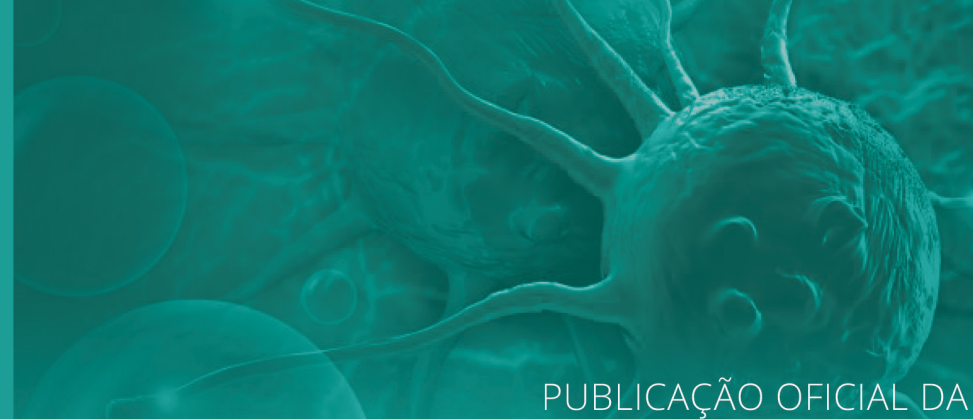

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CANCEROLOGIA

Sociedade Brasileira de Cancerologia

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EDITORIAL

Revista da Sociedade Brasileira de Cancerologia

A Sociedade Brasileira de Cancerologia é a mais antiga e tradicional do Brasil. Desde a década de 40 vem trabalhando em prol do desenvolvimento do ensino e ajudando na luta contra o câncer. Recentemente, tivemos as eleições para a nova diretoria onde a chapa vitoriosa do Dr. Enaldo Melo assumiu neste mês de agosto. Com isso, mantém-se a estratégia de gestão voltada para o apoio ao ensino e a educação na área de cancerologia, bem como lutando por políticas públicas de acesso à inovação e tecnologia aos pacientes oncológicos do SUS, sistema único de saúde. Nesse ano de 2024, também começamos a organização do próximo Congresso Brasileiro de Cancerologia, a ser realizado em 2025 e presidido pelo Dr. Ricardo Antunes. No âmbito da revista científica da Sociedade Brasileira de Cancerologia, aguardamos a indexação da plataforma LILACs, o que nos trará um valoroso reconhecimento. Recebemos artigos de médicos do Brasil e do mundo com foco na pesquisa em cancerologia. Eu convido você a ler a edição atual da nossa revista e a colaborar submetendo artigos científicos nas próximas edições.

Ramon Andrade B de Mello
Editor-chefe da Revista da SBC
Vice-Presidente da SBC

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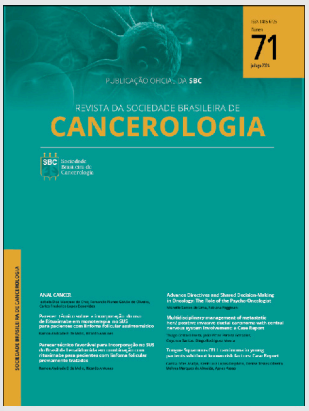
Sociedade Brasileira de Cancerologia



PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE CANCEROLOGIA, COM A PARTICIPAÇÃO DA SOCIEDADE BRASILEIRA DE PSICO-ONCOLOGIA

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SUMÁRIO

ARTIGO ORIGINAL I *ORIGINAL ARTICLES*

ANAL CANCER

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ABSTRACT

Anal cancer treatment involves a multidisciplinary approach encompassing surgery, chemotherapy, and radiation therapy. The primary goal of treatment is to achieve disease control while preserving anal function and minimizing treatment-related toxicities. Surgery is often utilized for early-stage anal cancer, where the tumor is localized and has not spread to nearby lymph nodes. Procedures such as local excision or abdominoperineal resection may be performed to remove the tumor and surrounding tissue. In cases where the cancer has spread to nearby lymph nodes, lymph node dissection may be necessary to prevent further spread of the disease. Chemotherapy is commonly used in combination with radiation therapy for both early and advanced stages of anal cancer. Chemotherapy drugs such as 5-fluorouracil and mitomycin C are typically administered to help maximize the effectiveness of radiation treatment and target any remaining cancer cells. Radiation therapy plays a crucial role in the treatment of anal cancer by delivering high-energy radiation to the affected area to kill cancer cells and shrink tumors and external beam radiation therapy is the most common approach. Overall, the optimal treatment plan for anal cancer depends on the stage of the disease, the patient's overall health, and individual factors. Close collaboration between oncologists, surgeons, radiation oncologists, and other healthcare professionals is essential to tailor treatment to each patient's specific needs and optimize outcomes. Early detection and prompt intervention are critical in improving the prognosis for individuals diagnosed with anal cancer.

Key-words: anal cancer, anal carcinoma, chemoradiation, systemic treatment, radiotherapy.

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ANAL CANCER

Anal cancers are typically classified into two categories, depending on the location of the initial tumor: those originating in the anal canal, which are found above the anal verge, and those originating in the perianal skin, located below the anal verge, which were formerly referred to as anal margin cancers. The treatment approach can vary based on the cancer's location. However, It is important to note that anal cancers can occasionally spread from one area to another, making it challenging to identify their exact origin. In this section, we will explore the treatment options for the most common histological type of anal cancer, squamous cell carcinoma.

1. EPIDEMIOLOGY AND CLINICAL FEATURES

Anal cancer is a rare malignancy, accounting for roughly 0.5% of new cancers diagnosed in the United States annually, with an overall incidence rate of 2.0 per 100,000 persons. It´s incidence has gradually risen over the past decade of available data (2010–2019), increasing on average by approximately 2.2% each year[1].

Rectal bleeding stands out as the most prevalent initial symptom of anal cancer, experienced by around 45 % of patients. Anorectal pain or the feeling of a mass in the rectal area is reported by 30 % of individuals, while 20 % do not exhibit any tumor-related symptoms. Essential to note that bleeding originating from a mass near or just above the anal sphincter might mistakenly be linked to hemorrhoids, potentially leading to a delay in diagnosis[1].

In cases of anal squamous cell carcinoma (SCC), a significant number of gay men, approximately 50 %, have a history of anorectal condyloma, with this history being less common in women and straight men, at fewer than 30 %. These percentages notably surpass those found in normal controls, which typically range from 1 to 2 %. Moreover, tumors affecting the perianal skin, such as Bowen's disease or Paget disease, can manifest with symptoms like pruritus ani or a bleeding, reddened eczematoid plaque[2–5].

Anal cancer risk factors encompass a variety of epidemiological and clinical considerations. However, infection with high-risk strains of human papillomavirus (HPV), particularly HPV types 16 and 18, have been strongly linked to the development of anal cancer. Additional risk factors may involve engaging in receptive anal intercourse, having a weakened immune system due to conditions such as HIV/AIDS or organ transplantation, and a history of certain sexually transmitted infections, such as genital warts. Other contributing factors may include smoking, a history of cervical, vaginal, or vulvar cancer, and older age.

The relationship between human papillomavirus (HPV) and anal cancer carcinogenesis is intricate and well-established. High-risk HPV types, particularly HPV 16 and 18, are known to play a significant role in the development of anal cancer. The process of HPV-related anal carcinogenesis typically begins with the viral infection of epithelial cells in the anus. HPV integrates its DNA into the host cell genome, leading to the dysregulation of cellular functions and promoting oncogenic transformation. After the integration, the expression of viral oncoproteins E6 and E7 plays a pivotal role in carcinogenesis. E6 inactivates the tumor suppressor protein p53, leading to uncontrolled cell proliferation, inhibition of apoptosis, and genomic instability. On the other hand, E7 disrupts the function of the retinoblastoma (Rb) tumor suppressor protein, further promoting cell cycle progression and inhibiting cell differentiation[2–6].

2. STAGING

The staging of anal cancer is crucial for determining the extent of the disease, guiding treatment decisions, and predicting outcomes. The most used system for staging anal cancer is the TNM system, which is maintained by the American Joint Committee on Cancer (AJCC). The 8th edition of this system assesses tumors based on three key criteria: the size and extent of the tumor (T), whether cancer cells have spread to nearby lymph nodes (N), and whether there are metastases, or spread of cancer to distant parts of the body (M)[7–9].

T (Tumor) Categories:

- TX: Primary tumor cannot be assessed.
- T0: No evidence of primary tumor.
- Tis: Carcinoma in situ (also called high-grade dysplasia, a pre-cancerous condition).
- T1: Tumor 2 cm or smaller in greatest dimension.
- T2: Tumor larger than 2 cm but not larger than 5 cm in greatest dimension.
- T3: Tumor larger than 5 cm in greatest dimension.
- T4: Tumor of any size that invades adjacent organs (e.g., vagina, urethra, bladder) without crossing the pelvic wall.

N (Lymph Nodes) Categories:

- NX: Regional lymph nodes cannot be assessed.
- N0: No regional lymph node involvement.
- N1: Metastasis in perirectal lymph node(s).

- N2: Metastasis in unilateral internal iliac and/or inguinal lymph node(s).
- N3: Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes.

M (Metastasis) Categories:
- M0: No distant metastasis.
- M1: Distant metastasis present.

Stage Grouping:
- Stage 0: Tis, N0, M0 (Carcinoma in situ)
- Stage I: T1, N0, M0
- Stage II: T2-3, N0, M0
- Stage IIIA: T1-2, N1, M0 or T3, N1, M0 or T4, N0, M0
- Stage IIIB: T4, N1, M0 or Any T, N2-3, M0
- Stage IV: Any T, Any N, M1

2.1. SURVIVAL ACCORDING TO STAGE

Accurate staging is essential for determining the most appropriate treatment approach and predicting the prognosis for patients with anal cancer. It enables oncologists to tailor treatment plans to the individual characteristics of each case, maximizing the chances of successful outcomes and quality of life for patients undergoing treatment. Early detection and proper staging are key factors in optimizing treatment strategies and improving overall survival rates for individuals with anal cancer. Therefore, these outcomes should be pursuit.

Recently, AJCC staging system was revised and published in 9th edition. Both 8th and 9th staging groups are present in **table 1**.

Table 1. AJCC Version 9 and 8th Edition Clinical Stage Groups.

AJCC Version 9				AJCC 8th Edition			
T	**N**	**M**	**Stage Group**	**T**	**N**	**M**	**Stage Group**
T1	N0	M0	I	T1	N0	M0	I
T2	N0	M0	IIA	T2	N0	M0	IIA
T1	N1	M0	IIB	T3	N0	M0	IIB
T2	N1	M0	IIB	T1	N1	M0	IIIA
T3	N0	M0	IIIA	T2	N1	M0	IIIA
T3	N1	M0	IIIA	T4	N0	M0	IIIB
T4	N0	M0	IIIB	T3	N1	M0	IIIC
T4	N1	M0	IIIC	T4	N1	M0	IIIC
Any T	Any N	M1	IV	Any T	Any N	M1	IV

Adapted from: AJCC Cancer Staging System

Janczewski and colleagues analyze survival outcomes of AJCC 8Th edition staging system and validate the stage groups revision in generate 9th AJCC edition. Survival analysis revealed a lack of hierarchical order by clinical stage groups based on the AJCC 8th edition staging system for anal cancer as presented in **figure 1**. Overall survival at 5 years for stage I disease was 85.5%, followed by 78.5% for stage IIA disease, and 63.5% for stage IIB disease; however, patients with stage IIIA disease demonstrated a 73.7% survival at 5 years, followed by 59.3% for patients with stage IIIB disease, 60.0% for patients with stage IIC disease, and 22.1% for patients with stage IV disease. Thus, patients with stage IIIA disease had a better prognosis than those with stage IIB disease[10].

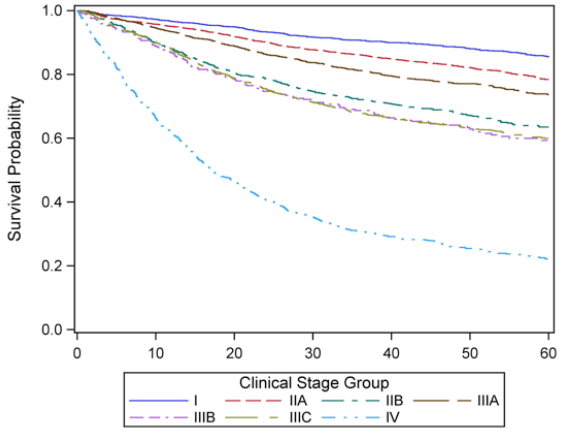

Figure 1. Survival outcomes used to generate version 9 American Joint Committee on Cancer staging system for anal cancer.

From: CA A Cancer J Clinicians, Volume: 73, Issue: 5, Pages: 516-523, First published: 28 April 2023, DOI: (10.3322/caac.21780)

Because of the lack of hierarchical prognostic order based on the eighth edition staging system for anal cancer, revised stage group definitions were applied. The authors describe a most accurate hierarchical order, where survival analyses using the new stage groupings demonstrate 5-year survival: 85.5% for stage I, 78.5% for stage IIA, 73.7% for stage IIB, 62.2% for stage IIIA, 59.3% for stage IIIB, 57.2% for stage IIIC, and 22.1% for stage IV as presented in **figure 2**.

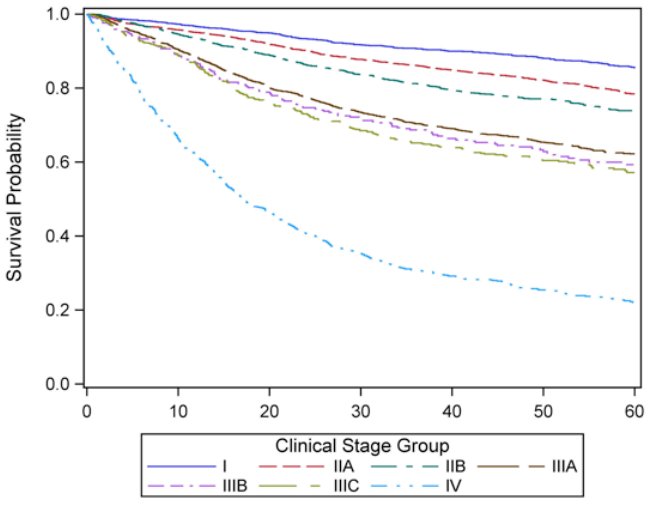

Figure 2. Survival outcomes used to generate version 9 American Joint Committee on Cancer staging system for anal cancer.

From: CA A Cancer J Clinicians, Volume: 73, Issue: 5, Pages: 516-523, First published: 28 April 2023, DOI: (10.3322/caac.21780)

Although the staging criteria utilized to create the AJCC version 9 staging system for anal cancer demonstrates hierarchical order, all current clinical data was retained from previous editions of AJCC system. Therefore, the extrapolation of these data to clinical decision should be taken with caution.

3. DIAGNOSIS

3.1. Medical History and Physical Examination

When assessing a lesion located in the anus, the initial step is to determine its true location, distinguishing between the anal canal region and the perianal region. This differentiation is crucial due to the more aggressive tumor biology encountered in anal canal lesions. Perianal lesions are defined as those within five centimeters of the anal margin, while lesions beyond this boundary are considered cutaneous in origin and require individualized assessment in cases of intermediate location between the anus and the female vulva.

During the medical history-taking, common symptoms include the presence of an expansive lesion and/or anorectal pain, bleeding, itching, tenesmus, mucus discharge, and involuntary fecal leakage. Physical examination, through inspection, allows for the identification of external lesions - in the case of perianal tumors or those with partial externalization - enabling the assessment of surface appearance, margins, extension, asymmetries in perineal anatomy, secretion drainage, and coloration. Some lesions may present with a strong characteristic odor associated with necrosis. At this evaluation stage, emphasizing the lesion's lateralization, distance from the anal margin, and any extension into the anal canal is crucial. Digital rectal examination complements the evaluation, providing information on consistency, pain presence, mobility, extension into the anal canal - including measurement of this distance -, involvement of sphincter muscles, presence of ulcerations, and friability. Anoscopy follows the physical examination, when feasible and tolerated by the patient, allowing for a complete visualization of the anal canal, and facilitating on-the-spot biopsies if there is a lesion above the anorectal transition[1,7,11].

In the case of malignant anal canal lesions, the physical examination necessitates palpation of the inguinal lymph nodes, the site of lymphatic drainage from this organ, to assess lymphadenopathy.

3.2. Additional Tests

Upon clinical diagnosis of anorectal tumors, systemic staging is carried out, alongside the need for biopsies to confirm etiology. Most of these neoplasms are histologically characterized as squamous cell carcinomas due to their epithelial origin, with occasional occurrences of adenocarcinomas, undifferentiated tumors, or melanomas.

Recommended investigations include chest and abdominal computed tomography (CT), abdominal and pelvic magnetic resonance imaging (MRI), gynecological examination for assessing synchronous cervical neoplasms, and HIV serology in patients with unknown immune status. In addition to these assessments, the association of HPV co-infection with squamous cell carcinoma of the anal canal has prompted the inclusion of subtype investigation as part of the evaluation of patients with these lesions, with subtype 16 being most associated with malignancies.

Based on the obtained data, the clinical staging, according to the AJCC 8th edition, classifies the pathology based on its primary location and the pres-

ence of nodal or metastatic disease, followed by the completion of clinical staging.

For clinical purposes, it's important to understand the role and accuracy of various imaging tests used in the staging of anal cancer. Staging is a critical step in cancer management as it determines the extent of cancer spread and guides treatment planning. Here is an overview of the key imaging tests used in anal cancer staging, alongside considerations of their accuracy and utility[3,7–9,12–14].

3.2.1. Magnetic Resonance Imaging (MRI)

MRI is particularly useful for evaluating the local extent of anal cancer, including tumor depth, involvement of surrounding tissues, and the anal sphincter complex. It's crucial for planning both surgical and non-surgical treatment approaches.

MRI offers high-resolution images and can provide detailed information about tumor size, location, and the involvement of adjacent structures. Its sensitivity and specificity in assessing the local extent of anal cancer make it a preferred choice for initial staging and surgical planning.

3.2.2. Computed Tomography (CT) Scan

CT scans are widely used for the staging of anal cancer, especially for detecting distant metastases in the liver, lungs, and other parts of the body. They are also used to assess lymph node involvement.

While CT scans are less sensitive than MRI for defining local tumor invasion and involvement of the anal sphincter or other local structures, they are effective for identifying enlarged lymph nodes and distant metastatic disease. However, CT scans may not distinguish between cancerous and non-cancerous lymph nodes solely based on size, which can sometimes lead to inaccuracies in staging.

3.2.3. Positron Emission Tomography (PET/CT)

PET/CT combines the metabolic imaging of PET with the anatomical imaging of CT, providing comprehensive information about tumor metabolism and structure simultaneously. It is particularly useful for detecting metastatic disease and assessing lymph node involvement, as well as for detecting recurrence.

PET/CT is more sensitive than CT alone for identifying metastatic disease, especially in cases where distant metastasis is small or in unusual locations. It improves the accuracy of staging by detecting active cancer cells that may not yet have led to anatomical changes visible on CT or MRI. However, it can sometimes produce false positives in the presence of inflammation or infection.

3.2.4. Endoanal Ultrasound (EAUS)

Endoanal ultrasound is primarily used for evaluating the local invasion of anal cancer, specifically the involvement of the anal sphincter complex and the depth of tumor penetration into the surrounding tissues.

EAUS provides detailed images of the layers of the anal canal wall, making it highly accurate for assessing tumor depth and local extent. However, its utility is limited for detecting distant metastases or assessing non-local lymph nodes.

The choice of imaging test is often based on multiple factors, including the specific details needed for staging, the availability of technology, and institutional preferences. The accuracy of these tests significantly impacts the staging and, thereby, the management plan for anal cancer, emphasizing the importance of selecting the most appropriate imaging modality based on the clinical scenario.

4. TREATMENT

4.1. Local Excision

Superficially Invasive Squamous Cell Carcinoma (SISCC) lesions are typically treated with surgical excision, often incidentally during the resection of anorectal lesions, with histological findings confirming clear margins. Regular clinical evaluations, physical examinations, and complementary tests allow for meticulous monitoring. For perianal lesions, excision should include obtaining one-centimeter safety margins, encompassing the deep component. Careful analysis is required due to the risk of sphincter muscle involvement and potential anal margin deformities affecting continence[15].

4.2. Radiotherapy and systemic treatment

Historically, abdominoperineal resection of the rectum was the standard treatment for this condition. However, in the 1970s, Nigro and colleagues published evidence of complete pathological response using a combination treatment of radiotherapy (RT), 5-fluorouracil (5FU), and mitomycin C, leading to a paradigm shift in locoregional disease therapy. Initial treatment for the disease typically involves this regimen, with alternative schemes combining mitomycin and capecitabine or 5FU and cisplatin, always in conjunction with RT. Treatment response evaluation should occur between eight to twelve weeks, primarily based on physical examination, including digital rectal examination. Post-evaluation, follow-up flow depends on the identified outcomes:

a) Complete remission: quarterly anorectal and inguinal clinical evaluations, progressing to semi-annual assessments over five years; anoscopies every six to twelve months for three years; annual imaging studies for three years
b) Persistent disease: reevaluation after four weeks; if remission initiates, reassessment at three months; if persistence or growth occurs, follow disease progression algorithm
c) Disease progression: confirmatory biopsy; systemic restaging; surgical salvage for non-metastatic patients; palliative chemotherapy for metastatic patients, with potential for immunotherapy as a subsequent regimen.

4.2.1. Chemoradiation therapy

4.2.1.1. Nigro regimen

Chemotherapy plays a significant role in the treatment of anal cancer, especially when combined with other modalities such as radiation therapy. The standard chemotherapy regimen typically used for anal cancer is a combination of 5-fluorouracil (5-FU) and mitomycin C.

Several clinical studies and guidelines support the use of 5-FU and mitomycin C as a standard of care for anal cancer treatment. The National Comprehensive Cancer Network (NCCN) guidelines and the European Society for Medical Oncology (ESMO) guidelines both recommend this combination regimen for the management of anal cancer.

The main strategy for combination therapy is Nigro protocol, which demonstrated the efficacy of concurrent chemoradiation with 5-FU and mitomycin C in anal cancer, have contributed to the widespread adoption of this chemotherapy regimen.

Although the original regimen, described as the "Wayne State or Nigro regimen," used infusional FU 1000 mg/m2 on days 1 to 4 and 29 to 32 (plus mitomycin 10 to 15 mg/m2 on day 1 only) concurrent with RT, The National Comprehensive Cancer Network (NCCN) guidelines recommend the modified regimen as was used in the Radiation Therapy Oncology Group (RTOG) 98-11 trial . It consists of infusional FU 1000 mg/m2 on days 1 to 4 and 29 to 32 plus mitomycin 10 mg/m2 on days 1 and 29, maximum 20 mg per dose. ESMO guidelines suggest the infusional 5FU plus mitomycin regimen but offering the option of utilizing mitomycin 12 mg/m2 on day 1 only (maximum 20 mg single dose), as was used in the ACT II trial.

Taken these strategies together, the use of combined chemoradiotherapy results in local failure rates of 14 to 37 %, five-year overall survival rates of 72 to 89 %, and five-year colostomy-free survival rates of 70 to 86 %[6,16–18].

4.2.1.2. Comparison of cisplatin versus mitomycin

In certain nations, such as Brazil, the widespread availability of mitomycin is constrained, thereby necessitating the substitution of cisplatin in specific instances.

Comparative studies and trials have not conclusively demonstrated a significant difference in overall survival (OS) and disease-free survival (DFS) between cisplatin and mitomycin C regimens when used as part of chemoradiation therapy for anal cancer. The choice between these regimens often hinges on factors such as patient tolerance, potential side effects, and individual patient or physician preference.

In Intergroup trial (RTOG 98-11), induction chemotherapy plus concurrent chemoradiotherapy using cisplatin and 5FU (with RT begun after two courses of cisplatin and 5FU) was compared with the standard Nigro (mitomycin, 5FU, and concurrent RT). The chemotherapy drugs in both arms were given during weeks 1 and 5 of RT. The trial enrolled 682 non-HIV-infected patients with SCC of the anal canal, 27% >5 cm, and 26% clinically node positive. There were significant differences favoring 5FU plus mitomycin in five-year disease-free survival (68 versus 58%, p = 0.006), overall survival (78 versus 71%, p = 0.026), and colostomy-free survival (72 versus 65 %, p = 0.05). 5FU plus mitomycin was also associated with a statistically nonsignificant trend toward fewer locoregional failures (LRFs; 20 versus 26%) and fewer colostomies (cumulative rate of colostomy failure 12 versus 17 %). Hematologic toxicity was higher in the mitomycin group, but nonhematologic toxicity and late radiotherapy toxicity were similar in both groups[19].

The ACT II trial is one of the largest phase III studies comparing mitomycin C versus cisplatin, both combined with 5FU and radiotherapy, for the treatment of anal cancer. As follows, the trial found no significant difference in overall survival, disease-free survival, or toxicity between the two regimens[18].

In this trial, 940 non-HIV-infected patients with anal SCC (30 % node positive, 43% T3/4) [29]. Treatment consisted of RT in both arms (50.4 Gy in 28 fractions) with concurrent infusional FU (1000 mg/m2 per day on days 1 to 4 and 29 to 32) and either cisplatin (60 mg/m2 on days 1 and 29) or mitomycin (12 mg/m2 day 1 only. As result, the three-year colostomy-free survival rate was similar in patients treated with mitomycin or cisplatin and those treated with and without maintenance treatment (72 to 75 % in all groups). The complete response rate at six months was 90.5 versus 89.6% with mitomycin and cisplatin, respectively. At a median follow-up of 5.1 years, three-year progression-free survival was similar with cisplatin

versus mitomycin, and overall survival was also similar (hazard ratio [HR] for death with cisplatin versus mitomycin 1.05, 95% CI 0.80-1.38). Patients receiving mitomycin had more acute grade 3 or 4 hematologic toxicity (26 versus 16%), but no higher rates of febrile neutropenia (3% in both groups) during chemoradiotherapy. Rates of grade 3 or 4 nonhematologic toxicity were similar (62 versus 68%)[20].

European guidelines (ESMO) include both strategies (mitomycin or cisplatin) as options for anal cancer treatment but consider the Nigro regimen the standard of care. Therefore, choice between cisplatin and mitomycin C in the chemoradiation treatment of anal cancer should be individualized, considering the efficacy, side effect profiles, and patient-specific factors[3].

4.2.2. Chemoradiation versus Radiation therapy alone

Current guidelines and standards of care for the treatment of anal cancer favor chemoradiation as the primary therapeutic modality for locally advanced disease due to its superiority in improving survival outcomes and preserving organ function. Radiotherapy alone is now generally reserved for cases where chemotherapy is contraindicated or for specific patient populations that may not tolerate chemoradiation. The data supporting this statement is discussed below.

The United Kingdom Coordination Committee on Cancer Research (UKCCCR) Anal Cancer Trial Task Force randomly enrolled 585 patients diagnosed with Stage T1 to T4 squamous cell carcinoma (SCC) of the anal canal or margin. These patients were divided to either receive solely radiotherapy (RT) at a dose of 45 Gy delivered via external beam in 20 or 25 sessions across four to five weeks, with an additional boost of 15 Gy via external beam or 25 Gy through brachytherapy, or to receive RT complemented by concurrent 5-fluorouracil (5FU) infusion (1000 mg/m2 across four days or 750 mg/m2 over five days during the initial and final weeks of RT) along with a single dose of mitomycin (12 mg/m2 on the first day). The group receiving chemoradiotherapy exhibited markedly lower rates of local failure (59 to 36 percent) and reduced mortality related to the disease (28 to 39 percent). Although more acute complications, including six fatalities, were observed with the combined therapy, late morbidity rates remained consistent across both groups[21].

Despite similar overall survival rates between the groups, an initial rise in deaths not related to anal cancer within the first five years was noted, which evened out by the tenth year. Post-five years, merely 11 patients in the chemoradiotherapy cohort experienced a locoregional recurrence as their primary post-treatment complication.

In another research by the European Organization for the Research and Treatment of Cancer EORTC, 110 patients with advanced-stage (T3-4 or N1-3) anal cancer were randomized to either RT alone (45 Gy with a 15 or 30 Gy boost) or RT with concurrent FU infusion (750 mg/m2 daily from days 1 to 5 and 29 to 33) plus a single dose of mitomycin (15 mg/m2 on day 1). The chemoradiotherapy group showed significantly improved outcomes, including an 80 percent versus 54 percent pathologic complete response rate, 18 percent improved locoregional control after five years, 32 percent higher colostomy-free survival rate, and better event-free and progression-free survival, though there was no significant difference in overall survival. Unlike the findings from the UKCCCR, this trial observed no significant differences in acute and late side effects or treatment-associated mortality rates between the groups[3,21].

4.3. Treatment in patients living with HIV

Individuals with HIV living with anal squamous cell carcinoma (SCC) can often achieve curability through combined modality therapy, generally receiving treatment akin to those without HIV. Notably, a low CD4 count doesn't always equate to increased treatment-related toxicity. Yet, those experiencing active HIV/AIDS-related health issues or with a history of such conditions (for instance, opportunistic infections or other cancers) might not withstand the standard therapy dosage or could necessitate dose modifications.

Evidence largely indicates that therapeutic response, disease management, and survival rates in patients with HIV under potent antiretroviral therapy (ART) mirror those observed in individuals not infected with HIV. In certain studies, higher instances of acute therapy-induced toxicity have been reported, especially with radiation therapy (RT) doses exceeding 30 Gy, though this finding isn't consistent across all research and seems not to affect long-term results. Approximately 6 to 12 percent of patients might require a diverting colostomy or abdominoperineal resection (APR) to manage these toxicities. The effect of CD4 counts on tolerating treatment has been the focus of a few small-scale observational studies.

An initial study involving 17 individuals before the advent of contemporary ART highlighted that none with a pre-treatment CD4 count ≥200 cells/microL necessitated hospital care during treatment. Conversely, those with counts below 200 cells/microL exhibited an increased need for hospitalization due

to complications such as myelosuppression, diarrhea, or moist desquamation, with four undergoing colostomies for treatment-related issues or ongoing/recurrent disease. This pattern has been echoed in subsequent research.

Subsequent analyses involving 59 patients in the modern ART era did not reveal a significant link between CD4 count and therapy-related toxicity, even with CD4 counts under 200 to 300 cells/microL.

Overall, individuals with HIV should receive treatment comparable to those who are HIV-negative. However, those with active HIV/AIDS-related health challenges or a history of opportunistic infections or other HIV-associated cancers might be less able to endure standard therapy or mitomycin, necessitating dose adjustments or alternative treatments excluding mitomycin. Current data do not support the addition of cetuximab, known to boost RT effectiveness in HPV-related oropharyngeal SCC, as enhancing outcomes in HIV-related anal SCC when combined with standard chemoradiotherapy[2,22,23].

4.4. Surgical Salvage Treatment

Abdominoperineal resection of the rectum is the treatment for persistent disease or local recurrence. The appropriate technique involves en bloc excision of the rectosigmoid - starting with ligation of the inferior mesenteric artery at its origin and the inferior mesenteric vein, followed by pelvic rectal dissection to preserve mesorectal integrity, and the excision of the anus and anal canal containing the sphincter apparatus, preceded by marking of perineal skin margins. Wound closure can be achieved with sutures along remaining anatomical planes or may require the use of muscle flaps and/or synthetic meshes for pelvic floor reconstruction. In cases necessitating sphincter apparatus removal, definitive terminal colostomy completes the oncological surgical procedure[3,7,9].

5. METASTATIC DISEASE

Systemic therapy represents the conventional modality for addressing metastatic anal squamous cell carcinoma (SCC), though a specific, albeit limited, cohort of patients presenting with solely hepatic metastases may derive advantage from surgical resection. Yet, the criteria for such candidate selection remain to be established.

The prevalence of distant metastases, predominantly in the liver, is notably higher. Nonetheless, the incidence of distal metastases among SCC of the anal canal patients has generally remained low.

For instance, in the trials conducted by the UKCCCR and the EORTC, distant metastases manifested post-combined modality therapy in 10 and 17 percent of cases, respectively.

Furthermore, in the ACT II trial, a mere 22 percent out of the 209 patients who experienced relapse were confronted with distant metastases.

It appears, however, that this scenario may be evolving. Epidemiological evidence indicates that, at least within the United States, the prevalence of distant-stage SCC witnessed a threefold increase from 2001 to 2015, marked by an average annual percentage rise of 8.6 percent among men and 7.5 percent among women.

Fortunately, while advanced disease is less common in anal carcinoma, it presents a significant challenge in clinical practice, with many patients experiencing a wide range of symptoms, from pain and bleeding to bowel obstruction.

5.1. Chemotherapy

5.1.1. Cisplatin and fluorouracil

The predominant treatment protocol for metastatic conditions typically involves a combination of cisplatin and 5FU. Despite reports indicating response rates as high as 60 to 65 percent, these responses are often transient. Optimal results seem to be observed in individuals receiving a comprehensive, multidisciplinary approach to manage their metastatic disease. According to a study, patients who underwent multidisciplinary care exhibited a median survival of 53 months, contrasting with 17 months for those solely receiving palliative systemic chemotherapy. Nevertheless, concerns regarding toxicity and treatment logistics, particularly the use of infusional 5FU, have led to its decreased utilization[3].

5.1.2. Paclitaxel and carboplatin

In the InterAACT trial, the effectiveness of the paclitaxel and carboplatin regimen was examined in 91 patients diagnosed with advanced anal squamous cell carcinoma (SCC) who had not previously received treatment. Patients were randomly divided into two groups: one receiving carboplatin (AUC 5 on day 1 every 28 days) along with weekly paclitaxel (80 mg/m2 on days 1, 8, and 15 every 28 days), and the other receiving cisplatin (60 mg/m2 on day 1 every 21 days) alongside infusional fluorouracil (FU) (1000 mg/m2 per 24 hours on days 1 through 4 every 21 days). The primary endpoint was the response rate[24].

The results demonstrated that the carboplatin plus weekly paclitaxel group exhibited response

rates comparable to those of the cisplatin plus FU group (59% versus 57%) but achieved superior median overall survival (20 versus 12.3 months) and a more favorable toxicity profile, with fewer serious adverse events reported (36% versus 62%).

5.2. Immunotherapy

Immunotherapy has emerged as a promising resource in the treatment of anal cancer, offering a novel approach to harness the immune system in combating cancer cells. Clinical trials have explored the efficacy of immunotherapeutic agents, particularly immune checkpoint inhibitors, in patients with anal cancer.

5.2.1. Pembrolizumab

The KEYNOTE-028 phase Ib trial investigated the use of pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, in patients with PD-L1-positive advanced solid tumors, including anal cancer. The results showed promising antitumor activity with an overall response rate of 17% in patients with advanced anal cancer who had previously received at least one line of treatment[25,26].

Furthermore, the KEYNOTE-158 trial expanded on these findings by evaluating pembrolizumab in patients with advanced solid tumors, including anal cancer, regardless of PD-L1 expression status. At a median time from first dose to data cutoff of 34.7 months, there were 12 objective responses (11,4%) and 6 were complete. When analyzed according to PD-L1 expression, responses were more frequent in those with a combined positive score of 1 or higher (15 versus 3%). Median duration of response was not reached at the time of data cutoff (range 6.0+ to 33.9+ months) but by Kaplan-Meier estimation, 90 percent of the responders had response duration ≥24 months. Although median progression-free survival was only 2.1 months, median overall survival in the entire cohort was 11.9 months. Toxicity was manageable; although approximately 61 percent had a treatment-related adverse event, and 22 percent of patients experienced at least one immune-mediated adverse effect, only five discontinued the drug for side effects[25,26].

5.2.2. Nivolumab

The absence of a standardized treatment protocol for metastatic disease prompted an exploration of the anti-PD-1 antibody nivolumab in a clinical trial setting. The study, a single-arm, multicentre phase 2 trial conducted at ten academic centers across the USA, enrolled patients with refractory metastatic SCCA who received nivolumab every 2 weeks (3 mg/kg). The primary outcome measure was response. Among the 39 patients screened, 37 were enrolled and treated with nivolumab. Out of these, nine patients (24% [95% CI 15-33]) displayed responses, including two complete responses and seven partial responses. Grade 3 adverse events, such as anaemia (n=2), fatigue (n=1), rash (n=1), and hypothyroidism (n=1) were reported, with no incidences of serious adverse events noted. Nivolumab demonstrated good tolerability and efficacy as a monotherapy for patients with metastatic SCCA, suggesting that immune checkpoint blockade holds promise as a potential approach for treating this rare disease[27].

While further research is needed to optimize patient selection and treatment strategies, immunotherapy holds promise as a valuable therapeutic option for patients with anal cancer.

6. FOLLOW-UP

After completing primary treatment for non-metastatic anal cancer, surveillance and follow-up strategies for perianal and anal canal cancer are similar. Patients are typically re-assessed with a Digital Rectal Examination (DRE) between 8- and 12-weeks post-completion of chemoradiotherapy (chemoRT). Depending on the evaluation, patients are categorized into complete remission, persistent disease, or progressive disease status. Patients with persistent disease that is not progressing may undergo close monitoring, with a follow-up in 4 weeks to observe potential improvements.

In the National Cancer Research Institute's ACT II study, which compared different chemoRT regimens, no significant differences were found in Overall Survival (OS) or Progression-Free Survival (PFS). Notably, a significant portion (72%) of patients who did not achieve a complete response by 11 weeks post-treatment ultimately reached complete remission by week 26. Patients demonstrating a complete response at 26 weeks exhibited superior 5-year survival rates. Consequently, the recommendation is to consider monitoring patients with persistent anal cancer for up to 6 months after completing radiation and chemotherapy, if there is no sign of disease progression during this monitoring period.

Persistent disease can continue to regress for up to 6 months post-treatment initiation, potentially avoiding the need for further aggressive procedures such as Abdominoperineal Resection (APR) in some cases. The guidance includes observation and reevaluation at 3-month intervals for these patients. Metabolic guided images is often unhelpful in this scenario

and NCCN guidelines advise against utilizing PET/CT imaging in the reevaluation due to concerns about false-positive results caused by radiation-induced inflammation, which may lead to unnecessary surgeries. Biopsy-confirmed disease progression should prompt more intensive treatment strategies.

Although histologic confirmation is required for assessing progressive disease, patients may be classified as being in complete remission without biopsy if there is no clinical evidence of disease. For these patients, regular evaluations every 3 to 6 months for 5 years are recommended, including DRE and assessment of inguinal nodes. Anoscopic evaluation should be conducted every 6 to 12 months for 3 years. Chest, abdominal, and pelvic imaging with contrast or without contrast should be performed annually for 3 years for patients initially diagnosed with stage II–III disease[3,7,9].

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ARTIGO ORIGINAL I *ORIGINAL ARTICLES*

Parecer técnico sobre a incorporação do uso de Rituximabe em monoterapia no SUS para pacientes com linfoma folicular assintomático

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RESUMO

O presente parecer técnico tem como objetivo analisar a incorporação do uso de Rituximabe em monoterapia no SUS para pacientes com linfoma folicular assintomático. Trata-se de uma doença que afeta o sistema linfático e, mesmo em estágios iniciais, pode trazer complicações a longo prazo. A utilização do Rituximabe tem se mostrado eficaz no tratamento dessa condição, proporcionando melhores resultados clínicos. Além disso, é importante ressaltar que a utilização desse medicamento em monoterapia traz benefícios econômicos ao sistema de saúde, pois reduz a necessidade de outros tratamentos mais invasivos e custosos. Dessa forma, a incorporação do Rituximabe em monoterapia no SUS para pacientes com linfoma folicular assintomático se mostra uma medida necessária e benéfica para a melhoria da qualidade de vida desses pacientes.

1. Introdução

O linfoma folicular é uma neoplasia maligna do sistema linfático que afeta um número significativo de pessoas no Brasil. Apesar dos avanços na terapia do câncer, ainda há desafios no tratamento dessa doença, principalmente no estágio inicial assintomático. Nesse sentido, é de extrema importância a avaliação da incorporação do uso de Rituximabe em monoterapia no Sistema Único de Saúde (SUS) para pacientes com linfoma folicular assintomático, a fim de proporcionar uma opção terapêutica eficaz e segura[1].

Este parecer técnico tem como objetivo fornecer uma análise precisa e embasada sobre a viabilidade e os benefícios dessa incorporação, considerando os estudos clínicos e a análise fármaco-econômica disponíveis, a fim de subsidiar a tomada de decisão das autoridades de saúde.

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2. Estudos clínicos

Os estudos clínicos são fundamentais para avaliar a eficácia e segurança do rituximabe em monoterapia para pacientes com linfoma folicular assintomático[2]. Diversos ensaios clínicos randomizados têm demonstrado os benefícios dessa abordagem terapêutica. Um estudo multicêntrico conduzido por Marcus et al. (2012) comprovou que o tratamento com rituximabe em monoterapia resultou em remissão completa duradoura em 77% dos pacientes[3]. Além disso, um estudo adicional realizado por Salles e outros (2017) demonstrou uma taxa de resposta objetiva de 92% entre os pacientes que receberam tratamento com rituximabe. Esses resultados promissores evidenciam a eficácia do rituximabe quando utilizado como monoterapia no tratamento do linfoma folicular assintomático, destacando assim o seu potencial para aprimorar a qualidade de vida dos pacientes.

3. Estudos fármaco-econômicos

Os estudos de fármaco-economia mostram a viabilidade econômica da incorporação desta tecnologia proposta no SUS do Brasil[4]. Embora o ICER não seja diretamente calculado para o threshold brasileiro, podemos ver que a tecnologia é viável. Os resultados dos estudos de custo-efetividade do tratamento com rituximabe como monoterapia serão descritos neste estudo[5]. Com base nessas informações, será realizada uma análise de custo-efetividade para determinar se a inclusão do rituximabe como monoterapia é uma opção economicamente viável e sustentável para o sistema de saúde brasileiro[6].

4. Conclusão

Com base na análise dos estudos clínicos e na avaliação fármaco-econômica realizada, concluímos que a incorporação do uso de Rituximabe em monoterapia no SUS para pacientes com linfoma folicular assintomático é altamente recomendada. Os estudos clínicos demonstraram eficácia significativa do Rituximabe na redução da progressão da doença e aumento da sobrevida livre de progressão, proporcionando benefícios clínicos relevantes para os pacientes. Além disso, a análise fármaco-econômica revelou que o uso do Rituximabe em monoterapia representa um custo-benefício favorável, considerando a redução de internações hospitalares e os potenciais ganhos em qualidade de vida. Portanto, acreditamos que a inclusão do Rituximabe em monoterapia no SUS é essencial para garantir o acesso igualitário a um tratamento eficaz e melhorar os desfechos clínicos dos pacientes com linfoma folicular assintomático.

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ARTIGO ORIGINAL I *ORIGINAL ARTICLES*

Parecer técnico favorável para incorporação no SUS do Brasil da Lenalidomida em combinação com rituximabe para pacientes com linfoma folicular previamente tratados

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1. Introdução

O linfoma folicular é uma neoplasia hematológica maligna, sendo o segundo tipo mais comum de linfoma não-Hodgkin. Embora tenham ocorrido avanços significativos no tratamento dessa doença, muitos pacientes apresentam recorrência ou resistência aos tratamentos convencionais. Por esse motivo, há uma necessidade de novas opções terapêuticas para melhorar os resultados e a qualidade de vida desses pacientes. Neste contexto, a lenalidomida em combinação com rituximabe tem se destacado como uma alternativa promissora, demonstrando eficácia significativa em estudos clínicos[1]. Este parecer técnico tem como objetivo avaliar a viabilidade de incorporação dessa terapia no SUS do Brasil, com base em evidências clínicas e científicas.

2. Objetivo

O objetivo deste parecer técnico é avaliar a possibilidade de incorporação no Sistema Único de Saúde do Brasil (SUS) da Lenalidomida em combinação com rituximabe para pacientes com linfoma folicular previamente tratados. Será realizado uma análise criteriosa baseada em estudos clínicos da literatura científica com o intuito de justificar a eficácia e benefícios dessa terapia para os pacientes, levando em consideração os dados disponíveis sobre sua segurança, eficácia, efetividade e custo-efetividade.

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3. Estudos clínicos

Os estudos clínicos realizados com lenalidomida em combinação com rituximabe para pacientes com linfoma folicular previamente tratados demonstraram resultados promissores[2]. Um estudo randomizado de fase 2 avaliou a eficácia e segurança dessa combinação em 178 pacientes, onde foi observada uma taxa de resposta global de 92%. Além disso, a sobrevida livre de progressão mediana foi de 37 meses e a taxa de resposta completa foi de 72%[1]. Outro estudo avaliou o impacto da adição da lenalidomida à terapia padrão em 656 pacientes. Nesse estudo, foi observada uma melhora significativa na sobrevida global, com uma mediana de 83 meses para o grupo tratado com a combinação, em comparação com 47 meses para o grupo tratado apenas com a terapia padrão. Esses resultados evidenciam o potencial da lenalidomida em combinação com rituximabe para o tratamento do linfoma folicular, oferecendo uma opção terapêutica eficaz e segura para os pacientes[3].

4. Estudos fármaco-econômicos

Os estudos fármaco-econômicos realizados demonstram a viabilidade e o impacto positivo da incorporação da Lenalidomida em combinação com rituximabe no tratamento de pacientes com linfoma folicular previamente tratados[4]. De acordo com esses estudos, a utilização desses medicamentos resulta em maior efetividade terapêutica, retardando a progressão da doença e aumentando a sobrevida dos pacientes. Além disso, a adoção dessa terapia combinada também se mostra financeiramente vantajosa, uma vez que reduz os custos associados aos tratamentos convencionais, como internações hospitalares e procedimentos invasivos. Portanto, a inclusão da Lenalidomida em combinação com rituximabe no SUS do Brasil é uma medida estratégica e responsável, capaz de proporcionar benefícios clínicos significativos aos pacientes com linfoma folicular, ao mesmo tempo em que otimiza a utilização dos recursos públicos de saúde[5].

5. Conclusão

A lenalidomida em combinação com rituximabe apresentou resultados promissores em estudos clínicos para o tratamento de pacientes com linfoma folicular previamente tratados. Os estudos demonstraram taxas de resposta objetiva e sobrevida global superiores em comparação com outras opções terapêuticas disponíveis. Além disso, a combinação foi bem tolerada pelos pacientes, com um perfil de segurança favorável. Considerando esses resultados, recomenda-se a incorporação da lenalidomida em combinação com rituximabe no SUS do Brasil como uma opção terapêutica eficaz e segura para pacientes com linfoma folicular previamente tratados.

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ARTIGO ORIGINAL I *ORIGINAL ARTICLES*

Advance Directives and Shared Decision-Making in Oncology: The Role of the Psycho-Oncologist

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OBJECTIVE

To analyze scientific articles available in online journals to explore the importance of Advance Directives (ADs) and shared decision-making in the trajectory of cancer patients.

METHOD

Literature review, with data collection conducted in March 2024, using the Connect Papers tool and searches in Scielo, PubMed, and Google Scholar databases, focusing on publications from the last five years.

RESULTS

Twelve publications were selected, and their textual analysis allowed reflection on three thematic areas: patient autonomy in decision-making, effective communication and facilitation of discussions, and psychological support in decision-making.

CONCLUSION

Despite the availability of current scientific publications on the topic, there is a gap in the engagement of psycho-oncologists in debates related to Advance Care Planning (ACP) and the preparation of Advance Directives (ADs). Although the studies analyzed recognize the importance of addressing patient's emotional aspects, only one study specifically investigated the role of psychologists in the construction of these documents. This discrepancy highlights the urgent need for more research and interventions that actively incorporate the expertise of psycho-oncologists in the process of constructing and executing ADs in collaboration with patients and oncologists. This is essential to ensure patient-centered cancer care, promoting assistance that fully considers each patient's unique needs and preferences.

Keywords: Advance Directives, Psycho-Oncology, Shared Decision Making

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INTRODUCTION

Advance Care Planning (ACP) is a practice that empowers patients to express their care preferences for future situations in which they may be unable to make decisions for themselves. This practice centers the patient in the health and disease process, ensuring that their values and wishes are respected, providing a more personalized care approach that benefits patients, families, and healthcare teams.

Advance Directives (ADs) are particularly relevant in oncology, where decisions about intensive and palliative treatments must align with each patient's personal beliefs. Colli and Souza highlight that ADs allow patients to establish their treatment preferences in advance, facilitating communication between the healthcare team and family members, and preventing unwanted or misunderstood medical interventions in the advanced stages of the disease.

The trajectory of discussions about ADs reveals difficulties in implementing them due to organizational needs and understanding by healthcare institutions, which may hinder effective implementation. Continuing education for healthcare professionals helps break down stigmas and taboos about death, promoting education on communication and shared decision-making. The experience of advanced cancer requires professionals to be prepared to develop this advanced care plan, which involves more than just the medical treatment challenge.

The implementation of ADs also faces challenges such as the need for team integration, lack of technical/professional knowledge, contextual obstacles, resistance to learning new concepts, high workload, the severity of the patient's clinical condition, and the requirement for specific legal/juridical bases. Contextual obstacles include some patients' passivity towards the disease and their low educational level, resulting in little or no adherence. Additionally, healthcare professionals may face difficulties, considering the instrument an overload of tasks due to their workload.

The challenges of discussing terminality have increased over time as advances in curative measures or the reversal of previously incurable diseases like cancer have led to more people seeking treatment, even when available resources are limited, prolonging suffering and disrespecting patient autonomy, especially in terminal stages.

Incorporating ADs in the management of cancer patients aims to promote a sincere approach with compassionate and clear communication, considering the risks and benefits of each choice, and reflecting on possibilities for better quality of life, dignity, and autonomy in cancer care. Respecting one's autonomy and that of others implies recognizing the right to have opinions, make choices, and act according to personal values. Disrespecting this treats individuals as means to others' goals, morally violating their capacity to determine their own destiny, as autonomous individuals are ends in themselves.

Furthermore, psycho-oncological interventions help patients and families navigate the emotional complexities that this decision-making process entails. Effective communication is crucial and acts as a barometer for professionals to address the distress naturally brought on by decision-making, considering the suffering caused by the crisis of illness.

In Brazil, few studies focus on patient perspectives regarding AD practices. Beyond all the legal and juridical implications involved in documenting ADs, subjective issues such as anxiety and depression can impair patients' ability to engage effectively in ACP and make informed decisions about their final care. Therefore, it is necessary to offer practical recommendations to mitigate these impacts, highlighting the importance of early identification and proper management of anxiety and depression symptoms, as well as continuous support for patients and their families during the ACP process and end-of-life decision-making.

Promoting early discussions about palliative care is highly beneficial, but it is crucial to avoid withholding information or violating patient autonomy. Research suggests that married individuals and those with higher education levels are more receptive to these conversations. However, advanced cancer patients tend to participate less in them. Patients value open communication, clarification of palliative care concepts, and discussions that empower them, eliminating misunderstandings. It is essential to redouble efforts to reach patients with little knowledge on the subject, especially those with advanced cancer, to increase their receptivity and enable informed decision-making.

Palliative care planning is still in its early stages in the current context, facing various challenges in practice while striving to humanize care. A suggestion to improve integration is to adopt the interconsultative model, allowing collaboration between

different specialties.

Discussing terminality is a taboo, and few people talk with their families, friends, and healthcare professionals about their care preferences in severe and advanced disease cases. Although most people desire care that prioritizes quality of life and alleviation of suffering at the end of life, the healthcare system tends to offer interventions focused on maintaining life, often without improving the patient's quality of life. When there are no conversations about prognosis, treatment goals, and expectations, patients lose the opportunity to express their values and preferences. This often leads to medical decisions that do not align with the patients' priorities and desires. Encouraging these discussions is the basis for ensuring that the care provided respects the patients' wishes, offering a more dignified end-of-life experience in line with their desires.

FINAL CONSIDERATIONS

The effective implementation of ADs in healthcare institutions faces significant obstacles. Although psycho-oncologists support patients and their families during the decision-making process, especially in advanced disease stages, this is not evident in current scientific research. Promoting a patient-centered care approach that effectively integrates ACP and ADs is important for advancing the quality of cancer care. This article emphasizes the need to advance health policies, institutional practices, and professional training to fully embrace the potential of ADs in improving end-of-life care, respecting patients' wishes, and promoting a more dignified and respectful care experience. It also challenges psycho-oncologists to consider the importance of their role in this sensitive moment for their patients.

Future studies should focus on various aspects, including the effectiveness of communication strategies employed by psycho-oncologists to help patients understand and express their advance care preferences. Additionally, it is important to investigate how these practices influence health outcomes, patient satisfaction, and emotional well-being throughout cancer treatment.

Ultimately, expanding the evidence base in this area will not only enhance clinical practices but also inform health policies and clinical guidelines, promoting a more effective and compassionate approach to cancer care.

Multidisciplinary management of metastatic her2-positive invasive ductal carcinoma with central nervous system involvement: a Case Report

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RESUMO

Introdução: O câncer de mama metastático HER-2 positivo é uma doença desafiadora, especialmente na presença de múltiplas metástases cerebrais, devido à dificuldade de penetração da barreira hematoencefálica pelos medicamentos mais tradicionais. Entretanto, novas tecnologias, como o conjugado trastuzumab-deruxtecan (T-DXd) e os inibidores de tirosina quinase (ITK) de nova geração, como o Tucatinibe, têm demonstrado maior eficiência na penetração da barreira hematoencefálica e respostas terapêuticas mais profundas e duradouras neste sítio de disseminação. Além disso, procedimentos de radioterapia de alta precisão e alta entrega de dose, como a radiocirurgia, tratam as lesões de forma focal, preservando o parênquima cerebral em contraste com a radioterapia cerebral total tradicionalmente empregada nos casos de metástases múltiplas. No entanto, todas essas tecnologias são indisponíveis no Sistema Único de Saúde (SUS), o que é extremamente desanimador. **Relato de Caso**: Uma paciente de 38 anos, atendida exclusivamente no SUS, apresentou trombose venosa em membros inferiores em fevereiro de 2019. Após os exames iniciais para investigação de trombofilia secundária, realizou mamografia com achado de microcalcificações na mama esquerda. Submetida à biópsia, confirmando-se carcinoma ductal invasivo grau 2, HER2 positivo. A paciente iniciou quimioterapia neoadjuvante com Adriamicina e Ciclofosfamida, seguida de Paclitaxel e Trastuzumabe. Submetida à mastectomia esquerda em novembro de 2019. Iniciou acompanhamento a partir de 2020, com detecção de recidiva pleural em 2021 e múltiplas metástases cerebrais (13 lesões) em fevereiro de 2022. Paciente foi submetida à radioterapia cerebral total seguido de quimioterapia com protocolo Docetaxel, Pertuzumabe e Trastuzumabe (CLEOPATRA). Evoluiu bem, mas apresentou progressão cerebral da doença em agosto de 2022, quando foi modificado tratamento para Trastuzumabe-Deruxtecano por via judicial. Houve boa resposta cerebral e sistêmica ao tratamento, mas evoluiu com nova progressão em 3 lesões encefálicas. Paciente realizou radiocirurgia nestas lesões em cenário privado e manteve o Trastuzumabe-Deruxtecano devido boa resposta sistêmica. Evoluiu bem até que em fevereiro de 2024 apresentou progressão pulmonar agressiva com óbito por insuficiência respiratória. **Discussão e Conclusão**: O caso relata uma paciente com múltiplas metástases cerebrais que inicialmente recebeu tratamento pelo sistema público e, posteriormente, teve acesso a tecnologias e trata-

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mentos mais avançados por via judicial ou privada. O acesso a tecnologias e tratamentos personalizados modernos possibilitou o controle das lesões cerebrais, com melhora na qualidade de vida e prolongamento da sobrevida. Apesar do número de lesões, foi possível tratar a doença de forma focal mesmo após radioterapia cerebral total, preservando a paciente de altas doses de radiação e minimizando as toxicidades inerentes ao tratamento com bom controle local de doença. Conclui-se que o acesso à tecnologia de ponta em todos os cenários terapêuticos é capaz de garantir sucesso ao tratamento oncológico, mesmo no cenário paliativo, e deveria ser uma realidade para todos os pacientes brasileiros em equidade aos pacientes da saúde suplementar.

Palavras-chave: Câncer de mama Her-2 positivo, metástase cerebral de câncer de mama, radiocirurgia

ABSTRACT

Introduction: HER-2-positive metastatic breast cancer is a challenging disease, especially in the presence of multiple brain metastases, due to the difficulty of penetration of the blood-brain barrier by most traditional drugs. However, new technologies, such as trastuzumab-deruxtecan conjugate (T-DXd) and new-generation tyrosine kinase inhibitors (TKIs), such as Tucatinib, have demonstrated greater efficiency in penetrating the blood-brain barrier and deeper and longer-lasting therapeutic responses at this site of dissemination. In addition, high-precision and high-dose delivery radiotherapy procedures, such as radiosurgery, treat lesions focally, preserving the brain parenchyma in contrast to whole-brain radiotherapy traditionally used in cases of multiple metastases. However, all these technologies are unavailable in the Unified Health System (SUS), which is extremely discouraging. **Case Report:** A 38-year-old patient, treated exclusively by the SUS, presented venous thrombosis in the lower limbs in February 2019. After initial examinations to investigate secondary thrombophilia, she underwent a mammogram with finding of microcalcifications in the left breast. She underwent biopsy, confirming grade 2 invasive ductal carcinoma, HER2 positive. The patient started neoadjuvant chemotherapy with Adriamycin and Cyclophosphamide, followed by Paclitaxel and Trastuzumab. She underwent left mastectomy in November 2019. She started follow-up in 2020, with detection of pleural recurrence in 2021 and multiple brain metastases (13 lesions) in February 2022. The patient underwent whole brain radiotherapy followed by chemotherapy with the Docetaxel, Pertuzumab and Trastuzumab protocol (CLEOPATRA). The patient progressed well, but presented cerebral progression of the disease in August 2022, when the treatment was changed to Trastuzumab-Deruxtecan through legal means. There was a good cerebral and systemic response to the treatment, but the disease progressed with new progression in 3 brain lesions. The patient underwent radiosurgery for these lesions in a private setting and continued on Trastuzumab-Deruxtecan due to a good systemic response. The patient progressed well until February 2024 when she presented aggressive pulmonary progression and died due to respiratory failure. **Discussion and Conclusion**: The case reports a patient with multiple brain metastases who initially received treatment through the public system and later had access to more advanced technologies and treatments through legal or private means. Access to modern personalized technologies and treatments made it possible to control the brain lesions, improving quality of life and prolonging survival. Despite the number of lesions, it was possible to treat the disease focally even after whole brain radiotherapy, sparing the patient from high doses of radiation and minimizing the toxicities inherent to the treatment with good local control of the disease. It is concluded that access to cutting-edge technology in all therapeutic scenarios is capable of guaranteeing success in oncological treatment, even in the palliative setting, and should be a reality for all Brazilian patients in equal measure to supplementary health patients.

Keywords: Her-2 positive breast cancer, brain metastasis of breast cancer, Radiosurgery

INTRODUCTION

Breast cancer, a major global health challenge, exhibits substantial heterogeneity in its biological and clinical presentation (Weigelt et al., 2010; Łukasiewicz et al., 2021). HER2-positive breast cancers, representing approximately 15-20% of all breast cancer cases, are characterized by the overexpression of the human epidermal growth factor receptor 2 and are associated with more aggressive disease and poorer prognosis (Guarneri et al., 2010; Siegel et al., 2022). The introduction of targeted therapies, such as trastuzumab, has significantly improved survival rates for patients with HER2-positive metastatic

breast cancer, exceeding 50 months from the diagnosis of advanced disease (Deluche et al., 2020).

Advancements in molecular understanding have led to the development of novel therapeutic agents and strategies. The use of antibody-drug conjugates, like trastuzumab-deruxtecan, and the emergence of treatments targeting HER2-low metastatic breast cancer, have expanded the scope of therapeutic options (Modi et al., 2022). Additionally, the heterogeneity within HER2-positive breast cancer, including the influence of hormone receptor co-expression and genetic mutations like PIK3CA, has a significant impact on treatment responses and survival outcomes (Dieci et al., 2020). The molecular complexity and dynamics of metastasis in HER2-positive breast cancer, especially in the brain, present a substantial challenge (Hosonaga; Saya; Arima, 2020). Brain metastases, prevalent in advanced stages of HER2-positive breast cancer, necessitate innovative approaches, with radiosurgery emerging as a crucial modality for local control (Bailleux; Eberst; Bachelot, 2021).

Recent trends in breast cancer management emphasize the need for personalized medicine, driven by a deeper understanding of molecular markers and histological types (Sun et al., 2021). The case of a 38-year-old female patient, presenting with grade 2 invasive ductal carcinoma and brain metastases, exemplifies the challenges in managing advanced HER2-positive breast cancer. The evolution of her condition, despite systemic control, underscores the complexity of treatment, involving a combination of targeted therapy, chemotherapy, and advanced techniques like radiosurgery. This case highlights the importance of integrating novel therapeutic strategies and the critical role of radiosurgery in managing cerebral metastases in HER2-positive breast cancer.

CASE PRESENTATION

In February 2019, a 38-year-old female presented to our facility with lower extremity edema without claudication and associated symptoms. The patient also had a venous Doppler of the lower limbs which confirmed deep vein thrombosis, highlighting the proactive steps taken to understand her condition. It is crucial to acknowledge that the patient is dependent on the public health system for her healthcare needs. This dependency has posed significant barriers to accessing more advanced treatment options, framing the context of her treatment journey within the systemic limitations of public healthcare access.

The Initial workup included a mammogram on 08/02/2019 that showed dense breast tissue with microcalcifications in the left breast, rated BIRADS 4. Biopsy on 02/13/2019 confirmed grade 2 invasive ductal carcinoma. Immunohistochemistry indicated estrogen receptor (ER) negative, progesterone receptor (PR) negative, and HER2 3+. On a subsequent chest computed tomography (CT) an oval-shaped image with liquid density and a hydro-air level was observed in the anterior left thoracic wall, measuring approximately 3.2 cm in the left breast. Additionally, a contrast-enhancing nodule measuring about 3.3 cm was observed, heterogeneous due to interspersed calcifications. Ultrasound of the axillae demonstrated the absence of involvement in the region and absence of bone metastasis.

Treatment commenced on 06/05/19 with neoadjuvant chemotherapy, involving Adriamycin and Cyclophosphamide, followed by Paclitaxel. Herceptin (trastuzumab) therapy was initiated on 07/29/19. The treatment plan, following the completion of chemotherapy and surgical intervention, was to continue trastuzumab therapy for a total duration of one year to complete the recommended course of treatment. Despite chemotherapy, imaging on 09/17/19 showed multiple nodular images in the left breast, necessitating a left mastectomy on 11/07/19. Post-operative pathology revealed a 1.0x0.5 cm residual invasive ductal carcinoma, with 1 out of 8 lymph nodes positive, indicating a need for further treatment. She completed adjuvant radiotherapy in February 2020.

Throughout 2020 and the beginning of 2021, the patient was monitored through regular laboratory and imaging tests. In May 2021, a chest CT scan showed moderate left pleural effusion, causing compressive atelectasis of the adjacent lung. There was also lymphadenopathy in the internal thoracic chains, with a necrotic center, measuring up to 2.2 x 1.0 cm, indicating pleural recurrence. A thoracotomy and pleurodesis were performed on 29/06/21. Pathology from 06/16/21 and immunohistochemistry from 06/23/21 confirmed grade 3 carcinoma, HER2 3+. Due to these findings, she underwent palliative chemotherapy with Docetaxel starting 07/09/21. However, treatment was complicated by elevated transaminase levels, necessitating adjustments in chemotherapy scheduling. The second cycle had to be rescheduled to 08/20/21 and it continued monthly until the sixth cycle on 11/26/21. Simultaneously, starting on 08/27/2021, Trastuzumabe and Pertuzumabe were used, with a twenty-one day interval between cycles, until 11/26/21, the fifth cycle. In the first cycle, the patient experienced a severe

allergic reaction, which was prevented in the following cycles with antiallergics. Zoledronic acid therapy was initiated on 10/29/21, and in reality, it was continued every twelve weeks to manage bone lesions.

Patient's condition further progressed with the development of multiple cerebral metastases (13 lesions) by February 2022. Magnetic Resonance Imaging (MRI) of the brain on 02/01/22 indicated multiple solid nodules up to 1.5 cm in the encephalic parenchyma. She underwent whole brain radiotherapy (WBRT) - 30 Gy in 10 fractions, 3D conformal - from 02/11 to 02/28/2022. Despite radiotherapy, her condition evolved with progression in the central nervous system's lesions, as indicated by a brain MRI on 06/06/22, showing reduction and negative volumetric variation of some lesions, however, with a volumetric increase of others, along with increased vasogenic edema (a finding that implies disease progression).

Owing to these observations, she underwent radiosurgery and chemotherapy with Trastuzumab deruxtecan starting 08/23/2022. Given the 13 metastatic lesions, the radiosurgery therapeutic plan used two different approaches, depending on the size of the nodule (**Figure 1**). Thus, for smaller nodules, a single fraction was chosen, while for larger nodules, hypofractionation was used (3 fractions of 3 × 9 Gy). After the procedures, the patient denied having seizures and stated that she tolerated the diet and maintained preserved physiological habits.

On 02/13/2023, a brain MRI showed considerable reduction in the number and size of nodules previously identified in infra- and supratentorial encephalic structures, as well as diminished vasogenic edema. There was a decrease in lesion enhancement, along with changes in their signal characteristics, many of them indicating residues of hemorrhagic and/or calcific nature, indicating good response to treatment. In July 2023, despite systemic disease control, her condition evolved with progression in three CNS lesions by July 2023, as indicated by an MRI on 06/09/23 showing increased nodular size and new intra-axial enhancement foci.

The patient underwent radiosurgery on these lesions in a private setting and continued taking Trastuzumab-Deruxtecan due to a good systemic response. He progressed well until, in February 2024, he presented aggressive pulmonary progression and died due to respiratory failure.

DISCUSSION AND CONCLUSIONS

In analyzing the epidemiological landscape of brain metastases, it is noted that while lung cancer is the predominant primary source across genders, breast cancer emerges as the leading cause in females. Particularly, HER2-positive and triple-negative breast cancers exhibit a heightened predisposition for central nervous system involvement, a pattern observed in the patient discussed herein (Yuzhalin; Yu, 2024).

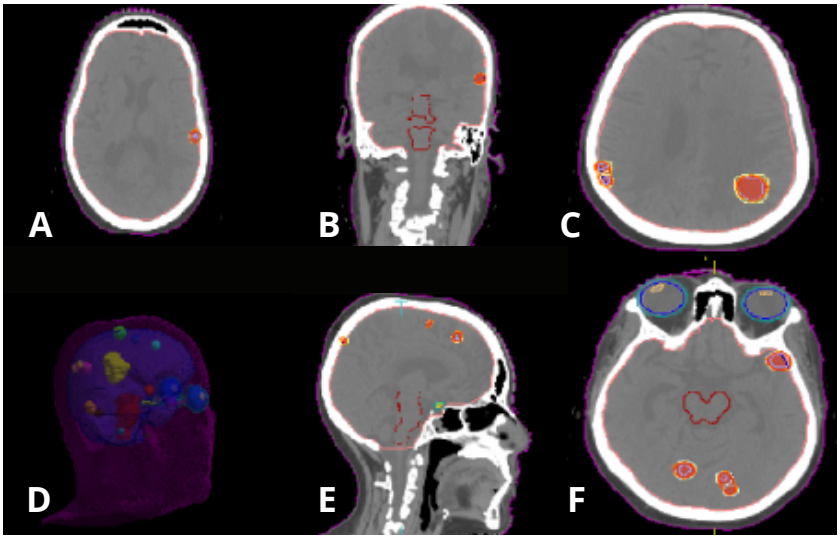

Figure 1: Stereotactic radiosurgery (SRS) planning. **A**: Coronal CT scan with a lesion in the left cerebral hemisphere. **B**: Coronal CT scan with lesions in the right and left cerebral hemispheres. **C**: Coronal CT scan with lesions in cerebral hemispheres. **D**: Three-dimensional planning based on CT scan. **E**: Sagittal CT scan with lesions in a cerebral hemisphere. **F**: Coronal CT scan at the midbrain level with lesions in cerebral hemispheres.

The prognosis for patients with brain metastases can be effectively stratified using the Graded Prognostic Assessment (GPA) index. This tool integrates critical factors such as cognitive function (via the Karnofsky Performance Status - KPS), cancer subtype, and patient age to forecast outcomes (Sperduto et al., 2012; Valiente et al., 2018). Based on the study presented by Sperduto et al. (2012), patients with brain metastasis from breast cancer can score by (a) KPS (0 if KPS ≤50; 0.5 if =60; 1 if between 70-80; 1.5 if it is between 90-100; by (b) subtype (0 for basal; 1.0 for luminal-A; 1.5 for HER2-positive; 2.0 for luminal-B; and by (c) age (0 if ≥ 60 years; 0.5 if <60 years). The final sum represents the median survival in months, namely, 3.4 months (GPA between 0-1.0), 7.7 months (GPA between 1.5-2.0), 15.1 months (GPA between 2.5- 3.0) and 25.3 months (GPA between 3.5-4.0). Therefore, for the case at hand, a GPA score of 3.5 signals an anticipated median survival of 25.3 months, indicating a relatively favorable prognosis under appropriate management.

Although GPA can be used as a reference for therapeutic planning (Susko et al., 2016) between WBRT, Stereotactic Radiosurgery (SRS) or both concomitantly, currently, there is a greater preference for treatment using only SRS. Based on the results of 289 patients with brain metastases >2 cm presented by Minniti et al. (2016), the use of SRS, more specifically multifraction SRS (MF-SRS), presents a better prognosis regarding local control (LC) and risk of radiation-induced brain necrosis. Therefore, the therapeutic plan chosen for the patient's larger brain lesions corroborates the study findings, since the greatest differences in LC were in lesions ≥3 cm, comparing MF-SRS and single-fraction SRS (SF-SRS). Concomitantly, the patient's smaller lesions were treated as single metastases, given the high risk of radiation-induced brain necrosis, as she had previously been subjected to high doses of radiation by WBRT.

This study, however, used the size of the lesions as a comparative object and not the number of brain metastasis. This is a limitation of the case presented, since the patient had 13 CNS lesions. The decision-making, with the number of brain injuries as its object, was based on the study carried out by Yamamoto et al. (2019). This study followed the evolution of 934 patients divided between patients with 2 to 9 brain lesions and patients with more than 10 lesions. From the results presented, there was no statistically significant difference between the groups, proving the non-inferiority of SRC in relation to WBRT in patients with more than 10 lesions, as in the patient in this case. Additionally, in this study, 89.1% died from non-neurological causes.

The benefits of WBRT in controlling new brain lesions are normally limited to between 6 and 8 months, however, some patients can live for more than 12 months, depending on several prognostic factors, including multiple lesions. (Yamamoto et al., 2019). Reported cases of CNS metastases must increase in prevalence given advances in imaging exams and greater survival rates of cancer patients. Furthermore, given the complexity and singularity of each patient, decision-making regarding therapeutic guidance may involve factors that are not directly listed in current guidelines, as occurred in the case presented, when relating multiple lesions with lesions of distinct size patterns. Thereat, it is up to the oncology team to have the ability to group different scientific findings for the best decision.

Although there was a rationale for using only SRS, the therapeutic recommendation for the patient encounters the practical challenges inherent in cancer treatment within the Sistema Único de Saúde (SUS), the Brazilian Unified Health System. Despite the incorporation of SRS into the SUS Table of Procedures, Medications, Orthoses, Prostheses, and Special Materials (Brasil, 2018), empirical evidence derived from DataSUS indicates that this specific procedure has yet to be executed within the public healthcare network in the city of Salvador.

Updated knowledge in radiotherapy is of fundamental clinical and prognostic importance for patients with brain metastasis, as it avoids excessive doses of radiation, bringing positive practical results in local control, cognitive and survival rates. However, such theoretical updating must be accompanied by technological updating of health equipment for oncological treatment in Brazilian public health, such as offering SRS across the country.

Otherwise, thousands of patients with brain metastases will continue to receive high doses of radiation through WBRT with all the toxicities inherent to the method, especially cognitive deficit.

It is concluded that access to cutting-edge technology in all therapeutic scenarios is capable of ensuring success in oncological treatment, even in the palliative setting, and should be a reality for all Brazilian patients, equally with supplementary health patients.

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Tongue Squamous CELL carcinoma in young pacients whithout known risk factors: Case Report

Carcinoma espinocelular de língua em paciente jovem e sem exposição aos fatores de risco: Relato de Caso

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RESUMO

Uma maior ocorrência do carcinoma espinocelular de boca em pacientes jovens e sem fatores de risco vem sendo observada, sendo a língua o local de maior frequência nessa população. O objetivo deste trabalho é relatar o caso clínico de um paciente jovem, sem vícios, diagnosticado com carcinoma espinocelular de língua. **Relato de caso**: Paciente de 45 anos, sexo masculino, motorista, procurou a clínica odontológica com a queixa principal de um caroço na língua. Durante a anamnese, não relatou vícios, como tabagismo ou etilismo. Ao exame físico intra-bucal, observou-se a presença de um nódulo localizado em borda lateral e posterior da língua, indolor e sem relação de trauma, com tempo de evolução de aproximadamente 1 mês. Diante dos aspectos clínicos observados, procedeu-se à biópsia incisional e o diagnóstico final foi de carcinoma espinocelular de língua. Embora incomum, o presente caso clínico evidencia um diferente perfil da doença, acometendo pacientes jovens, sem vícios e cujo prognóstico ainda é incerto. Sugere-se uma influência genética na etiopatogenia da doença, porém, ressalta-se a importância da investigação de novos fatores etiológicos associados, visto o aumento de casos em pacientes sem vícios. Este caso clínico reforça a importância do diagnóstico precoce das lesões bucais, especialmente o CEC. Além disso, há a necessidade de uma profunda investigação sobre novos hábitos em pacientes jovens diagnosticados com carcinoma espinocelular, uma vez que os fatores etiológicos desse grupo ainda são incertos.

Palavras-chave: Neoplasias da língua. Carcinoma de células escamosas. Adultos.

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ABSTRACT

A rising incidence of oral squamous cell carcinoma (OSCC) in younger patients without traditional risk factors has been observed, with the tongue being the most commonly affected site in this population. This study aims to report a case of tongue squamous cell carcinoma in a young patient. **Case Report**: A 45-year-old male driver presented at the university dental clinic with the chief complaint of a nodule on the tongue. During the anamnesis, the patient reported no addictions, such as smoking or alcohol consumption. Intraoral examination revealed a painless nodule on the lateral and posterior border of the tongue, unrelated to trauma, with approximately one month of evolution. An incisional biopsy was performed, and histopathological examination confirmed a diagnosis of tongue squamous cell carcinoma. Although uncommon, this case highlights a different profile of the disease, affecting young patients without typical risk factors, with an uncertain prognosis. Genetic influences may contribute to the etiopathogenesis of the disease, but further investigation into new associated risk factors is necessary given the increasing number of cases in patients without traditional risk factors. It is crucial to raise awareness among dentists regarding the importance of a detailed analysis of oral lesions, as early diagnosis directly impacts prognosis.

Key-words: Tongue tumors. Squamous cell carcinoma. Adults.

1. INTRODUCTION

Squamous cell carcinoma (SCC) of the tongue is the most common site of cancer within the oral cavity and also the site with the poorest prognosis[1,2]. The incidence is higher among men over 40 years of age, smokers, and alcohol abusers[3]. Only 4-5% of these lesions are diagnosed in individuals under 40 years of age. However, recent studies have reported an increasing incidence of tongue cancer in young individuals, especially women, without the primary associated risk factors[1,2,3,4,5,6,7].

The clinical behavior and pathophysiology of SCC of the tongue in young patients appear to differ from those in older patients; the association with major risk factors such as alcohol and smoking is not as prevalent[7,8]. Another notable clinical aspect in this group is the higher occurrence on the lateral border[3,9] of the tongue and recurrence at the primary tumor site[3]. Although a relationship with the human papillomavirus (HPV) may be suggested for tumors of the oropharynx, tonsils, and base of the tongue, its influence on tongue cancer in young patients has not been established[3,7,8].

Several studies suggest a worse prognosis for SCC in young patients, associated with more aggressive disease behavior, higher rates of lymph node metastasis and lymphatic invasion, and poorer overall and disease-free survival rates[1,2,3,5,8]. However, results for this group remain heterogeneous, partly due to the lack of a consistent age cut-off for defining young patients, which ranges from 30 to 45 years[1,3,7].

Given the rising incidence of tongue cancer in young patients without associated risk factors, this study aims to report a case of SCC of the tongue diagnosed in a young patient without the major associated risk factors.

2. CASE REPORT

A 45-year-old male with fair skin presented to the university clinic with the primary complaint of a change in his tongue. During anamnesis, he denied any history of smoking, alcohol use, or systemic health issues. Intraoral examination revealed a painless nodule on the lateral and posterior border of the tongue, unrelated to trauma. The lesion had raised borders, a reddish color with interspersed whitish areas, a rough and irregular surface, and measured approximately 1.5 cm in diameter (**Figure 1**).

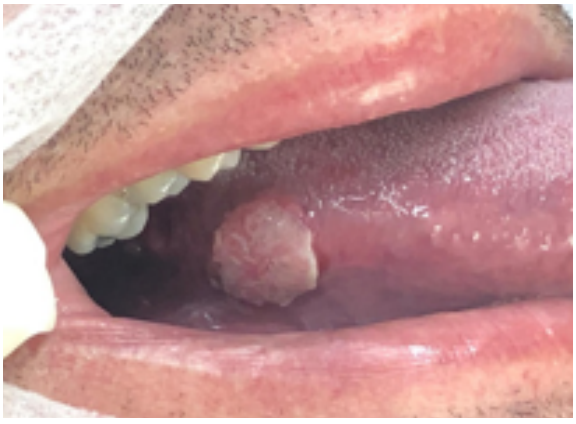

Figure 1 - Initial clinical appearance of the lesion.

The reported evolution time was approximately one month. Based on the observed clinical features, an incisional biopsy was performed, and the specimen was submitted for histopathological analysis. Microscopic examination revealed the presence of

nests of neoplastic epithelial cells with mild pleomorphism, hyperchromatism, an altered nucleus-cytoplasm ratio, dyskeratosis, keratin pearls, and mitotic figures invading the underlying connective tissue and destroying striated muscle fibers (**Figure 2A - 2D**).

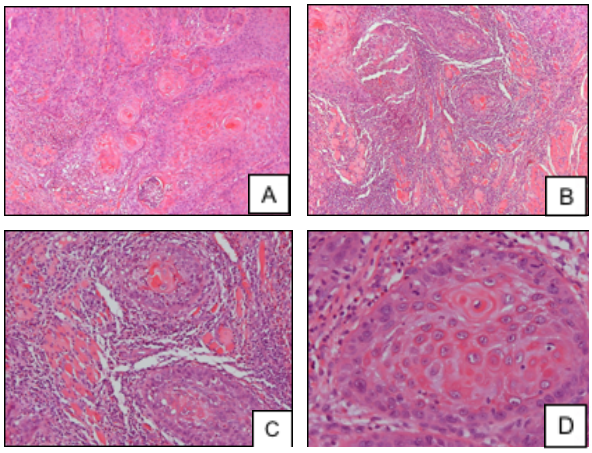

Figure 2: Islets of neoplastic epithelial cells (A - H&E, 5x, B- H&E, 10x) with discrete pleomorphism, hyperchromatism, altered nucleus-cytoplasm ratio, dyskeratosis, corneal pearls and mitosis figures invading the underlying connective tissue and destroying skeletal striated muscle fibers (C- H&E, 20x). In D, the presence of atypical mitoses can be seen (D- H&E, 40X).

Given the clinical and microscopic findings, a final diagnosis of tongue SCC was made, and the patient was referred to an oncology center for treatment, where total surgical removal of the lesion and cervical lymph node dissection were performed. At the 8-month post-surgical follow-up, no signs of recurrence were observed (**Figure 3**).

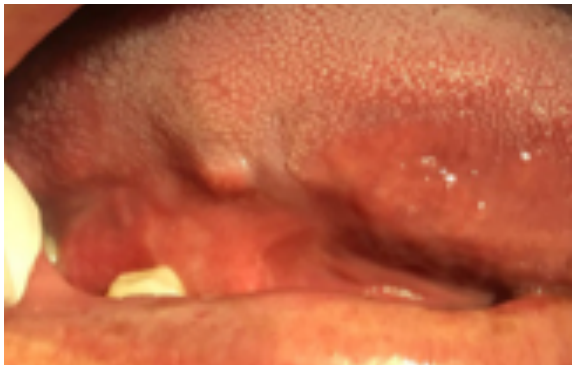

Figure 3 - 8-month post-surgical follow-up.

3. DISCUSSÃO

Squamous cell carcinoma is the most prevalent malignant neoplasm in the oral cavity[10]. Its etiology is multifactorial but is commonly associated with traditional risk factors such as tobacco use and frequent alcohol consumption[11]. The incidence is higher in males over 45 years of age[11]. However, the epidemiological profile is shifting, with a significant increase in cases of tongue SCC in young patients and women[1,7,11].

Advanced age is a major predisposing factor for SCC, primarily due to the accumulation of genetic mutations over time and prolonged exposure to carcinogenic risk factors[13]. However, the etiopathogenesis of this cancer in younger patients remains controversial[7,11,12].

Despite extensive research on oral SCC, few studies focus on the clinical, etiological, and pathogenic profiles of this neoplasm in patients under 45 years of age[7,10]. Compared to older populations, young patients with SCC exhibit lower smoking prevalence and higher alcohol consumption[14]. This suggests that unidentified genetic predispositions may play a key role in the onset and progression of SCC in young patients, independent of risk habits, as demonstrated in this case report[7,10,15,16].

A recent review by Tran et al. (2023) proposed several factors potentially associated with the etiopathogenesis of SCC in young, non-smoking, non-alcoholic patients, including genetic mutations, alterations in the bacterial microbiota, Fanconi anemia, and viruses such as Epstein-Barr and β-HPV. Deneuve et al. (2022) suggested possible risk factors including a history of leukoplakia, alcoholism, and cannabis use, although further research is needed to confirm these associations.

There is growing evidence of the involvement of specific proteins in the pathogenesis of malignant neoplasms such as SCC, indicating a correlation between molecular differences and the biological behavior of this cancer in young patients, potentially influencing their prognosis[7,18]. Some studies suggest a poor prognosis for SCC of the tongue in patients under 45 years, with higher rates of metastasis and lymphatic invasion. However, other studies have found no significant differences in survival rates between younger and older patients with tongue SCC [1,14,16,19,20].

Notably, the recurrence rate of tongue SCC in young, non-smoking patients is twice as high as in older, smoking populations[7,23]. Therefore, the therapeutic approach to the disease should be tailored to the tumor's stage and histological grade[11,7].

However, in these cases, surgical management with wide safety margins and neck dissection is often justified[7,24].

It is well-established that late diagnosis of SCC leads to lower survival rates and reduced quality of life due to higher rates of mutilation and psychological distress[16,25]. In contrast, early diagnosis significantly improves survival outcomes for all patients, regardless of age[10,15]. Consequently, public health strategies aimed at preventing late diagnosis are crucial for reducing morbidity and mortality[26].

To achieve this, the epidemiological, histological, clinical, and morphological characteristics of tongue SCC should be considered in the design of these strategies to increase the number of early-stage diagnoses[10,26]. Furthermore, dental surgeons play a crucial role in using semiotechnical resources to enhance the diagnosis of potentially malignant oral disorders, such as leukoplakia[25]. Comprehensive inspection and palpation of all oral structures and the lymph node chain in the head and neck are fundamental for identifying lesions that may affect the oral cavity[12].

It is important to note that SCC, specifically of the tongue, can be almost exclusively associated with young, non-smoking individuals[27]. Therefore, even though oral SCC is generally uncommon in patients under 45, this condition should be included in the differential diagnosis of potentially malignant oral disorders (PMODs), regardless of age[15].

Although several cases of SCC in young patients have been reported, the lack of specificity and heterogeneity in studies on this topic make it challenging to establish a clinical and epidemiological profile for this neoplasm in younger individuals[7,12,14]. Reaching a consensus on the classification of this patient population is also essential for standardizing data comparisons[17].

Given these considerations, this article emphasizes the need for further studies specifically addressing the incidence of SCC in patients under 45, enabling the literature to better understand the mechanisms underlying the disease in young individuals.

4. CONCLUSION

This case highlights the importance of early diagnosis of oral lesions, particularly SCC. Patient education on the prevention and monitoring of these lesions is essential, and the role of the dental surgeon in their diagnosis is crucial. Additionally, further research is needed to explore new habits in young patients diagnosed with SCC, as the etiological factors in this group remain uncertain.

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Título: O título do artigo deve ser curto, claro e conciso para facilitar sua classificação e deve ser enviado em inglês.

Autor(es): O(s) nome(s) completo(s) do(s) autor(es) e seus títulos e ligações à Sociedade ou Instituições, (Universidades, Faculdades, Hospital ou Departamento, Mini-currículos não serão aceitos) . Autor de correspondência : Nome, endereço, CEP, cidade, estado, país e endereço eletrônico.

Resumo: Deverá conter no máximo 250 palavras e elaborado de forma estruturada. Para artigos de Pesquisa e Ensaios Clínicos incluir: Justificativa e Objetivos, Métodos, Resultados e Conclusões. Incluir até seis descritores. Recomenda-se a utilização do DeCS – Descritores em Ciência da Saúde da Birene, disponível e, http://desc.bvs.br/.

Abstract: A versão do resumo em inglês deve ser encaminhada junto ao artigo. Incluir até seis keywords.

Corpo doTexto: Organizar o texto de acordo com os tipos de artigos descritos abaixo. Em artigos originais com humanos ou animais deve-se informar os aspectos éticos além do nº do processo e ano do Comitê ou Comissão de ética da Instituição.

CATEGORIA DE ARTIGOS

Além dos artigos originais que tem prioridade, a Revista da Sociedade Brasileira de Cancerologia, publica revisões, atualizações, relato de casos e cartas ao editor. Nomes genéricos dos fármacos devem ser usados. Quando nome comerciais são usados na pesquisa, esses nomes devem ser incluídos entre parênteses no capítulo MÉTODOS .

Artigos originais: são contribuições destinadas a divulgar resultados de pesquisa original inédita, que possam ser replicadas e ou generalizadas. Devem atender os princípios de originalidade e clareza da questão norteada, Justificativa e Objetivos. Introdução, Métodos, Resultados, Discussão, Conclusão, Figuras e Tabelas e Referências Bibliográficas.

Revisões: Avaliação crítica sistematizada da literatura e ou reflexão sobre determinado assunto, devendo conter conclusões. O procedimento adotado e a delimitação do tema devem estar incluídos. Para artigos de revisão destacar: Justificativa e Objetivos, Conteúdo e Conclusão.

Relato de casos: estudos avaliativos, originais ou notas prévias de pesquisa contendo dados inéditos e relevantes no fenômeno estudado. A apresentação deve acompanhar as mesmas normas exigidas para artigos originais.

Descritores: Para todos os artigos, indicar os Descritores. Recomenda-se a utilização do DECS – Descritores em Ciência da Saúde da Bireme, disponível em http://decs.bvs.br/.

Summary: A versão do resumo para o inglês deve ser enviado.

Texto: Iniciar o texto de acordo com o tipo de artigo.

Deve ser estruturado da seguinte forma: Introdução, Conteúdo, Conclusão e Referências. Não deve exceder a 40 referências.

ABREVIAÇÕES

Por favor, lembre que, apesar de muitos de nossos leitores serem especialistas, eles podem não ser especialistas na sua área e, assim é necessário explicar toda a terminologia e acrônimos a primeira vez que eles são usados. Por favor, providencie uma lista alfabética de todas as abreviações.

Referências: A Revista da Sociedade Brasileira de Cancerologia adota as "Normas Vancouver", disponível em http://www.icmje.org, como referência para a veiculação de seus trabalhos. Use as abreviações de revistas encontradas no Index Medicus/MedLine.

Elas devem ser dispostas no texto em ordem sequencial numérica, sendo obrigatória a sua citação (sobrescritas, sem parêntesis). Evitar a citação do nome do autor em destaque. Não se recomenda a citação de trabalho não publicado ou apresentado em Eventos Médicos. As referências com mais de cinco anos, de livros texto e resumo de congressos, devem limitar-se às que são fundamentais. Incluir referências acessíveis aos leitores. Quando a citação for de artigo já aceito para publicação, incluir "em processo de publicação", indicando a revista e o ano. Comunicações pessoais não são aceitas.

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Exemplos de referências:
Artigos de revistas:

1 autor - Wall PD. The prevention of postoperative pain. Pain 1988;33(1):289-90.

2 autores - Dahl JB, Kehlet H.The value of pre-emptive analgesia in the treatment of postoperative pain. Br J Anaesth 1993;70(1):434-9. -

Mais de 3 autores - Gimenes RO, Previato BL, Claudio PDS, et al. Impacto do programa escola de coluna em indivíduos com hérnia de disco lombar. Rev Dor 2008;9(2):1234-41.

ILUSTRAÇÕES

É obrigatória a sua citação no texto. Enumerar gráficos, figuras, tabelas e quadros em algarismos arábicos, elas deverão conter título e legenda. Indicar no texto, o local preferencial de entrada de cada ilustração (Entra Figura x, por exemplo). O mesmo resultado não deve ser expresso por mais de uma ilustração. Sinais gráficos utilizados nas tabelas ou gráficos devem ter sua correlação mencionada no rodapé. Gráficos, Figuras e Tabelas devem ser enviadas separadas do texto principal do artigo. A qualidade dos gráficos e figuras é de responsabilidade dos autores.

FORMATO DIGITAL

A Carta de submissão, o manuscrito, e tabelas deverão ser encaminhadas no formato DOC (padrão Windows Word); figuras em barras ou em linhas deverão ser encaminhadas em Excel (extensão XLS). Fotos deverão ter resolução mínima de 300 DPI, em formato JPEG.

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