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REVIEW ARTICLE

MALIGNANT PHYLLODES TUMOR: A SYSTEMATIC REVIEW OF THE LITERATURE

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ABSTRACT

Phyllodes Tumor of the Breast (PT) is an uncommon type of fibroepithelial neoplasm of the breast that affects mainly black women. It usually presents itself painlessly and with accelerated growth of the neoplastic mass. This growth will vary according to the biological behavior assumed by the tumor, and may be benign, borderline or malignant. The form of diagnosis is based on a tripod, consisting of clinical, laboratory and imaging exams. Surgery is still the main approach to treating the disease. The work developed is a systematic review of the literature on Malignant Phyllodes Tumor of the Breast (MPT). For this review, we searched the literature in PubMed and MEDLINE databases. In this way, we seek to provide an update on the approaches taken and advances made over the last five years.

KEYWORDS: BREAST TUMORS; MALIGNANT BREAST TUMORS; BREAST PHYLLODES TUMOR; MALIGNANT PHYLLODES TUMOR OF BREAST; RECURRENC

INTRODUCTION

Breast cancer is currently considered a public health problem not only in developed countries such as the United States and Western European countries, but also in developing countries such as Brazil. Non-epithelial malignant neoplasms represent less than 5% of all breast tumors. Among the main non-epithelial neoplasms of the breast are the Phyllodes Tumor[1].

The Phyllodes Tumor of Breast was first described in 1774 as "a giant type of Fibroadenoma". The first author to use the name "philistine cystosarcoma" was Johannes Muller in 1838. However, its cystic component nor its potential for malignancy had yet been reported. In 1981, the World Health Organization abandoned the term cystosarcoma and adopted the term "Phyllodes Tumor"[2-5].

The Phyllodes Tumor (PT) is part of the so-called fibroepithelial lesions. These lesions comprise a heterogeneous group of biphasic tumors that have different epithelial and stromal components in their morphology (demonstrating a widely variable clinical behavior), they include Fibroadenomas and Phyllodes Tumors. Therefore, Phyllodes Tumor represents 2.5% of all fibroepithelial tumors and 0.5% to 1.0% of all breast tumors[6]. Histologically, Phyllodes Tumors are similar to Fibroadenomas in that the epithelial-lined spaces are also surrounded by cell stroma. However, in Phyllodes Tumors, stromal cells are monoclonal and neoplastic[7].

Phyllodes Tumors are categorized as benign, borderline and malignant according to the World Health Organization (WHO). Most phyllodes tumors are benign, accounting for 60 to 75% of cases. Borderline and malignant phyllodes tumors are less frequent, accounting for 15% to 20% and 10% to 20%, respectively, of all cases. Benign disorders predominate in young premenopausal women and malignancy rates increase with advancing age [8-10].

Most cases of Phyllodes Tumor of the Breast occur in women between the third and fifth decade of life, and it affects mainly black women and for its diagnosis a triple evaluation is necessary. This evaluation consists of encompassing clinical, radiological and histopathological investigation of suspicious breast nodules. This disease usually manifests as voluminous tumors, typically larger than 5 cm, painless, with a firm consistency, a raised or lobulated surface, well defined, mobile and without involvement of the skin or deep tissues. Phyllodes Tumors also have the potential for local recurrence, being common in malignant Phyllodes Tumor (MPT) with reported frequencies ranging from 10 to 65% of cases. Furthermore, distant metastases occur due to systemic dissemination and, despite being rare, they are highly severe and mainly affect the lungs, bones, liver and brain [11-14].

With regard to treatment, surgical excision with neg-

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ative margins is the main form and is associated with high disease-free survival, long life expectancy, and low recurrence rate. Currently, breast-conserving surgery is an appropriate treatment option, which must have free margins and, thus, obtain an acceptable cosmetic result. In addition to this form of treatment, there is also radiotherapy, which is frequently used, since the Phyllodes Tumor tends to be locally aggressive [15-17].

In view of the above, we believe that the analysis and literary review of the Malignant Phyllodes Tumor of the Breast is pertinent, since this biological behavior is the least frequent and presents high health risks, especially when not addressed at its beginning and in an adequate way. In addition, in our studies it was possible to observe the scarcity of articles that are specifically directed to the Malignant Phyllodes Tumor and, with that, this study can help and expand the sources of knowledge on this subject.

OBJECTIVES

Conduct a systematic review presenting the most recent information on Malignant Phyllodes Tumor of the Breast.

Bring an updated view, from the last five years, on the diagnosis, treatment and metastatic and recurrence events of Malignant Phyllodes Tumor.

METHODOLOGY

A systematic review of the literature was carried out, using the PubMed and Virtual Health Library (VHL) platforms as a source of search strategy. Through these means, articles were searched with the keywords "phyllodes", "tumor" and "breast" (with the connective "AND") in the period from January 2016 to December 31, 2020, covering the last five years. In addition, on the PubMed platform, filters were selected that directed the articles to humans and English and Portuguese languages. In the VHL, the MEDLINE database and the English and Portuguese languages were selected. As a result, a total of 668 articles were analyzed, and in the end only 37 articles actually met our criteria (Diagram 1).

The articles analyzed were included when they met the pre-established criteria. Among them are matters related to Malignant Phyllodes Tumor of Breast such as clinical-pathological characteristics, diagnostic methods, treatment, metastases and local recurrence. And, among the exclusion criteria are articles outside the established period, duplicate references, gene analysis (molecular), male gender, articles that evaluated the three biological behaviors together (benign, borderline and malignant), pregnant or lactating women and children and adolescents under 18 years of age (following the Child and Adolescent Statute – Law 8069 of 1990).

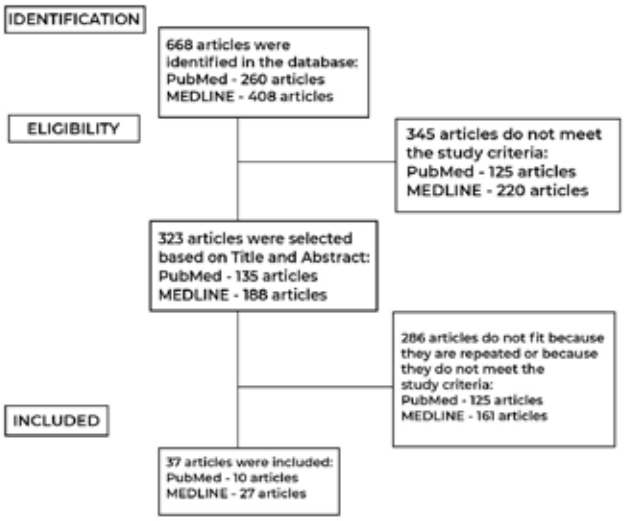

Diagram 1: Methodology followed in the analysis of articles.

RESULTS

Article	Study Methodology	Country	Surgery	Metastasis	Main Results
IMORI et al, 2017	Case report	Japan	Partial Mastectomy and Total Mastectomy	-	Patient 48 years old, PT in left breast. 6 episodes of relapses, all of which were MPT. Radiotherapy (RT) was performed. Currently without recurrence and metastasis.
WU et al, 2020	Case report	USA	Mastectomy	Bone	Patient 58 years old, PT in the right breast.She had 2 fibroadenoma relapses and 1 MPT. After bone metastasis, she refused treatment and later died.
LIEW et al, 2018	Retrospective Study	Malaysia	7 – Mastectomy and 4 – Breast Conserving Surgery	-	Study of 11 patients with MPT with a mean age of 45 years. Of these patients, 6 received RT and 8 developed local recurrence.

Article	Study Methodology	Country	Surgery	Metastasis	Main Results
WANG et al, 2017	Case report	China	Extensive tumor resection	-	A 27-year-old patient with PT in the right breast. She had 2 recurrences of fibroadenomas and the third MPT. She underwent radiotherapy. The patient was in good general condition, with no recurrence.
SHAN et al, 2016	Case report	USA	Partial Mastectomy	Pelvic cavity	A 30-year-old patient with PT on the left breast. She had 5 local relapses, 3 times pelvic metastasis. She underwent chemotherapy. The patient died 72 months after the diagnosis of PT.
SERA et al, 2017	Case report	Japan	Partial Mastectomy	Tonsillar and Pulmonary	A 57-year-old patient with a mass in the left breast. Without relapses and with refusal of treatment, the patient died 1 month after diagnosis.
CHANG et al, 2017	Case report	South Korea	Radical Mastectomy	Pulmonary	A 31-year-old patient with a mass in the right breast. She had several relapses at the surgical margins and metastasis after palliative radiotherapy (RT). Patient died.
RAJESH e FAROOQ, 2017	Case report	India	Mastectomy	-	27-year-old female, PT in the right breast, with 2 relapses, with no recurrence and current metastasis.
CHEN, 2017	Case report	Taiwan	Total Mastectomy	-	A 22-year-old female, PT in the right breast with symptoms of bloody nipple discharge, without recurrence.
WARNER et al, 2017	Case report	USA	Mastectomy	-	45-year-old female with a left breast mass. Patient with stable disease and stable sclerotic lesions were observed in their lumbar vertebral bodies.
WOLBERT et al, 2018	Case report	USA	Mastectomy	-	Female, 46 years old, left breast, diagnosed at an early stage without relapses and metastasis. Performs follow up correctly.
ALBALAWI, 2018	Case report	Saudi Arabia	Total Mastectomy	-	41-year-old female, left breast mass. With a 30 cm tumor, she was referred for RT and chemotherapy.
DURGA et al, 2018	Case report	India	Simple Mastectomy	Ovary	A 33-year-old patient with a mass in the right breast. RT for bone lesions and palliative chemotherapy.
NASRI et al, 2020	Case report	Tunisia	Mastectomy	Pancreas, gallbladder, lung and brain	A 51-year-old patient with an affected left breast. She died 5 weeks after the discovery of brain metastasis.
ABE et al, 2020	Case report	Japan	Mastectomy	Lymph node	A 44-year-old patient with an affected right breast. She had chemotherapy, but died 4 months after the mastectomy.
LEE SE et al, 2020	Case report	South Korea	Breast Conserving Surgery, Mastectomy and Wide Excision	`Pancreas	A 48-year-old patient with a mass on the right. She underwent adjuvant therapy with an immunomodulatory substance.
MORIOKA et al, 2020	Case report	Japan	Nipple Conserving Mastectomy	-	A 28-year-old patient with an affected left breast. She did not undergo radiotherapy and progressed well with no cases of recurrence.
ZHAO et al, 2020	Retrospective Study	China Popular Republic	564 – Mastectomy and 789 – Breast Conserving Surgery	1.3% - Lymph nodes	A total of 1353 patients with MPT participated in the study. Among these 226 received adjuvant RT and 1127 did not. No protective role of adjuvant RT was observed in patients.
LIU HP et al, 2020	Case report	Taiwan	Total Mastectomy	Stomach and brain	82-year-old patient with affected left breast. She had two recurrent local tumors and went on to undergo adjuvant RT. She died after two months.

Article	Study Methodology	Country	Surgery	Metastasis	Main Results
LEE HJ et al, 2020	Case report	South Korea	Breast Conserving Surgery	Scalp, lung and kidney	A 58-year-old patient with a mass in the left breast. She underwent palliative systemic chemotherapy and radiotherapy. Patient presented progressive disease and died 16 months after the initial diagnosis of distant metastases.
ATHAMNAH et al, 2020	Case report	Jordan	Nipple Conserving Mastectomy	-	A 23-year-old patient with a mass in the left breast. Patient underwent adjuvant RT.
NGUYEN et al, 2020	Case report	USA	Simple Mastectomy	-	A 26-year-old patient with an affected right breast. She received adjuvant radiotherapy to the breast and was monitored for recurrence.

Article	Study Methodology	Country	Surgery	Metastasis	Main Results
SHAFI et al, 2020	Case report	Saudi Arabia	Radical Mastectomy	Bilateral lymph node, chest wall and lung	A 45-year-old patient with an affected right breast. There was no local recurrence, but her lung nodules were increasing in number and size despite chemotherapy.
YAMAMOTO et al, 2019	Case report	Japan	Total Mastectomy	Lung	A 48-year-old patient with a mass in the right breast. Chemotherapy was performed. However, her condition suddenly worsened and she died shortly thereafter.
GREGSTON et al, 2019	Case report	USA	Radical Mastectomy	Lung and brain	A 32-year-old patient with a mass in the left breast. Patient received chemotherapy, however, died 20 months after diagnosis.
KHANAL et al, 2018	Case report	Nepal	Radical Mastectomy	Brain, adrenal and lung	A 37-year-old patient with an affected left breast. There was no local relapse.

Article	Study Methodology	Country	Surgery	Metastasis	Main Results
PARK et al, 2019	Retrospective Study	South Korea	43 – Cirurgia Conservadora de Mama e 27 – Mastectomia	Lymph node	Mean age 42 years, showed that adjuvant RT in treatment reduces local or distant relapse..
MOON et al, 2019	Case report	USA	Mastectomy	Lymph nodes and lung	48 year old woman, presented PT in the left breast, with complete remission after adjunctive treatment with chemotherapy.
SU et al, 2017	Case report	Taiwan	Radical Mastectomy	-	2 cases of PT in the left breast, with local recurrence, showed good results with RT and chemotherapy.
SHAH-PATEL, 2017	Case report	USA	Mastectomy	-	An 89-year-old female presented with PT in the left breast with rapid tumor progression.
SCHILLEBEECKX et al, 2016	Case report	Belgium	Total Mastectomy	-	A 57-year-old female presented with PT with heterologous lipo sarcomatous differentiation in the left breast.

Article	Study Methodology	Country	Surgery	Metastasis	Main Results
LIU M et al, 2016	Case report	China	Simple Mastectomy	-	43-year-old female with a giant tumor in the right breast.
EL OCHI et al, 2016	Case report	Morocco	Mastectomy	Bone	Two patients, one 40 years old and the other 48 years old, had a mass in the left breast.
DITSATHAM et al, 2016	Case report	Thailand	Simple Mastectomy	-	A 58-year-old female presented with a rare ruptured PT of the left breast.
JOHNSON et al, 2016	Case report	USA	Mastectomy	Lymph nodes, brain and lung	Female 66 years old, left breast affected. She underwent surgery with tumor cytoreduction and lumbar spinal fusion.
YOGI e SINGH, 2019	Retrospective Study	India	3 – Breast Conserving Surgery, 8 – Wide local excision and 4 – Mastectomy	-	Mean age of the study was 33 years. It shows that adjuvant RT has a significant role in preventing recurrence.
GAO et al, 2018	Case report	China	-	Lung	A 45-year-old patient with a left breast tumor.

DISCUSSION

Phyllodes tumors (PT) are classified as benign, borderline and malignant. Benign represents respectively between 60 and 75% of cases and the remainder is divided between the borderline and malignant subtypes, estimated at 10 to 30%[18-20].

In the current literature, Phyllodes Tumors are known to occur in women aged between 35 and 55 years, who are typically 10 to 20 years older than the peak incidence of fibroadenoma. Previous studies have reported a more frequent occurrence of malignant phyllodes tumor (MPT) in older patients with a mean age of 45 to 54 years[21].

It is estimated that the incidence of malignant PT is 2.1 cases in a million women, with a higher frequency in Latin and Asian women [22-25]. The tumor was almost equally distributed in the right and left breasts in all subtypes. A similar pattern of equal distribution was observed in several other studies. Two studies, however, described a left breast dominance pattern of 71% and 58%[26-28].

The manifestation of Phyllodes Tumor is through voluminous masses, of firm consistency. The size of the tumor can vary from a few centimeters to large lesions that involve the entire breast, with an average of 5 cm[29-31].

Phyllodes Tumors (PT) are categorized as benign, borderline and malignant according to the World Health Organization (WHO). This evaluation consists of encompassing clinical, radiological and histopathological investigation of suspicious breast nodules. Unlike breast carcinomas, PT predominantly start outside the ducts and lobules, in connective tissue, called the stroma, including the fatty tissue and ligaments that surround the ducts, lobules, blood vessels, and lymphatics of the breast. Generally, the clinical picture of the PT is manifested as a single nodule, with a smooth surface and not adherent to adjacent planes, lobulated, painless, pseudo-encapsulated or firm consistency, well defined, and without involvement of the skin or deep tissues, they are voluminous, fast-growing tumors, typically larger than 5 cm[32-36]. These tumors are painless in most cases, but can become painful, smooth, mobile, and with circumscribed edges, from 1 to 10 cm in diameter or even larger. Due to their rapid growth and the ability to reach large volumes as we witness, they can compromise the entire mammary gland. As they increase in volume, they can distend the adjacent skin, making it smooth and shiny, as well as favoring the visibility of the ecstatic venous reticulum and causing mild hyperemia to ulceration [37-39]. They have central cystic areas, most commonly located in the upper quadrant of the breast, bilaterality and multicentricity are exceptional. Axillary adenopathy is common, but it is usually inflammatory in nature, since metastases to axillary lymph nodes are uncommon, even in the malignant variety of the tumor [40-45].

Phyllodes Tumors are sometimes seen with a fibroadenoma-like structure where fibrocystic changes, adenosis, epithelial hyperplasia or atypical hyperplasia can occur, and their actual components are hyperproliferative interstitial cells, ie fibroblasts. Fibroblasts can also differentiate into fat cells, cartilage, smooth muscle, and striated muscle. These cells have lost their normal arrangement and are braided, mesh or spiral-shaped. Tumor cells may be evenly dispersed, with unequal density in different regions and varying degrees of atypia and a variable number of mitotic figures. There may be mucoid degeneration and necrosis or hemorrhage. All of these components can develop into a Sarcoma, the presence of these components indicates a poor prognosis. Invasive Ductal Carcinoma, Lobular Carcinoma and Carcinoma In Situ can also occur in PT, but they are very rare. The Phyllodes Tumor of the Breast has rich and difficult to predict biological characteristics. According to the histopathological criteria defined by the WHO, margin involvement, stromal cellularity, mitotic index and cellular pleomorphism should be observed. Imaging diagnosis by means of ultrasonography or mammography is not considered a routine standard due to the difficulty in differentiating Phyllodes Tumors from fibroadenomas; therefore, the histopathological examination is the gold standard for diagnosis[46].

Thus, ultrasound (USG) is used at first, due to the low cost of the exam and because it is not invasive. The PT appears on ultrasound as a voluminous lobulated mass, with clear boundaries, internally mostly solid hypoechoic uneven echoes, potentially with scattered echo-free zones. Malignant breast phyllodes tumor does not follow the general rules of other types of breast cancer in terms of echo attenuation, and microcalcification is common. Breast X-ray findings are related to the size of the tumor. Smaller tumors are nodules with smoother edges, while larger tumors have more irregular but clear lobulated edges, with greater density than normal glands. Magnetic resonance imaging (MRI) can clearly show the scope of the tumor. Mammary Phyllodes Tumor has low signal based on T1W1 single scan and higher signal based on T2W1. Dynamic lesion with contrast in time signal intensity curve is increasing more and more and the type of platform making it easier to differentiate with fibroadenoma. Among the types of biopsies available, fine needle puncture is not very specific, its accuracy is 23%, with a low predictive value, probably due to the volume of the tumor and the frequent presentation of areas of hemorrhagic infarction, making diagnosis and the distinction between tissues. Core biopsy has a specificity of 65%, being able to differentiate a Phyllodes Tumor from an adenocarcinoma, however, it does not discriminate between benign and malignant characteristics, being more effective in smaller tumors. Most studies suggest that the diagnostic accuracy rate by biopsy for mammary Phyllodes Tumor is around 50%. Thus, the anatomopathological evaluation of the complete piece is the most effective. Even with specific pathological criteria available, a definitive preoperative diagnosis is still difficult in some cases. Some immunohistochemical markers are studied in order to predict the three types, in an attempt to predict their biological behavior and thus better plan the

therapeutic approach. It also serves, in some cases, for the differential diagnosis with fibroadenoma. Ki-67 and p53 stand out, which are fibroblast and vascular endothelial growth factors. Ki-67 is a biomolecular marker that may be useful in differentiating between malignant Phyllodes Tumor and borderline fibroadenoma cases. Ki-67 is expressed much more in the stroma than in the epithelium of the Phyllodes Tumor, due to the large stromal growth, high stromal cellularity, presence of atypia and high rate of mitosis. Ki-67 positivity is also related to the positivity of another marker, p53. Thus, it can be said that the low expression of this marker is more related to favorable prognosis. The proto-oncogene that encodes the tyrosine kinase receptor (CD117) is present in 50% of malignant Phyllodes Tumors and in 5% of benign ones, it also has a higher expression in areas of stromal proliferation[47].

The Malignant Phyllodes Tumor (MPT) macroscopically presents itself as voluminous, bumpy tumors, with an elastic, firm consistency and a grayish-white surface, frequently interspersed with areas of hemorrhage, necrosis and degeneration, responsible for the cystic areas. In histopathology, malignant tumors are derived from periductal or intralobular stroma, their basic structure is similar to intracanalicular fibroadenoma, but with stromal hypercellularity, therefore, it can be called hypercellular fibroadenoma. They have marked stromal cellularity and atypia, high mitotic rate, with more than 10 mitoses per 10 high-power fields, infiltrative tumor margins with the presence of papillary projections lined up in the connective tissue, as well as the presence of stromal overgrowth. Sometimes figures of malignant mitosis can be seen and there may be bleeding, necrosis and multiple recurrence after surgery with poor prognosis. Some studies have shown that malignant Phyllodes Tumor has a larger diameter compared to benign and borderline tumors. In addition, other studies suggest that those with a diameter of 10 cm or more are defined as a large lobulated tumor. There were also studies that showed that some authors subdivide malignant Phyllodes Tumor into high and low grade varieties. This subdivision is based on criteria for stromal growth, margins, mitosis numbers and stromal atypia. Low grade malignant Phyllodes Tumor would have infiltrative margins, 11 to 20 mitoses per 10 high power fields and moderate degree of cellular atypia. The high-grade tumor would have clearly infiltrative margins and a very evident stromal growth, with more than 20 mitoses per 10 high-power fields and marked cellular atypia. This type of subdivision is important in the elaboration of prognosis for different types of Phyllodes Tumor. Immunohistochemical markers are associated with varying degrees of tumor malignancy, such as growth factors, mainly stromal, such as Ki-67, p53 and CD117 (which are more expressed in areas of stromal proliferation)[48].

The treatment of Malignant Phyllodes Tumor is well established regarding the need for excision of the neoplastic mass present in the breast. This excision can be through surgery such as a mastectomy (simple or radical) or breast-conserving surgery (BCS). In addition, radiotherapy, chemotherapy and hormone therapy are used as a complementary therapy, as they seek to help prevent local recurrence and metastasis.

Surgical excision is the first treatment option for Phyllodes Tumor, according to current National Comprehensive Cancer Network guidelines for breast cancer, regardless of the nature of the tumor (benign, borderline, or malignant). This determination is mainly valid for phyllodes tumors larger than 3 cm with free margins greater than or equal to 1 cm. Although some studies mark the extent of margins as controversial, since the tumor penetrates healthy tissue, most state the need for wide local excision to guarantee negative margins of 1 to 2 cm. And if wide local excision (breast-conserving surgery) fails to reach the designated margins, the preferred surgery is simple mastectomy. On the other hand, one of the analyzed studies, by ZHAO et al (2020), showed an improvement in patients undergoing breast-conserving surgery than those undergoing mastectomy, regardless of receiving adjuvant radiotherapy or not ($p < 0.001$). However, patients who underwent mastectomy tended to have higher risk factors. Breast-conserving surgery is feasible in the context of a good cosmetic and oncological outcome for patients with Malignant Phyllodes Tumor[49-50].

Phyllodes Tumor does not have its own guideline regarding adjuvant therapy. Wide local excision is recommended, adopting a margin of 1 cm, with no recommendation of radiotherapy, chemotherapy or hormone therapy as there are no direct guidelines for this. However, the use of adjuvant radiotherapy is indicated due to the higher rate of local recurrence, having relevant value, especially after breast-conserving surgery. This therapeutic approach stands out in cases of Phyllodes Tumors with more than 20 mitoses per 10 high-power fields, larger than 5 cm in size, with stromal overgrowth or with positive margins [49-50]. The use of adjuvant radiotherapy is still controversial, some studies do not show an improvement in the prognosis, while others show a better local control. In patients with Malignant Phyllodes Tumor measuring more than 2 cm after lumpectomy or tumors larger than 10 cm after mastectomy, adjuvant radiotherapy is strongly recommended in order to control the high rate of local recurrence in more than 15% of cases. However, even with this local control, neither disease-free survival nor overall survival are altered 50. The retrospective study by ZHAO et al (2020) also did not show significant benefits regarding survival in the application of adjuvant radiotherapy among patients with Malignant Phyllodes Tumor. Thus, although the use of radiotherapy has recently increased due to the high risk of recurrence, there is no evidence to support this practice [49-50].

The role of chemotherapy still remains unclear in relation to Malignant Phyllodes Tumor, since its effectiveness is unknown. However, the National Comprehensive Cancer Network currently recommends that recurrent metastatic Phyllodes Tumor cases follow treatment guidelines for met-

astatic soft tissue sarcomas. As Phyllodes Tumors are considered soft tissue sarcomas, adjuvant chemotherapy with doxorubicin plus dacarbazine may provide some benefits for patients with large (> 5.0 cm) high-risk tumors [11-14]. Moreover, the usefulness of anthracycline- and ifosfamide-based regimens, as well as high-capacity ifosfamide or anthracyclines plus granulocyte-macrophage colony-stimulating factor, has been reported for the treatment of soft tissue sarcomas. Therefore, our study analyzed situations in which chemotherapy was used, obtaining some positive responses and others that it was not effective. GREGSTON et al (2019) presented a case report in which the patient received AIM chemotherapy (Adriamycin®, ifosfamide and mesna) for six cycles and, despite initially showing a partial response, then the metastatic disease began to progressively advance, evidencing the ineffectiveness of chemotherapy. In the case of YAMAMOTO et al (2019), a benefit was shown with doxorubicin-ifosfamide (AI) therapy before surgery and showed its usefulness for cases of recurrent Phyllodes Tumor. Another case report, by MOON et al (2019), noted the effectiveness of treatment with surgery and chemotherapy. In this case, palliative chemotherapy with doxorubicin plus ifosfamide was used and a complete remission of the patient with lung metastases from a Malignant Phyllodes Tumor was evaluated. Doxorubicin and dacarbazine have been reported to be effective when given with cisplatin or ifosfamide, with ifosfamide being considered the most active agent for metastatic Malignant Phyllodes Tumors. In addition, the combination of doxorubicin plus cisplatin, cyclophosphamide, or ifosfamide may improve median survival in patients with metastatic Phyllodes Tumors. Furthermore, in the neoadjuvant setting, one study found that the combination of bevacizumab with chemotherapy increased the percentage of patients with non-metastatic breast cancer who achieved a pathological complete response. Thus, he evaluated sufficient tumor reduction and an efficacy of neoadjuvant treatment for Malignant Phyllodes Tumor [40-45].

Hormone therapy still does not have in-depth studies that determine it. The practical role of the expression observed in hormone receptors remains unclear, without proof of its real help as an adjuvant treatment [35-40].

Routine lymphadenectomy is not indicated, as Phyllodes Tumors propagate mainly hematogenously and rarely to lymph nodes (<1% have pathological lymph nodes). Sentinel lymph node biopsy is recommended in patients with a palpable lymph node, large phyllodes tumor, or suspected involvement in preoperative imaging. Therefore, if there is no evident clinical involvement of the axillary lymph nodes, dissection is not necessary [11-14].

The treatment for Malignant Phyllodes Tumor is complex and despite the techniques of surgery and adjuvant therapy (radiotherapy and chemotherapy) it still weakens the patient, which can lead to the appearance of local recurrence and metastases. Its difficult management leads to 5- and 10-year survival rates of 82 and 42% for malignant Phyllodes Tumor, respectively [35-40].

The subclassification of Phyllodes Tumor is of paramount importance, since local recurrence can occur in all categories of Phyllodes Tumor [25-30].

High local recurrence is the most important prognostic feature of this condition, with an overall recurrence rate of up to 40% of all histological types of mammary Phyllodes Tumors [47-50].

The type of surgery for Phyllodes Tumor with multiple recurrences separately is rarely reported in the literature. Kapiris et al., did not find in patients with malignant phyllodes tumor (MPT) the statistical significance of expanded local resection and mastectomy, and suggested the importance of negative surgical margin to control MPT recurrence and distant metastases [49-50].

Thus, the current approach to prevent local recurrence and metastasis is surgical resection with wide margins. Wide local excision with negative margins of at least 1 cm is recommended. If negative margins cannot be obtained, simple mastectomy is preferred. The effectiveness between wide local excision and mastectomy is indistinct. Although the possibility of local recurrence has decreased in patients who underwent mastectomy, overall survival did not improve when performing this surgery [40-45].

However, even with extensive surgical resection, the local recurrence rate remains high, ranging from 8 to 36%. The recurrence rate of malignant phyllodes tumors occurred in up to 25% of patients according to a review involving 5,530 patients[7-10].

On the other hand, the exact effect of adjuvant radiotherapy for the local control of different histological types of Phyllodes Tumor recurrence has been focused on by many researchers, but progress is still very small. Studies have shown that adjuvant radiotherapy can reduce local recurrence rates in malignant Phyllodes Tumor, without significant influence on survival [11-14].

Local recurrence is a risk factor for distant tumor metastases. Most distant metastases of Phyllodes Tumor of the breast occurred after local recurrence. However, other investigators have not observed an association between local recurrence and systemic spread. In addition, local recurrence can be rescued by secondary surgery. It is not yet known whether local recurrence is a predictive factor for metastasis of Phyllodes Tumor of the breast, since metastasis can appear without the coexistence of local recurrence [37-40].

Phyllodes Tumor metastasis can occur in all categories: Benign, Borderline and Malignant. Being very rare, the general rates of distant metastases in Phyllodes Tumor vary from 1.7% to 27.1%, with an average of 5.6%, according to the grade of the tumor30. Aggressive malignant phyllodes tumors are prone to rapidly growing metastatic spread. Thus, about 25% of TFM give rise to metastasis [40-44].

Usually, the spread of malignant phyllodes tumors is through the hematogenous route, and not through the lymphatic route. Metastases most often involve: lung (66%), bones (28%) and liver (15%), but almost all other

organs can be affected[45].

Lymphatic metastases are rare, with less than 5% of cases. For this reason, the removal of regional ganglion chains is not recommended, unless preoperative tests reveal the presence of tumors. Thus, axillary surgery is rarely indicated in patients diagnosed with Phyllodes Tumors [30-35].

Distant metastases occur after an average period of 18 months (range 2–57 months). The longest interval between a primary Phyllodes Tumor and the onset of metastasis was seven years. Most patients present with metastases within three years of the initial breast treatment35.

Once Phyllodes Tumor metastasis develops, the prognosis is poor, no long-term survival has been reported. Survival after metastatic disease is low, with several case series reporting a median survival ranging from 4 to 17 months, with wide variability based on the site of metastatic disease. And 5-year disease-free survival rates of 96% for benign phyllodes tumors and 66% for malignant phyllodes tumors[1-5].

It can be seen through this study that there are several articles from the last five years, most being case reports of malignant Phyllodes Tumor with metastasis. In short, these were rare cases of metastasis. SHAN et al (2016) reported metastasis to the pelvic cavity, NASRI et al (2020) pancreas and gallbladder (being the seventh report of pancreatic metastasis and the first of gallbladder in the literature), LIU et al (2020) stomach metastasis with manifestation of anemia (being the second in the literature) and LEE HJ et al (2020) reported a case of metastasis to the scalp. As they are infrequent cases, they should be considered as possible differential diagnoses in cases of previously diagnosed MPT.

The most frequent lung and bone metastases were reported, in most cases, associated with Malignant Phyllodes Tumor along with other rare metastases. SERA et al (2017) reported MPT with pulmonary and tonsillar metastasis, the second reported in the literature, in this case the patient refused treatment and died a month later. DURGA et al (2018), refer to bilateral pulmonary and ovarian dissemination and in several other places, being the first reported case of Phyllodes Tumor metastasizing to the ovaries. OHNSON et al (2016) reported bone, brain, lung, and lymph node metastasis. Only one case similar to this has been previously reported in the literature. KHANAL et al (2018), reported a case of pulmonary, brain and adrenal metastasis. There are only two cases of MPT with simultaneous involvement of these organs.

Some studies have considered tumor size, stromal overgrowth, tumor necrosis, infiltrating margins, mixed mesenchymal components, high mitotic rate, and stromal atypia as important factors in predicting metastatic spread. Another study also considers surgical margins and malignant Phyllodes Tumor [11-14].

For the treatment of metastatic Phyllodes Tumors, few data discuss the relationship between radiotherapy and metastasis. CHAO et al (2019), in a meta-analysis with 696 patients enrolled in 17 studies, found that radiotherapy is effective in achieving local disease control and suggested that radiotherapy may be effective in preventing metastases. This fact is due to the fact that they evaluated that their calculated metastasis rate is 4% in patients treated by radiotherapy, compared to a metastasis rate of 8% in patients receiving only surgical treatment[6-9].

CONCLUSION

Malignant Phyllodes Tumor is a neoplasm of variable biphasic behavior, occurring in approximately 10 to 20% of cases of Phyllodes Tumors.

In order to determine its diagnosis, margin involvement, stromal cellularity, mitotic index and cellular pleomorphism should be observed. Histopathological examination is the gold standard for diagnosis. Imaging diagnosis by means of ultrasound or mammography is common and presents microcalcifications, not following the general rules. Fine needle puncture is not very specific, with an accuracy of 23%. Core biopsy, on the other hand, has a specificity of 65%. However, the anatomopathological evaluation of the complete piece is the most effective to date. The most observed characteristic immunohistochemical markers with malignancy in the study were Ki-67 and p53 related to stromal growth and the CD117 proto-oncogene related to stromal proliferation.

Surgical treatment with resection margins greater than 1 cm is the approach of choice. Adjuvant radiotherapy has been widely used and some articles have highlighted its importance to avoid the risk of metastasis and local recurrence. Chemotherapy has also shown its relevance in helping to control metastases and promoting total tumor remission after surgery. Recurrence of aggressive malignant phyllodes tumors and risk of metastasis can be influenced not only by a negative margin, but also by histological grade, such as stromal overgrowth, high mitotic index, sarcomatous stroma, and infiltrative margin. Thus, our study highlighted the need for an early, complementary approach and regular follow-up to control this aggressive tumor, avoiding recurrence and metastasis.

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