumors and cervical LNs of patients with oral SCC. *CK19* was detected in 40% of control LNs, whereas *CK13* and *CK20* were undetectable. *CK13* and *CK19* were expressed in all primary tumors, whereas *CK20* was present in only 40%. Of 13 positive LNs, all expressed *CK13*, one did not express *CK19*, and six had undetectable *CK20* levels. Of 166 negative LNs, *CK13* was expressed in 14.4%, *CK19* in 54.4%, and *CK20* in 3.0%[30].

DISCUSSION

In cN0 patients, SLN biopsy has proven a valuable tool in selecting pN+ in cN0 patients for neck dissection and avoiding surgery for those with negative SLNs, associated with decreasing morbidity in pN0 patients compared with upfront neck dissection. However, this strategy has a sensitivity of 50–85%[16,17], with a negative predictive value of 97%[31]. However, for 29% of patients[31], the SLN could come positive, and a second-stage neck dissection would be necessary. Intraoperative diagnosis of SLN with frozen section has low sensitivity compared with permanent sectioning and demands special microtomes. To avoid a second-stage approach intra-operatively, molecular markers are potential tools for evaluating SLNs in patients with HNSCC if executed within an acceptable time with good reliability.

E48 is an antigen expressed in normal, malignant, and transitional squamous epithelial cells[8]. Nieuwenhuis et al.[32] investigated the diagnosis of micrometastases in LN aspirates. It showed real-time qRT-PCR and greater sensitivity in the cytological examination. Subsequently, the same authors investigated *E48* as a potential marker for detecting HNSCC in LN samples by RT-PCR and compared the results with histopathological examination. *E48* was detected in 22% of pN0 patients and 56% of pN+ patients in at least one histologically tumor-negative LN. There was nodal upstaging in 7 of 15 patients with *E48*-positive LNs[8].

Ferris et al.[17] compared the qRT-PCR results obtained for *PVA*, *PTHrP*, and *TACSTD1* with pathological examination using hematoxylin-eosin and immunohistochemistry staining. Despite demonstrating *PVA's* ability to detect micrometastases in LNs, the same authors pointed out possible limitations[17,21]. In 103 LNs, of which 43 were positive, the assay for *PVA* and *TACSTD1* failed to identify three metastatic LNs with 5% or fewer tumor cells on only one section. The authors' hypothesis for these false-negative LNs was sampling error[17].

Solassol et al.[27] evaluated the applicability and accuracy of real-time RT-PCR with *PVA*, *SCCA*, and *CK17* (Table 2) by comparing it with histopathological examination of 78 SLNs obtained from 22 patients with HNSCC and 11 control LNs from patients without cancer. *PVA* was the only marker distinguishing LNs with micrometastases from negative LNs. No false-negative cases were observed for *PVA*, whereas one and three patients were misclassified with *SCCA* and *CK17*, respectively. None of the markers differentiated ITC from negative LNs, which the authors attributed to a possible sampling error[27].

Hamakawa et al.[6] investigated *SCCA* gene expression using RT-PCR to detect cervical micrometastases from HNSCC by comparison with histopathological examination of 212 LNs obtained from 21 patients. Of 198 histologically negative LNs, *SCCA* mRNA was positive in 37 (18.7%) and upstaged the N-stage of 14 patients[6]. In a later study, Hamakawa et al.[33] evaluated 10 patients with cN0 oral SCC who had undergone SLN biopsy. One-half of each LN was subjected to frozen section analysis, while the other half was subjected to qRT-PCR for *SCCA* quantification. The method was performed manually within 2 h and 30 min, and no gene amplification of *SCCA* was observed in negative control LNs, but the automated process could speed up the analysis. Histopathological evaluation detected micrometastases in two LNs from different patients. *SCCA* was positive in these two LNs and staged as pN+. Moreover, even 2 h and 30 min is still faster than conventional histopathological evaluation with hematoxylin-eosin, step serial section, and immunohistochemistry as standard protocol for assessing SLN.

Shores et al.[25] investigated the use of *CK14* qRT-PCR to detect occult metastases in 153 cervical LNs from 13 patients with HNSCC. One portion of each LN was subjected to histopathological examination, while the rest was subjected to RT-PCR. All histopathological positive LNs expressed *CK14*. The authors established an arbitrary cutoff value for *CK14* detection to avoid false-positive results. Thus, *CK14* had a sensitivity of 100% and a specificity of 96%, with five possible false positives. However, sampling error may have occurred, and the study methodology could not confirm conflicting results between the two analyses[25].

Garrel et al.[16] assessed the accuracy of qRT-PCR in staging SLNs by targeting *CK5*, *CK14*, and *CK17* and using immunohistochemistry as the reference test. The mean duration of qRT-PCR was 180 min. There was no significant difference in the levels of the three markers between controls and negative LNs. *CK17* and *CK14* showed a significant difference in positive LNs compared with negative LNs. *CK5* showed no significant difference between the groups. *CK17* performed better, with 100% sensitivity and specificity, based on the cutoff value determined by the authors. The positive and negative predictive values were 100% for a 41.18% prevalence of SLN invasion. *CK17* failed to detect two micrometastases in two patients, but its staging accuracy was not compromised due to the detection of metastases in other SLNs[16].

Tao et al.[10] evaluated the presence of occult micrometastases in 1,328 LNs from 31 patients with HNSCC by real-time *CK19* qRT-PCR and compared the results with histopathological examination. The LN metastatic rates determined by histopathology and RT-PCR were 16.3 and 36.0%, respectively. The N-stage of 42% of patients would have changed if the molecular analysis had been considered.

Furthermore, *CK19* expression levels were significantly higher in positive than negative LNs[10].

In addition to *SCCA*, Hamakawa et al.[30] investigated the expression of *CK13*, *CK19*, and *CK20* by RT-PCR in primary tumors and neck LNs of patients with oral SCC. They concluded that *CK20* has less value in diagnosing cervical metastasis due to the low detection rate in primary tumors and positive LNs. *CK19* has a high detection rate in negative cervical LNs, possibly due to illegitimate gene expression of leukocytes, *CK19* pseudogene of tissue, or gene expression from ectopic salivary glands. *CK13* would change the N-stage of 100% of pN0 patients[30].

The few studies assessing molecular markers for detecting LN metastasis in HNSCC used different methodologies with small sample sizes and have sometimes been conducted in the context of SLN evaluation. A limitation of this method is the possibility of false positives due to the presence of ectopic salivary glands[6,16,21,26,30]. Hamakawa et al.[6,33] acknowledge that normal salivary glands express *SCCA* in a small volume, which is insufficient to achieve a certain cutoff value. Also, none of the ectopic salivary glands in cervical LNs expressed *SCCA*[6]. However, the same authors showed *CK13* and *CK19* expression in salivary glands[30]. Sampling error has also been considered a limitation in several studies[16,17,26].

Another crucial point is the time spent on genetic testing. Based on the results of our equipment, it took us approximately 2 h and 30 min to run the assay manually. The shorter the assay duration, the greater the benefit in the intraoperative study for LN metastases through SLNs. Ferris et al.[17] described using an automated system to analyze *PVA* and *TACSTD1* genes, in which the assay was completed in approximately 35 min. We contacted the company's representative and were informed that the Ferris et al.[17] cartridges were customized and compounded. Currently, only closed, pre-loaded diagnostic cartridges are available for purchase. For the manufacture of personalized cartridges, additional time would have to be added for production and import.

Although the intraoperative frozen section has been used to evaluate SLN, its sensitivity reported is variable, the accuracy depends on the experience of the pathologist[21,22], and the loss of material can lead to false-negative results[16]. If validated, qRT-PCR is potentially more sensitive than histopathology as it can be used to sample the entire LN or a significant portion of it. Furthermore, qRT-PCR is an objective method that does not depend on the examiner's interpretation and removes any doubt of potential human error with the sample processing. Finally, SLN samples can be processed to permit both qRT-PCR and routine pathological evaluation in parallel on adjacent tissue sections.

The ability to stage the cN0 neck has great clinical application accurately and rapidly to avoid the morbidity associated with open neck dissection in pN- or a second surgery in pN+ patients. These studies show that molecular tumor markers can be used with qRT-PCR to accurately predict nodal metastases in SLN samples in the intraoperative time frame during the procedure to remove the primary tumor or the closure of incisions. Although they are pilot studies, such an analysis is innovative. All showed excellent sensitivity, specificity, and accuracy rates of molecular analysis compared with conventional histopathological and immunohistochemical analysis, with variations of 60–100%, 81.2–100%, and 86.3–100%, respectively.

The lack of accurate diagnosis in the intraoperative frame time of SLNs is a topic of intense interest in the head and neck oncologic community. A delayed pN diagnosis compels pN+ patients to undergo further additional surgery with an increased risk of postoperative complications, damaged function, and worse outcomes. The advent of molecular markers and the development of rapid and precise molecular techniques can fill the gap in evaluating SLNs for identifying and treating LN metastases in HNSCC. If the molecular marker confirms metastases in SLN, the patient will not need a second surgical procedure, and the neck dissection could be done in the same procedure avoiding time delay to adjuvant treatment if required and second hospitalization, which could be a problem in the context of reschedule of another surgery in the same patient.

CONCLUSION

The estimated time for molecular analysis of an SLN biopsy sample by qRT-PCR was approximately 2 h and 30 min. Despite the limitations and few studies, molecular analysis for the diagnosis of lymphatic metastasis in SLN of oral cancer is a promising tool that can help guide surgeons' decision-making in the intraoperative diagnosis of SCC metastasis in SLNs.

ETHICAL APPROVAL

The study was approved by the Research Ethics Committee of our institution (protocol number 24763919.9.0000.5404, approval number 4.070.277).

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AUTHORS' CONTRIBUTIONS

EVC: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resoures, Visualization, Writing – original draft. **FL:** Investigation, Writing – review & editing. **FPG:** Investigation, Writing – review & editing. **DT:** Writing – review & editing. **CSB:** Methodology, Software. **CTC:** Conceptualization, Methodology, Project administration, Resoures, Supervision, Writing – review & editing.

REFERENCES

1. Patel V, Martin D, Malhotra R, Marsh CA, Doçi CL, Veenstra TD, et al. DSG3 as a biomarker for the ultrasensitive detection of occult lymph node metastasis in oral cancer using nanostructured immunoarrays. Oral Oncol. 2013;49(2):93-101. https://doi.org/10.1016/j.oraloncology.2012.08.001
2. Jones AS, Roland NJ, Field JK, Phillips DE. The level of cervical lymph node metastases: their prognostic relevance and relationship with head and neck squamous carcinoma primary sites. Clin Otolaryngol Allied Sci. 1994;19(1):63-9. https://doi.org/10.1111/j.1365-2273.1994.tb01150.x
3. Clark JR, Naranjo N, Franklin JH, Almeida J, Gullane PJ. Established prognostic variables in N0 oral carcinoma. Otolaryngol Head Neck Surg. 2006;135(5):748-53. https://doi.org/10.1016/j.otohns.2006.05.751
4. Alvi A, Johnson JT. Extracapsular spread in the clinically negative neck (N0): implications and outcome. Otolaryngol Head Neck Surg. 1996;114(1):65-70. https://doi.org/10.1016/S0194-59989670285-1
5. Hart RD, Nasser JG, Trites JR, Taylor SM, Bullock M, Barnes D. Sentinel lymph node biopsy in N0 squamous cell carcinoma of the oral cavity and oropharynx. Arch Otolaryngol Head Neck Surg. 2005;131(1):34-8. https://doi.org/10.1001/archotol.131.1.34
6. Hamakawa H, Fukizumi M, Bao Y, Sumida T, Onishi A, Tanioka H, et al. Genetic diagnosis of micrometastasis based on SCC antigen mRNA in cervical lymph nodes of head and neck cancer. Clin Exp Metastasis. 1999;17(7):593-9. https://doi.org/10.1023/a:1006732911057
7. Becker MT, Shores CG, Yu KK, Yarbrough WG. Molecular assay to detect metastatic head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg. 2004;130(1):21-7. https://doi.org/10.1001/archotol.130.1.21
8. Nieuwenhuis EJ, Leemans CR, Kummer JA, Denkers F, Snow GB, Brakenhoff RH. Assessment and clinical significance of micrometastases in lymph nodes of head and neck cancer patients detected by E48 (Ly-6D) quantitative reverse transcription-polymerase chain reaction. [Published correction appears in Lab Invest. 2003;83(12):1917. Kummer A [corrected to Kummer JA]]. Lab Invest. 2003;83(8):1233-40. https://doi.org/10.1097/01.lab.0000083532.46536.56
9. Peigné L, Godey F, Gallo M, Gall F, Fautrel A, Morcet J, et al. One-step nucleic acid amplification for detecting lymph node metastasis of head and neck squamous cell carcinoma. Oral Oncol. 2020;102:104553. https://doi.org/10.1016/j.oraloncology.2019.104553
10. Tao L, Lefèvre M, Ricci S, Saintigny P, Callard P, Périé S, et al. Detection of occult carcinomatous diffusion in lymph nodes from head and neck squamous cell carcinoma using real-time RT-PCR detection of cytokeratin 19 mRNA. Br J Cancer. 2006;94(8):1164-9. https://doi.org/10.1038/sj.bjc.6603073
11. Alkureishi LW, Burak Z, Alvarez JA, Ballinger J, Bilde A, Britten AJ, et al. Joint practice guidelines for radionuclide lymphoscintigraphy for sentinel node localization in oral/oropharyngeal squamous cell carcinoma. Ann Surg Oncol. 2009;16(11):3190-210. https://doi.org/10.1245/s10434-009-0726-8
12. Trivedi S, Mattos J, Gooding W, Godfrey TE, Ferris RL. Correlation of tumor marker expression with nodal disease burden in metastatic head and neck cancer. Otolaryngol Head Neck Surg. 2013;149(2):261-8. https://doi.org/10.1177/0194599813486876
13. Seethala RR. Current state of neck dissection in the United States. Head Neck Pathol. 2009;3(3):238-45. https://doi.org/10.1007/s12105-009-0129-y
14. Merritt RM, Williams MF, James TH, Porubsky ES. Detection of cervical metastasis. A meta-analysis comparing computed tomography with physical examination. Arch Otolaryngol Head Neck Surg. 1997;123(2):149-52. https://doi.org/10.1001/archotol.1997.01900020027004
15. Bondt RB, Hoeberigs MC, Nelemans PJ, Deserno WM, Peutz-Kootstra C, Kremer B, et al. Diagnostic accuracy and additional value of diffusion-weighted imaging for discrimination of malignant cervical lymph nodes in head and neck squamous cell carcinoma. Neuroradiology. 2009;51(3):183-92. https://doi.org/10.1007/s00234-008-0487-2
16. Garrel R, Dromard M, Costes V, Barbotte E, Comte F, Gardiner Q, et al. The diagnostic accuracy of reverse transcription-PCR quantification of cytokeratin mRNA in the detection of sentinel lymph node invasion in oral and oropharyngeal squamous cell carcinoma: a comparison with immunohistochemistry. Clin Cancer Res. 2006;12(8):2498-505. https://doi.org/10.1158/1078-0432.CCR-05-2136
17. Ferris RL, Xi L, Seethala RR, Chan J, Desai S, Hoch B, et al. Intraoperative qRT-PCR for detection of lymph node metastasis in head and neck cancer. Clin Cancer Res. 2011;17(7):1858-66. https://doi.org/10.1158/1078-0432.CCR-10-3110
18. Terada A, Hasegawa Y, Yatabe Y, Hyodo I, Ogawa T, Hanai N, et al. Intraoperative diagnosis of cancer metastasis in sentinel lymph node of oral cancer patients. Oral Oncol. 2008;44(9):838-43. https://doi.org/10.1016/j.oraloncology.2007.11.006
19. Tschopp L, Nuyens M, Stauffer E, Krause T, Zbären P. The value of frozen section analysis of the sentinel lymph node in clinically N0 squamous cell carcinoma of the oral cavity and oropharynx. Otolaryngol Head Neck Surg. 2005;132(1):99-102. https://doi.org/10.1016/j.otohns.2004.09.010
20. Trivedi NP, Ravindran HK, Sundram S, Iyer S, Kekatpure V, Durah S, et al. Pathologic evaluation of sentinel lymph nodes in oral squamous cell carcinoma. Head Neck. 2010;32(11):1437-43. https://doi.org/10.1002/hed.21345
21. Ferris RL, Stefanika P, Xi L, Gooding W, Seethala RR, Godfrey TE. Rapid molecular detection of metastatic head and neck squamous cell carcinoma as an intraoperative adjunct to sentinel lymph node biopsy. Laryngoscope. 2012;122(5):1020-30. https://doi.org/10.1002/lary.22467
22. Tu GY. Upper neck (level II) dissection for N0 neck supraglottic carcinoma. Laryngoscope. 1999;109(3):467-70. https://doi.org/10.1097/00005537-199903000-00023
23. Schilling C, Stoeckli SJ, Haerle SK, Broglie MA, Huber GF, Sorensen JA, et al. Sentinel European node trial (SENT): 3-year results of sentinel node biopsy in oral cancer. Eur J Cancer. 2015;51(18):2777-84. https://doi.org/10.1016/j.ejca.2015.08.023
24. Broglie MA, Haile SR, Stoeckli SJ. Long-term experience in sentinel node biopsy for early oral and oropharyngeal squamous cell

carcinoma. Ann Surg Oncol. 2011;18(10):2732-8. https://doi.org/10.1245/s10434-011-1780-6

25. Shores CG, Yin X, Funkhouser W, Yarbrough W. Clinical evaluation of a new molecular method for detection of micrometastases in head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg. 2004;130(8):937-42. https://doi.org/10.1001/archotol.130.8.937
26. Diest PJ, Torrenga H, Meijer S, Meijer CJ. Pathologic analysis of sentinel lymph nodes. Semin Surg Oncol. 2001;20(3):238-45. https://doi.org/10.1002/ssu.1039
27. Solassol J, Burcia V, Costes V, Lacombe J, Mange A, Barbotte E, et al. Pemphigus vulgaris antigen mRNA quantification for the staging of sentinel lymph nodes in head and neck cancer. Br J Cancer. 2010;102(1):181-7. https://doi.org/10.1038/sj.bjc.6605470
28. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method. Methods. 2001;25(4):402-8. https://doi.org/10.1006/meth.2001.1262
29. Ferris RL, Xi L, Raja S, Hunt JL, Wang J, Gooding WE, et al. Molecular staging of cervical lymph nodes in squamous cell carcinoma of the head and neck. Cancer Res. 2005;65(6):2147-56. https://doi.org/10.1158/0008-5472.CAN-04-3717
30. Hamakawa H, Fukuzumi M, Bao Y, Sumida T, Kayahara H, Onishi A, et al. Keratin mRNA for detecting micrometastasis in cervical lymph nodes of oral cancer. Cancer Lett. 2000;160(1):115-23. https://doi.org/10.1016/s0304-3835(00)00574-7
31. Bosch S, Czerwinski M, Govers T, Takes RP, Bree R, Al-Mamgani A, et al. Diagnostic test accuracy of sentinel lymph node biopsy in squamous cell carcinoma of the oropharynx, larynx, and hypopharynx: a systematic review and meta-analysis. Head Neck. 2022;44(11):2621-32. https://doi.org/10.1002/hed.27175
32. Nieuwenhuis EJ, Jaspars LH, Castelijns JA, Bakker B, Wishaupt RG, Denkers F, et al. Quantitative molecular detection of minimal residual head and neck cancer in lymph node aspirates. Clin Cancer Res. 2003;9(2):755-61. PMID: 12576446
33. Hamakawa H, Onishi A, Sumida T, Terakado N, Hino S, Nakashiro KI, et al. Intraoperative real-time genetic diagnosis for sentinel node navigation surgery. Int J Oral Maxillofac Surg. 2004;33(7):670-5. https://doi.org/10.1016/j.ijom.2004.01.009

REVIEW ARTICLE

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Cancer diagnosis in the post-coronavirus disease era: the promising role of telepathology and artificial intelligence

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INTRODUCTION

Cancer is one of the main public health challenges worldwide, being one of the leading causes of death and representing a significant barrier to increasing life expectancy. In many countries, cancer is the first or second leading cause of premature death before the age of 70. Cancer incidence and mortality are on the rise worldwide[1]. This increase is a result of demographic and epidemiological transitions taking place globally. From a demographic perspective, there is a reduction in the fertility rate and infant mortality, resulting in an increase in the proportion of elderly people in the population. The epidemiological transition, on the other hand, reflects the gradual shift from mortality from infectious diseases to deaths related to chronic diseases. Population aging and changes in behavior and environment, such as structural changes affecting mobility, recreation, diet, and exposure to environmental pollutants, contribute to increased cancer incidence and mortality[2].

In countries with a high human development index (HDI), impacts on incidence and mortality rates have been observed through effective actions for the prevention, early detection, and treatment of cancer. On the contrary, in countries in transition, these rates continue to increase or, at most, remain stable. The challenge for less developed countries is to make more effective use of available resources and efforts to control cancer.

According to estimates by the Global Cancer Observatory (Globocan), prepared by the International Agency for Research on Cancer (IARC), in 2020, there were about 19.3 million new cases of cancer worldwide (excluding cases of non-melanoma skin cancer, which totaled 18.1 million). It is estimated that one in five people will get cancer in their lifetime[1,3]. The 10 most common cancers account for more than 60% of new cases. Female breast cancer is the most common cancer globally, with 2.3 million (11.7%) new cases, followed by lung cancer, with 2.2 million (11.4%); colon and rectum, with 1.9 million (10.0%); prostate, with 1.4 million (7.3%); and non-melanoma skin, with 1.2 million (6.2%) new cases.

For Brazil, the estimate for the three-year period from 2023 to 2025 indicates that there will be approximately 704,000 new cases of cancer, 483,000 of which are cases of non-melanoma skin cancer when cases of non-melanoma skin cancer are excluded. Non-melanoma skin cancer is estimated to be the most prevalent, accounting for about 220,000 cases (31.3%). Next is breast cancer, with 74,000 cases (10.5%); prostate, with 72,000 cases (10.2%); colon and rectum, with 46,000 cases (6.5%); lung, with 32,000 cases (4.6%); and stomach, with 21,000 new cases (3.1%)[4].

When analyzing the most frequent types of cancer in men, there is a predominance of non-melanoma skin cancer, with 102,000 cases (29.9%); followed by prostate cancer, with 72,000 cases (21.0%); colon and rectum, with 22,000 cases (6.4%); lung, with 18,000 cases (5.3%); stomach, with 13,000 cases (3.9%); and oral cavity, with 11,000 cases (3.2%).

In women, the most common cancers are non-melanoma skin cancers, with 118,000 cases (32.7%); breast, with 74,000 cases (20.3%); colon and rectum, with 24,000 cases (6.5%); cervix, with 17,000 cases (4.7%); lung, with 15,000 cases (4.0%); and thyroid, with 14,000 cases (3.9%)[4].

The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on health and the global economy. As of October 2023, there were a total of 771,191,203 confirmed cases of COVID-19, with 6,961,014 deaths[5]. In the field of health, the impact was significant. The health system in several countries has been overwhelmed, with an urgent need for hospital beds, personal protective equipment, and health workers.

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Many hospitals and health facilities have worked beyond their maximum capacity, struggling to care for all patients affected by the disease. COVID-19 has proven to be a serious health threat, especially for vulnerable groups such as the elderly and people with pre-existing conditions. In addition to health, the pandemic has also had a devastating impact on the global economy. Business closures, travel restrictions, and lockdown measures have resulted in a collapse in tourism, retail, entertainment, and many other sectors. Millions of people lost their jobs and faced financial hardship. Governments around the world have had to take urgent action to contain the impact on the economy by implementing financial stimulus packages, aid programs, and support for businesses. Despite these efforts, economic recovery has been an ongoing challenge, with long-lasting consequences for many industries and individuals. Vaccination has been a key tool in the fight against the disease. As of October 5, 2023, a total of 13,516,185,809 vaccine doses had been administered. Mass vaccination was a hope to control the spread of the virus, lessen the severity of the disease, and reduce the number of deaths[5].

In May 2020, the American Society of Clinical Oncology (ASCO) published a special report recommending the postponement of any clinic visits and any cancer screening, diagnosis, or staging-related procedures if this postponement does not pose a risk of disease progression or worsening prognosis[6]. Some international studies show that the decrease in cancer diagnoses in the first months of the pandemic was 65.2% of new cancer cases[6]. Screening for some cancers has been hampered, with data showing that breast, colon, and rectal cancers were the most affected, with 89.2 and 84.5%, respectively. In a study carried out in the United Kingdom, the lockdown caused the suspension of cancer screenings, compromising the early diagnosis of numerous patients. Only in this case were patients with critical and symptomatic clinical conditions directed to diagnostic intervention. Cancer records from the National Health Service (NHS) were used through hospital databases with patients aged 15–84 years diagnosed with breast cancer (35583), colorectal cancer (24,975), and esophageal cancer (6,744) in 2010 with follow-up until 2014. In patients with primary lung cancer (29,305), 2012 was used as the year of diagnosis and 2015 as the final follow-up date. Using a flowchart to define the pathways of cancer patients within the NHS, an estimate was made to assess the consequences of delayed diagnosis in this group of patients over a period of 12 months, starting in March 2020 (lockdown date), contextualizing its impact 1, 3, and 5 years after the initial diagnosis. In this methodology, three pathways or flows of these patients were considered, corresponding to the best to the worst scenario. Based on this, the actual impact of survival at 1, 3, and 5 years after diagnosis was estimated, thus calculating the total number of deaths attributed to cancer and the total number of years of life lost compared with pre-pandemic data[7].

In Brazil, there are several articles reporting the impact of the pandemic on anatomical and pathological diagnoses of cancer, especially in the public health system. The Brazilian Society of Pathology (SBP) was one of the first societies to warn about the problem of cancer diagnosis in the midst of the pandemic. In an article published in Folha de São Paulo on April 17, journalist Claudia Colucci interviewed several representatives of medical societies, among which Dr. Clóvis Klock, at the time President of the Advisory Board of SBP., warned that many pathology services had a 70–80% decrease in cancer diagnoses at the beginning of the pandemic[8]. Subsequently, many articles have demonstrated these aspects of the prediction and impact of the decrease in diagnoses, both in Brazil and in other countries. This impact has been greater in some countries, especially in the case of the most vulnerable people[9-12].

In all scenarios, an increase of 7.9–9.6% in breast cancer deaths was estimated within 5 years after diagnosis, meaning 281–344 more deaths, respectively. In colorectal cancer, the increase was from 15.3% (1,445) to 16.6% (1,563), and in lung cancer, the increase was from 4.8% (1,235) to 5.3% (1,372). And finally, the increase seen in patients with esophageal cancer was 5.8% (330) to 6% (342). These data show that there has been a significant increase in preventable deaths in the United Kingdom, likely due to restrictive measures and social isolation[8]. Another study[13] observed a 40% reduction in the weekly incidence of cancer in the Netherlands and 75% in the United Kingdom since the beginning of the COVID-19 pandemic. This study used a methodology similar to ours, evaluating the records in a database from January to April 2019 comparing them with the same period in 2020.

Delays in cancer diagnosis can occur at different levels of health care: the patient level, primary care, and secondary care. Late diagnoses of more advanced neoplastic diseases may occur when patients are slow to recognize and act on suspicious symptoms[6]. Lack of awareness about early cancer symptoms is the main reason for late presentation, especially when symptoms are atypical[6]. In addition, the high demand for specialized medical services can create an additional barrier, delaying diagnosis, especially in public health services[4].

The COVID-19 pandemic has had significant impacts on cancer diagnosis and treatment, with delays in detection and overburdening health systems. In this context, telepathology and artificial intelligence (AI) emerge as promising tools to overcome these challenges and provide accurate and timely

diagnoses[14]. Telepathology allows the remote analysis of pathological samples, especially slides, whether hematoxylin and eosin, or special techniques, such as immunohistochemistry, facilitating access to specialists and collaborative interpretation of complex cases[15]. With telepathology, it is possible to send scanned images of slides to specialists anywhere in the world, allowing for accurate and rapid assessment. This is especially relevant in resource-constrained areas or during public health crises such as the COVID-19 pandemic[14]. Telepathology can be used in several stages of cancer diagnosis, including screening, primary diagnosis, and second opinion, providing greater agility and access to specialized care. AI, through advanced algorithms, can analyze large amounts of data quickly and accurately. In cancer diagnosis, AI has shown promising results in early detection, differentiation between benign and malignant lesions, classification of cancer subtypes, and selection of personalized therapies. These capabilities can help speed up the diagnostic process and improve accuracy, allowing for more appropriate and timely treatment for patients[16-18].

The use of telepathology and AI in cancer diagnosis can bring several benefits to overcoming the challenges posed by the COVID-19 pandemic. These technologies make it possible to carry out remote consultations, avoiding the need for patients to travel and reducing the risk of contamination[14]. In addition, AI's ability to analyze quickly and accurately contributes to decreasing diagnostic delays and providing reliable results. Implementing these technologies can improve access to healthcare services, particularly in remote or resource-limited areas[18].

The use of telepathology and AI in cancer diagnosis raises important ethical and regulatory considerations. Resolution No. 2,264/2019[19] regulates the use of telepathology in Brazil. It is necessary to ensure the privacy and protection of patient data, informed consent for the use of technologies, and the appropriate regulation of companies that develop and market telepathology and AI solutions, following the General Data Protection Law (Law No. 13,853) of 2019[20]. In addition, it is essential to ensure that these technologies are used as an auxiliary tool for physicians, respecting the expertise and clinical judgment of healthcare professionals.

Cancer diagnosis faces significant challenges in the context of the COVID-19 pandemic. Telepathology and AI emerge as promising solutions for early detection and accurate diagnosis, overcoming delays and reducing the need for patients to travel. The implementation of these technologies requires appropriate ethical and regulatory considerations to ensure their responsible and effective use. Going forward, telepathology and AI are expected to continue to evolve, providing significant advancements in cancer diagnosis and treatment, regardless of public health crises like COVID-19.

In addition, it is important to highlight that telepathology and AI can also be useful in the monitoring and follow-up of cancer patients, enabling the early identification of recurrences and the adjustment of treatments in a personalized way. These technologies have the potential to revolutionize the approach to cancer by offering more accurate, efficient, and accessible medicine. Therefore, investments in research, development, and implementation of telepathology and AI in the context of cancer are essential to improve treatment outcomes and quality of life for patients.

Telepathology and AI are promising tools in cancer diagnosis, especially in the post-COVID-19 pandemic context. These technologies can provide accurate and timely diagnoses, overcoming delays caused by social distancing measures and overburdening healthcare services. However, it is critical to ensure the protection of patient data, proper regulation, and responsible use of these technologies. With continued investments and advancements, telepathology and AI are expected to play a crucial role in improving access to healthcare services and optimizing cancer diagnosis and treatment, achieving better outcomes for patients worldwide.

AUTHORS' CONTRIBUTIONS

CK: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **FAS:** Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
2. Wild CP, Weiderpass E, Stewart BW, editors. World cancer report: cancer research for cancer prevention. Lyon: International Agency for Research on Cancer; 2020.
3. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53. https://doi.org/10.1002/ijc.31937

4. Santos MO, Lima FCS, Martins LFL, Oliveira JFP, Almeida LM, Cancela MC. Estimativa de incidência de câncer no Brasil, 2023-2025. Rev Bras Cancerol. 2023;69(1):e-213700. https://doi.org/10.32635/2176-9745.RBC.2023v69n1.3700
5. World Health Organization. 2023. Available from: https://covid19.who.int/
6. London JW, Fazio-Eynullayeva E, Palchuk MB, Sankey P, McNair C. Effects of the COVID-19 pandemic on cancer-related patient encounters. JCO Clin Cancer Inform. 2020;4(4):657-65. https://doi.org/10.1200/CCI.20.00068
7. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol. 2020;21(8):1023-34. https://doi.org/10.1016/S1470-2045(20)30388-0
8. folha.uol. 2020. Available from: https://www1.folha.uol.com.br/equilibrioesaude/2020/04/pandemia-leva-a-cancelamento-de-cirurgias-e-exames-de-doentes-com-cancer.shtml
9. Klock JCM, Borges, GS, Ogata DC, Klock C. O impacto da pandemia de covid 19 no diagnóstico de câncer em um serviço de patologia do sul do Brasil. Rev Científica Multidiscip Núcleo Conhecimento. 2021;182-90. https://doi.org/10.32749/nucleodoconhecimento.com.br/saude/servico-de-patologia
10. Breast Screening Working Group (WG2) of the Covid-19 and Cancer Global Modelling Consortium, Figueroa JD, Gray E, Pashayan N, Deandrea S, Karch A, et al. The impact of the COVID-19 pandemic on breast cancer early detection and screening. Prev Med. 2021;151:106585. https://doi.org/10.1016/j.ypmed.2021.106585
11. Labaki C, Bakouny Z, Schmidt A, Lipsitz SR, Rebbeck TR, Trinh QD, et al. Recovery of cancer screening tests and possible associated disparities after the first peak of the COVID-19 pandemic. Cancer Cell. 2021;39(8):1042-4. https://doi.org/10.1016/j.ccell.2021.06.019
12. Liss DT, Baker DW. Understanding current racial/ethnic disparities in colorectal cancer screening in the United States: the contribution of socioeconomic status and access to care. Am J Prev Med. 2014;46(3):228-36. https://doi.org/10.1016/j.amepre.2013.10.023
13. Kaufman HW, Chen Z, Niles J, Fesko Y. Changes in the number of US patients with newly identified cancer before and during the coronavirus disease 2019 (COVID-19) pandemic. JAMA Netw Open. 2020;3(8):e2017267. https://doi.org/10.1001/jamanetworkopen.2020.17267
14. Cimadamore A, Lopez-Beltran A, Scarpelli M, Cheng L, Montironi R. Digital pathology and COVID-19 and future crises: pathologists can safely diagnose cases from home using a consumer monitor and a mini PC. J Clin Pathol. 2020;73(11):695-6. https://doi.org/10.1136/jclinpath-2020-206943
15. Alami H, Fortin JP, Gagnon MP, Pollender H, Têtu B, Tanguay F. The challenges of a complex and innovative telehealth project: a qualitative evaluation of the eastern Quebec telepathology network. Int J Health Policy Manag. 2018;7(5):421-32. https://doi.org/10.15171/ijhpm.2017.106
16. Bulten W, Kartasalo K, Chen PC, Ström P, Pinckaers H, Nagpal K, et al. Artificial intelligence for diagnosis and Gleason grading of prostate cancer: the PANDA challenge. Nat Med. 2022;28(1):154-63. https://doi.org/10.1038/s41591-021-01620-2
17. Parwani AV. Next generation diagnostic pathology: use of digital pathology and artificial intelligence tools to augment a pathological diagnosis. Diagn Pathol. 2019;14(1):138. https://doi.org/10.1186/s13000-019-0921-2
18. Shafi S, Parwani AV. Artificial intelligence in diagnostic pathology. Diagn Pathol. 2023;18(1):109. https://doi.org/10.1186/s13000-023-01375-z
19. CFM. 2019. Available from: https://sistemas.cfm.org.br/normas/arquivos/resolucoes/BR/2019/2264_2019.pdf
20. Presidência da República. 2018. Available from: https://www.planalto.gov.br/ccivil_03/_ato2015-2018/2018/lei/l13709.htm

REVIEW ARTICLE

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Childhood and adolescent cancer: early diagnosis challenges

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INTRODUCTION

Childhood and adolescent cancers differ from adult cancers in terms of both the type of normal cellular counterpart involved and the mechanisms underlying malignant transformation[1,2].

Malignant neoplasms in children and teenagers predominantly affect blood cells and supporting tissues. Leukemia, central nervous system (CNS) tumors, and lymphomas are most observed in this age group. However, the global incidence of these conditions varies significantly, largely influenced by demographic and socio-economic factors in the regions under study[1,2].

Contrary to adult cancers, childhood and adolescent cancers typically exhibit shorter incubation periods and more rapid dissemination. These cancers are generally invasive but tend to be more responsive to chemotherapy[1]. Strategies to enhance early diagnostic capabilities should be implemented to facilitate appropriate treatment options and to increase the probability of survival while optimizing quality of life.

Given that the signs and symptoms of childhood and adolescent cancers frequently mimic those of common benign conditions in this age group, medical professionals must exercise rigorous scrutiny to promptly recognize the presence of neoplasia. In this context, the presence of a pediatrician at all levels of healthcare networks becomes a top priority. In instances of clinical suspicion, patients should be promptly referred to a specialized pediatric oncology center[1,2].

In this context, numerous studies have evaluated the factors contributing to delayed diagnosis of pediatric cancer, categorizing them based on the following[3]:

- Disease characteristics: onset, tumor site, and aggressiveness of the neoplasm;
- Patient/parental attributes: patient age, ethnicity, parental educational level, parental occupation, and family religious background;
- Accessibility to healthcare.

Regarding patient age, older children, who are less frequently supervised during activities such as dressing or showering, may experience delayed recognition of the signs and symptoms of the disease. Additionally, teenagers may be reticent to discuss health-related concerns with their parents or caregivers, which could impede early diagnosis[3,4].

EPIDEMIOLOGY

According to the International Agency for Research on Cancer (IARC), approximately 280,000 children and adolescents between the ages of 0 and 19 years were diagnosed with cancer globally in 2020. Of these, an estimated 110,000 succumbed to the disease. The actual incidence may be significantly higher, given that many countries encounter challenges in accurately diagnosing childhood cancers[5].

In Brazil, the National Cancer Institute (INCA) projects an estimated 7,930 new cases of childhood and adolescent cancer annually for the 2023–2025 triennium. This corresponds to an estimated risk of 134.81 cases per million children and adolescents. Annually, new cases are estimated to be 4,230 among males and 3,700 among females. These figures translate to an estimated risk of 140.50 new cases per million male children and 128.87 new cases per million female children[6].

In Brazil, neoplasms in infants constitute 6.3% of all cancer cases among patients in the 0–14 years age group. In this age group, the most diagnosed types of cancer are provided in descending order of frequency: neuroblastoma, leukemia, CNS tumors, retinoblastoma, germ cell tumors, sarcomas, renal tumors, and hepatoblastomas[7,8].

The biological behavior of cancer in adolescents diverges from that observed in both childhood and adult malignancies. These biological variants encompass divergent genetic risks,

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histological subtypes, as well as distinct pathways for oncogenic activation and regulation. The cancer in adolescents constitutes 2–6% of the total number of cancer cases. The histological types most encountered in teenagers are Hodgkin lymphoma, osteosarcoma, and testicular cancer[9].

In terms of anatomical location, specifically in the head and neck region, retinoblastoma, neuroblastoma, and rhabdomyosarcoma are more frequent in infants up to 3 years. In children aged 3–11 years, lymphoma and rhabdomyosarcoma are the most common, while among teenagers and young adults, lymphoma and soft tissue sarcomas prevail[3].

Globally, more than 100,000 children and teenagers under the age of 20 years succumb to cancer annually. Of these, approximately 75,000 are children aged 0–14 years, while around 27,000 are adolescents aged 15–19 years. The mortality rate is generally lower in high- and middle-income countries, largely attributable to more extensive access to precise diagnostic tests and treatment modalities[2].

In Brazil, although cancer in children and adolescents is relatively rare, it represents the leading cause of death due to disease, not considering causes due to accidents and violence, among individuals aged 1–19 years[1].

Trends in mortality rates are influenced by fluctuations in both incidence and survival rates, which, in turn, are shaped by the healthcare system's effectiveness in cancer management, including capabilities for early diagnosis and access to efficacious treatments[1].

RISK FACTORS

Most childhood cancer cases are not attributed to hereditary DNA mutations but rather arise from DNA alterations that occur early in the child's life, occasionally even prenatally. These mutations are somatic in nature, localized exclusively to the neoplastic cells, and are not heritable by offspring[1,2,10].

In childhood and adolescent cancer, there is no scientific evidence to support a significant etiological role for environmental or exogenous factors. However, high dose ionizing radiation and prior chemotherapy are recognized causes. For a substantial number of childhood cancer cases, existing research on etiology is either inconsistent or insufficient to permit a meta-analysis[2,10].

The minority of childhood cancer cases (5–10%) are caused by inherited predisposition. However, the percentage of inherited contribution varies significantly by cancer type and may be compounded by other genetic factors, as observed in adrenocortical carcinoma, choroid plexus carcinoma, optic nerve glioma, and retinoblastoma[2].

The chromosomal syndromes most associated with an elevated risk of neoplasm development include Trisomy 21, WAGR syndrome, and syndromes related to chromosomal instability, such as ataxia telangiectasia, Fanconi anemia, Bloom syndrome, Nijmegen syndrome, dyskeratosis congenita, and xeroderma pigmentosum[1,2].

Advances in genomics underscore the importance of conducting meticulously designed studies to identify the risk factors for cancer in childhood and adolescence, facilitated by the development of innovative analytic techniques. However, such studies necessitate larger sample sizes, which can only be attained through enhanced collaborative efforts[2].

In this context, in the Brazilian state of Paraná, the incidence of tumors in the adrenal cortex in children is 15–18 times higher compared with that in the United States and Europe. Additionally, in the states of Santa Catarina and São Paulo, this neoplasm has also been observed with greater frequency. The higher incidence is associated with an R337H mutation of the *p53* tumor suppressor gene. It is crucial for doctors in general and pediatricians specifically, to remain vigilant for early signs of puberty, particularly during the first years of life, to diagnose adrenal carcinoma in its initial stages—when surgical intervention alone has a near 100% survival rate[1].

DIAGNOSIS

Given the current minimal evidence supporting a significant etiological role for environmental or exogenous factors in childhood cancer, it is imperative to prioritize early diagnosis. However, if medical professionals do not consider the possibility of cancer, this could lead to delayed diagnosis. As a form of secondary prevention, cancer screening in children is either ineffective or applicable only to a limited subset of patients[1,2].

The exclusion of childhood and adolescent cancer as a diagnostic consideration often leads to delayed diagnosis in various neoplasias, such as bone tumors. In our experience, patients with osteosarcoma typically take an average of 4–5 months to seek medical attention for pain symptoms originating from tumors. In some instances, this period can extend up to 1 year, marked by a diagnostic odyssey involving different medical consultations.

In this context, medical professionals must exercise heightened vigilance, giving special attention to certain signs and symptoms (Table 1) that may be associated with at least 85% of childhood and adolescent cancer cases[1,3].

It is relevant to conduct a detailed clinical history, based on the chief complaint, as well as a thorough physical examination to assist in the identification of the disease in its early stages.

Table 1. Signs and symptoms of childhood and adolescent cancer.

Signs and symptoms	Possibility
Volume increase in soft tissue (although a history of trauma is frequently observed, no causal relationship has been established)	Sarcoma, leukemia
Increase in testicle volume	Leukemia, germ cell tumor
Persistent morning headaches, possibly associated with neurological alterations, diabetes insipidus, neurofibromatosis, or prior leukemia radiation therapy	Central nervous system tumor Langerhans cell histiocytosis
Abdominal pain, abdominal mass	Solid tumors, differentiation from hepatosplenomegaly
Refractory odontalgia	Lymphoma, rhabdomyosarcoma
Back pain that exacerbates in a supine position, with or without signs of spinal cord compression	Lymphoma, neuroblastoma, primitive neuroectodermal tumor, rhabdomyosarcoma, leukemia
Bone or joint pain, particularly if persistent and causing nocturnal awakening in the child, may be accompanied by edema, a palpable mass, or functional limitation	Leukemia, malignant bone tumor, and neuroblastoma
Ecchymoses, petechiae, and other forms of hemorrhage	Spinal cord involvement by leukemia, lymphoma, and neuroblastoma
Strabismus, nystagmus	Retinoblastoma
Excessive weight gain	Adrenocortical carcinoma
Exophtalmos, palpebral ecchymosis	Neuroblastoma (raccoon eyes), rhabdomyosarcoma, Langerhans cell histiocytosis
Fever of unknown origin persisting over an extended period	Lymphoma, leukemia, neuroblastoma, Ewing sarcoma
Hematuria, sistemic hypertension	Wilms tumor
Hepatosplenomegaly	Leukemia, lymphoma
Heterochromia, anisochromia	Neuroblastoma
Leukocoria or "white pupillary reflex"	Retinoblastoma
Asymmetric lymphadenopathy, similar to "potato bag"	Hodgkin lymphoma
Low cervical lymphadenopathy in teenagers	Thyroid carcinoma
Lymphadenopathy, particularly in the posterior auricular, epitrochlear, and supraclavicular regions	Leukemia and lymphoma
Altered nevi, particularly in areas subject to friction or sun exposure	Melanoma (rare in children)
Chronic otalgia and/or otorrhea, particularly if associated with seborrheic dermatitis	Langerhans cell histiocytosis, rhabdomyosarcoma
Pallor, fatigue	Anemia secondary to spinal cord involvement
Unexplained weight loss	Hodgkin lymphoma, Ewing sarcoma
Pruritus, nocturnal hyperhidrosis	Hodgkin lymphoma
Precocious pseudopuberty	Adrenocortical carcinoma
Vaginal bleeding	Rhabdomyosarcoma
Chronic non-productive cough	Leukemia or lymphoma, with mediastinal mass

Source: Silva et al.[1].

Family history and the presence of genetic or constitutional diseases can also aid in diagnostic formulation[1,2].

Some situations, such as oncological emergencies and urgencies, can manifest as initial symptoms of the disease, develop during treatment, or occur during its progression or recurrence. These conditions include hyperleukocytosis, tumor lysis syndrome, superior vena cava syndrome, superior mediastinal syndrome, intracranial hypertension, spinal cord compression, and febrile neutropenia. These oncological emergencies and urgencies require rapid identification and appropriate treatment to minimize mortality and sequelae in this patient population[1,3].

In retinoblastoma, the most commonly occurring intraocular tumor in children, diagnosis is confirmed through retinal examination with dilated pupil and specific findings in imaging exams. Direct biopsy of the tumor is contraindicated due to the risk of disease dissemination[1,3].

In malignant neoplasms requiring biopsy, several general principles should be adhered to for accurate diagnosis:

obtaining sufficient tissue without jeopardizing subsequent therapy, favoring excisional biopsy when malignancy involves an organ or lymph node, and ensuring proper preservation of the biopsy material[1,3].

The use of minimally invasive techniques is increasing, with successful results for both diagnostic tissue acquisition and research investigations. Fine-needle aspiration biopsy (FNAB) is commonly employed in adult cancer diagnosis. However, limitations regarding sample size and the potential need for repeat procedures restrict its utility among children[3].

Percutaneous image-guided needle biopsy, facilitated by either ultrasound or CT scan, is increasingly being employed for the diagnosis of malignant tumors in pediatric patients, particularly when complete tumor resection is unfeasible. Numerous studies have demonstrated that this approach is accurate, safe, and cost-effective for diagnosing solid tumors in pediatric populations[3].

Alterations in the hemogram, such as leukocytosis or leukopenia—primarily associated with neutropenia or pancytopenia—may indicate neoplastic infiltration of the bone marrow. These are typically observed in conditions such as leukemia, lymphoma, and neuroblastoma and less commonly in retinoblastoma[1,3].

Indications for bone marrow aspiration (myelogram) include the following[1,3]:

- Significant and unexplained reduction of one or more hematologic lineages;
- Presence of blasts or leukoerythroblastic alterations in peripheral blood;
- Unexplained association with lymphadenopathy or hepatosplenomegaly;
- Association to anterior mediastinal mass.

A crucial consideration for all doctors is to avoid corticosteroids prior to establishing a definitive diagnosis, as these drugs may obscure clinical presentation, select for resistant leukemia cells, and adversely affect patient prognosis[1].

TREATMENT AND PROGNOSIS

Many pediatric malignancies have high cure rates, and early diagnosis in certain histological subtypes may correlate with improved prognosis, reduced therapy intensity, and fewer disease- or treatment-related complications[3].

Therapeutic options are diverse, encompassing chemotherapy, surgery, radiation therapy, immunotherapy, targeted therapy, hematopoietic stem-cell transplantation, and organ transplantation. Each modality should be individualized based on the histological type and clinical extent of the disease[1].

Significant variability exists in survival rates among children and teenagers diagnosed with different neoplasms, depending on factors such as natural history, affected organ, extent of dissemination, and responsiveness to antineoplastic therapies. With advancements in technology, treatment is becoming increasingly individualized through the application of precision medicine and the development of targeted therapy[1].

In response to the need for cancer management across all age groups, including children, the World Health Organization (WHO) launched the Global Initiative for Childhood Cancer Control in 2018, supported by IARC and other global partners. The initiative aims to achieve a minimum global survival rate of 60% by 2030[1,11].

Avoidable deaths from childhood and adolescent cancer in low- and middle-income countries can be attributed to factors such as underdiagnosis, delayed or incorrect diagnoses, limited healthcare access, treatment abandonment, higher rates of treatment-related toxicity, and increased recurrence[5,11].

CONCLUSION

Although survival rates are contingent on histological diagnosis, 80–85% of all childhood and adolescent cancer types have the potential for cure if detected early and treated at specialized pediatric oncology centers that adhere to cooperative protocols.

If cancer is suspected in a child or teenager, prompt referral to a specialized center is essential for timely diagnosis, clinical staging, and immediate treatment initiation, given that early intervention can mitigate morbidity and disease-related complications.

AUTHORS' CONTRIBUTIONS

DBS: Conceptualization, Investigation, Writing – review & editing. **MADP:** Conceptualization, Investigation, Writing – review & editing. **MTFC:** Conceptualization, Writing – review & editing.

REFERENCES

1. Silva DB, Barreto JHS, Pianovski MAD. Epidemiologia e diagnóstico precoce do câncer infantojuvenil. In: Silva LR, Solé D, Silva CAA, Constantino CF, Liberal EF, Lopez FA, editors. Tratado de Pediatria. 5th ed. São Paulo (SP): Manole; 2022. p. 447-53.
2. Scheurer ME, Lupo PJ, Schüz J, Spector LG. Epidemiology of childhood cancer. In: Blaney SM, Adamson PC, Helman L, editors. Pizzo and Poplack's pediatric oncology. 8th ed. Philadelphia: Wolters Kluwer Health; 2021. p. 80-113.
3. Allen-Rhoades W, Steuber CP. Clinical assessment and differential diagnosis of suspected childhood cancer. In: Blaney SM, Adamson

PC, Helman L, editors. Pizzo and Poplack's pediatric oncology. 8th ed. Philadelphia: Wolters Kluwer Health; 2021. p. 370-89.

4. Ni X, Li Z, Li X, Zhang X, Bai G, Liu Y, et al. Socioeconomic inequalities in cancer incidence and access to health services among children and adolescents in China: a cross-sectional study. Lancet. 2022;400(10357):1020-32. https://doi.org/10.1016/S0140-6736(22)01541-0
5. Wild CP, Weiderpass E, Stewart BW, editors. World cancer report: cancer research for cancer prevention. Lyon: International Agency for Research on Cancer. 2020. [cited on 2023 Aug 31]. Available from: http://publications.iarc.fr/586
6. Instituto Nacional de Câncer (Brasil). Estimativa 2023: incidência de câncer no Brasil / Instituto Nacional de Câncer. Rio de Janeiro (RJ): INCA; 2022. p. 160.
7. Pianovski MAD, Silva DB, Belfort Neto R, Singh A. Neoplasias no lactente. In: Silva LR, Solé D, Silva CAA, Constantino CF, Liberal EF, Lopez FA, editors. Tratado de pediatria. 5th ed. São Paulo (SP): Manole; 2022. p. 495-502.
8. Wechsler DS editor. Neonatal malignant disorders, an issue of clinics in perinatology. v. 48. Amsterdã: Elsevier; 2021. p. 240.
9. Gorender EF, Barreto JHS. Câncer no adolescente. In: Silva LR, Solé D, Silva CAA, Constantino CF, Liberal EF, Lopez FA, editors. Tratado de pediatria. 5th ed. São Paulo (SP): Manole; 2022. p. 503-9.
10. Silva DB, Barreto JHS, Pianovski MAD. Câncer infantojuvenil e fatores de risco. In: Silva LR, Solé D, editors. Diagnóstico em pediatria. 2nd ed. São Paulo (SP): Manole; 2022. p. 1128-40.
11. World Health Organization. WHO report on cancer: setting priorities, investing wisely and providing care for all. Geneva: World Health Organization; 2020. [cited on 2022 Aug 30]. Available from: https://apps.who.int/iris/handle/10665/330745

REVIEW ARTICLE

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Interfaces between oncology and psychiatry

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INTRODUCTION

Cancer caused nearly 10 million deaths worldwide in 2020, or one-sixth of all deaths. Cancer is a difficult disease with many physical and psychological effects. Pain, weariness, and appearance changes may occur. They may struggle with depression, anxiety, and hopelessness. The sickness and its treatment raise life situations and existential and spiritual questions. The patient and their family and friends suffer during this long and difficult journey[1,2].

Mental problems are 30–60% more common in cancer patients. In addition, 29–43% of these individuals fulfill mental illness diagnostic criteria[3-5] with 1.28 more chance than controls[6]. Depression, adjustment difficulties, anxiety disorders, and delirium are common in these people. Advanced disease patients have a greater frequency and worse prognosis for these disorders[3-5]. Unfortunately, the occurrence of these common disorders, which have the potential for successful treatment, is underestimated and undertreated in cancer patients. Only 10% of these persons are referred for mental health services, according to empirical evidence[3-5]. The problems of stigma and discrimination, poorer dignity, poorer health behavior, and lack of integration in health-care services for people with severe mental disorders need to be addressed and solved in cancer care[7-9].

Interdisciplinary collaboration across medical disciplines is needed to advance cancer research and improve clinical care due to its complexity. Allowing cancer patients to communicate their fears might induce psychological distress management. Cognitive-behavioral therapy, crisis intervention, problem-solving, supportive, and group psychotherapy have been shown to reduce distress and improve the quality of life in cancer patients[10]. Psychotropic drugs and a psychiatrist are needed for severe and long-lasting symptoms. Mental condition differential diagnosis requires a thorough and specialized examination to distinguish between main and secondary causes[4].

Despite the importance of recognizing and correctly managing mental disorders in cancer patients, there is still less information in the literature on the subject. Therefore, this article aims to present a narrative review regarding the interfaces between oncology and psychiatry, in addition to discussing how the psychiatrist can assist the oncologist and other professionals who deal with oncological diseases in the correct management of mental disorders with a focus on in improving the prognosis and quality of life.

METHODS

A narrative review was carried out using the following keywords according to Mesh: oncology AND mental disorders. There was no restriction by language or date. The following articles were included: meta-analysis, systematic and non-systematic review, guidelines, clinical trials, cohorts, case-control, and cross-sectional studies. The following were excluded: case reports, case series, editorials, letters to the editor, and abstracts in event annals. Based on their technical knowledge and experience, the authors selected articles for inclusion in the final text for convenience.

RESULTS

Many cancer patients have psychological anguish after their diagnosis and treatment, regardless of stage. Distress includes unfavorable experiences impacted by cognitive, behavioral, emotional, social, spiritual, and physical variables. It can impair cancer management, including symptoms and therapy. Distress ranges from vulnerability, sadness, and anxiety to severe suffering and psychological and social impairment, which may indicate a mental disease[11-13]. Stress can result from cancer diagnosis

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and the many changes that occur during treatment and afterward. Despite advances in cancer detection and treatment, the prevalence of long-term side effects outweighs the efficacy of cancer treatments in improving survival rates across all age groups. Patients' everyday activities are hindered by weariness, discomfort, worry, and sadness[11-13].

Those with a history of mental illness, depression, or substance abuse are more likely to experience moderate or severe discomfort. Cognitive impairment, major concomitant diseases, uncontrolled symptoms, communication issues, and social barriers increase risk. Younger age, living alone, having young dependents, and earlier trauma and abuse—physical, sexual, emotional, and verbal—are social challenges and risk factors. Understanding cancer genetics is linked to emotional and cognitive distress. Distress has been linked to non-adherence to oncological treatment, increased difficulty making treatment decisions, increased medical appointment frequency, prolonged hospital stays, decreased quality of life, decreased surveillance examination participation, reduced physical activity, and limited smoking cessation progress[11-13].

Support from a psychiatrist and differential and early diagnosis help with a better prognosis and improved quality of life and can prevent the emergence of a mental disorder or its worsening when it already exists.

Management of mental disorders in oncology

Delirium

Neurocognitive impairment caused by brain dysfunction is sometimes called delirium. Changes in consciousness occur suddenly in this state. Patients may develop the neurocognitive and behavioral syndrome at any stage of cancer development, including at diagnosis. This condition may result from cancer, medicine, surgery, or nonmalignant diseases including myocardial infarction[14,15]. Advanced-stage cancer patients have a 90% chance of developing delirium in their final hours, days, and weeks. The most used screening tool is the Confusion Assessment Method (CAM). Delirium's four main symptoms—sudden start and fluctuating course, lack of attention, decreased cognitive functioning, and consciousness changes—form the basis for CAM diagnosis. The CAM method requires criteria (1), (2), and (3) or (4) to diagnose delirium[14,15].

Delirium is treated with pharmaceutical and nonpharmacological methods. Doctors, nurses, and caretakers must collaborate on nonpharmacological treatments. Healthcare practitioners try to alleviate patient stress while guaranteeing patient safety and integrity. Patient and staff safety must always come first. To prevent patient, caregiver, and staff harm, lines and catheters must be repaired immediately[15,16]. A recommended routine includes bed exercises and walking. Physical constraints can worsen symptoms and cause psychological distress; thus, they should be minimized. Patients' needs, including toilet access, must be met immediately. Superfluous procedures and annoying inputs such as light, noise, and bustle should be reduced. Eyeglasses and hearing aids can remedy visual or auditory impairments. To ensure comfort and familiarity, a familiar person should be positioned near the patient. Family and carers should be informed about delirium and its progression[15,16]. This effort educates caregivers and family members on patient support and agitation management. Medical experts should deliver this instructional intervention. Before starting medication, delirium's multiple causes must be identified and treated. Opioids and other risky drugs should be avoided. To eliminate kidney metabolites, infections and hydration must be treated. Antipsychotics including olanzapine, quetiapine, and aripiprazole may help cancer patients with delirium by increasing calm[15,16].

Anxiety disorders

Threats cause psychological and bodily anxiety. Cancer is a life-threatening condition that can cause worry in many individuals. In one research, 77% of 913 patients experienced anxiety within 2 years of medication. Anxiety disorders have several symptoms. Quantitatively excessive reactions, such as anxious adjustment disorder, often occur within a month of stress[17,18]. Generalized anxiety disorder (GAD) requires more symptoms than anxious adjustment disorder and symptom persistence for 6 months. In these conditions, anxiety often seems free-floating, without a precipitant or intensification pattern. Panic disorder causes anxiety to build to a peak. Phobic anxiety only responds to certain triggers, causing anticipatory avoidance. Medical facilities and therapies can cause phobias, and animal and social phobias may precede cancer. A descriptive classification of anxiety disorders is common. Regardless of its qualities, aberrant anxiety caused by an organic stimulation is called organic anxiety. Drugs like interferon can cause organic anxiety in cancer patients. Depression and anxiety might arise. Cancer specialists are responsible for diagnosing cancer patients' anxiety. Cancer specialists are still poor at recognizing and treating patients with mental disorders. Many questionnaires have been used to measure psychological discomfort and depression in cancer patients. All these procedures perform poorly when compared with standardized psychiatric interviews, and their use does not improve depression or anxiety outcomes. The explanation for these poor results is inadequate. Several self-report

surveys measure anxiety specifically[17,18]. However, their relative effectiveness in detecting elevated anxiety levels is unclear. Identifying high-risk populations may help discover anxiety disorders. Younger people, women, and the disadvantaged are more likely to worry. Anxiety symptoms rise following a cancer diagnosis but decrease with time. Several contextual variables affect cancer patients' anxiety. Cancer research has traditionally examined anxiety as a continuum rather than pathological levels, making it unclear how cancer-related conditions affect anxiety disorders or adaptive normal anxiety. People with such symptoms must consult a doctor. Scales aid identification. The nosological diagnosis should guide treatment, which includes psychotherapy, with cognitive-behavioral psychotherapy being the most common, and psychotropic medicines of various durations[17,18].

Mood disorders

Mood disorders pose a substantial health and economic burden across the globe[19]. Due to their chronic, often recurrent nature and common pathophysiological pathways, mood disorders have been associated with a host of physical conditions and illnesses, including cardiovascular disease, diabetes, gastroesophageal reflux disease, asthma, arthritis, and bone fracture. Moreover, mortality rates among those with mood disorders have been estimated to be 35% greater than in the general population, with most of these deaths due to comorbid chronic physical conditions. In the case-control study (n=807), mood disorder was documented for 18 of the 75 (9.3%) cancer cases and among 288 controls (24.0% vs. 39.3%)[20].

Suspicion should arise not only in the presence of mood symptoms (e.g., hypothymia, euphoria, or mixed state) but also in a previous history of mood disorder. Reduced pleasure, difficulties with sleep, changes in appetite, reduced expectations about the future, and ideas of death (with or without planning) may suggest the presence of depression. Increased energy, reduced need for sleep, accelerated thinking, and grandiosity may suggest mania. When conducting the case, it is important to share with the psychiatrist the investigation of possible primary or secondary causes. Examples of the latter include medications, the inflammatory process itself, and hormonal changes (such as the euphoria caused by increased serotonin production in carcinoid tumors or the effects of thyroid hormone supply in preventing recurrence in thyroid neoplasms)[21-23]. Treatment will depend on the diagnosis: depressive disorder (psychotherapy and antidepressants), mania, or mixed state (mood stabilizers and/or atypical antipsychotics)[22,24,25].

Psychotic disorders

Studies have noted that people with schizophrenia or mental disorders are most diagnosed in advanced stages of cancer[4,26,27]. Some symptoms of schizophrenia can emerge secondary to brain tumors and chemotherapy and can be confused with symptoms of delirium[4,26,27]. The preexisting or recent-onset psychosis can have a negative impact on the quality of care, continuity of care, and reaching remission as it is noted that a significant number of people are lost to follow-up in 1 year[4,26,27]. The quality of care is further poor in the homeless and institutionalized psychiatric patients. Treatment involves the use of antipsychotics; however, it is important that the team is aware of the limitations of these patients who have a distorted sense of reality[28]. Such patients will need support from their family members to make decisions. Delusional symptoms should not be confronted directly. At the same time, careful guidance is necessary regarding the state of health and the steps of the entire treatment[4,26,27,29].

Suicide behavior

Mental problems such as mood, substance use, psychotic, personality, and anxiety disorders can lead to suicidal behavior. Suicide risk among cancer patients who have mood disorders or anxiety and somatoform disorders is higher than for those without mental disorders[30]. A unified framework for describing suicidal conduct must include thought, planning, and attempt[31-33]. This improves situational management. Risk factors for suicide behavior must be categorized by the individual's condition, genetic predisposition, demographics, psychological variables, physical well-being, and health status, including chronic diseases. Also, the person's history of suicidal conduct, including non-suicidal self-harm, should be evaluated[31-33]. The examination of a mental disorder requires a safety plan that includes counseling, research, and monitoring to protect the individual. Suicide-risk persons must be monitored. Hospitalization may be necessary to protect their health in high-risk scenarios such as repeated attempts or a set strategy[31-33].

DISCUSSION

As previously discussed, the prevalence of mental illnesses in cancer patients is significant, underscoring the criticality of effectively managing these conditions. The presence of stress associated with illness is a risk factor that requires attention, as it has been identified as a contributing element in the onset of mental disorders. There is a limited body of literature pertaining to this subject, and the current knowledge on differential diagnosis and therapy draws upon the same

information utilized for other patient populations. When formulating a treatment plan, it is crucial to carefully evaluate any secondary reasons (such as drugs and clinical disorders) to see if they may be reversed before taking any psychiatric medication. The management of such circumstances typically entails psychotherapy or pharmacotherapy and necessitates the involvement of a psychiatrist collaborating with the oncology team.

CONCLUSION

The prevalence of mental illnesses among individuals diagnosed with cancer is significant, necessitating the crucial involvement of a psychiatrist in their treatment. These subjects exhibit considerable research potential, as there is a dearth of specialized investigations within this particular cohort.

AUTHORS' CONTRIBUTIONS

ALST: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **LB**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **AGS**: Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **VSL**: Data curation, Formal Analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **ALPB**: Data curation, Formal Analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **FVR**: Data curation, Formal Analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. WHO. Cancer. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer
2. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: an overview. Int J Cancer. 2021. https://doi.org/10.1002/ijc.33588
3. Tada Y, Matsubara M, Kawada S, Ishida M, Wada M, Wada T, et al. Psychiatric disorders in cancer patients at a university hospital in Japan: descriptive analysis of 765 psychiatric referrals. Jpn J Clin Oncol. 2012;42(3):183-8. https://doi.org/10.1093/jjco/hyr200
4. Venkataramu VN, Ghotra HK, Chaturvedi SK. Management of psychiatric disorders in patients with cancer. Indian J Psychiatry. 2022;64(Suppl 2):S458-S472. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_15_22
5. Anuk D, Özkan M, Kizir A, Özkan S. The characteristics and risk factors for common psychiatric disorders in patients with cancer seeking help for mental health. BMC Psychiatry. 2019;19(1):269. https://doi.org/10.1186/s12888-019-2251-z
6. Vehling S, Mehnert-Theuerkauf A, Philipp R, Härter M, Kraywinkel K, Kuhnert R, et al. Prevalence of mental disorders in patients with cancer compared to matched controls - secondary analysis of two nationally representative surveys. Acta Oncol. 2022;61(1):7-13. https://doi.org/10.1080/0284186X.2021.1992008
7. Grassi L, Riba M. Cancer and severe mental illness: bi-directional problems and potential solutions. Psychooncology. 2020;29(10):1445-51. https://doi.org/10.1002/pon.5534
8. Silva AG, Baldaçara L, Cavalcante DA, Fasanella NA, Palha AP. The impact of mental illness stigma on psychiatric emergencies. Front Psychiatry. 2020;11:573. https://doi.org/10.3389/fpsyt.2020.00573
9. Bentson TM, Fløe LE, Bruun JM, Eriksen JG, Johnsen SP, Videbech P, et al. Barriers in cancer trajectories of patients with pre-existing severe mental disorders-a systematic review. Psychooncology. 2023;32(6):862-74. https://doi.org/10.1002/pon.6138
10. Currier MB. The interface of psychiatry and oncology. Int Rev Psychiatry. 2014;26(1):1-3. https://doi.org/10.3109/09540261.2013.871800
11. Oh HM, Son CG. The risk of psychological stress on cancer recurrence: a systematic review. Cancers (Basel). 2021;13(22):5816. https://doi.org/10.3390/cancers13225816
12. National Cancer Institute. Stress and cancer. NIH. 2022. Available from: https://www.cancer.gov/about-cancer/coping/feelings/stress-fact-sheet
13. Riba MB, Donovan KA, Andersen B, Braun I, Breitbart WS, Brewer BW, et al. Distress management, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17(10):1229-49. https://doi.org/10.6004/jnccn.2019.0048
14. Majzoub I, Abunafeesa H, Cheaito R, Cheaito MA, Elsayem AF. Management of altered mental status and delirium in cancer patients. Ann Palliat Med. 2019;8(5):728-39. https://doi.org/10.21037/apm.2019.09.14
15. Bush SH, Lawlor PG, Ryan K, Centeno C, Lucchesi M, Kanji S, et al. Delirium in adult cancer patients: ESMO clinical practice guidelines. Ann Oncol. 2018;29(Suppl 4):iv143-iv165. https://doi.org/10.1093/annonc/mdy147
16. Baldaçara L, Diaz AP, Leite V, Pereira LA, Santos RM, Gomes Júnior VP, et al. Brazilian guidelines for the management of psychomotor agitation. Part 2. Pharmacological approach. Braz J Psychiatry. 2019;41(4):324-35. https://doi.org/10.1590/1516-4446-2018-0177
17. Stark D, Kiely M, Smith A, Velikova G, House A, Selby P. Anxiety disorders in cancer patients: their nature, associations, and relation to quality of life. J Clin Oncol. 2002;20(14):3137-48. https://doi.org/10.1200/JCO.2002.08.549
18. Traeger L, Greer JA, Fernandez-Robles C, Temel JS, Pirl WF. Evidence-based treatment of anxiety in patients with cancer. J Clin Oncol. 2012;30(11):1197-205. https://doi.org/10.1200/JCO.2011.39.5632

19. National Institute of Health. Any mood disorder. NIH. 2024. Available from: https://www.nimh.nih.gov/health/statistics/any-mood-disorder
20. Cowdery SP, Stuart AL, Pasco JA, Berk M, Campbell D, Bjerkeset O, et al. Mood disorder and cancer onset: evidence from a population-based sample of Australian women. Braz J Psychiatry. 2021;43(4):355-61. https://doi.org/10.1590/1516-4446-2020-0932
21. Ismail MF, Lavelle C, Cassidy EM. Steroid-induced mental disorders in cancer patients: a systematic review. Future Oncol. 2017;13(29):2719-31. https://doi.org/10.2217/fon-2017-0306
22. Kishi T, Ikuta T, Matsuda Y, Sakuma K, Okuya M, Nomura I, et al. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. Mol Psychiatry. 2022;27(2):1136-44. https://doi.org/10.1038/s41380-021-01334-4
23. Miola A, Porto V, Meda N, Perini G, Solmi M, Sambataro F. Secondary Mania induced by TNF-α inhibitors: a systematic review. Psychiatry Clin Neurosci. 2022;76(1):15-21. https://doi.org/10.1111/pcn.13302
24. Malhi GS, Bell E, Bassett D, Boyce P, Bryant R, Hazell P, et al. The 2020 Royal Australian and New Zealand college of psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2021;55(1):7-117. https://doi.org/10.1177/0004867420979353
25. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97-170. https://doi.org/10.1111/bdi.12609
26. American Psychiatric Association. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia / Guideline Writing Group, Systematic Review Group, Committee on Practice Guidelines. 3rd ed. Washington (DC): American Psychiatric Association; 2021.
27. Wootten JC, Wiener JC, Blanchette PS, Anderson KK. Cancer incidence and stage at diagnosis among people with psychotic disorders: systematic review and meta-analysis. Cancer Epidemiol. 2022;80:102233. https://doi.org/10.1016/j.canep.2022.102233
28. Bertoni RA, Leal FM. revisão do tratamento da esquizofrenia: monoterapia vs associação de antipsicóticos. Debates em Psiquiatria. 2023;13:1-20. https://doi.org/10.25118/2763-9037.2023.v13.414
29. Cavagnoli NM, Merlo Medeiros P, Moraes FN, Aleixo ALB, Hofmeister CF, Leal KP. Síndrome de capgras como manifestação de tumor renal. Debates em Psiquiatria. 2022;12. https://doi.org/10.25118/2763-9037.2022.v12.431.
30. Choi JW, Park EC, Kim TH, Han E. Mental disorders and suicide risk among cancer patients: a nationwide cohort study. Arch Suicide Res. 2022;26(1):44-55. https://doi.org/10.1080/13811118.2020.1779156
31. Baldaçara L, Weber CAT, Gorender M, Grudtner RR, Peu S, Teles ALS, et al. Brazilian Psychiatric Association guidelines for the management of suicidal behavior. Part 3. Suicide prevention hotlines. Braz J Psychiatry. 2023;45(1):54-61. https://doi.org/10.47626/1516-4446-2022-2536
32. Baldaçara L, Rocha GA, Leite VDS, Porto DM, Grudtner RR, Diaz AP, et al. Brazilian psychiatric association guidelines for the management of suicidal behavior. Part 1. Risk factors, protective factors, and assessment. Braz J Psychiatry. 2021;43(5):525-37. https://doi.org/10.1590/1516-4446-2020-0994
33. Baldaçara L, Grudtner RR, Leite V, Porto DM, Robis KP, Fidalgo TM, et al. Brazilian Psychiatric Association guidelines for the management of suicidal behavior. Part 2. Screening, intervention, and prevention. Braz J Psychiatry. 2021;43(5):538-49. https://doi.org/10.1590/1516-4446-2020-1108

REVIEW ARTICLE

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From "dose erythema" to FLASH radiotherapy: impacts on clinical practice

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BRIEF HISTORY

After the discovery of X-rays in 1985 and radioactivity in 1986, the potential of these types of radiation was immediately recognized as an essential tool in medicine. At first, the biological effects and dose magnitudes of radiation were unknown; thus, the biological marker of the therapeutic dose was the redness of the skin after some time of exposure. This kind of dose measurement was known as "dose-erythema" based on which the therapeutic effect and tolerance of the tissues were estimated. During these first years, radiation was used in a variety of scenarios of malignant, benign, infectious, and inflammatory diseases among other applications such as cosmetic and other health-related aspects. Obviously, the hazards of this indiscriminate use started to appear. Only in the late 1930s, the ionization effect of radiation started to be better understood and it was this effect that became the basis for all future radiological dose measurements, allied with the studies of the biological effects of these radiation doses, called radiobiology.

Therefore, from a simple surface application of radiation with the evaluation of the effects based on the redness of the skin to a better knowledge of the dose–effects relationship of this radiation, almost half a century passed.

The first treatments were based on anatomical superficial surrogates and bone anatomy through X-ray images to define the target. Also, low-energy equipment (kilovoltage—kV) was used, which delivered a higher dose throughout the beam pathway and the skin surface, causing varied grades of skin reactions. To bypass this effect, the actual prescription dose was split into different radiation fields that were also defined according to surface anatomy and X-ray images. As the target or tumor location was set only indirectly, large margins were needed to avoid geographic miss and treatment failure. Later, megavoltage (MV) machines were developed and allowed delivery of higher doses to the target while better sparing the skin. Nevertheless, the same strategies for target definition were used for a long time. This irradiation technique may be called "conventional" or bidimensional and is still useful and used in many centers, mainly in middle- and low-income countries.

Technological advances in imaging tools, software, and hardware have made it possible to assess anatomy and dose distribution in three, or even four dimensions, providing more precise treatments and consequently with a lower risk of normal tissue damage. It is the era of three-dimensional or volume-based radiotherapy.

3D-CRT, IMRT, VMAT, IGRT, and 4D-RT[1]

The concept of three-dimensional conformal radiotherapy (3D-CRT) technique emerged in the 1960s and was the greatest step forward in radiotherapy. Volumetric imaging and computing sciences developments made it possible to visualize and quantify volumes rather than planar images for the definition of treatment targets and organs at risk and allowed improvement in dose distribution within the target volume while better sparing the surrounding tissues.

New hardware and software technologies were incorporated and permitted to consider the heterogeneous density of different tissues (different radiation absorption rates in bones and air, for example), according to the number of Hounsfield units of computed tomography (CT). Graphics and three-dimensional reconstructions have allowed the creation of increasingly individualized treatments according to the pathology and anatomy of each patient. In the 1990s and 2000s, other imaging data were integrated into planning systems (magnetic resonance imaging (MRI) and proton emission tomography (PET)). It then became possible to modulate the radiation delivery to better spare organs

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at risk of unnecessary irradiation. Combined with the creation of complex mathematical algorithms for inverse planning, this led to another major advance in radiotherapy, which is intensity-modulated radiotherapy (IMRT), when each tumor voxel is considered an individual target. Initially, with a rather slow dose delivery, the treatment became faster with the implementation of volumetric modulated arc therapy (VMAT).

With increasing precision, dose delivery needed to be assured. Real-time imaging systems were developed, such as oblique orthogonal radiographs performed in the treatment room and a CT scan coupled to the linear accelerator that can perform images while the patient is positioned in the treatment couch (cone-beam CT) to solve this issue. This strategy was called image-guided radiation therapy (IGRT), and even more precise technologies became available.

Simultaneously, and with the same concern for keeping high precision and treatment quality, four-dimensional (4D) CT scans, which account for respiratory motion, have been valuable for treating tumors that move with respiratory motion (e.g., lung and liver tumors), thus introducing the 4D radiotherapy (4D-RT) technique. When combined with IGRT, the level of precision allows the reduction of safety margins and increase of dose per fraction, thereby reducing the total number of fractions and giving rise to the concept of stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR).

SRS, and SABR/SBRT

Despite being an undeniable contribution to the technological evolution of using ionizing radiation for therapeutic purposes, radiosurgery (SRS) dates back to the 1950s when Lars Leksell, a neurosurgeon, developed a non-invasive method for destroying intra-cerebral lesions that were inaccessible through conventional neurological surgery[1]. It is worth noting that at that time, three-dimensional CT images were not available, so the treatment was limited to conditions that could be assessed through angiography, such as arteriovenous malformations, and the treatment location was defined by stereotaxis.

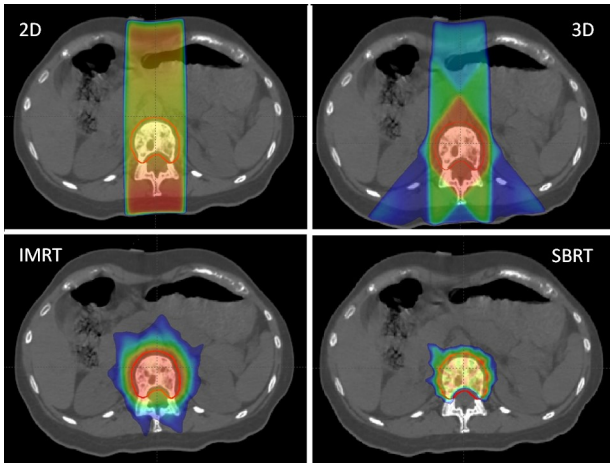
Radiosurgery, by definition, is the delivery of high doses of radiation to a specific volume in a single fraction. In general, multiple fields with lower doses converge at a single center, where a high dose is concentrated, and the dose rapidly decreases at the periphery of the lesion. As the size of the lesion to be treated increases, this dose falloff becomes smaller, potentially limiting the technique, mainly for lesions larger than 4–5 cm. In these cases, the treatment is administered in more than one fraction, when radiosurgery is then referred to as fractionated stereotactic radiotherapy.

SBRT or SABR is the technology that has presented the larger growth in recent years. It follows the same principles as cranial radiosurgery, namely, delivering a potent, ablative, or nearly ablative dose in a few fractions (five or fewer fractions). SBRT can be performed using any of the technologies already described (e.g., 3DCT, IMRT, VMAT, IGRT, and 4D-RT) with the goal of delivering a high dose while sparing the surrounding normal tissues. It has proven to be an interesting technique for treating early lung tumors and oligometastases, particularly because it is effective and allows for a shorter treatment period. This technology also allowed for curative intent radiation treatments that changed clinical practice. For early-stage lung cancer[2] and hepatocellular carcinomas[3], SBRT has proven to be a standard of care for patients with curative intent. It has also been used in patients with oligometastatic cancers, with promising results[4].

Figure 1 shows a comparison of the techniques' evolution.

ADAPTIVE RADIOTHERAPY

Tumor behavior during treatment, i.e., response or progression, can be mapped, and the radiation treatment can be adapted along the treatment, periodically: adaptive radiotherapy. Dose delivery can be changed and adapted according to the daily presentation or location of the lesion, to better assure the precision of dose delivery. However, not only the anatomical changes can be considered



[1]From now on, some titles will be presented with abbreviations that will be defined in the corresponding text. The reason for this format is that the different techniques are better known worldwide by their abbreviation, so the reader can be more acquainted with the specific terms.

Figure 1. Comparison of radiotherapy techniques in the same case of spinal metastasis. Hot colors (red, yellow) illustrate higher doses (prescribed dose), and cold colors (green, blue) illustrate low-dose areas. The red line defines the target. Note that the more advanced the technique (from 2D to 3D, IMRT/VMAT, and SBRT), the higher the normal tissue sparing, including a very precise sparing of the spinal cord with SBRT, where very high doses are delivered (white arrow).

but also the biological behavior of the tumor during treatment. The concept of multidimensional radiotherapy (MD-CRT) based on the "Biological Target Volume" (BTV) was introduced in 2000 by Ling et al.[5] and considers that the tumor has different active areas. These areas may be identified in functional exams (e.g., PET and scintigraphies), and thus, dose delivery can be shaped according to the areas that are more or less active at first, and if indicated, during treatment. This strategy has the potential to achieve better clinical outcomes. However, due to the complexity of the technique and availability of the method, it is not yet used worldwide and is the subject of many ongoing studies.

3D-IGABT

Brachytherapy is the radiation treatment where radioactive material is placed close, or in direct contact, or even inside the target lesion. This technique has also been described since the late 1800s and early 1900s, with several indications and applications. Gynecological (cervical and endometrial cancers) and prostate cancers are the ones where the technique is more often used nowadays. Remarks should be made mostly regarding the evolution of 2D brachytherapy, based only on indirect anatomic references available through simple X-rays, to 3D image-guided adaptative brachytherapy (3D-IGABT). The same principles used in volume-based external beam irradiation are now used for 3D-IGABT, where ultrasound, CT scans, and MRI images are used for treatment planning. The simple technical improvement led to more benefits than the association with chemotherapy, mainly for cervical cancer, where lower toxicity (acute and late) and survival improvement may be expected[6].

IORT

Intraoperative radiation therapy (IORT) is a treatment modality where radiation is delivered during surgery with the displacement of normal tissues away from the irradiated area. It can be performed using external beam radiation therapy equipment or brachytherapy. The main indications for IORT are for abdominal tumors surrounded by intestinal loops, and early-stage breast cancer, either as a single approach or combined with external beam irradiation[7].

HEAVY PARTICLES

Heavy particles can be neutral (neutrons) or charged (electrons, protons). Electrons are lightweight, negatively charged particles produced in the same treatment units as photons (linear accelerators). However, heavier particles require a very expensive infrastructure to be generated.

Among heavy particles, protons have the most prominent role in clinical practice. Due to the physical characteristics of these particles, the beams are particularly useful in treating structures deeply located within tissues while sparing structures surrounding the target volume that would interact with the radiation before reaching this volume.

Clinically, this allowed for the treatment of diseases that previously were treated with more modest outcomes, like chordomas of the base of the skull[8,9], or far more toxic results, as in lymphoma patients[10]. Particularly for pediatric patients[11], the use of proton therapy has proven to be highly effective and changed clinical practice where it is available.

This technology has been growing. However, despite numerous studies being published, the high cost of equipment and its large dimensions are significant drawbacks to the widespread use.

FLASH-RT

It is worth mentioning the FLASH technique, which is defined as radiation therapy delivered at an ultrahigh dose rate (≥40 Gy/s), resulting in treatment times 400 times shorter than conventional treatments. It is promising in terms of its high anti-tumor effect and better preservation of normal tissues. FLASH-RT was first used in humans in Switzerland in 2018[12] but remains an experimental treatment. However, it could become one of the primary radiation therapy technologies in clinical applications in the future.

COMBINED TREATMENTS

Different combinations of irradiation with systemic treatments (e.g., chemotherapy and hormone therapy) have been proven beneficial for patients. New targeted and immunotherapies are emerging, with promising results; some of them are combined with radiation treatment[13]. Identification of genetic mutations and molecular tumor profiles is increasing and will provide a better patient and treatment selection, for individualized approach.

Therefore, it is expected that the combination of all these advances will give better results and more hope for the population.

CLINICAL ASPECTS

All the technological advances in radiotherapy allowed, at first, better normal tissue sparing while providing better tumor coverage by the prescribed dose. Furthermore, target dose increments with higher precision and safety were possible, and better clinical results, with impact on local control and survival and less toxicity are being progressively achieved.

Allied with that, changes in radiobiological paradigms such as the sensibility of some tumors to radiation, such as breast[14,15] and prostate cancers[16], determined the development of successful hypofractionated radiotherapy regimens (higher dose/fraction with lower number of fractions)[17], with many advantages among better management of overloaded departments and more convenience for the patients[18].

In summary, the impacts of the radiotherapy advances in clinical practice involve the following:

- Improved treatment outcomes: Enhanced precision and accuracy in radiation delivery have led to improved tumor control rates and reduced toxicity, ultimately enhancing patient outcomes.
- Personalized medicine: The ability to tailor treatment plans based on individual patient characteristics and tumor dynamics has resulted in more personalized and effective treatments.
- Reduced side effects: By sparing healthy tissues and organs, modern radiotherapy technologies have significantly reduced the incidence and severity of treatment-related side effects, improving patients' quality of life.
- Expanded indications: Many of these innovations have expanded the range of treatable tumors, allowing for more comprehensive cancer care.
- Shorter treatment times: Techniques such as SBRT and FLASH radiation therapy offer shorter treatment durations, reducing the burden on patients and healthcare systems.

FINAL REMARKS

Technological advances in radiotherapy have revolutionized the field, offering clinicians a wide array of tools to treat cancer with unprecedented precision and efficacy. From IGRT to novel approaches like FLASH radiation therapy, these innovations continue to transform clinical practice by improving treatment outcomes, personalizing care, and minimizing side effects. As the landscape of radiotherapy technology continues to evolve, patients can expect even more refined and effective cancer treatments in the future. Radiotherapy remains a cornerstone of cancer care, and its future is brighter than ever.

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AUTHORS' CONTRIBUTIONS

HAC: Conceptualization, Formal Analysis, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MSC:** Conceptualization, Formal Analysis, Validation, Visualization, Writing – review & editing. **GPM:** Formal Analysis, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Roberge D, Salvajoli JV. Radiocirurgia e radioterapia estereotáxica. In: Salvajoli JV, Souhami L, Faria SL, editors. Radioterapia Em Oncologia. v. 1. 3rd ed. Atheneu; 2023. p. 239-70.
2. Ball D, Mai GT, Vinod S, Babington S, Ruben J, Kron T, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol. 2019;20(4):494-503. https://doi.org/10.1016/S1470-2045(18)30896-9
3. Dawson LA, Winter K, Knox J, Zhu AX, Krishnan S, Guha C, et al. NRG/RTOG 1112: randomized phase III study of sorafenib vs. stereotactic body radiation therapy (SBRT) followed by Sorafenib in hepatocellular carcinoma (HCC) (NCT01730937). Int J Radiat Oncol Biol Phys. 2022;114(5):1057. https://doi.org/10.1016/J.IJROBP.2022.09.002
4. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol. 2020;38(25):2830-8. https://doi.org/10.1200/JCO.20.00818
5. Ling CC, Humm J, Larson S, Amols H, Fuks Z, Leibel S, et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. Int J Radiat Oncol Biol Phys. 2000;47(3):551-60. https://doi.org/10.1016/s0360-3016(00)00467-3
6. Suzumura EA, Gama LM, Jahn B, Campolina AG, Carvalho HA, Soárez PC. Effects of 3D image-guided brachytherapy compared to 2D conventional brachytherapy on clinical outcomes in patients with cervical cancer: a systematic review and meta-analyses. Brachytherapy. 2021;20(4):710-37. https://doi.org/10.1016/j.brachy.2021.03.004
7. Pilar A, Gupta M, Ghosh Laskar S, Laskar S. Intraoperative radiotherapy: review of techniques and results. Ecancermedicalscience. 2017;11:750. https://doi.org/10.3332/ecancer.2017.750
8. Hong S, Mahajan A, Laack NN, Link MJ, Shinya Y, O'Brien E, et al. Comparison of tumor control after stereotactic radiosurgery or pencil beam proton therapy for newly diagnosed clival chordomas: a single-center retrospective study. World Neurosurg. 2023;178:e510-9. https://doi.org/10.1016/j.wneu.2023.07.109
9. Chhabra AM, Rice SR, Holtzman A, Choi JI, Hasan S, Press RH, et al. Clinical outcomes and toxicities of 100 patients treated with proton therapy for chordoma on the proton collaborative group prospective registry. Radiother Oncol. 2023;183:109551. https://doi.org/10.1016/j.radonc.2023.109551
10. Abbassi LM, Goudjil F, Arsène-Henry A, Dendale R, Kirova YM. Protontherapy versus best photon for mediastinal hodgkin lymphoma: dosimetry comparison and treatment using ILROG

guidelines. Cancer Radiother. 2019;23(8):922-5. https://doi.org/10.1016/j.canrad.2019.02.005

11. Ahmed SK, Keole SR. Proton therapy in the adolescent and young adult population. Cancers (Basel). 2023;15(17):4269. https://doi.org/10.3390/cancers15174269
12. Lin B, Gao F, Yang Y, Wu D, Zhang Y, Feng G, et al. FLASH radiotherapy: history and future. Front Oncol. 2021;11:644400. https://doi.org/10.3389/fonc.2021.644400
13. Carvalho HA, Villar RC. Radiotherapy and immune response: the systemic effects of a local treatment. Clinics (Sao Paulo). 2018;73(Suppl 1):e557s. https://doi.org/10.6061/clinics/2018/e557s
14. SBRT, Brazilian Society of Radiotherapy, Freitas NMA, Rosa AA, Marta GN, Hanna SA, Hanriot RM, et al. Recommendations for hypofractionated whole-breast irradiation. Rev Assoc Med Bras (1992). 2018;64(9):770-7. https://doi.org/10.1590/1806-9282.64.09.770
15. Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet. 2020;395(10237):1613-26. https://doi.org/10.1016/S0140-6736(20)30932-6
16. Morgan SC, Hoffman K, Loblaw DA, Buyyounouski MK, Patton C, Barocas D, et al. Hypofractionated radiation therapy for localized prostate cancer: an ASTRO, ASCO, and AUA evidence-based guideline. J Clin Oncol. 2018;36(34):JCO1801097. https://doi.org/10.1200/JCO.18.01097
17. Batumalai V, Delaney GP, Descallar J, Gabriel G, Wong K, Shafiq J, et al. Variation in the use of radiotherapy fractionation for breast cancer: survival outcome and cost implications. Radiother Oncol. 2020;152:70-7. https://doi.org/10.1016/j.radonc.2020.07.038
18. Irabor OC, Swanson W, Shaukat F, Wirtz J, Mallum AA, Ngoma T, et al. Can the adoption of hypofractionation guidelines expand global radiotherapy access? An analysis for breast and prostate radiotherapy. JCO Glob Oncol. 2020;6:667-78. https://doi.org/10.1200/JGO.19.00261

REVIEW ARTICLE

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Biopsy of bone tumors: a literature review

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INTRODUCTION

In the differential diagnosis of bone tumors, the following parameters are relevant: age, onset and duration of symptoms, lesion location (affected bone), affected part of the bone, radiographic aspect, and tumor growth pattern.

Clinical evaluation and conventional radiographic examination, together, allow correct diagnosis in >80% of patients. The investigation should proceed where: (a) clinical and imaging findings suggest biological aggressiveness; (b) findings are normal/indeterminate despite clinical presentation; or (c) it is necessary to restage the tumor. Additional imaging modalities are required, seeking accurate information on tumor tissue composition, its anatomical relationships, and metabolic and functional profiles, in addition to the presence of distant dissemination—bone biopsy constitutes the final stage of evaluation, completing the tumor staging[1,2].

The aim of bone biopsy is to obtain a representative tumor tissue sample that enables histopathological, immunohistochemical, cytogenetic, and molecular processing, defining the diagnosis and histological grading. An inadequate technique can make correct tissue analysis unfeasible, hinder definitive surgery, and increase local recurrence and metastase rates among other complications, in addition to potentially making it impossible to preserve the affected limb and/or reduce the patient's chances of survival. The biopsy should be performed by an experienced surgeon, preferably the one who will perform the definitive procedure[3-6].

More recently, we have observed the development of liquid biopsy, which, among other applications, has been used in the diagnosis and follow-up of bone and soft tissue sarcomas[7-9].

This paper updates the reader on the biopsy techniques currently employed in the diagnosis and graduation of bone tumors.

Planning of bone biopsies

A proper bone biopsy requires meticulous planning. The shortest distance to the lesion is not necessarily the ideal path for sample acquisition. Whichever technique is listed, it must follow fundamental principles for its execution[10] (Table 1).

Bone biopsy should be postponed until the imaging evaluation has been completed in order to (a) allow accurate collection planning, seeking the most representative area of the lesion, in line with definitive surgical access; (b) facilitate differential diagnosis, allowing histopathological correlation; and (c) avoid previous manipulation that generates edema and image artifacts[1,2].

It is critical to obtain a sufficient and representative tumor sample. Benign aggressive or malignant primary bone tumors are usually heterogeneous—multiple samples need to be collected to establish a diagnosis. Bone metastases from carcinoma and multiple myeloma, in contrast, are homogeneous, and it is usually sufficient to collect a single tissue sample or aspirate for diagnostic definition[11].

Samples should be collected from the peripheral area, which usually contains viable tumors. It is important to identify and avoid reactive areas and necrotic or hemorrhagic components.

Until proven otherwise, all bone lesions that require bone biopsy should be considered malignant—biopsy routes should always be considered contaminated, requiring complete subsequent removal, en bloc with the resected specimen, in definitive surgery (Figure 1). Anatomical dissection should be averted, as well as violating not affected compartments, intercompartmental planes, neurovascular bundles, and joints. Crossing soft tissue structures necessary for limb reconstruction should also be avoided. Therefore, it is important to plan the biopsy site along the planned access route for definitive surgery. The incision should follow the main axis of the segment being approached[3-6,11].

Perforation of the affected bone during biopsy can lead to iatrogenic fracture. This possibility should be minimized by making small oval or circular bone holes.

In addition to preoperative antibiotic prophylaxis, infections at the biopsy site should be prevented by adequate asepsis and antisepsis.

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Table 1. Fundamental principles of bone biopsies.

Principle 1	All biopsies should be located so that they can be resected en bloc with the operative specimen at the time of definitive surgery.	Performed along the access route planned for the definitive surgery; In the extremities, incisions should be made in the longitudinal direction, following the longest axis of the segments addressed. In other sites, use accesses that avoid contamination of more than one compartment and facilitate oncological resection of tumors. If the use of a drain is necessary, its exit hole should be located along and close to the skin incision (~1 cm).
Principle 2	Avoid contamination of compartments not involved by the tumor.	Avoid: Violation of compartmental barriers; Anatomical dissection; Hematoma; Traverse soft tissue structures necessary for reconstruction.
Principle 3	The material obtained through biopsy should provide a diagnosis.	Ensure that sufficient tissue is obtained; Ensure that a representative sample of the tumor (periphery of the lesion) is obtained; When considering the demand for differential diagnosis with osteoarticular infection, it is recommended to obtain samples for culture and antibiogram.
Principle 4	Avoid iatrogenic complications such as stress fractures or infection at the biopsy site.	The cortical orifice should be small, oval, or circular; Adequate asepsis and antisepsis; Preoperative antibiotic prophylaxis.
Principle 5	Rigorous hemostasis should be achieved prior to wound closure.	Identify history of bleeding disorders and the use of anticoagulants, among other conditions in the preoperative period; Occlude the cortical orifice after the procedure (polymethylmethacrylate, bone wax, or hemostatic sponge); If there is a demand for the use of a tourniquet, remove it before performing definitive hemostasis; If necessary, use a drain along and near the skin incision (~1 cm).

Source: adapted from Campanacci[10].

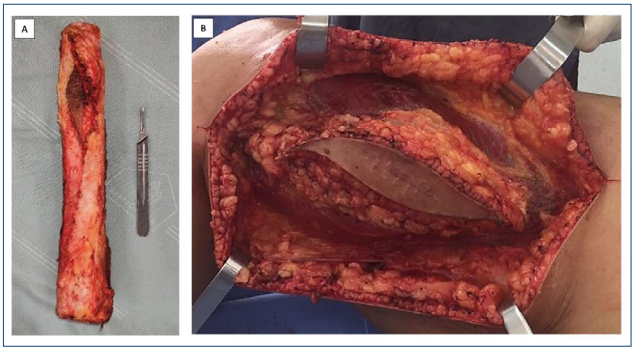

Figure 1. (A) Adamantinoma of the tibia: the piece was resected en bloc with the scar and biopsy path. (B) Osteosarcoma of the distal femur; intraoperative aspect of the procedure of wide tumor resection, biological reconstruction, and fixation - three-dimensional resection of the biopsy pathway, resected together with the specimen in sequence.

It is very important to establish absolute hemostasis to avoid hematoma, because of local dissemination risk, particularly in open biopsies—any hematoma around a tumor should be considered contaminated; large hematomas can dissect compartments, affecting the entire extremity and making it impossible to preserve the limb. It is of paramount importance to identify a history of bleeding disorders and the use of anticoagulants, among other conditions, before the biopsy is scheduled. If there is a need to use a tourniquet, venous emptying using an Esmarch band is contraindicated, due to the risk of proximal tumor dissemination through lymphatic and venous routes—gravitational emptying should be chosen. The tourniquet should be removed before wound closure, allowing adequate hemostasis. Drains generally are not used—in the rare cases where they are needed, their exit holes should be along and near (1 cm) the incision—the drainage path is considered contaminated and should be excised together with the surgical specimen, in the same way as the biopsy path. Bleeding through the bone orifice can be contained by occlusion with bone wax, hemostatic sponge, or polymethylmethacrylate[3-6,11].

Bone biopsy techniques

Diagnostic accuracy should be the most important parameter in defining the bone biopsy technique. There are two types: (a) percutaneous/closed biopsies, minimally invasive procedures, guided or not by images and (b) open biopsies, in which samples are obtained through bloody approach, incisional (lesion sample collection) or excisional (complete lesion resection).

The proximity of adjacent critical structures, the lesion topography, and comfort for the patient should influence the selection of the collection site. In the cases where multiple lesions are present, the most accessible or safest lesion should be chosen for biopsy accomplishment.

Closed or percutaneous bone biopsies

Image-guided percutaneous bone biopsy has become the preferred diagnostic method for a bone neoplasm. It is a minimally invasive procedure with a high level of diagnostic accuracy and a low rate of complications.

Planning a percutaneous biopsy often requires more time and effort than performing this procedure itself. Decisions regarding the selection of guiding modality, needle type, path, specific target in the lesion, and expected pathological findings should be defined before the procedure[12].

Fluoroscopy, computed tomography (CT), magnetic resonance imaging (MRI), single photon emission CT (SPECT), SPECT/CT, and positron emission tomography–CT (PET/CT) enable precise orientation of percutaneous bone biopsies. The quality and availability of imaging modalities vary between practices—logistical details may limit your choice[13-23].

Fluoroscopy (Figure 2) and CT are the preferred modalities for guided biopsies. In hard-to-reach sites (spine and waist belts), CT guidance, in addition to increasing diagnostic accuracy, reduces the rate of complications.

The use of MRI, SPECT, SPECT/CT, and PET/CT in staging has increased the diagnosis of occult bone lesions, defining anatomical landmarks that help to perform CT-guided biopsies, when not guided by these modalities per se.

Although MRI is devoid of ionizing radiation and provides superior characterization and delineation of lesions, MRI-guided biopsy is generally not feasible (equipment compatibility, patient positioning, cost, and execution time), or necessary.

Radionuclide-guided bone biopsy is highly accurate, achieving sensitivity and specificity of up to 100%. The use of a gamma probe is useful in differential diagnosis, especially to confirm or rule out metastatic disease, especially when it is not possible to define an appropriate site for biopsy using other imaging methodologies, in addition to providing limited exposure to ionizing radiation.

Fine-needle aspiration biopsy

In this modality, a thin, hollow needle is inserted directly into the lesion, obtaining a sample for cytological examination by aspirating[24].

Fine-needle aspiration biopsy obtains greater precision in homogeneous lesions (carcinoma metastases and multiple myeloma) and can be used in local recurrences or distant dissemination, in which cytological findings can be compared with those previously obtained.

It is a relatively atraumatic, minimally invasive outpatient procedure, with low cost and morbidity and lower contamination risk.

Its main limitation is that it does not allow the evaluation of tissue architecture, making it difficult or impossible to perform ancillary studies. The incidence of false-negative results is high, and even when results are positive, the diagnosis may not be accurate[3-6,24].

Core needle biopsy

A large needle is inserted through a small incision in the site planned for biopsy, preferably guided by imaging modalities[13-23].

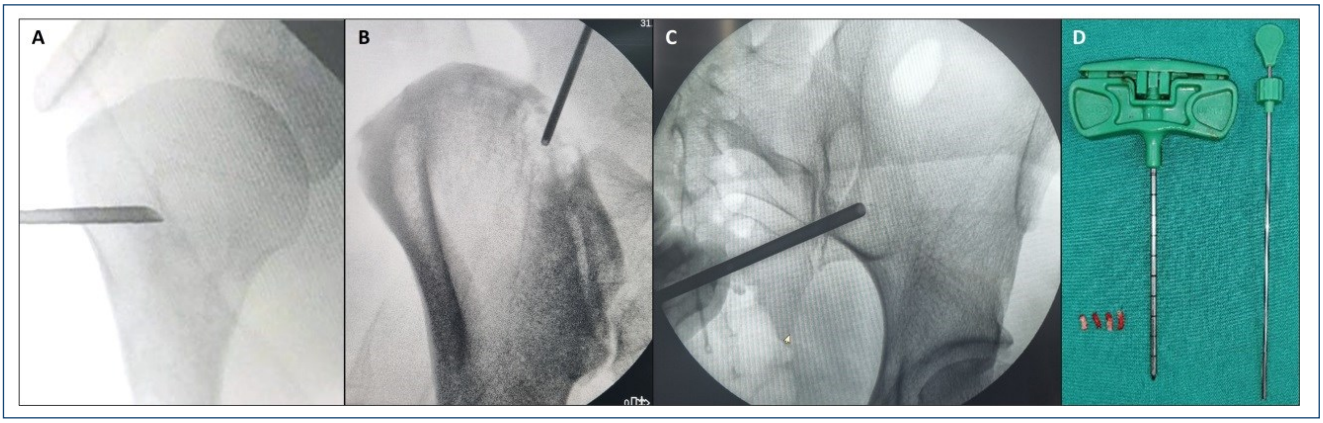

Figure 2. (A-D). Core needle biopsies. (A) A 40-year-old female patient with suspected enchondroma/chondrosarcoma in the proximal segment of the right humerus. A radioscopy-guided biopsy of the affected segment was performed with trephine. Diagnosis of grade 1 chondrosarcoma was confirmed. (B) A 52-year-old male patient with suspected metastatic lesion of undetermined origin in the right iliac. A radioscopy-guided biopsy with trephine was performed. Diagnosis of mesenchymal chondrosarcoma was made. (C) A 30-year-old female patient with a bone lesion in the left iliac. A radioscopy guided biopsy with trephine was performed. A diagnosis of simple bone cyst was made. (D) Jamshidi needle for bone biopsy mounted next to the extraction probe ("pusher"); chuck and trocar hinge at the T-handle; The trocar has a tapered stylet tip and the chuck features a "triple-crown" type cannula tip - these features provide a sharp and effective cutting tip for improved cortical penetration and medullary advancement that requires 25% less physical force. Appearance of the collection of four bone tumor samples.

Multiple samples are obtained, in different directions, through a single bone hole, reducing the risk of iatrogenic fracture.

This technique is useful in lesions in which a small sample is sufficient to confirm the diagnosis. The tissue architecture is preserved, allowing histological diagnosis, tumor grading, and ancillary analyses.

Recent studies suggest that the diagnostic yield of CNB is like that of incisional biopsy, reaching 70–98%. Yield can be maximized by collecting at least three samples; specimens >10 mm are 6.3 times more likely to allow a diagnosis than specimens <5 mm. Lesions ≥3 cm have a diagnostic yield five times higher than lesions <3 cm. Needles with a gauge of less than 18 mm may result in lower diagnostic yield.

The advantages of CNB are as follows: (a) minimally invasive, outpatient procedure; (b) lower cost; (c) low risk of route contamination; (c) tumor samples collection in places that are difficult to locate more safely and accurately, when guided by imaging tests; and (d) lower risk for complications than incisional biopsies (0–10% vs. 16%)[13-23,25].

Open bone biopsies

The open approach allows the collection of samples in greater quantity and of better quality, facilitating the pathologist's evaluation. However, it has greater potential for local contamination and systemic dissemination, as well as for other complications, such as hematoma, fracture, and infection[3-6].

Incisional bone biopsy

Incisional biopsy is indicated: (a) in the most difficult cases, where there is diagnostic uncertainty; (b) where accurate histological study requires a larger sample for diagnosis; or (c) when previously performed biopsy did not define the diagnosis.

This modality is still considered the "gold standard" for the diagnosis of musculoskeletal tumors because a diagnostic yield of 91–96% can be achieved.

Incisional biopsy can be performed in association with a frozen section, ensuring that a representative tumor sample has been obtained. It should be performed through wide access, along the incision line planned for the definitive treatment. It is mandatory to use the smallest incision compatible with obtaining an adequate sample, preferably in the affected compartment topography and, as far as possible, distal—especially in cases where amputation is envisaged. Transverse incisions are contraindicated because they require wider soft tissue resection at the time of definitive surgery. Following the same principle, more than one access should be avoided[3-6].

The disadvantages associated with this procedure include greater potential for contamination and a higher rate of local tumor recurrence, as well as complications related to the surgical wound (16%). In addition, it may require an increase in the extent of definitive resection, compromising the function of the affected limb[3-6].

Excisional bone biopsy

Excisional biopsy is a special form of open biopsy. Depending on the lesion location and size, marginal, or even wide, resection is achieved.

Excisional biopsies are indicated when the clinical/imaging characteristics (small tumors, with an unequivocally benign appearance and biological behavior) and the lesion topography (e.g., out of neurovascular bundle path) to be biopsied allow its wide resection in a single time and safely.

Liquid biopsy

Liquid biopsy consists of the collection of blood (most used) samples or other body fluids from which circulating tumor cells, cell-free nucleic acids, exosomes, and metabolites are extracted for analysis of any genomic, molecular, and metabolomic alterations. The collection is minimally invasive and circumvents many of the limitations of conventional biopsy. It can be performed at any time during cancer therapy, allowing dynamic monitoring of molecular changes in the tumor rather than relying on a static point in time[7-9].

This technique can provide a more accurate representation of the overall cancer genome than a single tissue biopsy. Longitudinal screening of genetic and epigenetic alterations through liquid biopsies has multiple applications. Liquid biopsy can better assess molecular heterogeneity, identify acquired tumor mutations, and characterize primary and recurrent tumors; monitor recurrence and metastases; predict treatment response; identify genetic determinants for targeted therapies; clarify the mechanisms of resistant tumor evolution in real time under treatment pressure; and screen asymptomatic individuals for early detection of cancer[7-9].

Liquid biopsy has been introduced into the routine diagnosis and follow-up of patients with bone and soft tissue sarcomas, establishing itself as a promising tool in the management of these neoplasms.

CONCLUSION

The domain of knowledge about bone biopsy planning is essential to obtain representative tissue samples, favoring tumor diagnosis and grading, as well as ancillary studies accomplishment (immunohistochemical, cytogenetic, and molecular processing), which allows defining the most adequate therapeutic protocol

for each case while avoiding unnecessary complications related to vices in procedure execution.

Liquid biopsy is a promising tool in the management of bone sarcomas, providing a more accurate representation of the overall cancer genome, with several therapeutic implications.

AUTHORS' CONTRIBUTIONS

AG: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **SAN:** Conceptualization, Supervision, Visualization, Writing – review & editing.

REFERENCES

1. Guedes A, Oliveira MBDR, Melo AS, Carmo CCMD. Update in imaging evaluation of bone and soft tissue sarcomas. Rev Bras Ortop (Sao Paulo). 2021;58(2):179-90. https://doi.org/10.1055/s-0041-1736569
2. Guedes A, Oliveira MBDR, Costa FM, Melo AS. Updating on bone and soft tissue sarcomas staging. Rev Bras Ortop (Sao Paulo). 2021;56(4):411-8. https://doi.org/10.1055/s-0040-1710331
3. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res. 1980;(153):106-20. PMID: 7449206
4. Errani C, Traina F, Perna F, Calamelli C, Faldini C. Current concepts in the biopsy of musculoskeletal tumors. ScientificWorldJournal. 2013;2013:538152. https://doi.org/10.1155/2013/538152
5. Garcia JG, Marques DS, Viola DCM, Petrilli MT, Alves MTS, Jesus-Garcia Filho R. Biopsy path contamination in primary bone sarcomas. Rev Bras Ortop (Sao Paulo). 2019;54(1):33-6. https://doi.org/10.1016/j.rbo.2017.09.006
6. Meek RD, Mills MK, Hanrahan CJ, Beckett BR, Leake RL, Allen H, et al. Pearls and pitfalls for soft-tissue and bone biopsies: a cross-institutional review. Radiographics. 2020;40(1):266-90. https://doi.org/10.1148/rg.2020190089
7. Castro-Giner F, Gkountela S, Donato C, Alborelli I, Quagliata L, Ng CKY, et al. Cancer diagnosis using a liquid biopsy: challenges and expectations. Diagnostics (Basel). 2018;8(2):31. https://doi.org/10.3390/diagnostics8020031
8. Cheung AH, Chow C, To KF. Latest development of liquid biopsy. J Thorac Dis. 2018;10(Suppl 14):S1645-51. https://doi.org/10.21037/jtd.2018.04.68
9. Li X, Seebacher NA, Hornicek FJ, Xiao T, Duan Z. Application of liquid biopsy in bone and soft tissue sarcomas: present and future. Cancer Lett. 2018;439:66-77. https://doi.org/10.1016/j.canlet.2018.09.012
10. Campanacci M. The wrong approach to tumors of the musculo skeletal system: what should not be done. Chir Organi Mov. 1999;84(1):1-17. PMID: 11569008
11. Panzica M, Lüke U, Mommsen P, Krettek C. [Biopsy and approach routes for bone tumors. Where and how much is sufficient?]. Unfallchirurg. 2014;117(6):501-9. https://doi.org/10.1007/s00113-013-2471-5
12. Kater EP, Boetzkes JA, Sakes A, Breedveld P. Bone biopsy devices - a patent review. Expert Rev Med Devices. 2023;20(11):919-28. https://doi.org/10.1080/17434440.2023.2254681
13. Santos LA, Lukeman JM, Wallace S, Murray JA, Ayala AG. Percutaneous needle biopsy of bone in the cancer patient. AJR Am J Roentgenol. 1978;130(4):641-9. https://doi.org/10.2214/ajr.130.4.641
14. Kandathil A, Subramaniam RM. PET/computed tomography and precision medicine: musculoskeletal sarcoma. PET Clin. 2017;12(4):475-88. https://doi.org/10.1016/j.cpet.2017.05.005
15. Matti A, Farolfi A, Frisoni T, Fanti S, Nanni C. FDG-PET/CT guided biopsy in angiosarcoma of bone: diagnosis, staging and beyond. Clin Nucl Med. 2018;43(2):e48-9. https://doi.org/10.1097/RLU.0000000000001918
16. Tomasian A, Hillen TJ, Jennings JW. Bone biopsies: what radiologists need to know. AJR Am J Roentgenol. 2020;215(3):523-33. https://doi.org/10.2214/AJR.20.22809
17. Meyenfeldt EM, Siebenga J, Pol HA, Schreurs WM, Hulsewe KW. Radionuclide-guided biopsy of bone lesions in cancer patients; a reliable, well-tolerated technique. Eur J Surg Oncol. 2014;40(2):193-6. https://doi.org/10.1016/j.ejso.2013.07.086
18. Spinnato P, Colangeli M, Rinaldi R, Ponti F. Percutaneous CT-guided bone biopsies: indications, feasibility and diagnostic yield in the different skeletal sites-from the skull to the toe. Diagnostics (Basel). 2023;13(14):2350. https://doi.org/10.3390/diagnostics13142350
19. Albano D, Messina C, Gitto S, Chianca V, Sconfienza LM. Bone biopsies guided by augmented reality: a pilot study. Eur Radiol Exp. 2023;7(1):40. https://doi.org/10.1186/s41747-023-00353-w
20. Cooke-Barber J, Brungardt JG, Sorger M, Pressey JG, Turpin B, Nagarajan R, et al. ASO visual abstract: pediatric and young adult image-guided percutaneous bone biopsy-a new standard of care? Ann Surg Oncol. 2023;30(6):3667. https://doi.org/10.1245/s10434-023-13167-2
21. Kovacevic L, Cavka M, Marusic Z, Kresic E, Stajduhar A, Grbanovic L, et al. Percutaneous CT-guided bone lesion biopsy for confirmation of bone metastases in patients with breast cancer. Diagnostics (Basel). 2022;12(9):2094. https://doi.org/10.3390/diagnostics12092094
22. Donners R, Fotiadis N, Figueiredo I, Blackledge M, Westaby D, Guo C, et al. Optimising CT-guided biopsies of sclerotic bone lesions in cancer patients. Eur Radiol. 2022;32(10):6820-9. https://doi.org/10.1007/s00330-022-09011-y
23. Masood S, Mallinson PI, Sheikh A, Ouellette H, Munk PL. Percutaneous bone biopsy. Tech Vasc Interv Radiol. 2022;25(1):100800. https://doi.org/10.1016/j.tvir.2022.100800
24. Chambers M, O'Hern K, Kerr DA. Fine-needle aspiration biopsy for the diagnosis of bone and soft tissue lesions: a systematic review and meta-analysis. J Am Soc Cytopathol. 2020;9(5):429-41. https://doi.org/10.1016/j.jasc.2020.05.012
25. Cooke-Barber J, Brungardt JG, Sorger M, Pressey JG, Turpin B, Nagarajan R, et al. ASO author reflections: minimizing time in hospital via bone biopsy or other means. Ann Surg Oncol. 2023;30(6):3666. https://doi.org/10.1245/s10434-023-13170-7

REVIEW ARTICLE

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Update on brown tumor of hyperparathyroidism

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BACKGROUND

On the right and left sides of the thyroid, the parathyroid glands are presented in the form of four nodules in total, two apical and two basal[1]. Topographic variations are common—the parathyroid glands can be located near the larynx or even in the mediastinum, near the thymus[1]. Microscopically, they are made up of two main types of cells, clear and oxyphilic; the former secrete parathyroid hormone (PTH), and the latter have a still obscure function—all are arranged in a chordonal arrangement, interspersed with lobes of fatty tissue[1,2].

Parathyroid hormone is a calcitonin antagonist that directly acts on renal tubule cells, inhibiting phosphate reabsorption and regulating phosphaturia[1]. In the bones, it acts by stimulating the action of osteoclasts which, by enzymatic action, reabsorb the matrix and solubilize calcium[1]. Therefore, PTH plays a key role in serum calcium homeostasis[1-3].

Excessive production of PTH[4-10] may occur due to primary hyperparathyroidism (PHP), phosphate retention, skeletal resistance to PTH, impaired PTH degradation, and altered calcium-PTH feedback regulation in secondary hyperparathyroidism (SHP) or persistent tertiary hyperparathyroidism (THP)[2,3,11,12]. Increased PTH production results in hypercalcemia[3], due to increased calcium absorption in the intestine, increased renal tubular reabsorption, and increased osteoclastic activity[4,5,11] which leads to bone demineralization, resulting in microfractures hemorrhage, hemosiderin deposition[13], and excessive vascular proliferation that give such lesions the characteristic brown staining, justifying the nomenclature brown tumor of hyperparathyroidism (BTH)[4,5].

Brown tumor of hyperparathyroidism has a female predominance[4,5,14] in a ratio of 3:18 and increases in frequency with aging (especially after the age of 50 years) and after menopause, which is related to hormonal effects[4,5]. It is very rare before puberty, and its incidence increases with age[2,10].

Hyperparathyroidism (HP) is a pathology characterized by an increase in PTH secretion despite an increase in calcium in the extracellular fluid[10]. The hormone acts by absorbing the calcium present in the bones through the action of osteoclasts and preventing the reabsorption of phosphate in the glomerular filtrate, which causes phosphaturia and hypophosphatemia[10]. It occurs more frequently in the white breed and is rare in the yellow breed, with an overall incidence of about 20/100,000[6]. In the United States, BTH occurs in less than 2% of all HP patients and is especially associated with the most severe forms of the disease and parathyroid carcinoma. The occurrence of HP in young people should raise the suspicion of hereditary diseases such as multiple endocrine neoplasia (MEN) syndrome[2,5].

Brown tumor of hyperparathyroidism secondary to PHP is very rare[6,15]—only 2–5% of its carriers have this condition, usually caused by massive PTH secretion[6,12,16,17]. PHP can occur due to parathyroid adenoma[4,5,10,13,16] (up to 85% of cases)[4,5,10]—benign but metabolically active[4,5], eventually ectopic lesion[7]; parathyroid carcinoma[4,5,10]—which, although a rare cause of PHP (<1% of cases), presents bone involvement (BTH) more frequently (up to 90% of cases) when compared with benign causes of PHP[4,5]; and hereditary factors (5–10% of cases) such as MEN type 1 (comprises up to 95% of hereditary cases of BTH) and 2A, HP-jaw tumor syndrome, and familial isolated HP that can result in BTH if undiagnosed[2,4].

Secondary hyperparathyroidism is a frequent result of chronic renal failure (CRF)[5,7,14,16], particularly in dialysis patients, leading to renal osteodystrophy, a clinical condition that commonly causes BTH[5,7,16] (present in up to 50% of cases)[5], with extensive bone marrow osteofibrosis and increased osteoclastic bone resorption[7]. The kidneys are unable to produce calcitriol, which promotes the entry of calcium into the bones. In calcitriol scarcity, PTH levels increase, promoting the removal of calcium from the skeleton. Several factors contribute to this, including bone strength to PTH, increased phosphorus retention, which causes malabsorption of calcium in the gut, and inhibition of 1,25(OH)2D production by increased phosphorus[4].

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Persistent tertiary hyperparathyroidism is characterized by excessive secretion of PTH after long-standing SHP, in which the stimulated parathyroids are no longer in reactive mode but have taken on quasi-autonomous function—not unlike PHP, leading to hypercalcemia[12]. In theory, THP occurs due to the monoclonal expansion of parathyroid cells that have acquired an altered setpoint of their calcium-sensing receptor, causing PTH to continue to be secreted despite high serum calcium levels[12]. Other rare causes of THP include X-linked hypophosphatemic rickets, adult-onset hypophosphatemic rickets (autosomal dominant), and oncogenic osteomalacia[12].

It is important to distinguish between primary parathyroid disorder, in which there is excessive and incomplete PTH secretion, as occurs in PHP, and physiological situations in which these glands respond to stimuli that lead to increased PTH secretion, as in SHP[12]. From a biochemical point of view, the main difference between primary and SHP is that in the former, there is an increase in serum calcium and a reduction in phosphate[16,17], and in the latter, there is normocalcemia[12] and hyperphosphatemia[16]. Although both SHP and THP result from chronic stimulation of PTH secretion, serum calcium is always normal in the former, while it is always elevated in the latter. The distinction between PHP and THP is usually evident to the extent that a clearly definable disorder is present, such as long-standing malabsorptive syndrome or chronic kidney disease (CKD), often after kidney transplantation[2,12].

Vitamin D deficiency may be associated with elevated PTH[12].

Drugs such as lithium and thiazide diuretics may be associated with an increase in PTH levels[12].

DIAGNOSIS

The diagnosis of BTH is based on clinical manifestations, laboratory tests, imaging evaluation, and anatomopathological study[9,18]. However, as these can be non-specific, it is necessary to maintain a high index of suspicion[9,18], especially in those patients who do not have a diagnosis of HP[2,18].

CLINICAL FINDINGS

Clinically, HP (particularly PHP)[16] presents as "stones, bones, and groans," where "stones" refer to recurrent kidney stones, "bones" refer to bone pain, loss of bone mass, and fractures, and "groans" describe psychic groans and gastrointestinal symptoms such as vomiting, nausea, peptic ulcers, and pancreatitis[3-5,12]. Other findings include hypercalcemia[5,12], anorexia[5,10], bloating[10], constipation[10], weight loss[5], muscle weakness[12], pruritus[12], soft tissue or vascular calcifications[12], polyuria[10], nocturia[10], polydipsia[10], and nephrolithiasis[10,12].

Brown tumor of hyperparathyroidism is an advanced HP finding[10]. Its clinical findings depend on the lesion's size and location and are nonspecific—some patients are asymptomatic. Bone fragility can lead to fractures[1,7,12,17] which, in turn, lead to pain and disability[7,12,18]. Injuries that affect the spine may be associated with spinal cord compression. Facial deformities can cause difficulty breathing and food swallowing[7].

LABORATORY FINDINGS

Laboratory findings include elevated serum PTH[5,9,11], elevated serum calcium[5,9,11], decreased serum phosphate[5], normal or elevated alkaline phosphatase[4,5], and elevated urate[4].

Many studies confirm that the clinical manifestations of HP are worse when there is a deficiency of vitamin D, making its dosage an important part of the screening of suspected vitamin D[14].

The anatomopathological examination is the gold standard modality for the definitive diagnosis[9,19] of BTH.

IMAGING EVALUATION

Brown tumor of hyperparathyroidism can present as diffuse osteopenia[4,5], osteoporosis[5,6], bone deformities[4,7], and circumscribed osteolytic lesions[4-6] (Figure 1). Bone resorption occurs due to increased osteoclastic activity that affects all bone surfaces in different sites, which may be subperiosteal, intracortical, endosteal, trabecular, subchondral, subligamentous, or subtendinosus[7]. Subperiosteal bone resorption[7,14,18] is the most striking radiographic feature of HP[7] and can be observed in the middle phalanges[4,5,7] (the most sensitive radiographic sign in the diagnosis of BTH)[7], distal radius[5], humerus[7], and clavicle[4-7,14,18]. Subchondral bone resorption is characterized by enlargement or pseudoenlargement of the joint[7] and occurs in different joints, such as the pubic symphysis and sacroiliac joints, sternoclavicular, and acromioclavicular. Intracortical and endosteal resorption may lead to endosteal clipping findings. The association of trabecular resorption (which causes loss of definition) and granular texture[7] leads to the "salt and pepper" pattern of the skull[2,4,5,7,9,14]. Subligamentous and subtendinous bone resorption can occur in the ischial tuberosities, trochanters, and insertions of the coracoclavicular ligaments[7]. Bone resorption[7] can lead to loss of the hard blade of the teeth[4,7,10] and lesions to the vertebral bodies[4]. BTH[4,5,7,10,14,18] can occur in the pelvis[4,6-9], ribs[4,6-9], long bones[4,6-9], maxilla[18], and clavicle[9]. In severe forms of BTH, bone deformities[7] and insufficiency

fractures may occur[7,9,14] (Figure 2). Excessive resorption of the terminal phalanges can lead to acroosteolysis[7,10]. Severe resorption in the sacroiliac joints can cause pelvic deformities that lead to inability to walk[7]. Thoracic vertebral fractures can lead to an increase in its anteroposterior diameter, leading the thorax to take on a "bell-bottom" shape[7]. Abnormal curvature and vertebral rotation can lead to thoracic deformities[7].

Multifocal involvement of the skeleton is usually present[4,6,14,20-23] on radiographs, technetium-99m bone scintigraphy (MDP-99mTc)[4,6,14], or positron emission tomography-computed tomography (PET-CT).

Computed tomography (CT)[5,8,24], MDP-99mTc bone scan[5,8,24] (Figure 3), and ultrasound[5,6,8] may be useful for detecting parathyroid gland disorders.

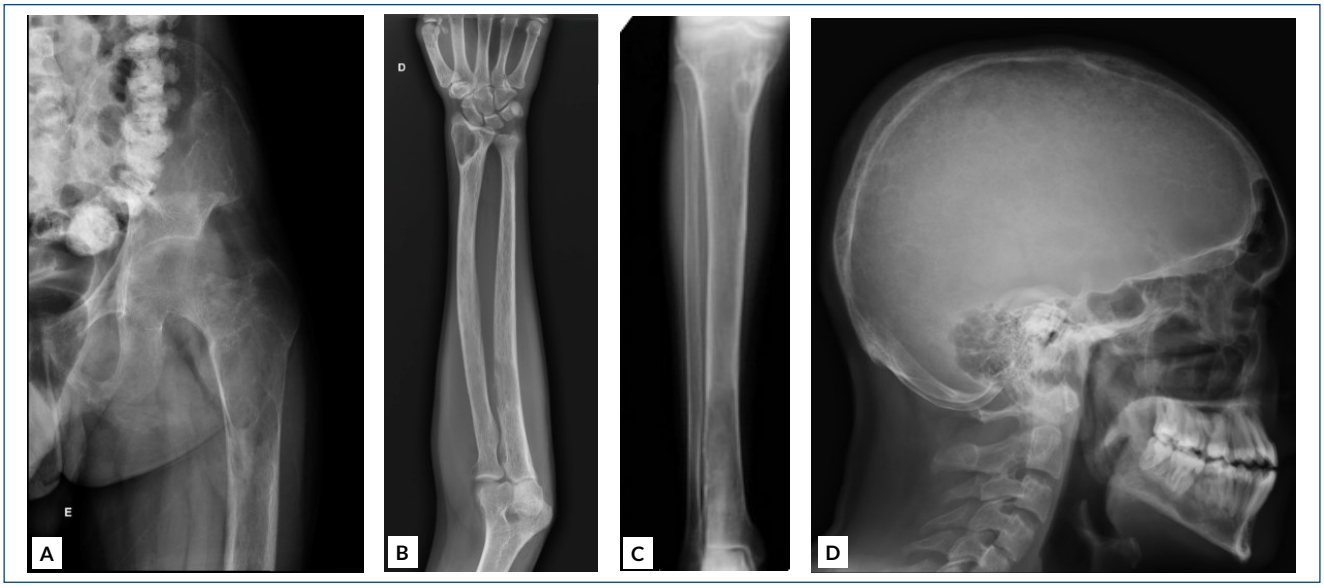

Figure 1. (A–D) A 23-year-old male patient with primary hyperparathyroidism due to parathyroid adenoma presenting disseminated osteolytic bone lesions.

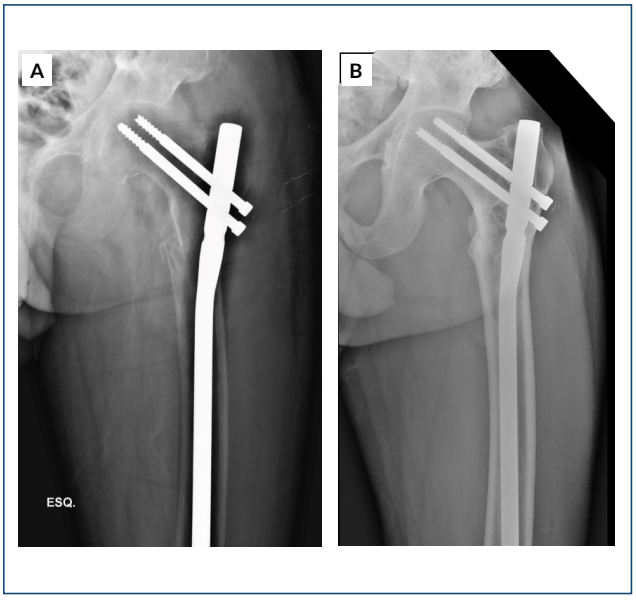

Figure 2. (A, B) A 23-year-old male patient with primary hyperparathyroidism due to parathyroid adenoma, evolving with a pathological fracture through the subtrochanteric bone lesion. (A) Fixation of the fracture with proximal femur nailing. (B) Appearance of the lesion after parathyroidectomy, shortly after fracture fixation.

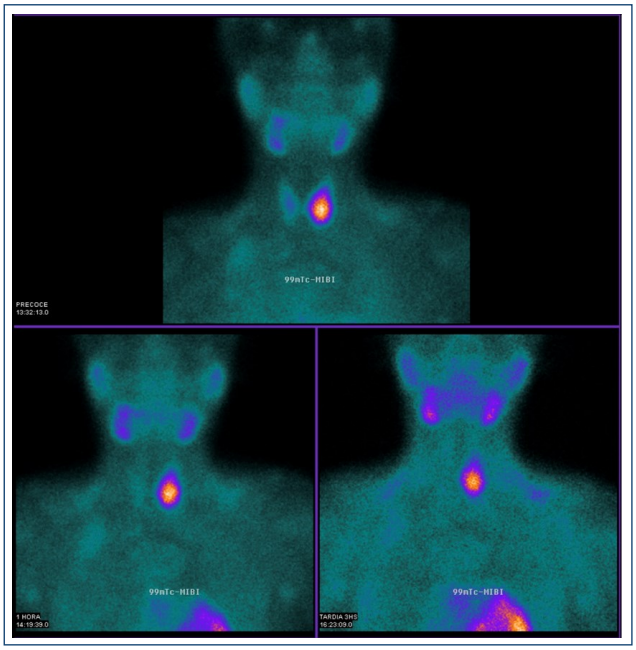

Figure 3. A 23-year-old male patient with a brown tumor of hyperparathyroidism secondary to parathyroid adenoma. Scintigraphy showing hyperuptake of the left parathyroid glands.

HISTOPATHOLOGY

Brown tumor of hyperparathyroidism consists of vascularized osteofibrous tissue, devoid of matrix. Microscopically, there is increased resorption of bony trabeculae, forming a "tunneling" or "dissection" pattern. Osteoclastic resorption[4,5,11,18,19] leads to microfractures and microhemorrhages that progressively produce a small vacuum that becomes confluent with others, making BTH visible macroscopically[3,5,6,8,11,16,18]. Osteoclasts consume the trabecular bone that osteoblasts establish, and this front of reparative bone deposition, followed by further resorption, can expand beyond the usual shape, from bone to the periosteum, and cause bone pain. Involvement of the bones by BTH weakens them, resulting in pathological fractures[4].

DIFFERENTIAL DIAGNOSIS

The imaging and histological features of BTH overlap with findings common to different diseases, making differential diagnosis difficult[9,11,14,18]. However, the clinical history of PHP or CRF with SHP usually establishes the diagnosis[4,6].

It is critical to distinguish BTH from other clinical conditions to avoid unnecessary surgical procedures[18].

The clinical picture "stones, bones, and groans" can be reproduced in malignant neoplasms such as paraneoplastic syndrome, due to the high levels of PTH-related peptides (PTHrP) that simulate the effect of PTH. In these cases, BTH can be mistaken for bone metastases[12].

If hypercalcemia is present, the first impression is often of a malignant lesion[14].

Giant cell tumor of bone[5,8,14,18,25], aneurysmal bone cyst[5,8,14,25], simple bone cyst[14], giant cell reparative granuloma[5,8], fibrous dysplasia[8], and non-ossifying fibroma[8] are included in the differential diagnosis of BTH. It can also be confused with a primary malignant bone tumor[14] or metastatic disease[5,8,9,14,25], based on radiographic findings, because it often presents with multiple disseminated osteolytic lesions[5,8,14,25].

Bone scintigraphy, which has hot spots and/or generally high absorption in PHP, lacks specificity as it can also be seen in a variety of other conditions associated with increased bone metabolism, such as trauma, infections, primary or secondary malignant bone lesions, osteomalacia, Paget's disease, and other osteometabolic diseases[14].

Positron emission tomography-computed tomography does not reliably distinguish malignant from benign skeletal lesions[14].

Even histology cannot guarantee a correct diagnosis, due to the large number of lesions with multinucleated giant cells[19]. Among the numerous lesions that present these characteristics on anatomopathological examination[11,14,18,19], the most challenging differential diagnosis occurs between the giant cell tumor and the BTH[9,11,18]. Other lesions, such as reparative cell granulomas, aneurysmal bone cysts, and some types of osteosarcoma, may present macroscopic and microscopic features similar to BTH[14,18].

TREATMENT

Treatment of BTH begins with the management of HP, usually by parathyroidectomy, and should occur after the correction of underlying metabolic issues[9,11]. After parathyroidectomy, most bone disorders resulting from BTH will resolve[2,9,11].

If surgery is not the best treatment option, medical treatment of hypercalcemia, vitamin D deficiency, and hyperphosphatemia may be performed. Serial evaluation of serum calcium, phosphate, PTH, and vitamin D determines the need for treatment[5].

Regarding the orthopedic approach to the lesions, some studies point to the previous fixation of the fractures, while others indicate the fixation after parathyroidectomy[15]. Prior treatment of fractures is appropriate in cases where there are severe bone lesions associated with hypercalcemia—surgery should be postponed until the manifestations of hypercalcemia are corrected, avoiding intraoperative adverse events[15]. If parathyroidectomy is defined to be performed prior to fracture fixation, one should be aware of the possibility of "starving bone" syndrome, a condition characterized by rapid, deep, and prolonged hypocalcemia, accompanied by hypophosphatemia and hypomagnesemia. Until hypocalcemia resolves, definitive fixation of fractures should be delayed[2,15].

PROGNOSIS

Bone changes constitute a late presentation of HP. Bone involvement in HP has shown a significant decrease in incidence in recent decades (from 80 to only 15%)[5], constituting a very rare presentation of PHP, especially in developed countries, where serum calcium measurement is routinely performed[14,18]. This fact is attributed to the early detection[4,5,8,14,15] of asymptomatic cases through the monitoring of serum calcium and the treatment[4,14] of PH in the early stages of the disease. Proactive therapeutic management has made the manifestation of BTH relatively more common in renal osteodystrophy[14], and 5% of PH cases develop this condition, which usually indicates prolonged or more severe disease[5].

Bone lesions resulting from BTH are usually resolved through parathyroidectomy. Proper management of HP results in decreased osteoclastic activity and new bone deposition[2,5].

AUTHORS' CONTRIBUTIONS

AG: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **RGB:** Visualization, Writing – review & editing. **SAN:** Visualization, Writing – review & editing. **AALG:** Writing – original draft.

REFERENCES

1. Próspero JD, Baptista PPR, Amary MFC, Santos PPC. Paratireóides: estrutura, funções e patologia. Acta Ortop Bras. 2008;17(2):53-7. https://doi.org/10.1590/S1413-78522009000200011
2. Jambeiro JES, Guedes A, Mattos ESR, Guedes AAL, Freire ANM, Freire MDM, et al. Osteíte fibrose cística. Rev Cient HSI. 2023;7(1):18-30.
3. Majumdar S, Uppala D, Kotina S, Alekhya B. Brown tumor of hyperparathyroidism with multiple lesions. J Oral Maxillofac Pathol. 2022;26(Suppl 1):S111-5. https://doi.org/10.4103/jomfp.jomfp_409_20
4. Kalathas T, Kalatha T, Boultoukas E. Brown tumors; a possible pitfall in diagnosing metastatic disease. Hell J Nucl Med. 2010;13(1):15-7. PMID: 20411164
5. Naji Rad S, Deluxe L. Osteitis fibrosa cystica. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020.
6. Xu W, Qu Y, Shi W, Ma B, Jiang H, Wang Y, et al. Multiple bone brown tumor secondary to primary hyperparathyroidism: a case report and literature review. Gland Surg. 2019;8(6):810-6. https://doi.org/10.21037/gs.2019.11.14
7. Lacativa PG, Franco FM, Pimentel JR, Patrício Filho PJ, Gonçalves MD, Farias ML. Prevalence of radiological findings among cases of severe secondary hyperparathyroidism. Sao Paulo Med J. 2009;127(2):71-7. https://doi.org/10.1590/s1516-31802009000200004
8. Wang X, Wang M, Zhang J, Zhu Y, Zhu M, Gao H, et al. Humeral brown tumor as first presentation of primary hyperparathyroidism caused by ectopic parathyroid adenomas: report of two cases and review of literature. Int J Clin Exp Pathol. 2014;7(10):7094-9. PMID: 25400803
9. Panagopoulos A, Tatani I, Kourea HP, Kokkalis ZT, Panagopoulos K, Megas P. Osteolytic lesions (brown tumors) of primary hyperparathyroidism misdiagnosed as multifocal giant cell tumor of the distal ulna and radius: a case report. J Med Case Rep. 2018;12(1):176. https://doi.org/10.1186/s13256-018-1723-y
10. Frischenbruder JA, Pereira GA. Hiperparatiroidismo: relato de um caso. Rev Bras Ortop. 1996;31(1):96-8.
11. Rossi B, Ferraresi V, Appetecchia ML, Novello M, Zoccali C. Giant cell tumor of bone in a patient with diagnosis of primary hyperparathyroidism: a challenge in differential diagnosis with brown tumor. Skeletal Radiol. 2014;43(5):693-7. https://doi.org/10.1007/s00256-013-1770-9
12. Jamal SA, Miller PD. Secondary and tertiary hyperparathyroidism. J Clin Densitom. 2013;16(1):64-8. https://doi.org/10.1016/j.jocd.2012.11.012
13. Hakkou F, Benjelloun L, Hallab L, Chbicheb S. Brown tumor of the jaw as a rare manifestation of hyperparathyroidism: two case reports and literature review. Int J Surg Case Rep. 2023;111:108823. https://doi.org/10.1016/j.ijscr.2023.108823
14. Misiorowski W, Bilezikian JP. Osteitis fibrosa cystica. JBMR Plus. 2020;4(9):e10403. https://doi.org/10.1002/jbm4.10403
15. Vanitcharoenkul E, Singsampun N, Unnanuntana A, Sirinvaravong S. Osteitis fibrosa cystica and pathological fractures-the classic but neglected skeletal manifestation of primary hyperparathyroidism: a case report. BMC Musculoskelet Disord. 2021;22(1):443. https://doi.org/10.1186/s12891-021-04326-1
16. Xie C, Tsakok M, Taylor N, Partington K. Imaging of brown tumours: a pictorial review. Insights Imaging. 2019;10(1):75. https://doi.org/10.1186/s13244-019-0757-z
17. Choi JH, Kim KJ, Lee YJ, Kim SH, Kim SG, Jung KY, et al. Primary hyperparathyroidism with extensive brown tumors and multiple fractures in a 20-year-old woman. Endocrinol Metab (Seoul). 2015;30(4):614-9. https://doi.org/10.3803/EnM.2015.30.4.614
18. Hamidi S, Mottard S, Berthiaume MJ, Doyon J, Bégin MJ, Bondaz L. Brown tumor of the iliac crest initially misdiagnosed as a giant cell tumor of the bone. Endocrinol Diabetes Metab Case Rep. 2020;2020(1):20-0029. https://doi.org/10.1530/EDM-20-0029
19. Próspero JD, Baptista PPR, Lima Júnior CLH. Doenças ósseas com células gigantes multinucleadas: diagnóstico diferencial. Rev Bras Ortop. 1999;34(3):214-23.
20. Santhanam S, Chandrasekaran S. Multifocal brown tumor: a case of primary hyperparathyroidism. J Clin Rheumatol. 2021;27(5):e166-7. https://doi.org/10.1097/RHU.0000000000001306
21. Facorat O, Fontaine C, Courtieu C, Trevillot V, Vidal C, Che H. Multiple brown tumors in primary hyperparathyroidism. J Clin Rheumatol. 2021;27(8S):S766-8. https://doi.org/10.1097/RHU.0000000000001504
22. Miwa S, Tanaka T, Aiba H, Yamada S, Otsuka T, Tsuchiya H. Multiple bone cysts caused by hyperparathyroidism: a case report and review of the literature. Cancer Diagn Progn. 2023;3(5):590-6. https://doi.org/10.21873/cdp.10259
23. Aldosari S, Alghamdi EA, Alragea A. Multiple brown tumors in primary hyperparathyroidism causing pathological fracture: a case report of a 21-year-old adult male. Cureus. 2023;15(3):e35979. https://doi.org/10.7759/cureus.35979
24. Hummel R, Weber T, Zoller H. Brown tumor. Dtsch Arztebl Int. 2021;118(42):712. https://doi.org/10.3238/arztebl.m2021.0071
25. Zhong Y, Huang Y, Luo J, Ye Y. Misdiagnosis of brown tumour caused by primary hyperparathyroidism: a case report with literature review. BMC Endocr Disord. 2022;22(1):66. https://doi.org/10.1186/s12902-022-00971-2

REVIEW ARTICLE

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Endoscopic diagnosis and management of superficial esophageal squamous cell carcinoma

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Brazilian Society of Digestive Endoscopy

INTRODUCTION

Esophageal neoplasia ranks seventh in incidence and sixth in mortality among all cancers worldwide[1]. Regarding histopathology, squamous cell carcinoma (SCC) accounts for **up to 90%** of cases and its distribution varies geographically, with a concentration in areas of greatest risk known as the **"esophageal cancer belt,"** which encompasses the region from northeast Iran, Central Asia, and northeast China[2] (Figures 1 and 2).

Smoking and alcohol consumption are major risk factors for esophageal squamous cell carcinoma (ESCC). Patients with head and neck squamous cell carcinoma (HNSCC) are at risk of developing a second primary tumor on the esophagus supporting the concept of field cancerization. Results of a screening program in high-risk patients showed that the frequency of a second primary tumor in this population occurred in 8% of patients with HNSCC, mostly superficial lesions amenable to endoscopic curative resection. In multivariate analysis, SCC of the oral cavity and oropharynx and the presence of esophageal low-grade dysplasia (LGD) were the **predictive factors of ESCC**[3].

Survival rates and choice of initial treatment are directly related to invasion depth. According to the Japanese Esophageal Society[4], superficial ESCC is defined as a cancer invading up to the submucosa, regardless of linfonodal invasion **(T1NxMx)**. On the contrary, early ESCC is the mucosal cancer **(T1aNxMx)** (Figure 3).

Management of ESCC has changed over the last few years, and endoscopic resection (ER) techniques have become increasingly important. Nevertheless, surgery continues to be the standard treatment, either alone or in combination with chemoradiotherapy. In addition to the tumor staging, the management of ESCC should be chosen according to patients' preferences and the availability of surgical and endoscopic approaches.

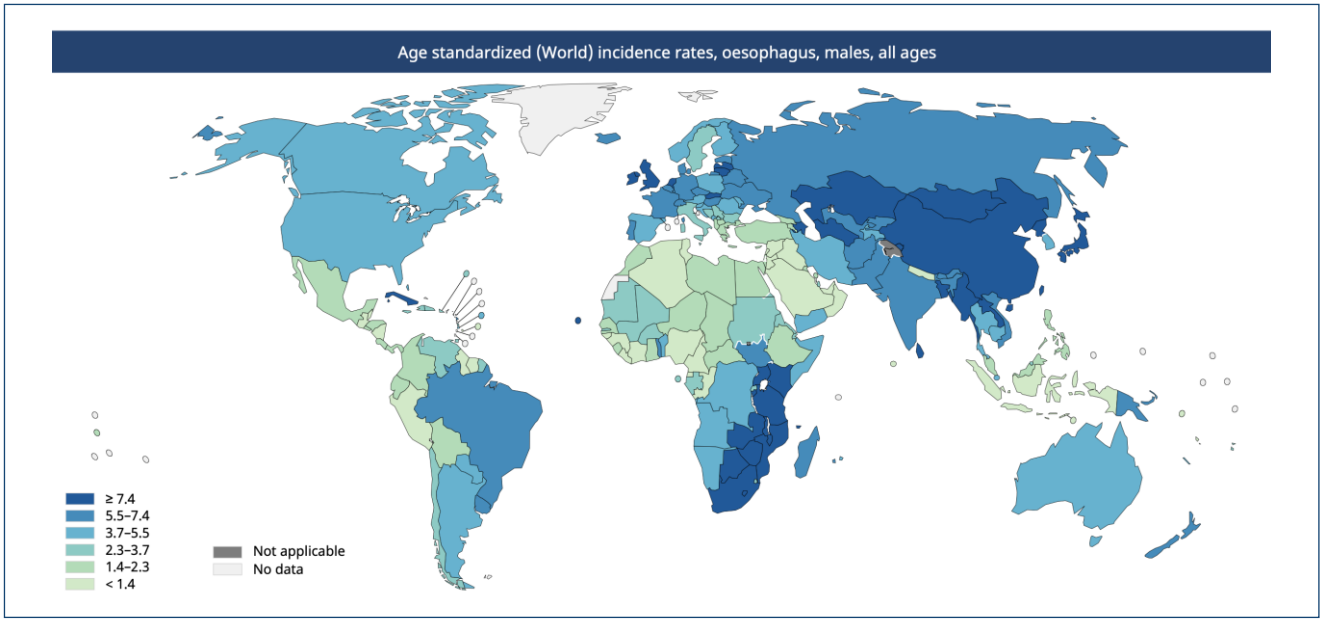

Figure 1. Incidence of esophageal cancer worldwide. Data source: GLOBOCAN 2020. Graph production: IARC (https://gco.iarc.fr/today) World Health Organization.

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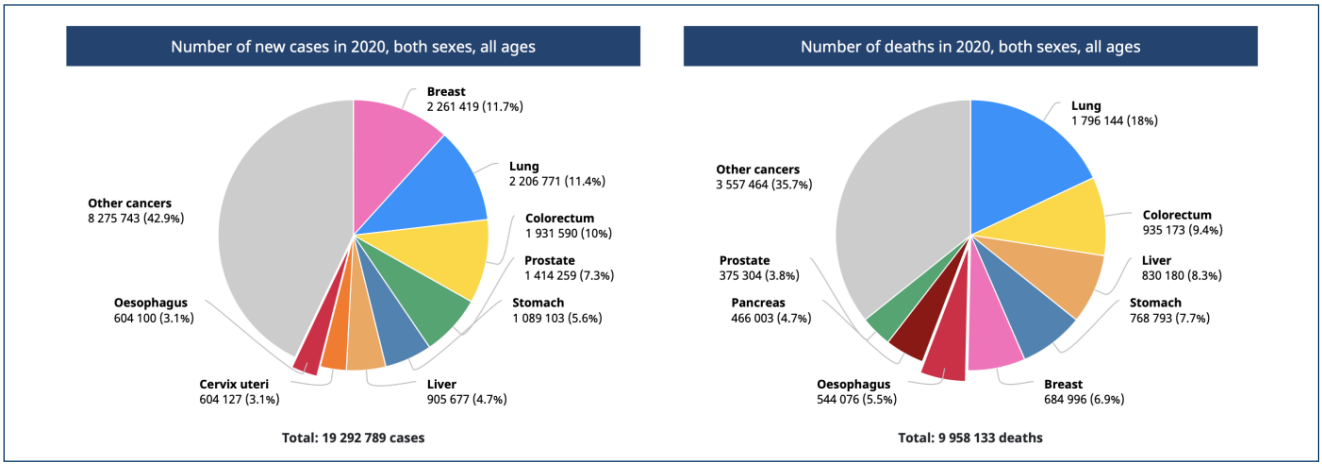

Figure 2. Number of new cases and deaths. Data source: GLOBOCAN 2020. Graph production: IARC (https://gco.iarc.fr/today) World Health Organization.

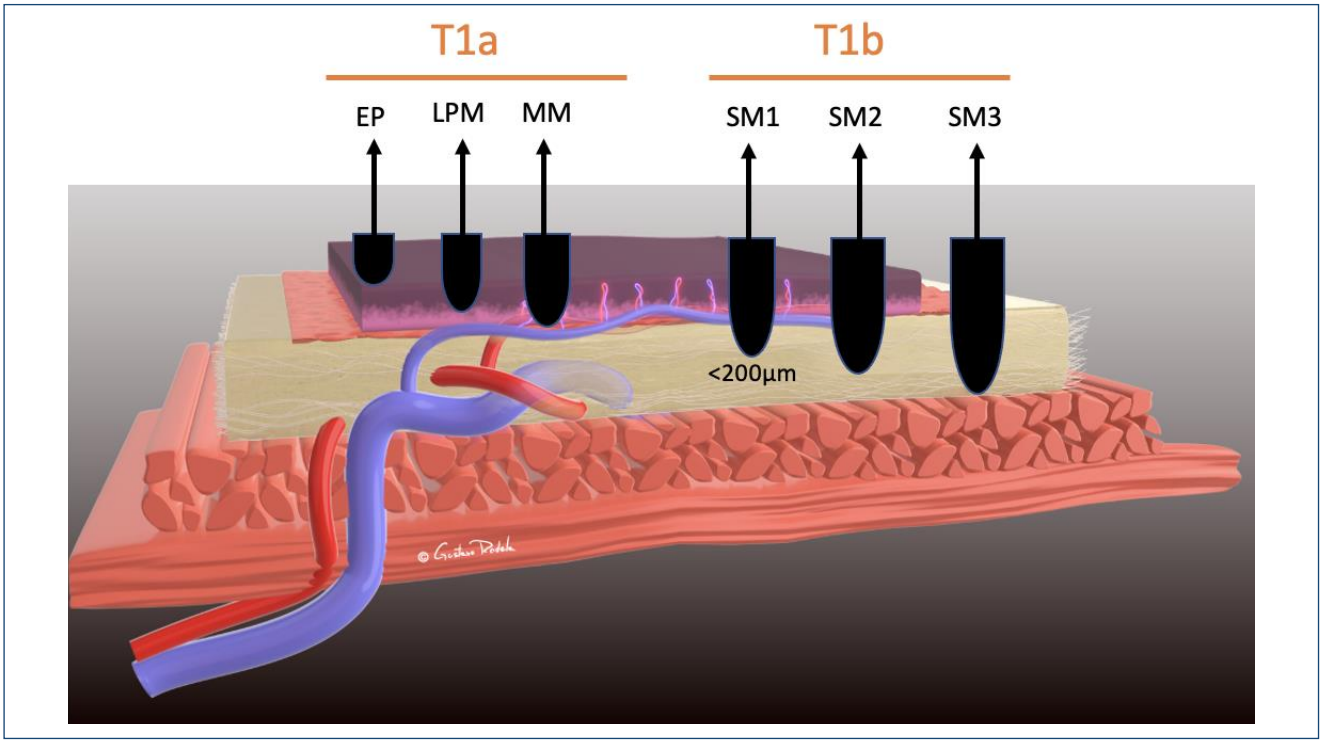

Figure 3. Subclassification for superficial cancer.

As the incidence of ESCC is increasing mainly because of improvements in endoscopic detection, this review will focus on the advances in diagnosis and endoscopic treatment strategies for superficial ESCC.

PRETREATMENT ASSESSMENT

ENDOSCOPY

Most patients with superficial ESCC do not have signs or symptoms caused by the neoplasia. It means that the diagnosis of superficial ESCC relies on endoscopy mostly indicated for unrelated gastrointestinal symptoms (e.g., dyspepsia) or in the context of screening programs[5].

The accurate evaluation of disease extent is crucial for the selection of the appropriate treatment strategy, and the endoscopic assessment of tumor depth is essential. Nevertheless, **mucosal changes associated with early cancers may be subtle and missed**. Therefore, the right preparation for an endoscopic examination is mandatory. The first step is to remove mucus and bubbles from the mucosal surface with mucolytics and/or defoaming agents. Adequate conscious sedation is

indicated. To avoid missing a lesion, it is essential to take time to evaluate the esophagus. It is estimated that high-definition, white light endoscopy (HD-WLE) has a **50% sensitivity** for the detection of ESCC. In this sense, Lugol chromo endoscopy was developed in the early 1990s. The principle is that iodine binds reversibly to glycogen, which is less abundant in immature and rapidly dividing cells such as those found in dysplasia and inflammation. Widely available today, Lugol's staining turned into an invaluable tool in characterizing the esophageal epithelial surface as a simple and cheap technique that improves the detection rate and helps to delineate margins. Compared with WLE, **Lugol's iodine chromoendoscopy significantly improved the sensitivity of ESCC**. However, this method has some drawbacks, namely, the lower specificity due to the non-differentiation of inflammatory changes and side effects such as chest pain[5-8]. A color change after iodine staining, from the initial yellow color to a pink color 2–3 min later, is known as the **pink-color sign** and is recognized as a valuable indicator for the diagnosis of ESCC[9,10] (Figure 4). This sign has been reported to dramatically improve specificity for HGIN and invasive cancer. Compared with HD-WLE, electronic and optic chromoendoscopy (i.e., NBI, BLI, FICE, and i-scan) have a higher sensitivity for the diagnosis of ESCC. However, Lugol chromoendoscopy has still a higher sensitivity for this purpose.

Because of its high specificity, the pink-color sign is a good indicator for choosing adequate biopsy sites in patients with multiple Lugol-void lesions (LVL), the so-called leopard print pattern (Figure 5).

The presence of multiple LVLs can indicate a high-risk condition for HGD and ESCC. Thus, the presence of multiple LVLs is important in clinical settings to assess the risk of development of ESCC[11].

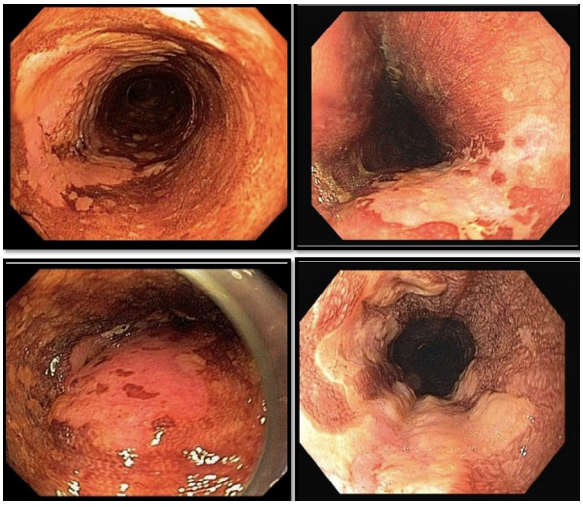

Figure 4. Lugol pink-color sign.

The pink-color sign is sometimes difficult to see because of its low intensity, whereas the metallic silver sign is clearly apparent with NBI. Its presence alone could indicate the presence of a cancerous lesion, regardless of macroscopic appearance or histopathologic characteristics[12] (Figure 6).

With HD-WLE, the macroscopic classification of Paris[13] may help predict the extent of invasion into the submucosa. Polypoid and excavated lesions, classified as Paris Ip and III, respectively, are easy to recognize, but they account for only 20% of early cancer and are more likely to contain invasive submucosal cancer in more than 80% of the cases. By contrast, most early esophageal cancer has a flat appearance with minimal impact on the contour of the mucosal surface (0-IIa, IIb, and IIc) (Figures 7 and 8).

Other macroscopic features of mucosal ESCC by HD-WLE are flat reddish areas with a smooth surface, slightly elevated or

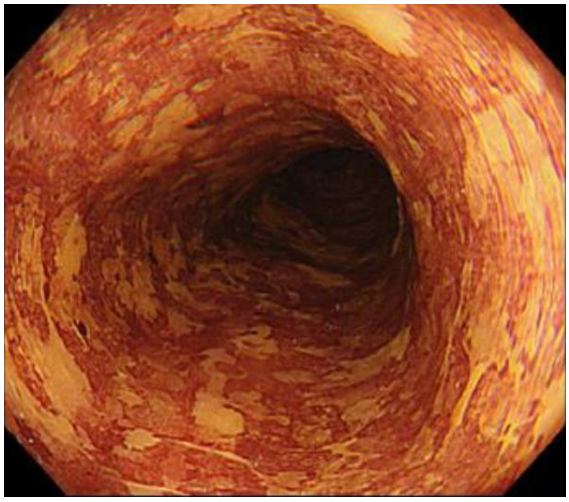

Figure 5. Leopard print pattern.

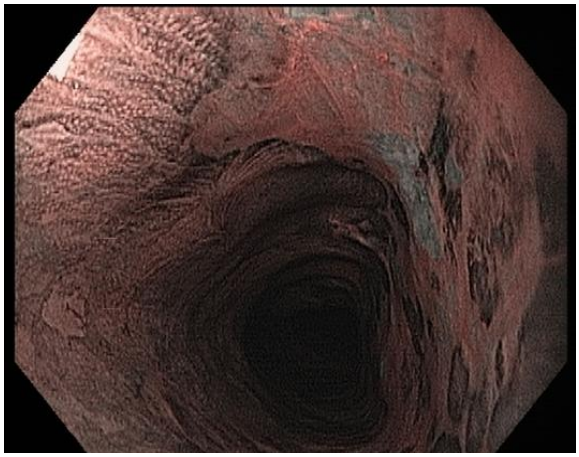

Figure 6. Metallic silver sign.

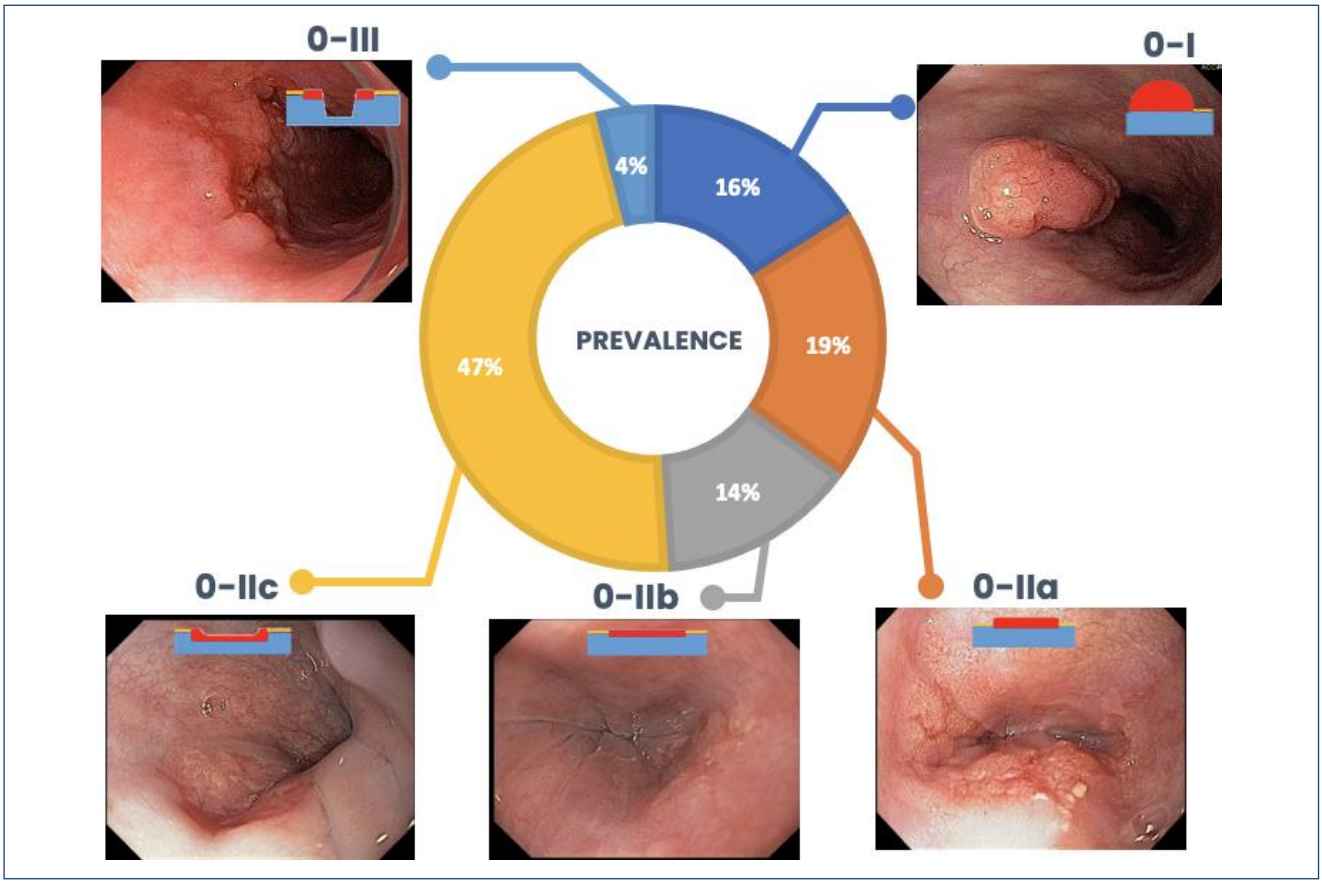

Figure 7. Macroscopic classification (the Paris Classification) and prevalence.

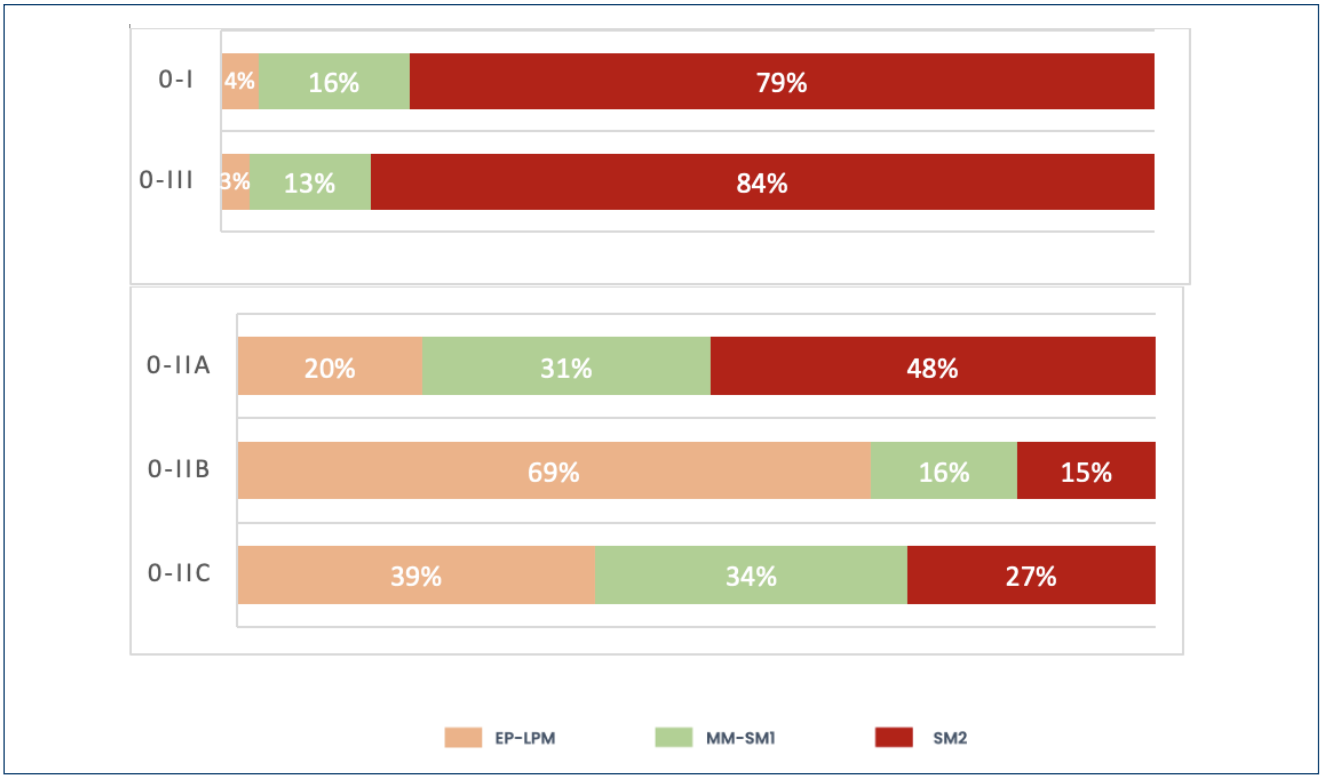

Figure 8. Invasion depth according to the Paris classification.

small depressed lesions with a slightly rough surface, or white granules (Figure 9). Submucosal ESCC may appear as irregular, protruded, and ulcerated lesions[14] (Figure 10).

However, the sensitivity of the Paris classification for the prediction of the depth of invasion is only 50% even among experienced endoscopists. Therefore, endoscopic diagnosis based solely on this gross, macroscopic appearance of a tumor is of limited value. It is essential, therefore, to have an additional, more accurate staging method.

Magnifying endoscopic assessment of the intrapapillary capillary loops (IPCLs) can predict the depth of invasion[15,16]. In ESCC, IPCL pattern changes present as dilatation, weaving, change in caliber, and variety in shape, the so-called **"four characteristic markers of cancer."** According to the Japanese Esophageal Society classification[17], microvessels are classified as type A if they have three or fewer factors and type B if they have all four. In this classification, vessels are classified into two categories: non-cancerous (normal epithelium, inflammation, and LGD) and cancerous (HGD and invasive SCC) epithelium. Type B1 is defined as type B vessels with a loop-like formation. B1 vessels normally appear as dot-like microvessels in a target area (Figure 11). When target lesions have only type B1 vessels, the histological invasion depth is predicted as T1a-EP (M1) or T1a-LPM (M2). B2 is defined as type B vessels without a loop-like formation that has a stretched and markedly elongated transformation. The B2 vessels often show a multilayered arrangement or irregularly branched/running pattern. This pattern is related to lesions invading muscularis mucosa (M3) and superficial submucosa (SM1, up to 200 micra). B3 is defined as highly dilated abnormal vessels whose caliber appears to be more than three times that of the usual B2 vessels and often appears green in color. The predicted invasion depth of the B3 pattern is deep submucosa.

ENDOSCOPIC ULTRASOUND

For locoregional staging of esophageal cancer of ESCC, endoscopic ultrasound (EUS) was extensively studied. It can be used for tumor (T) and node (N) staging (Figure 12). In general, EUS sensitivity and specificity rates for the correct evaluation of the

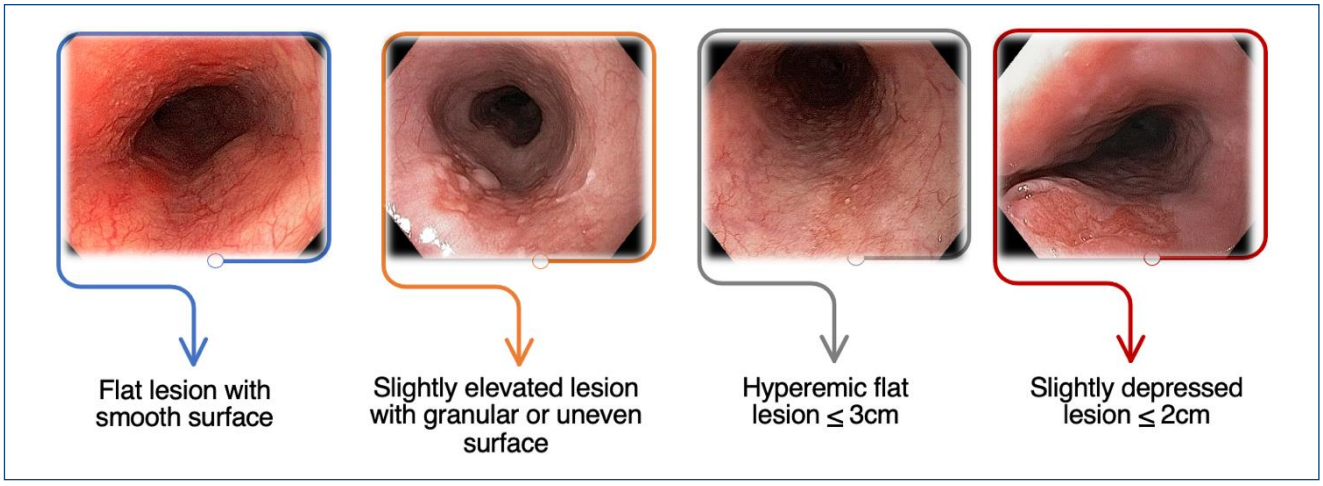

Figure 9. Macroscopic features of mucosal ESCC under HD-WLE.

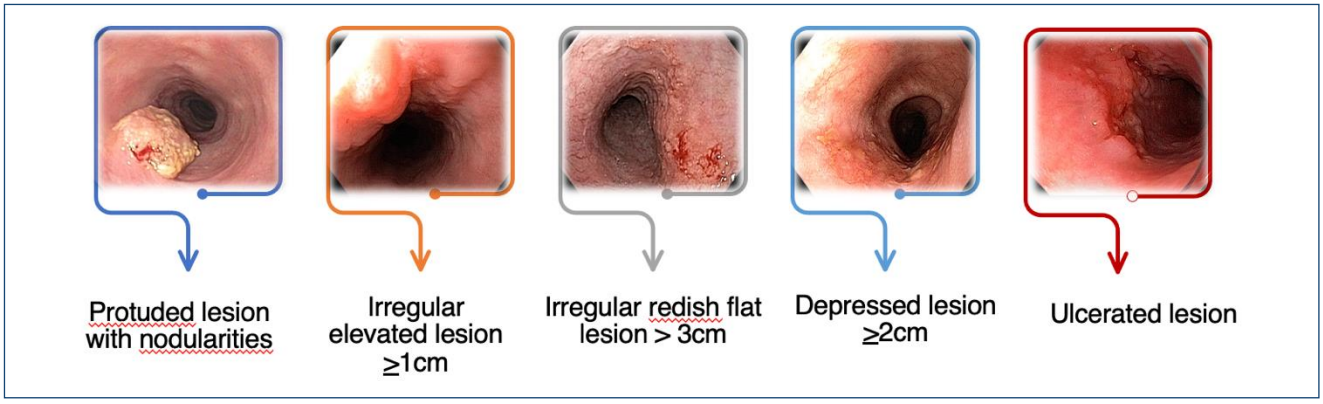

Figure 10. Macroscopic features of submucosal ESCC under HD-WLE.

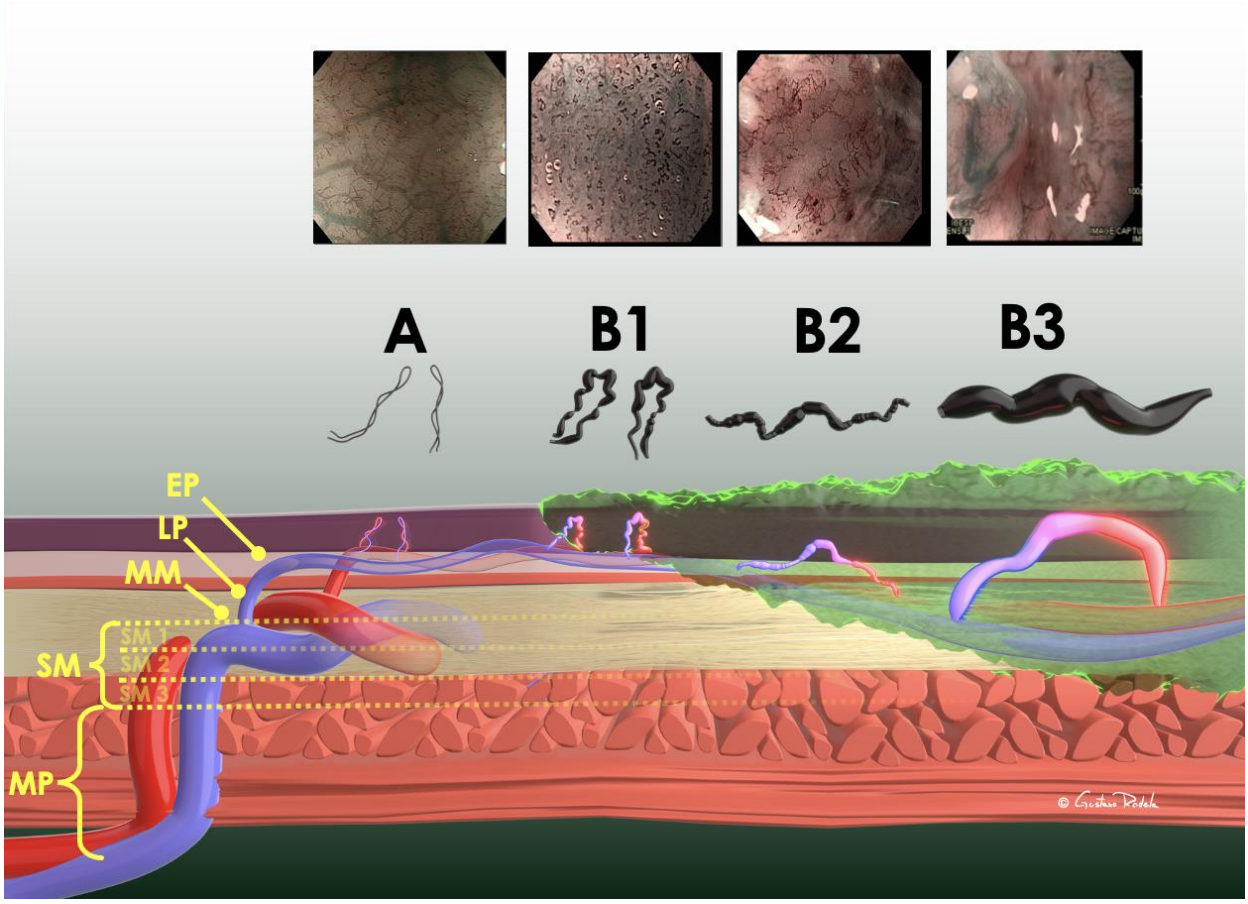

Figure 11. JES classification.

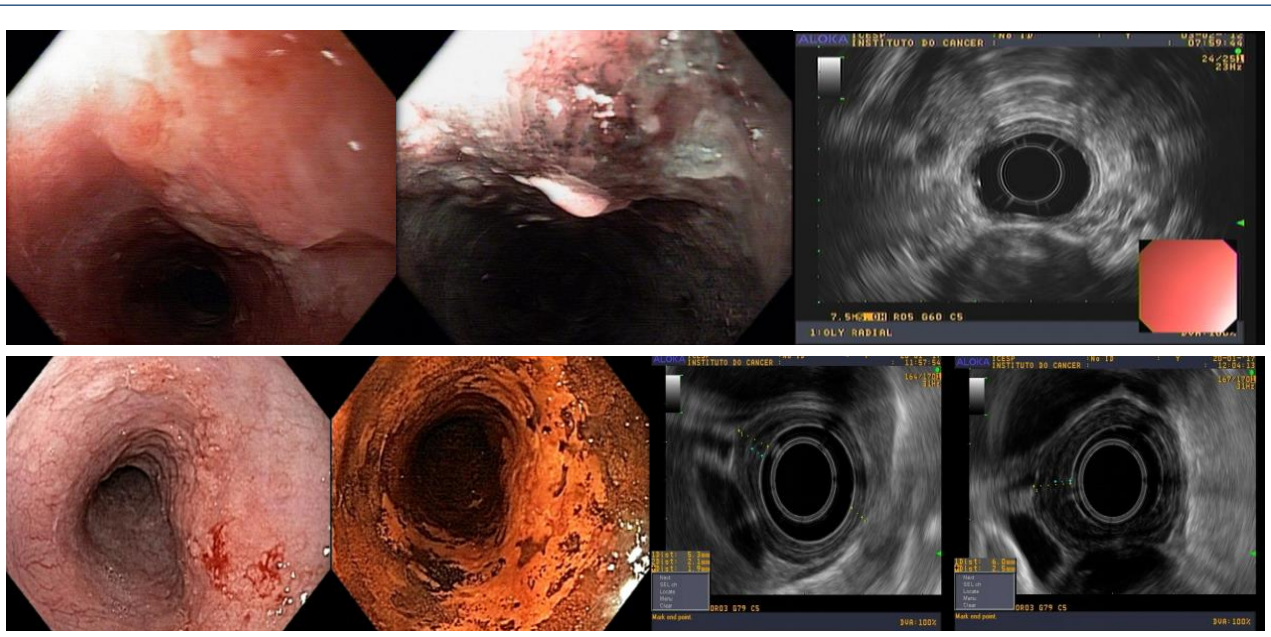

Figure 12. EUS assessment of T staging.

T stage are 81–92% and 94–97%, respectively[18]. The overall accuracy for N staging is 74% when used alone[19].

The usefulness of EUS in superficial cancer is controversial. An early meta-analysis of 19 studies and 1,019 patients with superficial esophageal cancer described an overall accuracy of 0.93 of EUS for T staging. However, the heterogeneity of this meta-analysis was high probably due to multiple factors including the location and type of lesion, the method and frequency of the EUS probe, and the experience of the endosonographer[20]. In our experience, **the EUS accuracy to differentiate T1a from T1b lesions is suboptimal** and we give preference to magnifying endoscopy. We indicate EUS in superficial ESCC when the findings of magnifying endoscopy are unclear aiming at a better T and N staging.

Moreover, in stenotic advanced tumors, EUS evaluation may not be technically possible. In a multicenter study involving 100 patients with stenotic esophageal neoplasms, the EUS scope could not traverse the stricture in 70. From them, all patients had T3Nx or T4Nx disease. This fact reduced the enthusiasm for tumor dilation to perform a complete EUS staging[21].

CROSS-SECTIONAL STUDIES

The evaluation for distant metastasis includes commonly computed tomography (CT) and/or positron emission tomography (PET-CT). These methods can also provide complementary information for T and N staging. Most superficial ESCCs are not detected on CT or PET-CT[22].

TREATMENT STRATEGY

The initial treatment strategy should take into consideration a multidisciplinary assessment of the patient's condition and choice, disease extension, metastatic status, invasion depth, tumor size, location, and circumferential extent (Figure 13).

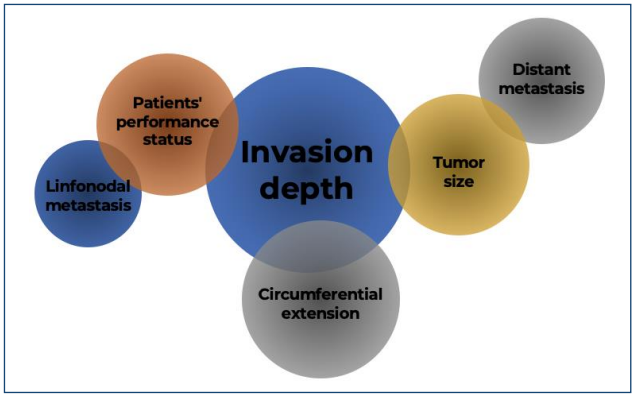

Figure 13. Therapeutic strategy for superficial esophageal squamous cell cancer.

Among these factors, cancer invasion depth correlates with the risk of metastasis and curability. A proposed algorithm for the treatment based on the TNM stage (according to the AJCC 8th edition) is discussed below[23] (Figure 14).

T1 (superficial) lesions are defined as those invading the mucosa (T1a) and submucosa (T1b). These lesions have been further categorized into three subtypes (M1–M3 and SM1–SM3, respectively) according to the depth of invasion.

Esophageal lesions classified as M1 (intraepithelial) or M2 (invades the lamina propria) have virtually no risk of lymph node involvement. This risk increases to 8–18% in lesions that invade the muscularis mucosa (M3), to 11–53% in lesions that invade the submucosa up to 200 μm (SM1), and 30–54% in deeper lesions (SM2)[17]. Additional characteristics that impact the risk of nodal involvement include vascular invasion, tumor size, and the degree of tumor differentiation (Figure 15).

Given the low risk of lymph node involvement, mucosal lesions classified as M1 and M2 (IPCL type B1) are absolute indications for ER. Lesions clinically classified as invading muscularis mucosa (M3) or superficial submucosa (SM1) can also be treated by ER. However, due to the risk of linfonodal metastasis, they are considered relative indications. Lesions with endoscopic features of deep submucosa invasion (more than 200 μm or ≥SM2) are associated with a risk of lymph node metastasis at a frequency of about 50% and should be treated similarly to advanced carcinomas[24-27].

Endoscopic techniques have been developed for curative resection of superficial neoplasms of the esophagus, such as endoscopic mucosal resection (EMR, Figure 16) and endoscopic submucosal dissection (ESD, Figure 17). Currently, **ESD is considered the preferred approach to manage superficial ESCC, enabling accurate *en bloc* resection with a lower recurrence rate and improved survival (Figure 18)**[28-31].

In a multicenter retrospective study that included 148 tumors (80 treated by EMR and 68 by ESD), the recurrence rate was significantly higher in the EMR group (23.7 versus 2.9%), and 5-year recurrence-free survival rates were worse (73.4 versus 95.2%)[3,32] in the EMR group.

In comparison with surgery, even though no randomized trials are available, evidence shows that the long-term outcomes of ESD and surgery are comparable. In a retrospective study, 116 T1a ESCCs larger than 2 cm treated either surgically (n=47) or endoscopically (n=69) were compared. The overall survival rate was similar (97.1% versus 91.5%, p=0.18), Procedure-related complications occurred more often in the surgical group (8.5% versus 0, p<0.05)[33].

In addition to the depth of invasion, the circumferential extent of the lesion should be taken into consideration because of the high risk of stenosis in lesions involving more than 75%

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Table 1 Cancer staging categories for cancer of the esophagus and esophagogastric junction

Category	Criteria
T category	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a*	Tumor invades the lamina propria or muscularis mucosae
T1b*	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a*	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b*	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis
Squamous cell carcinoma G category	
GX	Differentiation cannot be assessed
G1	Well-differentiated. Prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells. Tumor cells are arranged in sheets, and mitotic counts are low
G2	Moderately differentiated. Variable histologic features, ranging from parakeratotic to poorly keratinizing lesions. Generally, pearl formation is absent
G3‡	Poorly differentiated. Consists predominantly of basal-like cells forming large and small nests with frequent central necrosis. The nests consist of sheets or pavement-like arrangements of tumor cells, and occasionally are punctuated by small numbers of parakeratotic or keratinizing cells
Squamous cell carcinoma L category***	
LX	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including esophagogastric junction

*, subcategories; †, if further testing of "undifferentiated" cancers reveals a glandular component, categorize as adenocarcinoma G3; ‡, if further testing of "undifferentiated" cancers reveals a squamous cell component, or if after further testing they remain undifferentiated, categorize as squamous cell carcinoma G3; ***, location is defined by epicenter of esophageal tumor.

Table 2 Clinical (cTNM) stage groups

cStage group	cT	cN	cM
Squamous cell carcinoma			
0	Tis	N0	M0
I	T1	N0–1	M0
II	T2	N0–1	M0
	T3	N0	M0
III	T3	N1	M0
	T1–3	N2	M0
IVA	T4	N0–2	M0
	T1–4	N3	M0
IVB	T1–4	N0–3	M1

Figure 14. TNM stage according to the AJCC 8th edition. Available in Annals of Cardiothoracic Surgery, Vol. 6, No. 2, March 2017.

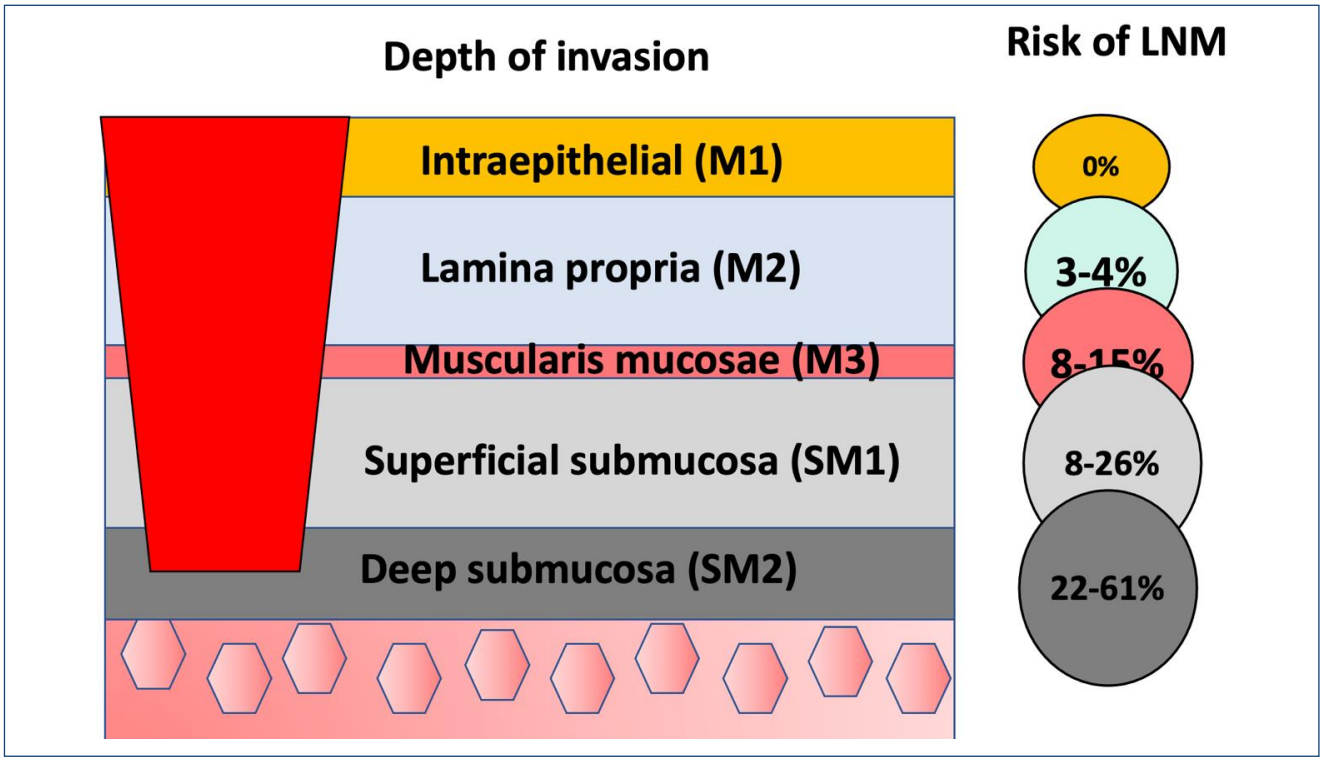

Figure 15. The correlation between superficial ESCC depth of invasion and the risk of lymph node metastasis.

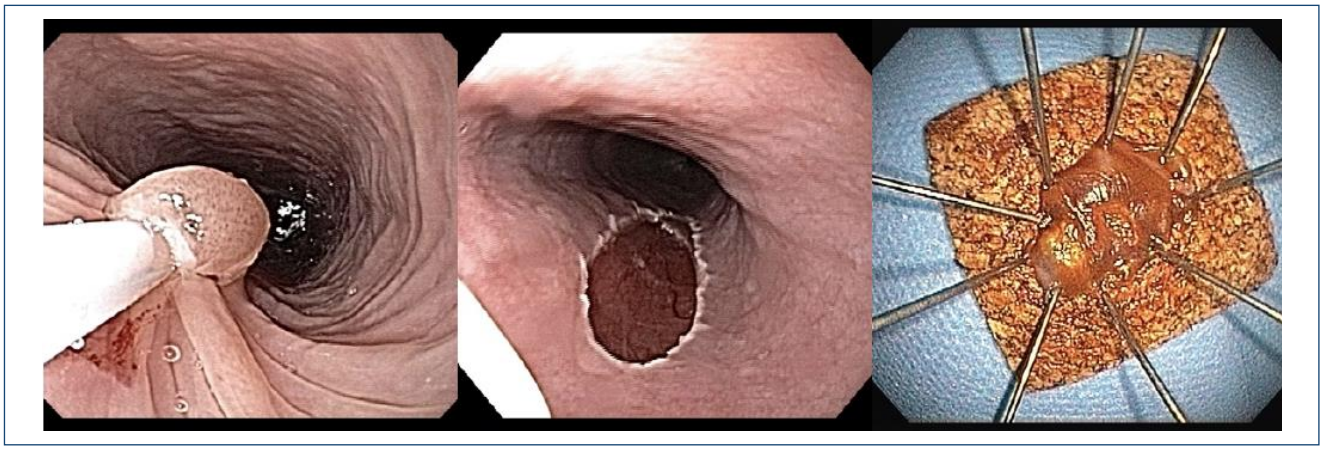

Figure 16. Esophageal endoscopic mucosal resection (EMR).

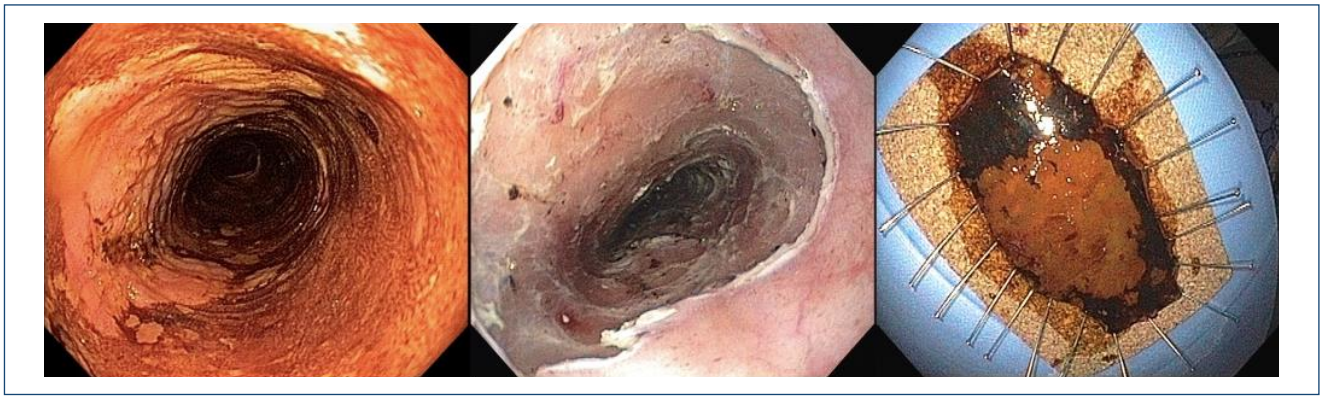

Figure 17. Endoscopic submucosal dissection (ESD).

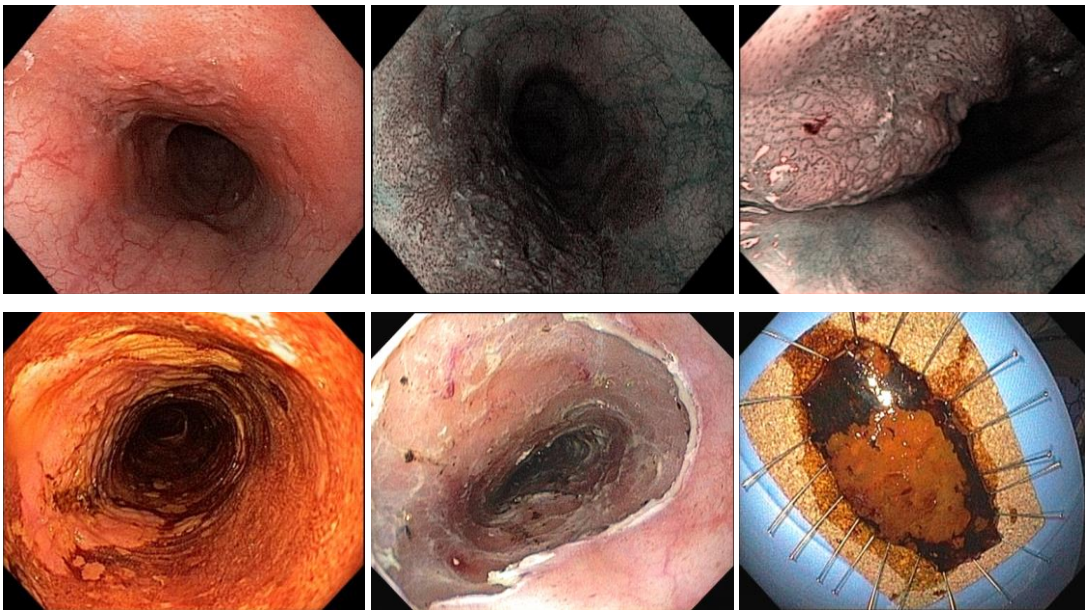

Figure 18. Circumferential ESD.

of the circumference. Nevertheless, more effective prophylaxis with oral and/or intravenous corticosteroids has recently been developed with promising results[34,35]. Furthermore, dilatation is another effective method to prevent stenosis following post-ESD stenosis. In terms of outcomes, the complete resection rate following circumferential esophageal ESD is reported to be as high as 100% and the curative resection rate is 70%[36-38].

It is important to highlight that the endoscopic diagnosis of the invasion depth has some limitations, mostly on extensive lesions and lesions with IPCL Type B2, where the JES classification accuracy is only 55.7%[26]. Accordingly, the assessment of the histological diagnosis of resected specimens is essential. In patients classified as having pT1a-epithelium/lamina propria mucosae disease (M1 or M2), follow-up should be scheduled. On the contrary, in patients with muscularis mucosa (M3) or superficial submucosa (SM1) and positive vascular invasion, an additional treatment (surgical or chemoradiotherapy) is required. Also, for lesions showing deep submucosal invasion, regardless of lymphovascular metastasis, additional esophagectomy or chemoradiotherapy is necessary[27]. The selection between surgery and chemoradiotherapy should be made after assessing the patient's clinical condition (Figure 19).

A Japanese trial[39] evaluated the efficacy of ER followed by chemoradiotherapy. Patients with histologically M3 lesions, positive vascular invasion, and negative resection margins or histologically SM invasion and negative resection margin underwent prophylactic chemoradiotherapy. Patients with SM invasion and positive resection margin underwent definitive chemoradiotherapy. Favorable results were obtained in the prophylactic chemoradiotherapy group, with a 3-year overall survival rate of 90.7% (90%CI 84.0–94.7%). That study showed that even when ER is not curative, a good prognosis can be expected if additional chemoradiotherapy is administered.

A multicenter study involving seven western centers reported a 25% residual/recurrence rate of esophageal cancer (both adenocarcinoma and ESCC) after ESD for T1b lesions (hazard ratio, 6.25; 95% confidence interval, 1.29–30.36; p=0.023). Those findings corroborate the limitation of ER for esophageal cancer with submucosa invasion[40].

CONCLUSION

Superficial ESCC diagnosis has been increasing worldwide. The endoscopic prediction of the depth of tumor invasion is the most important factor in selecting the treatment strategy and optimizing outcomes. ER techniques by EMR and ESD have become the most important treatment as provide high curative rates and organ preservation.

AUTHORS' CONTRIBUTIONS

RNM: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **FMF**: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

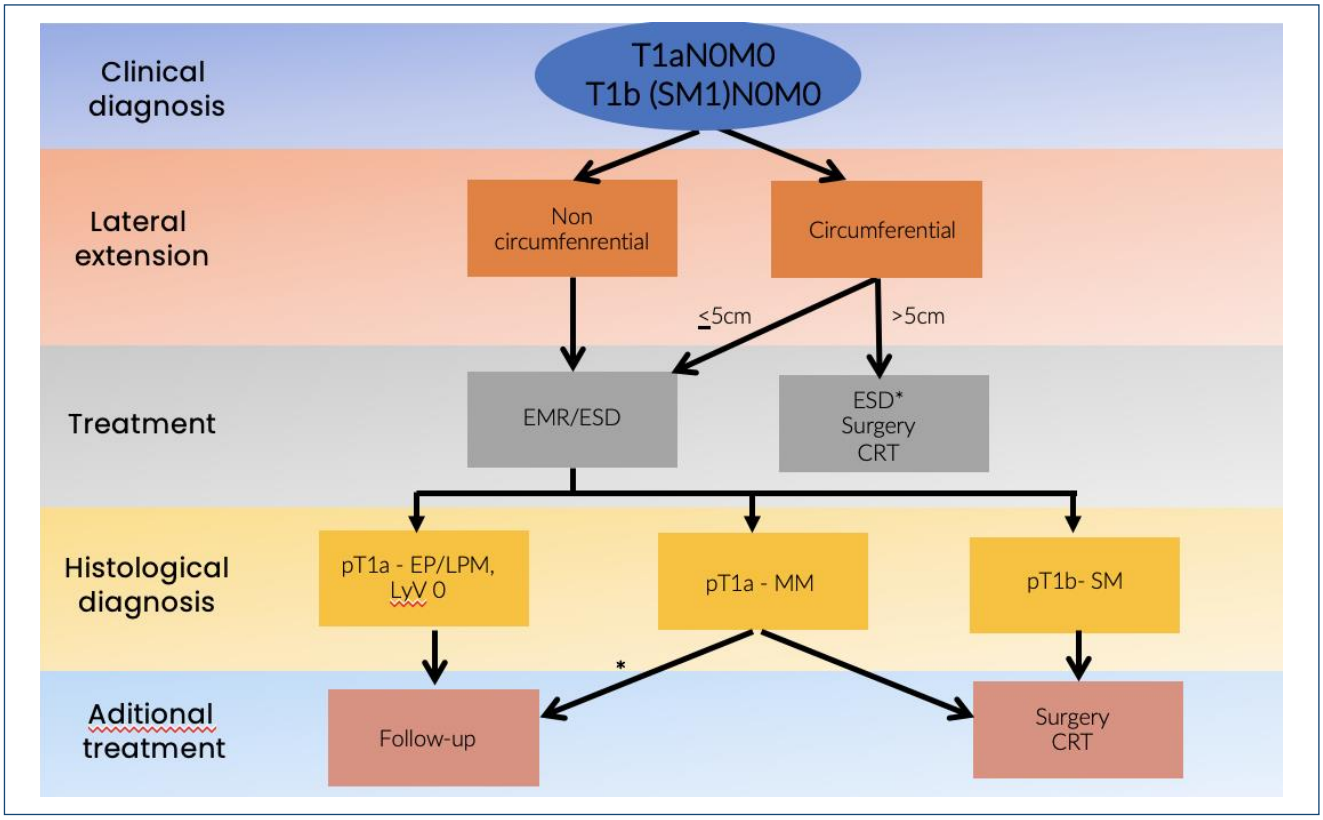

Figure 19. Therapeutic strategy for superficial ESCC. Adapted from Ishiara et al. Dig Endosc, 2020.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492
2. Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. Gastroenterology. 2018;154(2):360-73. https://doi.org/10.1053/j.gastro.2017.08.023
3. Nobre Moura R, Kuboki Y, Baba ER, Safatle-Ribeiro A, Martins B, Paulo GA, et al. Long-term results of an endoscopic screening program for superficial esophageal cancer in patients with head and neck squamous cell carcinoma. Endosc Int Open. 2022;10(2):E200-8. https://doi.org/10.1055/a-1675-2334
4. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edition: part I. Esophagus. 2017;14(1):1-36. https://doi.org/10.1007/s10388-016-0551-7
5. Codipilly DC, Qin Y, Dawsey SM, Kisiel J, Topazian M, Ahlquist D, et al. Screening for esophageal squamous cell carcinoma: recent advances. Gastrointest Endosc. 2018;88(3):413-26. https://doi.org/10.1016/j.gie.2018.04.2352
6. Fukuhara T, Hiyama T, Tanaka S, Oka S, Yoshihara M, Arihiro K, et al. Characteristics of esophageal squamous cell carcinomas and lugol-voiding lesions in patients with head and neck squamous cell carcinoma. J Clin Gastroenterol. 2010;44(2):e27-33. https://doi.org/10.1097/MCG.0b013e3181b31325
7. Hashimoto CL, Iriya K, Baba ER, Navarro-Rodriguez T, Zerbini MC, Eisig JN, et al. Lugol's dye spray chromoendoscopy establishes early diagnosis of esophageal cancer in patients with primary head and neck cancer. Am J Gastroenterol. 2005;100(2):275-82. https://doi.org/10.1111/j.1572-0241.2005.30189.x
8. Chung CS, Liao LJ, Lo WC, Chou YH, Chang YC, Lin YC, et al. Risk factors for second primary neoplasia of esophagus in newly diagnosed head and neck cancer patients: a case-control study. BMC Gastroenterol. 2013;13:154. https://doi.org/10.1186/1471-230X-13-154
9. Ishihara R, Kanzaki H, Iishi H, Nagai K, Matsui F, Yamashina T, et al. Pink-color sign in esophageal squamous neoplasia, and speculation regarding the underlying mechanism. World J Gastroenterol. 2013;19(27):4300-8. https://doi.org/10.3748/wjg.v19.i27.4300
10. Zheng JY, Chen YH, Chen YY, Zheng XL, Zhong SS, Deng WY, et al. Presence of pink-color sign within 1 min after iodine staining has high diagnostic accordance rate for esophageal high-grade intraepithelial neoplasia/invasive cancer. Saudi J Gastroenterol. 2019;25(2):113-8. https://doi.org/10.4103/sjg.SJG_274_18
11. Matsuno K, Ishihara R, Nakagawa K, Ohmori M, Iwagami H, Inoue S, et al. Endoscopic findings corresponding to multiple Lugol-voiding lesions in the esophageal background mucosa. J Gastroenterol Hepatol. 2019;34(2):390-6. https://doi.org/10.1111/jgh.14439
12. Maselli R, Inoue H, Ikeda H, Onimaru M, Yoshida A, Santi EG, et al. The metallic silver sign with narrow-band imaging: a new endoscopic predictor for pharyngeal and esophageal neoplasia. Gastrointest Endosc. 2013;78(3):551-3. https://doi.org/10.1016/j.gie.2013.03.1332

13. Gastrointestinal Endoscopy. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc. 2003;58(6 Suppl):S3-43. https://doi.org/10.1016/s0016-5107(03)02159-x
14. Ebi M, Shimura T, Yamada T, Mizushima T, Itoh K, Tsukamoto H, et al. Multicenter, prospective trial of white-light imaging alone versus white-light imaging followed by magnifying endoscopy with narrow-band imaging for the real-time imaging and diagnosis of invasion depth in superficial esophageal squamous cell carcinoma. Gastrointest Endosc. 2015;81(6):1355-61.e2. https://doi.org/10.1016/j.gie.2014.11.015
15. Kubo K, Fujino MA. Ultra-high magnification endoscopy of the normal esophageal mucosa. Gastrointest Endosc. 1997;46(1):96-7. PMID: 9260723
16. Inoue H, Kaga M, Ikeda H, Sato C, Sato H, Minami H, et al. Magnification endoscopy in esophageal squamous cell carcinoma: a review of the intrapapillary capillary loop classification. Ann Gastroenterol. 2015;28(1):41-8. PMID: 25608626
17. Oyama T, Inoue H, Arima M, Momma K, Omori T, Ishihara R, et al. Prediction of the invasion depth of superficial squamous cell carcinoma based on microvessel morphology: magnifying endoscopic classification of the Japan esophageal society. Esophagus. 2017;14(2):105-12. https://doi.org/10.1007/s10388-016-0527-7
18. Puli SR, Reddy JB, Bechtold ML, Antillon D, Ibdah JA, Antillon MR. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World J Gastroenterol. 2008;14(10):1479-90. https://doi.org/10.3748/wjg.14.1479
19. Krill T, Baliss M, Roark R, Sydor M, Samuel R, Zaibaq J, et al. Accuracy of endoscopic ultrasound in esophageal cancer staging. J Thorac Dis. 2019;11(Suppl 12):S1602-9. https://doi.org/10.21037/jtd.2019.06.50
20. Thosani N, Singh H, Kapadia A, Ochi N, Lee JH, Ajani J, et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. Gastrointest Endosc. 2012;75(2):242-53. https://doi.org/10.1016/j.gie.2011.09.016
21. Bang JY, Ramesh J, Hasan M, Navaneethan U, Holt BA, Hawes R, et al. Endoscopic ultrasonography is not required for staging malignant esophageal strictures that preclude the passage of a diagnostic gastroscope. Dig Endosc. 2016;28(6):650-6. https://doi.org/10.1111/den.12658
22. Aoyama J, Kawakubo H, Mayanagi S, Fukuda K, Irino T, Nakamura R, et al. Discrepancy between the clinical and final pathological findings of lymph node metastasis in superficial esophageal cancer. Ann Surg Oncol. 2019;26(9):2874-81. https://doi.org/10.1245/s10434-019-07498-2
23. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. J Thorac Oncol. 2017;12(1):36-42. https://doi.org/10.1016/j.jtho.2016.10.016
24. Kitagawa Y, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 1. Esophagus. 2019;16(1):1-24. https://doi.org/10.1007/s10388-018-0641-9
25. Kitagawa Y, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. Esophagus. 2019;16(1):25-43. https://doi.org/10.1007/s10388-018-0642-8
26. Ishihara R, Arima M, Iizuka T, Oyama T, Katada C, Kato M, et al. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. Dig Endosc. 2020;32(4):452-93. https://doi.org/10.1111/den.13654
27. Abe S, Hirai Y, Uozumi T, Makiguchi ME, Nonaka S, Suzuki H, et al. Endoscopic resection of esophageal squamous cell carcinoma: current indications and treatment outcomes. DEN Open. 2021;2(1):e45. https://doi.org/10.1002/deo2.45
28. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, Ceglie A, et al. Endoscopic submucosal dissection: European society of gastrointestinal endoscopy (ESGE) guideline. Endoscopy. 2015;47(9):829-54. https://doi.org/10.1055/s-0034-1392882
29. Ono S, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, et al. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. Gastrointest Endosc. 2009;70(5):860-6. https://doi.org/10.1016/j.gie.2009.04.044
30. Rizvi QU, Balachandran A, Koay D, Sharma P, Singh R. Endoscopic management of early esophagogastric cancer. Surg Oncol Clin N Am. 2017;26(2):179-91. https://doi.org/10.1016/j.soc.2016.10.007
31. Aadam AA, Abe S. Endoscopic submucosal dissection for superficial esophageal cancer. Dis Esophagus. 2018;31(7). https://doi.org/10.1093/dote/doy021
32. Berger A, Rahmi G, Perrod G, Pioche M, Canard JM, Cesbron-Métivier E, et al. Long-term follow-up after endoscopic resection for superficial esophageal squamous cell carcinoma: a multicenter Western study. Endoscopy. 2019;51(4):298-306. https://doi.org/10.1055/a-0732-5317
33. Yuan B, Liu L, Huang H, Li D, Shen Y, Wu B, et al. Comparison of the short-term and long-term outcomes of surgical treatment versus endoscopic treatment for early esophageal squamous cell neoplasia larger than 2 cm: a retrospective study. Surg Endosc. 2019;33(7):2304-12. https://doi.org/10.1007/s00464-018-6524-2
34. Isomoto H, Yamaguchi N, Nakayama T, Hayashi T, Nishiyama H, Ohnita K, et al. Management of esophageal stricture after complete circular endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. BMC Gastroenterol. 2011;11:46. https://doi.org/10.1186/1471-230X-11-46
35. Kataoka M, Anzai S, Shirasaki T, Ikemiyagi H, Fujii T, Mabuchi K, et al. Efficacy of short period, low dose oral prednisolone for the prevention of stricture after circumferential endoscopic submucosal dissection (ESD) for esophageal cancer. Endosc Int Open. 2015;3(2):E113-7. https://doi.org/10.1055/s-0034-1390797
36. Yamashina T, Ishihara R, Uedo N, Nagai K, Matsui F, Kawada N, et al. Safety and curative ability of endoscopic submucosal dissection for superficial esophageal cancers at least 50 mm in diameter. Dig Endosc. 2012;24(4):220-5. https://doi.org/10.1111/j.1443-1661.2011.01215.x
37. Miwata T, Oka S, Tanaka S, Kagemoto K, Sanomura Y, Urabe Y, et al. Risk factors for esophageal stenosis after entire circumferential endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. Surg Endosc. 2016;30(9):4049-56. https://doi.org/10.1007/s00464-015-4719-3
38. Tsujii Y, Nishida T, Nishiyama O, Yamamoto K, Kawai N, Yamaguchi S, et al. Clinical outcomes of endoscopic submucosal dissection for superficial esophageal neoplasms: a multicenter retrospective cohort study. Endoscopy. 2015;47(9):775-83. https://doi.org/10.1055/s-0034-1391844
39. Nihei K, Minashi K, Yano T, Shimoda T, Fukuda H, Muto M, et al. Final Analysis of Diagnostic Endoscopic Resection Followed by Selective Chemoradiotherapy for Stage I Esophageal Cancer: JCOG0508. Gastroenterology. 2023;164(2):296-99.e2. https://doi.org/10.1053/j.gastro.2022.10.002
40. Joseph A, Draganov PV, Maluf-Filho F, Aihara H, Fukami N, Sharma NR, et al. Outcomes for endoscopic submucosal dissection of pathologically staged T1b esophageal cancer: a multicenter study. Gastrointest Endosc. 2022;96(3):445-53. https://doi.org/10.1016/j.gie.2022.02.018