Systematic Review

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Management and Outcomes of Metastatic and Recurrent Malignant Phyllodes Tumors of the Breast: A Systematic Literature Review

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ABSTRACT

To summarize the evidence on the current management and outcomes for metastatic and recurrent malignant phyllodes tumors (MPTs) of the breast. A systematic literature review of all cases of metastatic or recurrent MPTs of the breast published between 2010 and 2021 was performed. In total, 66 patients from 63 articles were included. Fifty-two (78.8%) had distant metastatic disease (DMD subgroup), and 21 (31.8%) showed locoregional recurrent/progressive disease (LRPR subgroup). Locoregional recurrences in patients with no distant metastases were treated with surgical excision in all cases. Radiotherapy was administered in 8/21 cases (38.1%) and was combined with chemotherapy in 2/21 cases (9.5%). Metastatic disease was managed through metastases surgical excision, chemotherapy, radiotherapy, or a combination of these three in 84.6% of cases, while the remaining patients received no oncological treatments. Chemotherapy was proposed in 75.0% of cases. Anthracycline and alkylating agent-based combination regimens were most frequently administered. The median survival time was 24 (2.0–152.0) months, and 72.0 (2.5–98.5) months in the DMD and LRPR subgroups, respectively. Management of recurrent or metastatic MPTs is challenging. Surgery is the fundamental approach, but the use of adjuvant radio- and chemo-therapy remains controversial due to the lack of scientific evidence. Further studies and international registers are needed to implement new and more efficient treatment strategies.

Keywords: Phyllodes tumor; breast cancer; recurrence; local relapse; metastatic; adjuvant treatment

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Key Points

- Evidence and guidelines concerning the management of malignant phyllodes tumors (MPTs) of the breast are limited, especially in the case of recurrent or metastatic disease.
- This study reports current trends in managing MPTs, confirming inconsistent management approaches and a lack of evidence supporting treatment plans.
- Further studies and international registers are needed to implement new and more efficient treatment strategies.

Introduction

Phyllodes tumors of the breast are rare fibroepithelial neoplasms, representing less than 1% of all breast tumors (1). They are classified into benign, borderline, and malignant phyllodes tumors (MPTs) based on histologic characteristics (2). The rarity of this malignancy contributes to the difficulty in defining the most appropriate treatment. This uncertainty is even more marked for recurrent and metastatic MPTs, for which prognosis is significantly affected, and evidence is limited concerning their optimal management. In this study, all cases of metastatic and/or recurrent MPTs published in the last decade were reviewed to give an overall view of their current management and outcomes.

Materials and Methods

Search Strategy and Selection Process

This systematic literature review was conducted using a structured search protocol based on the PRISMA criteria (3). To find all cases of metastatic or recurrent MPTs of the breast reported over the last decade, PubMed, Embase, and Web of Science were searched using the terms "malignant phyllode/malignant phyllodes," "tumor/tumors,"

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and "breast" for all articles published from 1st January 2010 and 31st December 2021. We included all articles in English or French reporting metastatic or recurrent phyllodes tumors of the breast. We excluded articles reporting benign or borderline phyllodes tumors, patients aged <18 years, phyllodes tumors in men, studies or case series without individual data, and articles with unavailable full text. Sixty-three articles were selected and analyzed (4-66). The literature search protocol design is summarized in Figure 1.

Data Collection Process and Analysis

Two authors performed data extraction independently, results were compared, and any conflict was discussed with a third party. For each patient, any relevant demographic and oncological data concerning the initial treatment, follow-up, management, and outcomes in cases of metastatic or recurrent phyllodes tumors of the breast was extracted. When possible, corresponding authors were contacted to obtain missing or updated information.

SPSS, v20 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data were analyzed for the subgroups of patients presenting distant metastases at the time of diagnosis or as a progression/recurrence, designated the distant metastatic disease (DMD) subgroup and for those with locoregional progressive or recurrent disease, designated the locoregional progressive/recurrent (LRPR) subgroup. Since the difference between progression and recurrence was frequently difficult to clarify, these two entities were analyzed together. LRPR disease was considered to consist of lesions limited to the initially involved breast, skin, surgical scar, surrounding soft tissues, and ipsilateral thoracic wall (e.g., pectoral muscles), axillary and internal mammary lymph nodes, without any sign of distant metastases. DMD was considered in all cases presenting with lesions in any other location, with or without a concomitant LRPR disease. Patients who first presented with a locoregional progression/recurrence with no distant lesions that lately developed a metastatic disease were analyzed in both the LRPR and DMD subgroups. Continuous variables are presented as median with minimum and maximum values, and categorical variables as numbers and percentages (%). All missing information was considered as such, and no assumptions were made. Patients with missing data for a specific variable were not included in the statistical analysis. The Kaplan-Meier statistical method was applied for survival analysis, and the log-rank test was used to compare survival curves. Comparison between subgroups was not the objective of this study, but when reported, differences were compared using ANOVA, the Kruskal-Wallis test, or Fisher's exact test. A p-value <0.05 was considered statistically significant.

Results

In total, 66 patients from 63 series/case reports were included in the analysis. Fifty-two (78.8%) presented with a distant metastatic disease (DMD subgroup), and 21 (31.8%) showed locoregional recurrent/progressive disease (the LRPR subgroup). Seven patients first presented with locoregional progressions/recurrences with no distant lesions and

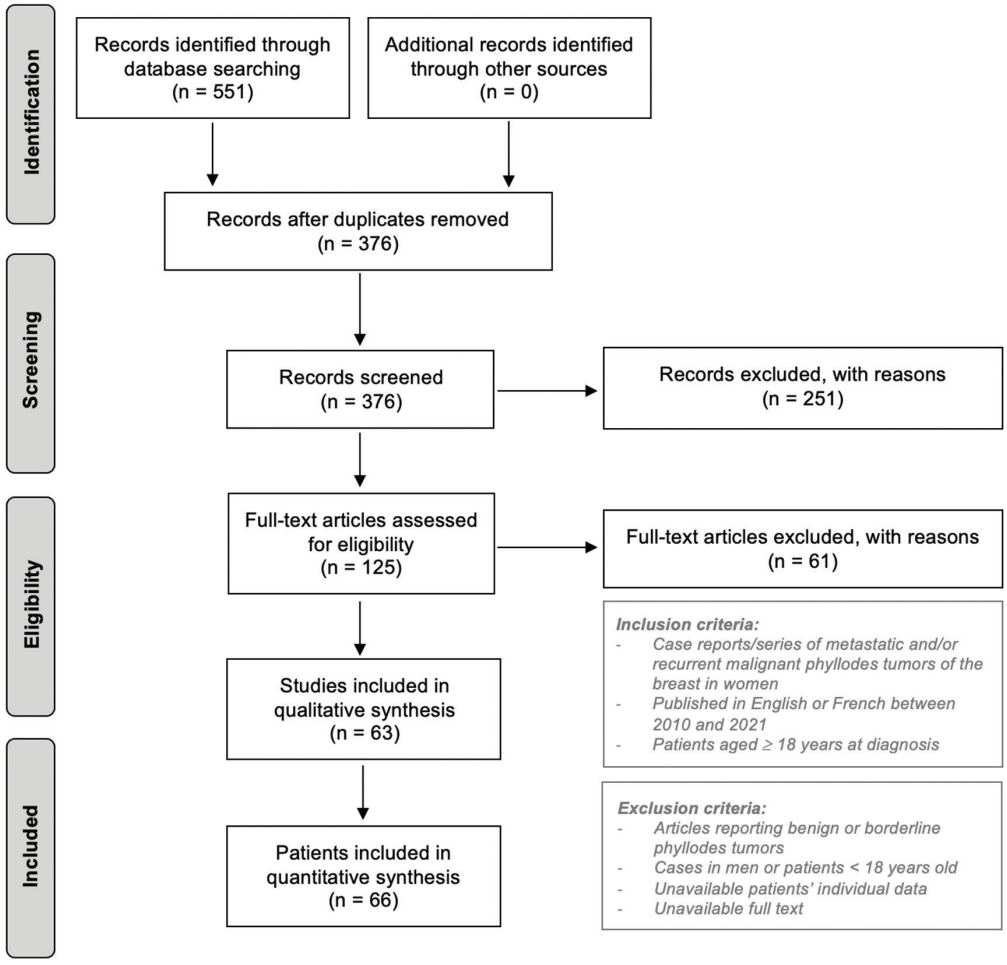

Figure 1. Selection flowchart showing the inclusion and exclusion process

later developed metastatic disease. These patients were analyzed in both the DMD and LRPR subgroups.

The median age was 50 (26–82) years in the DMD subgroup and 45 (18–82) years in the LRPR subgroup. The median tumor size was 100 (22–430) mm and 90 (30–300) mm in the DMD and LRPR subgroups, respectively. All except one patient (62/63, 94.4%) received primary breast surgery by mastectomy (51/63, 81.0%) or a lumpectomy (11/63, 17.5%). Histological characteristics, including surgical margin status, were reported in 25 patients (37.9%) and are summarized in Table 1. Following primary surgery, systemic chemotherapy was administered in 6/13 patients (46.2%) with distant metastasis at diagnosis and in 3/60 patients (5.0%) with no initial sign of metastatic disease. Chemotherapy was given as an adjuvant treatment except in one patient, who received neoadjuvant doxorubicin and cyclophosphamide before mastectomy for mass reduction (45). Adjuvant radiotherapy was administered in 1/13 patients (7.7%) with distant metastases at diagnosis and in 12/60 patients (20.0%) with no initial sign of metastases. Complementary data concerning initial observations and management are reported in Table 1.

Management of Locoregional Progressions/Recurrences

Locoregional progression/recurrence was observed in 21/21 patients (100%) in the LRPR subgroup and in 18/52 patients (34.6%) in the DMD subgroup. Overall, the median time after the initial breast surgery and the first locoregional progression/recurrence was 8.9 (1.0–36.0) months. No differences were observed between patients operated on by mastectomy or lumpectomy or relating to surgical margins status.

Locoregional progressions/recurrences in patients with no distant metastases were treated with surgical excision in all cases (21/21, 100%). Adjuvant radiotherapy was administered in 8/21 cases (38.1%) and was combined with chemotherapy in 2/21 cases (9.5%). In patients with associated distant metastases, locoregional lesions were surgically excised in 14/18 patients (77.8%). Adjuvant radiotherapy was given in 9/18 patients (50.0%) and was associated with adjuvant chemotherapy in 3/18 cases (16.7%).

Patients with initially limited locoregional recurrences/progressions (LRPR subgroup) subsequently developed distant metastases in 9/21 patients (42.9%) with a median interval between first local progression/recurrence and distant relapse of 2.0 (0.5–14.0) months.

Overall, multiple local progressions/recurrences were observed in 10 patients (15.9%), 4 patients (6.3%) presented with two progressions/recurrences, and 4 patients (7.9%) presented with more than two progressions/recurrences. The median interval between the first and the second and between the second and the third locoregional recurrences/progressions was 3.5 (0.5–40) months and 4 (0.5–14) months, respectively. All patients except three developed concomitant distant metastases and died of their disease in a median interval of 2 (0.5–34.5) months from the last locoregional recurrence/progression.

The three patients with multiple recurrences without distant metastases were treated with surgical excision in all cases (3/3, 100%) for both the second and third progressions/recurrences. Radiotherapy was also given in 1/3 of patients (33.3%), and chemotherapy was administered in 1/3 of cases (33.3%) for the second and third progression/recurrence, respectively. Median survival was 70.3 (68.5–72) months for these patients. Additional data concerning the management and outcomes of locoregional progressions/recurrences are reported in Tables 2 and 3.

Table 1. Data at the time of diagnosis and initial management

	Distant metastatic disease subgroup (n = 52)	Locoregional progressive/ recurrent subgroup (n = 21)
Age (years)	50 (26–82)	45 (18–82)
Brest tumor laterality		
Right	28/50 (56.0)	11/21 (52.4)
Left	22/50 (44.0)	10/21 (47.6)
Bilateral	-	-
Tumor size (mm)	100 (22–430)	90 (30–300)
Skin invasion	10/46 (21.7)	4/20 (20.0)
Thoracic wall invasion	9/46 (19.6)	2/20 (10.0)
Locoregional lymph node involvement	4/52 (7.7)	1/21 (4.8)
Axillary	4/52 (7.7)	1/21 (4.8)
Internal mammary	-	-
Breast surgery		
Mastectomy	41/48 (85.4)	13/21 (61.9)[b]
Lumpectomy	6/48 (12.5)	8/21 (38.1)[a]
ALND	14/48 (29.2)	4/21 (19.0)
None	1/48 (2.1)	-
Surgical margins		
Not involved	26/30 (86.7)	7/10 (70.0)
<1 cm	5/30 (16.7)	4/10 (40.0)
>1 cm	2/30 (6.7)	-
Involved	4/30 (13.3)	3/10 (30.0)
Histological characteristics	19/52 (36.5)	6/21 (28.6)
Marked stromal growth, marked stromal cellularity, >5 mitoses per 10 high-power field and/or necrosis	16/19 (84.2)	6/6 (100.0)
Heterologous elements		
Osteosarcomatous	5/19 (26.3)	-
Chondrosarcomatous	5/19 (26.3)	1/6 (16.7)
Angiosarcomatous	3/19 (15.8)	-
Fibrosarcomatous	3/19 (15.8)	-
Distant metastases at diagnosis	13/52 (25.0)	-
Localization		
Lung	11/13 (84.6)	-
Liver	1/13 (7.7)	-
Brain	1/13 (7.7)	-
Soft tissues lumbar region	1/13 (7.7)	-
Abdominal wall	1/13 (7.7)	-
Adjuvant treatment		

Table 1. Continued

Metastases surgical excision	2/13 (15.4)	-
Chemotherapy	6/13 (46.2)	-
Indicated, but refused	1/13 (7.7)	-
Radiotherapy	1/13 (7.7)	-
Indicated, but refused	-	-
Combined chemotherapy and radiotherapy	1/13 (7.7)	-
No (neo)adjuvant oncological treatment	6/13 (46.2)	-
No distant metastases at diagnosis	39/52 (75.0)	
Chemotherapy	1/39 (2.6)	2/21 (9.5)
Indicated, but refused	-	-
Radiotherapy	9/39 (23.1)	3/21 (14.3)
Indicated, but refused	2/39 (5.1)	1/21 (4.8)
Combined chemotherapy and radiotherapy	-	-
No (neo)adjuvant oncological treatment	28/39 (71.8)	16/21 (76.2)

ALND: axillary lymph node dissection; [a]: p-value <0.05, the difference is statistically significant compared with the distant metastatic disease subgroup; [b]: p-value is 0.538, the difference is not statistically significant compared with the distant metastatic disease subgroup

Management in Metastatic MPTs

Distant metastases were observed at the time of diagnosis in 13 patients. They were localized in the lungs (11/13, 84.6%), liver (1/13, 7.7%), brain (1/13, 7.7%), soft tissues in the lumbar region (1/13, 7.7%), and in the abdominal wall (1/13, 7.7%). Subsequent progressions/recurrences in other locations were observed in six cases (6/13, 46.2%) within a median interval of 2.0 (1.0–9.0) months. Lesions were observed in bones (1/13, 7.7%), brain (2/13, 15.4%), mediastinal lymph nodes (1/13, 7.7%), adrenal glands (1/13 7.7%), and in the oral cavity (2/13, 15.4%). Distant metastatic progressions/recurrences were observed in 39 patients within 9.0 (1.0–60.0) months from the initial diagnosis of locoregionally-confined disease. Metastases were more frequently observed in the lungs (29/39, 74.4%), the bones (10/39, 25.6%), and the brain (7/39, 17.9%). Data concerning all metastases localizations are summarized in Table 2.

Patients with distant metastases at the time of diagnosis received breast surgery in all cases but one (12/13, 92.3%), who was deemed a non-surgical candidate, given multiple sites of metastases and no local pain or open wounds (38). Operated patients received a mastectomy in all the cases reporting the type of surgery, with associated axillary lymph node dissection in 5/12 cases (41.7%). Distant metastases were surgically excised in two patients (2/13, 15.4%) through partial pulmonary thoracoscopic resection (1/13, 7.7%) and cerebral metastatic excision (1/13, 7.7%). Systemic chemotherapy was administered in 6/13 cases (46.2%) and was proposed but refused by the patient in one additional case (1/13, 7.7%). Chemotherapy was administered as adjuvant treatment in all cases but one (1/13, 7.7%), in which neoadjuvant paclitaxel was given before mastectomy (35). A combination of systemic chemotherapy and radiotherapy of the chest wall was reported in one case (1/13, 7.7%) (49).

Table 2. Data concerning recurrences/progressions

	Distant metastatic disease subgroup (n = 52)	Locoregional progressive/ recurrent subgroup (n = 21)
Locoregional progression/recurrence		
1st progression/recurrence	18/52 (34.6)	21/21 (100.0)
Interval diagnosis – progression/recurrence (months)	4.0 (1.0–77.0)	4.0 (1.0–36.0)
Surgical excision	14/18 (77.8)	21/21 (100.0)
Chemotherapy	5/18 (27.8)	2/21 (9.5)
Radiotherapy	9/18 (50.0)	8/21 (38.1)
Combined chemotherapy and radiotherapy	3/18 (16.7)	2/21 (9.5)
2nd progression/recurrence	4/52 (7.7)	3/21 (14.3)+
Interval diagnosis – progression/recurrence (months)	5.0 (1.5–10.0)	21 (11–31)
Surgical excision	1/4 (25.0)	3/3 (100)
Chemotherapy	-	-
Radiotherapy	-	1/3 (33.3)
Combined chemotherapy and radiotherapy	-	-
3rd progression/recurrence	-	3/21 (14.3)+
Interval diagnosis – progression/recurrence (months)	-	25.8 (12.5–39)
Surgical excision	-	3/3 (100)
Chemotherapy	-	1/3 (33.3)
Radiotherapy	-	-
Combined chemotherapy and radiotherapy	-	-
Distant metastatic progression/ recurrence*	45/52 (86.5)	9/21 (42.9)
Interval diagnosis – progression/recurrence (months)	11.0 (1.0–60.0)	8.0 (1.5–78)
Localization		
Lungs	29/52 (55.8)	6/21 (28.6)
Bones	11/52 (21.2)	4/21 (19.0)
Brain	9/52 (17.3)	3/21 (14.3)
Heart	5/52 (9.6)	1/21 (4.8)
Oral cavity (mandibular region, tonsil)	5/52 (9.6)	-
Liver	4/52 (7.7)	-
Pancreas	3/52 (5.8)	-
Bowel	3/52 (5.8)	-
Kidney	2/52 (3.8)	-
Pleural cavity	2/52 (3.8)	-

Table 2. Continued

Mediastinal lymph nodes	2/52 (3.8)	1/21 (4.8)
Stomach	2/52 (3.8)	-
Skin	2/52 (3.8)	-
Thyroid gland	1/52 (1.9)	-
Adrenal glands	1/52 (1.9)	-
Parotid gland	1/52 (1.9)	-
Subphrenic space	1/52 (1.9)	-
Intraperitoneal	1/52 (1.9)	-
Supraclavicular lymph nodes	-	-
Supraclavicular lymph nodes	-	1/21 (4.8)
Treatment		
Metastases surgical excision	16/45 (35.6)	6/9 (66.7)
Chemotherapy	28/45 (62.2)	4/9 (44.4)
Indicated but refused	6/45 (13.3)	-
Radiotherapy	15/45 (33.3)	1/9 (11.1)
Indicated, but refused	2/45 (4.4)	-
Combined chemotherapy and radiotherapy	14/45 (31.1)	-
No metastases treatment	7/45 (15.6)	1/9 (11.1)

⁺: Only patients with locoregional progressions/recurrences in the absence of distant metastases were analyzed; *: For patients with distant metastases at the time of diagnosis, other localization than initially observed metastases

Metastatic progressions/recurrences in patients with no distant lesions at diagnosis were treated through metastases surgical excision in 13/39 cases (33.3%), which in most cases represented partial pulmonary resections (6/39, 15.4%). Excisions of bowel, kidney, adrenal gland, and heart metastases were also reported. Chemotherapy was proposed in 32/39 cases (82.1%), administered in 26/39 cases (66.7%), and refused by 6/39 patients (15.4%). Combined radiotherapy was reported in 12/39 cases (30.8%), which was mainly used to irradiate the chest wall and axilla for concomitant locoregional progressions/recurrences (6/39, 15.4%). However, radiotherapy was also reported for irradiation of scalp, pancreatic, bone, and parotid metastases. Additional data concerning the management and outcomes of metastatic MPT are reported in Tables 2 and 3.

Overall, metastatic MPTs were managed through surgical excision, chemotherapy, radiotherapy, or a combination of these three in 84.6% of cases, and chemotherapy was proposed in 75.0% of cases. In 15.4% of cases, patients received no oncological treatments. Reasons for this decision, such as patient refusal, poor general conditions, and no expected benefits, were rarely reported.

Chemotherapeutic Agents

The type of chemotherapeutic agents used was reported in 32/38 cases (84.2%), and details concerning dosages, intervals, and the number of cycles were reported in 9/38 patients (23.7%). The most frequently used chemotherapeutic agents were doxorubicin and ifosfamide (14/38, 36.8%). Protocols comprised 6-8 cycles with doxorubicin 25 or 30 mg/m^2 days 1-2, and ifosfamide 2 or 7.5 g/m^2 days 1–5. Other chemotherapeutic agent combinations were only reported in one or two cases and comprised a vast heterogeneity of treatments summarized in Table 4. No differences were observed in survival between patients who received different chemotherapeutic agents. Chemotherapy was always administered as adjuvant treatment, except in two cases where chemotherapy was given before breast surgery (35, 45). Chemotherapeutic agents were always administered systemically, except in one case where epirubicin was injected as chemoembolization for breast mass reduction (62).

Table 3. Follow-up and Outcomes

	Distant metastatic disease subgroup (n = 52)	Locoregional progressive/recurrent subgroup (n = 21)
Follow-up		
Total time (months)	14.5 (2.0–152.0)	13.0 (2.5–98.5)
Status at last control		2/21 (9.5)
NED	-	12/21 (57.1)
AWD	18/51 (35.3)	9/21 (42.9)
DOD	33/51 (64.7)	72 (2.5–98.5)
Survival time (months)	24 (2–152)	9/15 (60.0)
2-year survival rate	19/39 (48.7)	6/12 (50.0)
5-year survival rate	7/33 (21.2)	

NED: no evidence of disease; AWD: alive with disease; DOD: died of disease

Radiotherapy

Radiotherapy was used to treat locoregional as well as distant progressions/recurrences. Information concerning the location, doses, and fractions was reported in 13/38 cases (34.2%). Locoregional radiotherapy on the remaining breast and/or chest wall was administered with a median dose of 60 (50–84) Gray and a median number of fractions of 28 (10–30). Locoregional radiotherapy was administered as adjuvant treatment following local excisions in all cases except one, in which neoadjuvant radiotherapy was administered before the excision of the lesion (33). Details concerning radiotherapy in other localization were only reported for single disparate cases and are not reported.

Long-Term Outcomes

In the DMD subgroup, data concerning outcomes were available in 51/52 patients (98.1%), and the median follow-up was 14.5 (2.0–152.0) months. At the last control, 18/51 patients (35.3%) were alive with the disease, and 33/51 (64.7%) died of the disease. The median survival time was 24.0 (2.0–152.0) months. The 2-year and 5-year survival rates were 48.7% and 21.2%, respectively.

In the LRPR subgroup, data were available in all patients, and the median follow-up was 13.0 (2.5–98.5) months. At last control, 8/21 patients (38.1%) presented with no evidence of disease, 4/21 patients (19.0%) were alive with the disease, and 9/21 (42.9%) died of the disease. The median survival time was 72.0 (2.5–98.5) months. The 2-year and 5-year survival rates were 60.0% and 50.0%, respectively. Patients in the LRPR subgroup who presented subsequent distant metastatic lesions had a 2-year and 5-year survival rate of 27.3% and 18.2%, respectively.

Table 4. Chemotherapeutic agents

	Distant metastatic disease subgroup (n = 52)	Locoregional progressive/ recurrent subgroup (n = 21)
1st line chemotherapy		
Doxorubicin and Ifosfamide	8/52 (15.4)	3/21 (14.3)
Doxorubicin, Ifosfamide and Dacarbazine	1/52 (1.9)	-
Doxorubicin and Cyclophosphamide	2/52 (3.8)	-
Doxorubicin and Bevacizumab	-	1/21 (4.8)
Epirubicin and Cyclophosphamide	1/52 (1.9)	-
Epirubicin, Cyclophosphamide and Fluorouracil	1/52 (1.9)	-
Liposomal Doxorubicin, Cisplatin and Paclitaxel	1/52 (1.9)	-
Paclitaxel	1/52 (1.9)	-
Gemcitabine and Docetaxel	1/52 (1.9)	-
Ifosfamide	-	-
Apatinib	-	-
2nd and 3rd line chemotherapy		
Doxorubicin and Ifosfamide	3/52 (5.8)	-
Paclitaxel and Bevacizumab	2/52 (3.8)	-
Pazopanib	2/52 (3.8)	-
Bevacizumab and Temzolomide	1/52 (1.9)	-
Doxorubicin and Cyclophosphamide	1/52 (1.9)	-
Gemcitabine and Carboplatin	1/52 (1.9)	-
Gemcitabine and Docetaxel	1/52 (1.9)	-
Gemcitabine and Taxotere	-	1/21 (4.8)
Docetaxel	1/52 (1.9)	-
Paclitaxel	1/52 (1.9)	-
Apatinib	1/52 (1.9)	-
Ifosfamide	1/52 (1.9)	1/21 (4.8)

The 5-year survival rate in the DMD subgroup was lower than the LRPR subgroup, although not significant (21.2% vs. 50.0%, p = 0.07). Comparisons concerning survival time and the 2-year survival rate between subgroups were not significant.

No survival differences were observed between patients managed with different therapeutic strategies in either subgroup. Data concerning outcomes are summarized in Table 3, and Kaplan-Meier survival curves are presented in Figure 2.

Discussion and Conclusion

MPTs of the breast constitute an uncommon condition and represent 0.03–0.3% of all breast cancers, with an annual incidence of about 2/1,000,000 (1). Surgery is the management of choice for the primary treatment of localized MPTs. However, due to its rarity, little is known about appropriate management in the case of metastatic or locally recurrent MPTs. In this study, we systematically reviewed all cases of metastatic and/or recurrent MPTs published in the last 10 years to give an overall view of their current management and outcomes.

The national cancer center network (NCCN) recommends treating primary MPTs with lumpectomy or mastectomy in cases of impossibility to adequately obtain 1 cm margins or for cosmetic reasons (67). Mastectomy did not prove superior to wide excision in terms of survival and, therefore, should not be routinely performed (68). Nodal involvement is very rare, and sentinel lymph node biopsy or axillary lymph node dissection are not indicated unless there is suspicion of lymph nodal metastases (67, 69). Adjuvant radiotherapy, chemotherapy, and hormonotherapy are not recommended for the primary treatment of localized MPTs (67).

Locoregional recurrences are common complications of MPTs and are observed in about 12–65% of cases (70, 71). In this systematic review locoregional recurrences were observed within a median time of 8.9 (1.0–36.0) months (70, 71). Positive surgical margins and large tumor size seem to be the main risk factors for locoregional recurrences (70, 72). In this review, these characteristics were found in about 2/3 of patients presenting with a locoregional recurrence.

Although adjuvant radiotherapy following primary surgery is not routinely indicated, in the case of locoregional recurrence, the NCCN recommends considering local irradiation following tumor excision (67). Adjuvant radiotherapy following primary surgery seems to reduce locoregional relapses but with no proven effect on overall survival, regardless of the surgical margin status (73-77). The role and impact of adjuvant radiotherapy for locoregional relapses are unclear due to limited evidence. In our review, 100% of tumor recurrences were surgically excised, while adjuvant radiotherapy was administered in just over a third of cases. Our review showed no survival differences in locoregional relapsing patients treated with or without adjuvant radiotherapy. No validated guidelines exist for radiation treatment for recurrent MPTs, and in our review, radiotherapy modalities were rarely reported, and no general agreement was found. Combined radio- and chemotherapy seem not indicated and have been reported only twice (22, 61). Multiple recurrences were rarely reported, and except for surgical excision, no consistent trends were observed in their adjuvant treatment. Surgical excision of the local lesion at each relapse seems appropriate (39), associated with a single course of radiotherapy. However, the role of adjuvant chemotherapy for multiple local recurrences is unclear and currently not indicated unless concomitant distant metastases are observed.

As previously observed (70), we found locoregional recurrence to be a strong predictor of distant metastases, with 42.9% of patients developing distant disease after a median time of 2.0 (0.5–14.0) months from their first locoregional recurrence. Yet, the relationship between local relapses and distant metastatic spread is unclear and often debated by authors (78). In our review, survival in patients with locoregional recurrent MPTs was similar to the reported overall survival in the case of MPTs (2, 70, 78, 79). However, the observed 5-year survival rate of 50.0% reduced dramatically to 18.2% in those patients who subsequently developed distant metastases. This highlights the relative controllability of localized MPTs and their locoregional recurrences but the difficulty in managing a distant metastatic spread.

Around 1.5% of MPTs present with metastatic disease at diagnosis, and 10–25% are associated with distant metastatic recurrences, with predominant hematogenous spread and lesions observed in nearly all

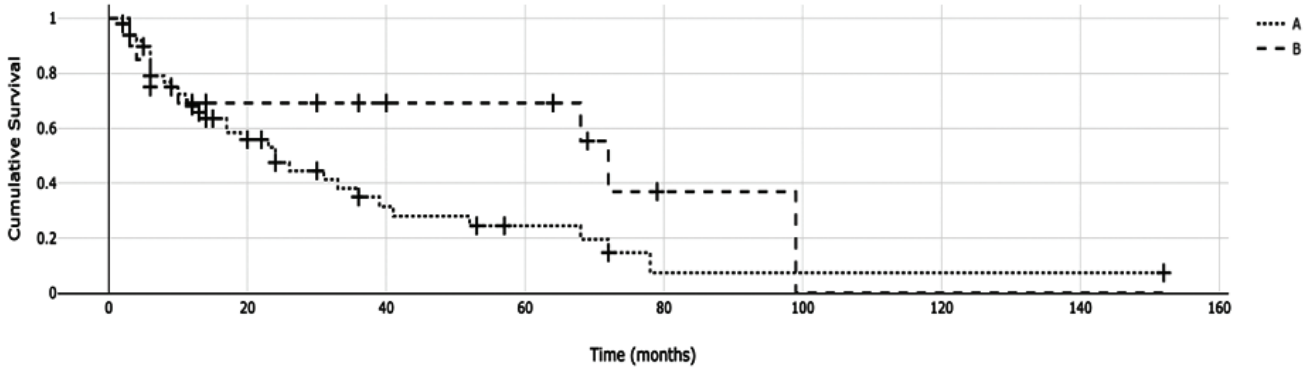

Figure 2. Kaplan-Meier survival curves

A: distant metastatic disease subgroup; B: locoregional progressive/recurrent subgroup

organs but predominantly in lungs and bones (1, 70, 79-82). In our review, metastatic recurrences were observed within a median time of 9.0 (1.0–60.0) months. Similar to other studies, the intervals between primary treatment and metastatic recurrences vary widely, from a few weeks to several years (70, 71). The main risk factors associated with the development of distant disease are large tumor size, infiltrative surgical margins, marked stromal overgrowth or cellularity, >5 mitoses per 10 high-power fields, and tumor necrosis (70, 79). In our study, these features were observed in about 3/4 of patients presenting with distant metastases. The presence of heterologous sarcomatous elements could predispose to the development of distant metastases (83), but this association was not universally shared (78). In our study, patients with metastatic recurrences presented with osteosarcomatous and/or chondrosarcomatous heterologous elements in about 70% of cases. However, the small sample size limits any possible suggestions of the relation between these histological features and metastatic MPTs. Patients with metastatic disease, whether at diagnosis or for relapses, should be treated in accordance with the guidelines for metastatic soft tissue sarcomas, as recommended by the NCCN (67). However, these patients frequently do not respond to chemotherapy and often have poor survival (84). In our review, chemotherapy was proposed in around 3/4 of cases with distant metastases, and a wide range of chemotherapy regimens was administered. Anthracycline and alkylating agent-based combination regimens were most frequently administered, and the combination of doxorubicin-ifosfamide was administered in more than one-third of cases. Protocols varied between 6–8 cycles with doxorubicin 25 or 30 mg/m^2 days 1-2, and ifosfamide 2 or 7.5 g/m^2. Due to limited data, there was no superiority in a specific treatment regimen over the others, as reported in earlier studies. Currently, there are no randomized clinical trials assessing the role of adjuvant chemotherapy in MPTs, and its role remains undefined (78, 79, 82). This uncertainty was highlighted by the fact that, in our review, more than 1/3 of patients with distant metastases were not offered or considered for chemotherapy. In part of these cases, metastases were managed through surgical excision and/or radiotherapy, but more than 20% of patients received no oncological treatments.

Overall, patients with MPTs have a 5-year survival rate of around 65% (2, 70, 78, 79), which, from our results, reduces to approximately 20% in case of metastatic disease. Conversely, patients with localized disease present a 10-year survival rate as high as 90% (85). In addition to distant metastases, survival seems to be affected by the tumor size, the surgical margin status, the stromal overgrowth and differentiation, and the presence of osteosarcomatous or chondrosarcomatous histological features (70, 86-89). Due to the limited sample size, we could not assess these features in this review. Characteristics predisposing to locoregional relapses, metastatic disease, and poor prognosis should be studied carefully in future research to identify possible indications for primary adjuvant chemo- and/or radiotherapy. In addition, due to the relative uncertainty and confusion around the optimal management of MPTs, more specific international and local guidelines for the management of MPTs are needed.

The main limitation of this study was its small sample size. In addition, analyzed data were extrapolated from case reports and small case series, which were rarely oriented toward metastatic or recurrent MPT, and which frequently reported only limited and incomplete data. This may have resulted in selection and information bias. However, to our knowledge, this study represents the only review of metastatic or recurrent MPT and could improve the general knowledge about the current trends in managing this rare condition.

Clinical and Research Consequences

Due to limited data and inconsistent results, this study carries no clinical consequences. However, we see an urgent need to create international registers and perform specific trials to improve evidence about treatment strategies for recurrent or metastatic MPTs of the breast.

Management of recurrent and metastatic MPTs is a challenge. Surgery remains the fundamental approach, but the role of adjuvant radio- and chemotherapy remains controversial due to the lack of evidence of their positive impact on survival. This study reports the current trends in managing MPTs, confirming inconsistent approaches and a lack of evidence supporting the superiority of one or some treatment options. Further trials and international registers are needed to gather evidence about treatment options, therapy response, and patient-reported outcomes to implement new management strategies.

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Authorship Contributions

Concept: Y.H., D.H.; Design: Y.H., D.H.; Data Collection and/or Processing: E.S., Y.H.; Analysis and/or Interpretation: E.S., Y.H., D.H.; Literature Searching: E.S., Y.H.; Writing: E.S., Y.H.

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