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ORIGINAL ARTICLE – BREAST ONCOLOGY

Impact of Metastasis Surgery and Alkylating-Agent-Based Chemotherapy on Outcomes of Metastatic Malignant Phyllodes Tumors: A Multicenter Retrospective Study

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ABSTRACT

Background. Metastatic phyllodes tumors have poor prognosis with median overall survival of 11.5 months. The objective of this study is to identify prognostic factors and the best options for management of metastatic malignant phyllode tumors (MMPTs).

Patients and Methods. A multicentric retrospective study, including cases of MMPT from 10 sarcoma centers, was conducted. The primary end-point was overall survival (OS), and the secondary end-point was the clinical benefit of chemotherapy (CBCT) rate.

Results. 51 MMPT patients were included. Median time from diagnosis to metastatic recurrence was 13 months. Management of MMPT consisted in surgery of the metastatic disease for 16 patients (31.3%), radiation therapy of the metastatic disease for 15 patients (31.9%), and chemotherapy for 37 patients (72.5%). Median follow-up was 62.1 months [95% confidence interval (CI) 31–80 months]. Median OS was 11.5 months (95% CI 7.5–18.7 months). On multivariate analysis, two or more metastatic sites [hazard ratio (HR) 2.81, 95% CI 1.27–6.19; $p = 0.01$] and surgery of metastasis (HR 0.33, 95% CI 0.14–0.78; $p = 0.01$) were independently associated with OS. The CBCT rate was 31.4% and 16.7% for the first and second lines. Polychemotherapy was not superior to single-agent therapy. Alkylating-agent-based chemotherapy, possibly associated with anthracyclines, was associated with a better CBCT rate than anthracyclines alone ($p = 0.049$).

Conclusions. The results of this study emphasize the impact of the number of metastatic sites on survival of MMPT patients and the leading role of metastasis surgery in MMPT management. If systemic therapy is used, it

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should include alkylating agents, which are associated with a better clinical benefit.

BACKGROUND

Malignant phyllodes tumors (MPT) are rare fibroepithelial tumors of the breast, accounting for less than 1% of all primary breast tumors.[1] They are aggressive tumors, with a metastatic recurrence risk of around 22% during follow-up.[2,3] The outcomes and management of metastatic MPT (MMPT) are poorly documented. Lungs followed by bones are the most common metastatic sites of MMPT.[3] However, literature includes a substantial number of case reports about unusual metastatic locations of MMPT, including stomach, intestine, pancreas, adrenal gland, mandible, and heart.[4]

To the best of the authors' knowledge, only two studies have reported several cases of MMPT.[5,6] The largest series reported 37 cases of MMPT, mainly managed by chemotherapy as first-line treatment.[5] The median time from diagnosis to metastatic recurrence was 21 months. Almost all patients received doxorubicin-based chemotherapy. The longest survival (9 months) was obtained with a combination of doxorubicin and ifosfamide. No effect of hormone therapy (testosterone) was reported in that series. The second study included only seven patients.[6] Poly-chemotherapy was also the main treatment of MMPT, with use of doxorubicin, ifosfamide, or cisplatin. Overall outcomes were poor, with six deaths reported and one patient still under treatment.

Surgery of the metastatic disease was not considered to be an effective treatment of MMPT by Mituś et al.[5] Indeed, its efficacy for metastatic disease in MMPT is rarely mentioned in literature, only in a few case reports.[4,7] However, the potential benefit of metastasectomy has been reported in sarcomas, especially in case of lung metastases.[8] Therefore, surgery of the metastatic disease is recommended in case of isolated lung metastases in the most recent European Society for Medical Oncology (ESMO)-European Reference Network for Rare Adult Solid Cancers (EURACAN) guidelines on soft tissue and visceral sarcomas.[9]

The objectives of the present study are to report the outcomes of MMPT patients and to identify prognostic factors. The impact of surgery of the metastatic disease in this rare type of sarcoma is also assessed. Finally, chemotherapy regimens were assessed for possible correlation with disease control and prolonged overall survival.

PATIENTS AND METHODS

Study Design and Patients

We retrospectively analyzed the medical charts of patients treated for MMPT between 1 January 2000 and 1 September 2016 in 10 centers of the French Sarcoma Group (GSF-GETO). The list of patients was obtained via the GSF database (Conticabase and Rreps databases). All sarcoma centers that had included at least one case in the GSF database were invited to participate in the study and include all the cases available in their center, according to the following inclusion criteria: (1) histological central review by an expert pathologist member of the GSF-GETO for MPT diagnosis, (2) data on initial treatment (between 1 January 2000 and 1 September 2016) and follow-up available, (3) no other concomitant uncontrolled cancer, and (4) confirmed diagnosis of metastases. Criteria for noninclusion were: no metastatic relapse and missing follow-up data.

The study was approved by the national institutional review board. Considering the retrospective character of the study, no informed consent was deemed necessary.

Assessments

The patients' characteristics at diagnosis included age, Eastern Cooperative Oncology Group (ECOG) performance status, family history of breast and ovarian cancer, and *BRCA* mutation. The following tumor characteristics were reported: tumor size, localization, multifocality, ulceration, mitotic count, necrosis, nodal and distant metastasis, and number and localization of metastases. The treatment characteristics reported included surgery of the metastatic disease, chemotherapy data (regimen, number of cycles and lines, and clinical benefit rate), and radiotherapy administration. The primary endpoint was overall survival (OS), and the secondary endpoint was the rate of chemotherapy clinical benefit (CBCT), defined as complete or partial response or stability superior to 6 months.

Statistical Analyses

For continuous variables, medians and ranges were computed. Median follow-up was calculated using the reverse Kaplan–Meier method. OS was defined as time from the metastatic event to death or last follow-up. Survival rates were estimated using the Kaplan–Meier method and are presented with their 95% confidence interval (95% CI). 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 backward stepwise analysis.

Prognostic factors of response to chemotherapy were selected using the log-rank test. Factors significantly associated with OS were included in a multivariate Cox regression analysis using the maximum-likelihood method and backward stepwise analysis. All tests were two sided, and p value< 0.05 was considered significant. All statistical analyses were performed using STATA13 software (Stata Corporation, College Station, TX).

RESULTS

Patients' Baseline Characteristics

Between 1 January 2000 and 1 September 2016, 51 among 212 patients (24%) were included from 10 participating centers (Table 1). Almost all patients had performance status of 0 (n = 33; 68.8%) or 1 (n = 13; 27.1%). Seven (13.7%) patients presented metastatic disease at diagnosis. For the other patients, the median time from diagnosis to metastatic recurrence was 13 months (range 1–130 months). Lung was the main metastatic site (n = 44, 86.3%), then bone (n = 12; 23.5%) (Supplementary Table S1).

MMPT Treatments

Management of MMPT consisted in surgery (n = 16; 31.3%), radiotherapy (n = 15; 31.9%), first-line chemotherapy (n = 37; 72.5%), second-line chemotherapy (n = 18; 49%), or third-line chemotherapy (n = 9; 24%) (Supplementary Table S2). Radiation therapy was performed as palliative treatment, for pain management, in almost all cases.

Chemotherapy and CBCT Rate

The majority of patients received anthracyclines, alkylating agent (ifosfamide and cyclophosphamide), or both as first-line chemotherapy. However, 10 MMPT patients (19.6%) received adjuvant chemotherapy with an anthracycline regimen for their initial treatment, preventing their use at the metastatic stage (Fig. 1). Thus, among them, six patients also received chemotherapy for the metastatic disease, but none with anthracyclines.

Among the 37 patients who received first-line chemotherapy, 35 reported an evaluable response. The response rate to chemotherapy and clinical benefit are summarized in Supplementary Table S2.

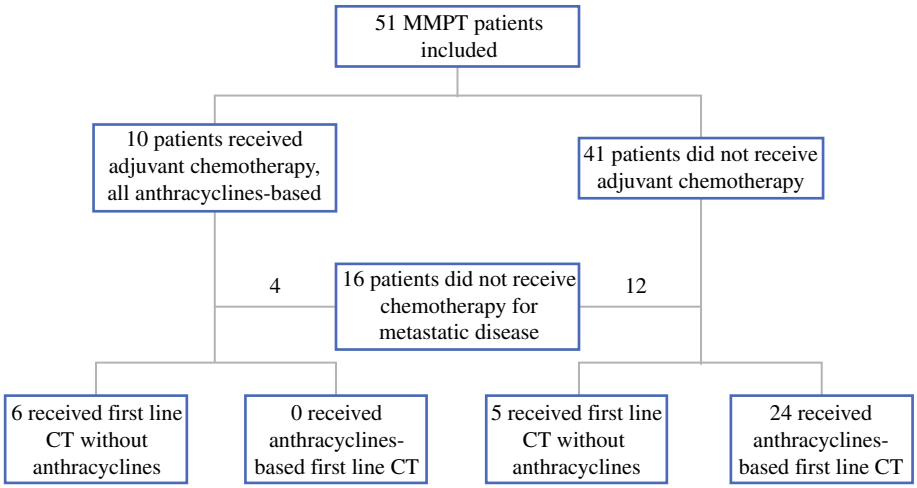
Polychemotherapy was not superior to single-agent therapy in terms of CBCT rate (Supplementary Table S3).

TABLE 1 Patients' characteristics

	n	Range or percentage
Age (median, years)	56.4	19.5–90.5
Weight (median, kg)	62.5	46–117
WHO performance status		
0	33	68.8%
1	13	27.1%
2–3	2	4.2%
Metastatic disease at diagnosis		
Yes	7	13.7%
No	44	86.3%
Time between diagnosis and metastatic recurrence		
$<$ 12 months	17	38.6%
$\geq$ 12 months	27	61.4%
Local recurrence		
No	36	72%
Yes	14	28%
Number of metastatic sites		
1	26	51%
$\geq$ 2	25	49%
Surgical treatment for metastatic disease	16	31.3%
Radiotherapy for metastatic disease	15	31.9%
Chemotherapy for metastatic disease	37	72.5%

WHO World Health Organization

FIG. 1 Flowchart



MMPT: Metastatic Malignant Phyllode Tumour; CT: Chemotherapy

As first-line treatment, the alkylating agent-based chemotherapy regimen, possibly associated with anthracyclines, was associated with a better CBCT rate than anthracyclines alone ($p = 0.049$). As second-line treatment ($n = 18$), the regimens used were more heterogeneous, including cisplatin–etoposide association, doxorubicin alone, regorafenib, taxanes, gemcitabine, and trabectedin. Three patients reported partial response when treated with cisplatin, doxorubicin, or regorafenib. Surprisingly, pazopanib was not reported to be used in this retrospective analysis.

TABLE 2 Prognostic factors for overall survival (univariate analysis)

	Hazard ratio	*p*-Value
Age (years)		
< 50	1.09	0.8
≥ 50	1	
Number of metastatic sites		
1	1	0.001
≥ 2	3.34	
Surgery for metastatic disease		
Yes	0.26	0.002
No	1	
Chemotherapy regimen		
Anthracycline-based chemotherapy	1.86	0.15
Alkylating-agent-based chemotherapy	1	
Clinical benefit of chemotherapy		
Yes	0.31	0.01
No	1	

Survival

Median follow-up was 62.1 months (95% CI 31–80 months, range 0.3–94 months). Median OS was 11.5 months (95% CI 7.5–18.7 months). The 1-year and 2-year OS rates were 49% (95% CI 35–62%) and 33% (95% CI 20–47%).

Prognostic factors assessed in univariate analysis are presented in Table 2. Fourteen (27.5%) patients presented a concomitant local recurrence, which was not associated with poorer OS. On univariate analysis, time to metastatic recurrence superior to 12 months (HR 0.86; $p = 0.64$) and metastatic disease at diagnosis (HR 1.09; $p = 0.2$) were not associated with OS. Two or more metastatic sites were associated with poorer OS (HR 3.34, $p = 0.001$), and CBCT and surgery of the metastatic disease were associated with better OS (HR 0.31, $p = 0.01$; HR 0.26, $p = 0.002$). Although linked to CBCT, alkylating-agent-based chemotherapy regimens did not reach significance for OS (HR 1.86; $p = 0.15$) (Fig. 2).

On multivariate analysis, factors independently associated with OS were two or more metastatic sites (HR 2.81; 95% CI 1.27–6.19; median 7.5 vs. 31.1 months; $p = 0.01$) and metastasis surgery (HR 0.33; 95% CI 0.14–0.78; median 25.9 vs. 9.9 months; $p = 0.01$) (Fig. 3).

DISCUSSION

This study reports poor prognosis for MMPT patients in this series, with median OS of 11.5 months (95% CI 7.5–18.7 months), concordant with the median OS of 7 months reported in Mitus' study.[5] This is less than the median survival of all metastatic soft tissue sarcomas, with median survival at the metastatic stage of 13 months,[10] although lung metastasis are also the most common

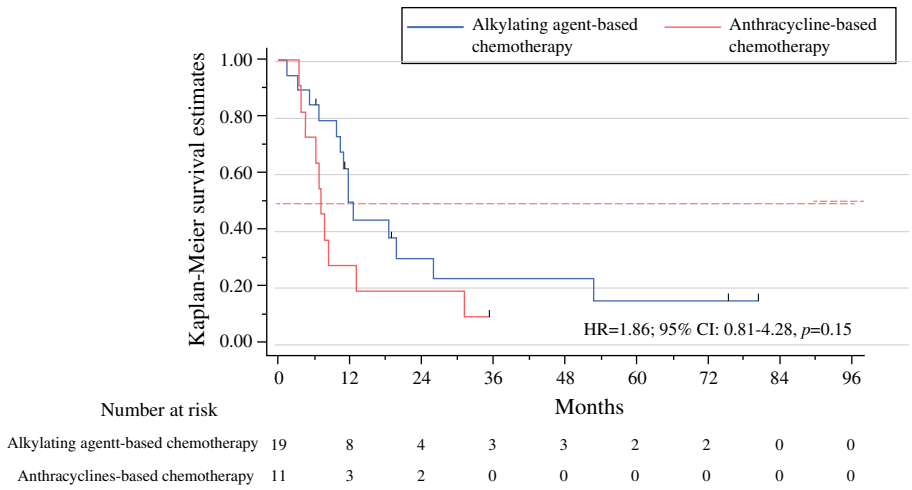


FIG. 2 Kaplan–Meier estimates of overall survival according to first-line chemotherapy regimen (univariate analysis)

HR: Hazard-ratio; 95% CI: 95% confidence interval

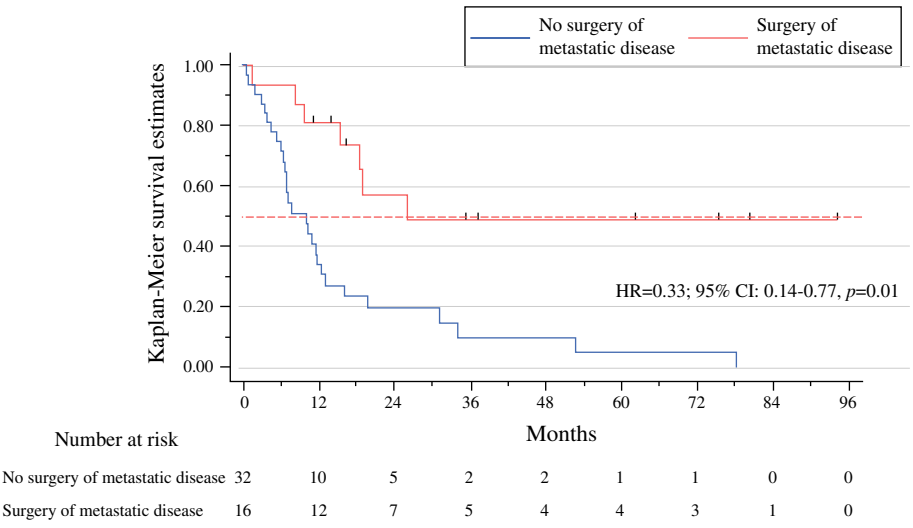


FIG. 3 Kaplan–Meier estimates of overall survival according to completion of surgery for metastatic disease (multivariate analysis)

HR: Hazard-ratio; 95% CI: 95% confidence interval

metastatic site for MMPT. The results of this study do not explain such poor prognosis compared with all soft tissue sarcomas.[11]

This study highlights the interest in treating patients with oligo-metastatic disease, including with surgery. Indeed, the number of metastatic sites and surgery of metastases have a major impact on overall survival, and independently so, thus strengthening their prognostic value. When surgery of metastases was performed, 50% of patients were still alive after 24 months. Long survival is reported only in patients who underwent metastasis surgery. Selecting good candidates for such surgery is a major issue requiring close collaboration between medical and surgical oncologists. However, performance of such selection inevitably leads to a bias in the survival analysis of these patients.

Except for some case reports, to the best of the authors' knowledge, no published study has specifically reported interest in metastasectomy in MMPT. However, several authors have reported results of metastasectomies in metastatic sarcoma patients. In 2017, Chudgar et al. published a series of 539 sarcoma patients who underwent 760 pulmonary metastasectomies,[12] reporting median OS of 33.2 months. The number of metastatic sites, number of metastases, and time to metastasis were prognostic factors of OS. The recurrence rate after metastasectomy was 74%, much higher than the 50% reported herein. In this study, the median OS of patients who underwent metastasis surgery was 31.1 months; half of these patients were long-time survivors without any event. Time to metastatic event was previously reported as a strong prognostic factor,[12] probably leading to less metastatic surgery for patients with synchronous compared with metachronous metastases.

Smolle et al. showed that metastasectomy was associated with prolonged survival in patients with metachronous metastases, even after using a propensity score to address the higher prevalence of favorable prognostic factors in the surgery group.[13]

In the work presented herein, patients with synchronous metastases had the same prognosis as patients with metachronous metastases, which is concordant with the study of Chudgar et al.[12] A recent study by Krishnan et al. reported a benefit of metastasectomies in patients with metastases at diagnosis.[14] The results of this study and of the two others encourage performance of surgery for metastatic disease (especially in case of isolated lung metastases) regardless of the time to metastatic event, as recommended in the most recent ESMO-EURACAN guidelines for soft tissue and visceral sarcomas.[9]

For unresectable MMPT, chemotherapy is the most used treatment (n = 37 patients, 72.5%, in this study). Alkylating-agent-based regimens seem to be effective in MMPT patients, offering better disease control compared with therapies based on anthracyclines alone. The antitumoral effect of alkylating agents has been suggested in some case reports.[6,15] A doublet of chemotherapy was not superior to single-agent chemotherapy, as also reported in literature on STS sarcomas.[10] This may be due to the good response rate to chemotherapies based on alkylating agents alone (50% disease control). The results presented herein suggest that alkylating agents should be considered for management of MMPT, in combination with anthracyclines or as single administration, although this needs to be confirmed in prospective studies.

Although the CBCT rate was low in second line (16.7%), we reported a case of partial response with cisplatin–etoposide, whose effectiveness was reported in 1989,[16] and a partial response with regorafenib, VEGF, PDGFr, FGFR, RAF, BRAF, TIE2, and FLT3 inhibitor. This finding correlates with recently published data on molecular profiling of MMPT.[17,18] Numerous alterations of molecular markers of angiogenesis, as well as *EGFR* and *TP53*, have been described and could represent an option to improve the poor outcomes currently obtained with conventional chemotherapies.

This study has some limitations, first among which is its retrospective design, with the associated rate of missing data. Although this is the largest study on MMPT, including a significant number of patients with this rare disease, the number of patients included is still too low to analyze the impact on OS of the different systemic regimens proposed for management of MMPT. Indeed, the sample size of the subgroups divided by regimen would be too small. As proposed by Confraveux et al., a common international database is essential to increase the number of patients available for inclusion in studies on such rare diseases.[19]

CONCLUSIONS

The results of this study emphasize the effect of the number of metastatic sites in MMPT patients on survival and the leading role of surgery of the metastatic disease, if achievable, for MMPT management. In other cases, the systemic treatment should include alkylating agents, considering their clinical benefit. Targeted therapies could also be effective and should be investigated in further studies.

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