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ORIGINAL ARTICLE – BREAST ONCOLOGY

Surgical Margins and Adjuvant Therapies in Malignant Phyllodes Tumors of the Breast: A Multicenter Retrospective Study

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ABSTRACT

Background. The optimal threshold of surgical margins for breast malignant phyllodes tumors (MPTs) and the impact of adjuvant chemotherapy and radiotherapy were investigated.

Patients and Methods. We conducted a multicenter nationwide retrospective study of all MPT cases with central pathological review within the French Sarcoma Group. Endpoints were local recurrence-free survival (LRFS), metastasis-free survival (MFS), and overall survival (OS) rates.

Results. Overall, 212 patients were included in the study. All non-metastatic patients underwent primary surgical treatment, including 58.6% of conservative surgeries. An R0 resection was achieved in 117 patients (59.4%: 26.9% of patients with 1–2 mm margins, 12.2% of patients with 3–7 mm margins, 20.3% of patients with≥8 mm margins). Ninety-four patients (45%) underwent a second surgery (SS) to obtain R0 margins, with a final mastectomy rate of 72.6%. Radiotherapy and chemotherapy were performed in 91 (43.1%) and 23 patients (10.9%), respectively, but were not associated with better outcomes. Mastectomy was significantly associated with better LRFS ($p<0.001$). Margins of 0, 1, or 2 mm with SS were associated with better MFS (hazard ratio [HR] 0.3, $p=0.005$) and OS (HR 0.32, $p=0.005$) compared with margins of 0–1–2 mm without SS. Wider margins (>8 mm) were not superior to margins of 3–7 mm (3–7 mm vs.>8 mm; HR 0.81, $p=0.69$). Age (HR 2.14, $p=0.038$) and tumor necrosis (HR 1.96, $p=0.047$) were found to be poor prognostic factors and were associated with MFS.

Conclusions. This study suggests that 3 mm margins are necessary and sufficient for surgical management of MPTs,

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and emphasizes the importance of SS to obtain clear margins in case of 0–1–2 mm margins. No impact of adjuvant chemotherapy or radiotherapy was detected in this study.

Phyllodes tumors (PTs) are rare fibroepithelial neoplasms of the breast that represent<1% of all breast primary tumors.[1] They are heterogeneous and are classified into three different entities—grades I, II, and III (which are also called malignant phyllodes tumors [MPTs]). The incidence of MPTs is about 2.1 per million among American women.[2] They were first described by Johann Müller in 1838.[3] and were considered a benign tumor. Local and metastatic recurrences were then described, which allowed the distinction between benign and malignant PTs.[4,5] The grading of MPTs is based on histological parameters, including stromal cellularity and atypia, mitotic count, stromal overgrowth, and nature of the tumor borders.[1] Diagnosis is particularly difficult on imaging and core needle biopsy, and a final diagnosis is thus often made on a surgical sample,[6] which may explain the high rate of non-optimal surgeries. In MPT patients, recurrences may occur in up to 50% of cases during the first 3 years.[7] The local recurrence risk varies between 15 and 40%[8,9] and the metastatic recurrence risk varies between 17 and 26%.[10–12]

Surgery is the current cornerstone of MPT treatment. The question regarding the type of surgery (conservative or mastectomy) has been widely studied for MPTs. A recent meta-analysis highlighted the impact of mastectomy and clear margins on local recurrence rates, especially for malignant tumors.[13] Breast-conserving surgery (BCS) is possible considering the low recurrence rate in small tumors, but mastectomy is often performed for tumors> 5 cm in size .[14] Small MPTs (<5 cm in size) have been defined both in the literature [15] and according to the soft tissue sarcoma staging classification;[16] however, the margin threshold and the impact of adjuvant therapy remain to be clarified. Indeed, a wide surgical margin (≥10 mm) is often recommended but this recommendation is based on old studies, including only a few patients with grade III PTs, or case reports.[17,18] Other studies showed no benefits of a wide surgical margin (≥10 mm) on overall survival (OS) or disease-free survival (DFS), compared with an R0 surgery without security margins.[19,20] With regard to adjuvant therapy, according to a recent study adjuvant radiotherapy is now also often used,[21] although no proven benefit was reported on survival. Only a benefit on the risk of local recurrence (hazard ratio [HR] 0.49, range 0.19–0.95)[11,21–23] has been shown in a few studies. For adjuvant chemotherapy, a single study showed no impact of adjuvant chemotherapy on OS.[24]

In this study, we report on our assessment of the prognostic factors of MPT occurrence, especially surgical margins and adjuvant therapy. Our objective was to define a threshold of surgical margins necessary and sufficient for the surgical management of MPTs and to evaluate the impact of adjuvant chemotherapy and radiotherapy in MPT treatment strategy.

METHODS

Study Design and Patients

The objective of our retrospective study was to evaluate the prognostic factors of local recurrence-free survival (LRFS), metastasis-free survival (MFS), and OS in patients with MPTs.

We retrospectively analyzed the medical charts of patients from the GSF databases (Conticabase and Rreps) aged>18 years and treated for an MPT between 1 January 2000 and 1 September 2016 in 13 centers of the French Sarcoma Group (GSF-GETO). All centers that had included more than one case in the GSF registry were invited to participate in the study and to include all their eligible cases, including those initially non-reported in the national registry. Inclusion criteria were (1) histological central review by an expert pathologist member of the GSF-GETO, for MPT diagnosis; (2) data on initial treatment started between 1 January 2000 and 1 September 2016 and follow-up available; and (3) no other concomitant uncontrolled cancer.

The study was approved by the local Institutional Review Board. Considering the retrospective character of the study, no informed consent was deemed necessary.

Assessments

Patient characteristics at diagnosis included age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), family history of breast and ovarian cancer, or BRCA mutation. The following tumor characteristics were reported: tumor size, localization, multifocality, ulceration, number of mitosis, necrosis, and nodal and/or distant metastasis.

Characteristics of initial treatment included presurgery data (imaging, diagnostic biopsy, and histology), type of surgery, concomitant axillary surgery, surgical margin status, second or third surgery to obtain clear margins, adjuvant or neoadjuvant chemotherapy, and radiotherapy.

Surgical margins were evaluated using three classes: margins<3 mm without second surgery (SS), margins< 3 mm with SS, and margins≥3 mm. This classification was retained after first statistical analysis to obtain balanced groups.

Statistical Analyses

For continuous variables, medians and ranges were computed. Median follow-up was calculated using the reverse Kaplan–Meier method,[25] and survival rates were estimated using the Kaplan–Meier method.[26] RFS and OS were defined as the time between diagnosis (surgery) to event or death/last follow-up, respectively. Patients who did not experience the event of interest were censored at their last follow-up. Univariate and multivariate analyses were conducted using a binary logistic regression model with a backward stepwise analysis. Prognostic factors of local relapse, metastatic relapse, and OS were selected using the log-rank test.[27] Factors significantly associated with respective endpoints were included in a multivariate Cox regression analysis using the maximum likelihood method and a backward stepwise analysis. All tests were two sided and a p value<0.05 was considered significant. The differences between the two groups were evaluated using the χ^2 test or Student's test. All statistical analyses were performed using STATA13 software (StataCorp LLC, College Station, TX, USA).

RESULTS

Patient Baseline Characteristics

Between January 2000 and September 2016, 212 patients treated in one of the 13 participating centers were included in the study. Three centers provided 54.3% of the patients included in this series. Median age was 52.8 years (range 16.8–90.5) (Table 1), and PS was 0 or 1 for 200/203 patients (98.5%). No known BRCA mutation was reported. A presurgery biopsy was performed in 183/206 (86.3%) patients, with only 38.8% (71/183) with a presurgical MPT diagnosis. The majority of misdiagnoses on this biopsy were non-malignant PTs. Performing a biopsy, whatever the result, was associated with R0 resection ($p=0.044$) and better LRFS ($p=0.012$). Metastatic disease at diagnosis was reported in 7/212 (3.3%) patients.

Median tumor size was 58 mm (range 15–300) and the tumor was unifocal in 90.3% of cases. Intratumoral necrosis and epidermic ulceration were observed in 33% and 9.1% of cases, respectively. Lymphovascular space invasion (LVSI) was reported in only 3/136 cases. Invasive breast carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ were associated with MPTs in 4, 11, and 7 cases, respectively. Immunohistochemistry (IHC) was scarcely performed (in 6–21% of cases according to the different antibodies) and its positivity was particularly found for p53 (65% of the tested cases) and CD10 (85% of the tested cases). The median proportion of cells stained for the nuclear antigen Ki67 was 30% (range 5–80). Detailed IHC results are presented in electronic supplementary Table 1.

All patients with a localized disease ($n=205$) underwent surgery. Overall, 41.4% (87/210) underwent a mastectomy, while 54/210 patients (25.7%) underwent an axillary procedure, with only 5.6% (3/54) having MPT lymph node metastasis. The impact of the first surgery (BCS vs. mastectomy) on MFS and OS is summarized in Fig. 1. R0 resection at first surgery was achieved in 117/197 patients (59.4%): 26.9% with 1–2 mm margins, 12.2% with 3–7 mm margins, and 20.3% with margins≥8 mm. Mastectomy at first surgery permitted margins≥3 mm more frequently than BCS (55.6% vs. 16.5%, $p<0.0001$). Patients with resection margins≥3 mm had bigger tumors ($p=0.006$) and higher rates of tumor necrosis ($p=0.002$). 94/210 patients (44.8%) underwent an SS to obtain clear margins, with a final mastectomy rate of 73.3% (154/210). Among patients with initial mastectomy ($n=87$), six (7%) underwent an SS to obtain clear margins.

Adjuvant Treatment Modalities

Overall, 28/209 patients (11%) received chemotherapy, among whom 5 underwent neoadjuvant chemotherapy (Table 2). The median number of chemotherapy cycles was 6 (range 3–6). Chemotherapy was administered as a doublet, associating doxorubicin and ifosfamide in 67.8% (19/28) of cases (electronic supplementary Table 2). The treatment center ($p=0.011$), mastectomy as first surgery ($p=0.002$), and tumor necrosis ($p=0.007$) were associated with chemotherapy administration. Margin category was not found to be correlated with the administration of adjuvant chemotherapy.

Adjuvant radiotherapy was administered to 91/210 (43.3%) patients, at a 50 Gy dose in 25 fractions in 80% of cases. Patients who underwent a mastectomy were more frequently treated with radiotherapy ($p=0.006$) and chemotherapy ($p=0.011$). The treatment center ($p=0.023$), mastectomy as first surgery ($p=0.002$), and tumor necrosis ($p<0.0001$) were associated with radiotherapy administration.

Margin category was not found to be correlated with the administration of adjuvant treatment radiotherapy: 32/80 (40.0%) patients with 0 mm margins, 23/53 (43.4%) patients with 1–2 mm margins, 12/24 (50%) patients with 3–7 mm margins, and 22/40 (55.0%) patients with margins≥8 mm ($p=0.44$).

Survival

Median follow-up was 4.1 years (range 3.2–4.9), and local recurrences occurred in 35/210 (16.6%) patients. The 2- and 5-year LRFS rates were 84.8% (95% confidence

TABLE 1 Patient characteristics

	N=212	Range or percentage
Median age, years	52.8	16.8–90.5
Median weight, kg	65	37–117
Personal history of breast cancer	14	6.6
Family history of breast cancer	46	21.7
WHO performance status		
0	166	81.8
1	34	16.7
2–3	3	1.5
Missing	9	
Metastatic disease at diagnosis		
Yes	7	3.3
No	205	96.7
Diagnosis		
Autopalpation	121	59
Physical examination	55	26.8
Screening	25	12.2
Fortuitous	3	1.5
Symptomatic metastasis	1	0.5
Missing	7	
Breast imaging before surgery		
Yes	207	97.6
Mammography	166	80.2
Ultrasound	168	81.6
MRI	33	15.9
Presurgical biopsy		
Yes	183	88.8
No	23	11.2
Missing	6	
Biopsy results (/183)		
Malignant phyllodes tumor	71	38.8
Borderline phyllodes tumor	39	21.3
Benign phyllodes tumor	21	11.5
Non-gradable phyllodes tumor	15	8.2
Fibroadenoma	11	6
Other lesion suspect of malignity	10	5.5
Doubtful	12	6.6
Others	4	2.2

WHO World Health Organization, *MRI* magnetic resonance imaging

interval [CI] 78–89) and 78% (95% CI 69–84), respectively. 48/210 (22.9%) patients developed distant metastases, localized in the lung and pleura (85%), bone (23%), node (16%), or liver (8%). The 2- and 5-year MFS rates were 85.5% (95% CI 79–90) and 75.9% (95% CI 68–82), respectively. The median LRFS, MFS, and OS were not reached. At last update, 44 patients (20.8%) had died, of whom 38 deaths were related to the disease. The 2- and 5-year OS rates were 89% (95% CI 84–93) and 76% (95% CI 67–82).

Prognostic Analyses

Local recurrence: Factors significantly associated with better LRFS in univariate analysis were presurgery biopsy realization, diagnosis of MPTs at presurgical biopsy,

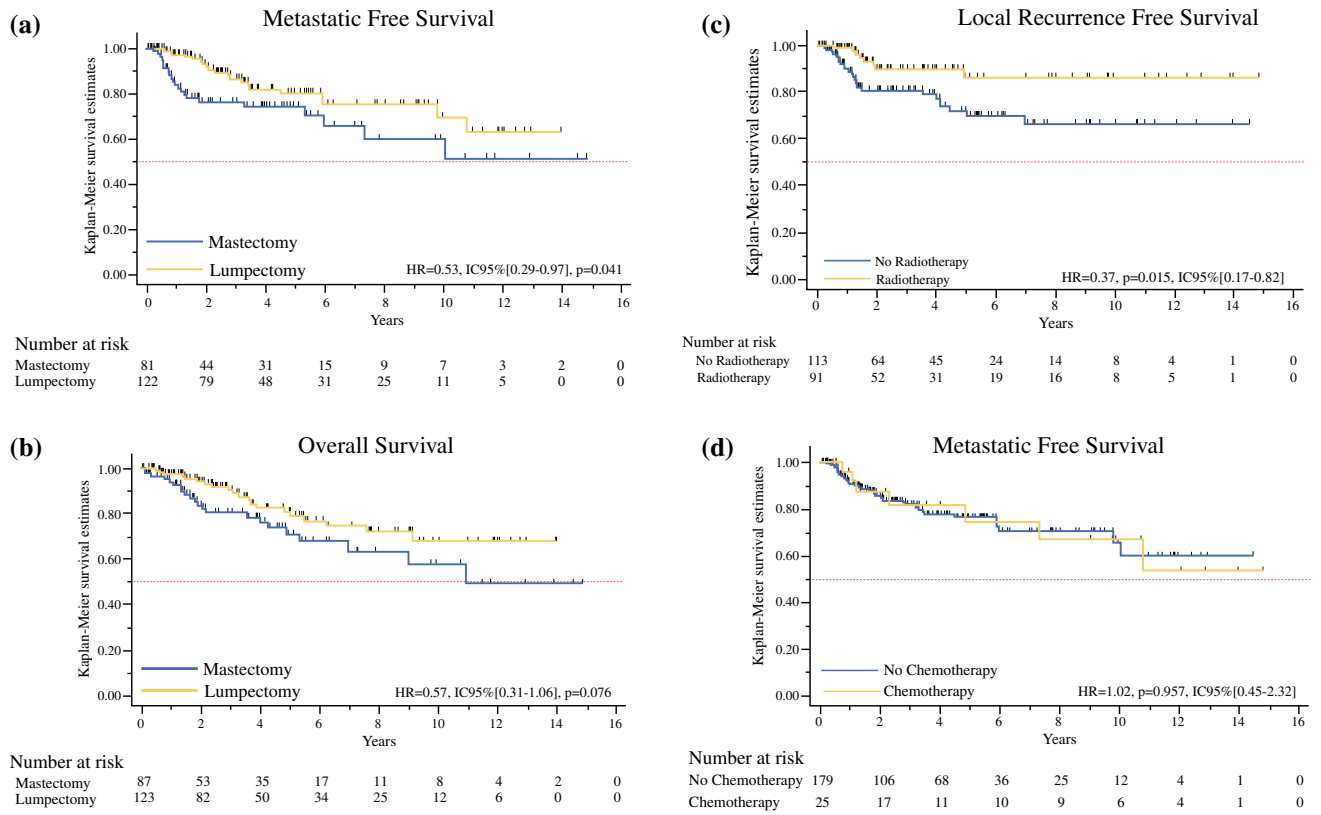


FIG. 1 Kaplan–Meier estimates of (**a**) metastatic-free survival and **b** overall survival according to the first surgery. **c** Kaplan–Meier estimates of local recurrence-free survival according to adjuvant radiation therapy status. **d** Kaplan–Meier estimates of metastatic-free survival according to adjuvant chemotherapy status. *HR* hazard ratio (univariate analysis), *CI* confidence interval

mastectomy as first or latter surgery, adjuvant radiotherapy and chemotherapy (Fig. 1c). Analyzing the effect of BCS or mastectomy with or without RT, BCS without RT was found to be inferior to other groups on LRFS ($p<0.001$) (Fig. 2). In multivariate analysis, mastectomy as first or second surgery was the only independent prognostic factor of better LRFS (Table 3).

Metastatic relapse: Factors significantly associated with poor MFS in univariate analysis were age≥50 years, diagnosis of MPTs at presurgical biopsy, mastectomy as first surgery, intratumoral necrosis, and 0/1/2 mm margins without SS. In multivariate analysis, age≥50 years, intratumoral necrosis, and margins 0/1/2 mm without SS were independent prognosis factors (Table 3). BCS was associated with better MFS (HR 0.53, 95% CI 0.29–0.97, $p=0.041$) but significance was not reached for OS (HR 0.57, 95% CI 0.31–1.06, $p=0.076$) (Fig. 1a, b). Adjuvant chemotherapy did not improve MFS (Fig. 1d).

Overall survival: Factors significantly associated with poor OS in univariate analysis were age≥50 years, diagnosis of MPTs at presurgical biopsy, presence of metastases at diagnosis, metastatic recurrence, and 0/1/2 mm margins without SS. In multivariate analysis, presence of metastases at diagnosis, metastatic recurrence, and 0/1/2 mm margins without SS were found to be independent prognostic factors (Table 3 and Fig. 3). Wider margins (>8 mm) were not associated with better outcomes (3–7 mm vs.>8 mm; HR 0.81, 95% CI 0.29–2.29, $p=0.69$). Contrary to distant metastatic occurrence, local recurrence was not statistically associated with poorer OS (HR 1.86, 95% CI 0.97–3.57, $p=0.06$) (Figs. 4a, b).

DISCUSSION

We present here the results of analysis of one of the largest series of MPT patients, and contribute to improving MPT management, which is crucially needed. Indeed, many issues on MPT management remain unanswered: prognostic factors are not well-identified, presurgery diagnosis is complex, no consensus on margin threshold is defined, and the role of adjuvant therapy and the management of metastatic disease are still unclear. In our study, rates of local and metastatic recurrences and deaths are comparable with those already published.[11,14] Presurgical diagnosis on biopsy is difficult and needs optimization, as confirmed by the 38.8% of well-diagnosed MPTs in our

TABLE 2 Surgical and medical management of malignant phyllode tumors

	N=212	%
Surgery	210	100
Breast-conserving surgery	123	58.6
Mastectomy	87	41.4
Missing	2	
Axillary procedure		
None	156	74.3
Axillary lymph node dissection	39	18.6
Sentinel lymph node biopsy	15	7.1
Missing	2	
Tumor size, mm		
<50	80	38.3
50–99	64	30.6
≥100	65	31.1
Missing	3	
Tumor necrosis	69	33.0
Missing	3	
Surgical margins, mm		
0	80	40.6
1–2	53	26.9
3–7	24	12.2
≥8	40	20.3
Missing	15	
Second surgery for clear margins	94	44.8
Missing	2	
Final mastectomy rate	154	73.3
Missing	2	
Adjuvant radiation therapy	91	43.1
Missing	2	
Adjuvant chemotherapy	23	11
Missing	3	
Local recurrence	35	16.6
Missing	1	
Metastatic recurrence	48	22.9
Missing	2	

study, a rate similar to those already published.[6] Our results also confirm the importance of performing the biopsy, as it was associated with R0 resection and better LRFS, and also emphasize the crucial role of surgery in MPT management. As previously described, BCS was safe in MPTs but the rate of optimal surgery was low: 133 patients (67.5%) had margins<3 mm, which led to 94 s surgeries (44.8%). Contrary to other sarcomas and epithelial breast cancer, an SS to obtain clear margins provides LRFS, MFS, and OS identical to cases with optimal initial surgery.[28,29] This effect is probably due to the breast anatomy; a second breast surgery (mastectomy) can resect all scars and dissection plans previously opened. Patients who underwent a first wide surgery (≥3 mm) do not show significantly better MFS or OS compared with patients with 0, 1, or 2 mm margins at initial surgery and without an SS. Indeed, these specific patients often present with bigger tumors with important necrosis. In accordance with previous studies,[2,15] first mastectomy was found to be a poor prognostic factor linked with tumor size.

In the literature, a 1 cm clear margin is often found for assessment of the quality of the MPT resection; however, this standard was set on relatively small series of patients.[8] In our study, a 3 mm threshold seemed sufficient for MPT surgery, with no impact of wide margins on OS. On the other hand, mastectomy does have a positive impact on LRFS. This superiority of mastectomy on LRFS is probably linked to the procedure. Indeed, mastectomy respects the sarcoma surgical rules, i.e. en bloc resection along the muscle fascia, more so than BCS. The lack of utility of nodal staging was also confirmed as nodal involvement was much too rare.[30]

Local recurrence was not associated with poorer survival, although patients treated with BCS reported more local recurrences compared with patients treated with mastectomy; tumors were smaller and less aggressive, with no LVSI or tumor necrosis. However, there is a trend towards an impact of a local recurrence on OS, as reported in a study of 235 MPT patients where a sixfold increase in metastatic recurrence after local recurrence was found.[31]

The effect of adjuvant treatment is unclear. Radiotherapy and chemotherapy were often administered in patients with large and necrotic tumors, although these patients had undergone previous mastectomy in most cases. A benefit was found for radiotherapy only in terms of LRFS in univariate analysis, but not in multivariate analysis, as recently reported in the Surveillance, Epidemiology, and End Results (SEER) database on PTs,[23] but this has been inconsistently reported.[21] The benefit of RT in our study seems to be strong for patients treated by BCS. Radiotherapy was proposed in patients with worse prognostic factors, including size or tumor necrosis. Chemotherapy was also indicated in patients with large and necrotic tumors and was not correlated with survival, which was concordant with previous studies.[24]

Overall, our multicenter study highlights the heterogeneity of MPT management within the participating centers, especially regarding adjuvant therapies.

Our study of 212 patients in 13 centers is one of the largest series including details on MPT management; the SEER database reported 821 MPTs during a 30-year period (updated in 2016, with 1974 MPTs reported), the IMPAC National Oncology Database (478 MPTs over 40 years), and the National Cancer Database (3120 patients over 11 years).[2,14,23] Contrary to these database studies, our

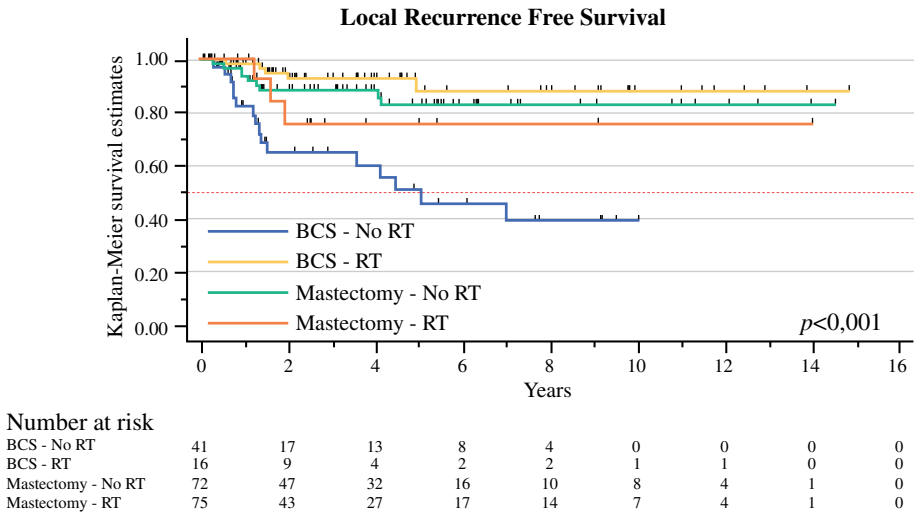


FIG. 2 Kaplan–Meier estimates of local recurrence-free survival according to the first surgery and adjuvant RT status (univariate analysis). *BCS* breast-conserving surgery, *RT* radiation therapy

TABLE 3 Prognostic factors for each endpoint (multivariate analysis)

	Variable		HR	95% CI	*p*-Value
LRFS	Mastectomy at first or second surgery	Yes	1	2.35–9.99	**<0.001**
		No	**4.85**		
	Margins, mm	0–1–2 without SS	1		
		0–1–2 with SS	0.82	0.38–1.79	0.62
		≥3	0.68	0.27–1.71	0.42
MFS	Age, years	<50	1	1.04–4.39	**0.038**
		≥50	**2.14**		
	Tumor necrosis	Yes	**1.96**	1.03–3.81	**0.047**
		No	1		
	Margins, mm	0–1–2 without SS	1		
		0–1–2 with SS	**0.3**	0.13–0.70	**0.005**
		≥3	0.75	0.37–1.53	0.43
OS	Metastatic disease at diagnosis	Yes	**5.27**	1.84–15.08	**0.002**
		No	1		
	Metastatic recurrence	Yes	**7.29**	3.56–14.92	**<0.001**
		No	1		
	Margins, mm	0–1–2 without SS	1		
		0–1–2 with SS	**0.32**	0.14–0.71	0.005
		≥3	0.55	0.28–1.12	0.099

LRFS local recurrence-free survival, *SS* second surgery, *MFS* metastatic-free survival, *OS* overall survival, *CI* confidence interval, *HR* hazard ratio

Significant variables are in bold

study, which only used the GSF-GETO database for patient listing, retrospectively collected data in each center, thus allowing the study of parameters such as margins or presurgical diagnosis, usually not reported in large databases.[14,23] Our data collection forms were specifically designed to answer difficult questions on MPT clinical management, so as to obtain results useful in clinical practice.

One of the limitations of our study is its retrospective design, together with patient selection and data management of such retrospective studies. However, carrying out prospective studies to identify prognostic factors and define a threshold for surgical margins in these very rare tumors would be both too expensive and very long. It seems, for the time being, that seriously conducted retrospective studies are the best way to obtain results on MPT

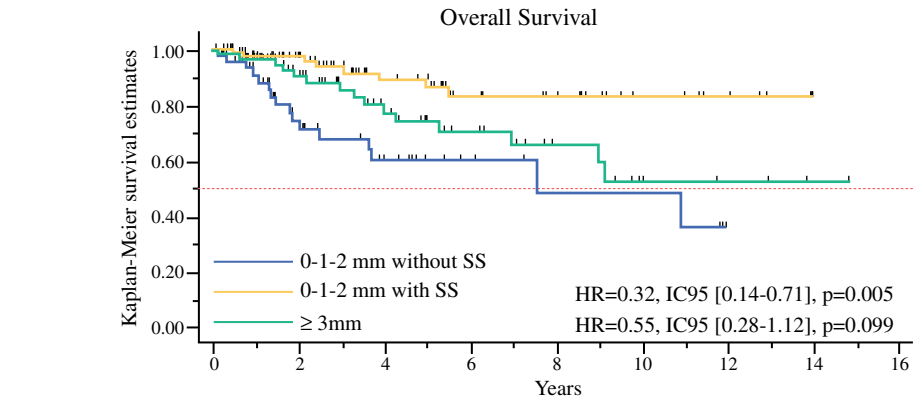


FIG. 3 Kaplan–Meier estimates of overall survival according to surgical margins. *HR* hazard ratio (multivariate analysis). *SS* second surgery, *HR* hazard ratio, *CI* confidence interval

Number at risk

0-1-2 mm without SS	49	25	14	7	4	4	0	0	0
0-1-2 mm with SS	84	58	36	23	19	9	5	0	0
≥ 3mm	63	43	27	17	10	4	3	1	0

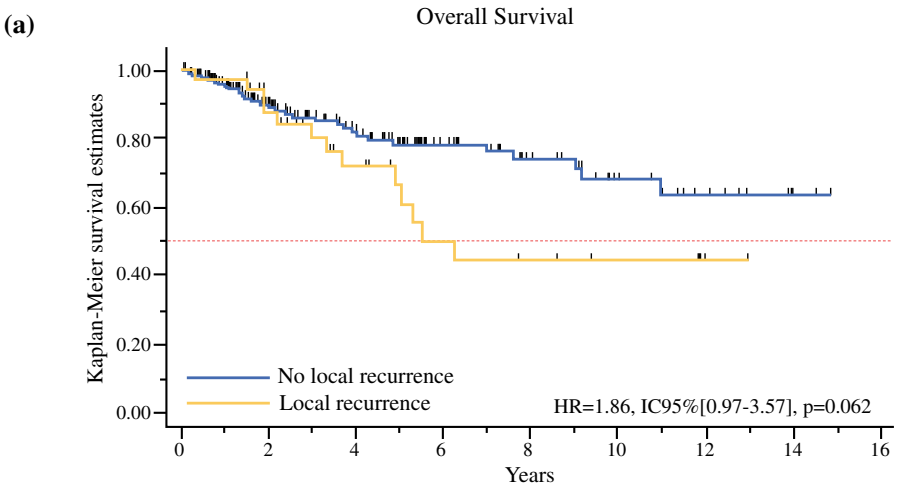
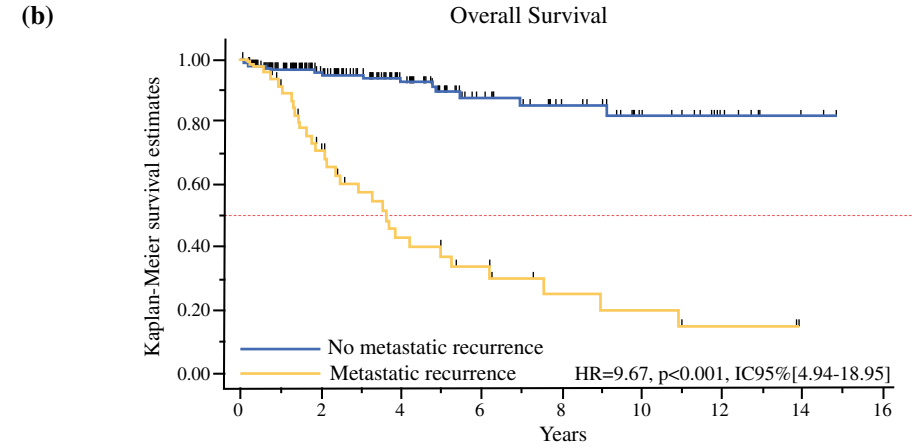


FIG. 4 Kaplan–Meier estimates of overall survival according to (**a**) local recurrence-free survival status or (**b**) metastatic-free survival status. *HR* hazard ratio (univariate analysis). *CI* confidence interval

Number at risk

No local recurrence	177	110	69	42	30	16	9	2	0
Local recurrence	35	26	16	9	6	4	1	0	0



Number at risk

No metastatic recurrence	164	106	70	41	31	16	8	2	0
Metastatic recurrence	48	30	15	10	5	4	2	0	0

management and to identify prognostic factors. Our 3 mm threshold for the surgical margins may allow setting-up a prospective study to evaluate the impact of adjuvant radiotherapy on event-free survival.

CONCLUSION

This study confirms surgery as the cornerstone of MPT treatment and management. We encourage using a 3-mm threshold for surgical margins and performing, when needed, second surgeries to obtain clear margins. BCS seems a viable option for small MPTs. The benefit of adjuvant radiotherapy and chemotherapy seems limited. Further studies are specifically needed to improve presurgical diagnosis on imaging and histology of these rare tumors of the breast.

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