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Metastatic feline mammary cancer: prognostic factors, outcome and comparison of different treatment modalities – a retrospective multicentre study

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Abstract

Objectives Although feline mammary carcinomas (FMCs) are highly metastatic, the literature and treatment options pertaining to advanced tumours are scarce. This study aimed to investigate the clinical outcome of metastatic FMC with or without adjuvant treatment.

Methods The medical records of 73 cats with metastatic FMC (stage 4) were reviewed and included in this study. Metastatic disease was detected by distinct imaging techniques (radiography, ultrasound and CT) and confirmed by cytology and/or histopathology. Cats with adjuvant chemotherapy treatment (n = 34) were divided into three groups: group 1 (n = 9) cats receiving maximum tolerated dose chemotherapy; group 2 (n = 15) cats receiving metronomic chemotherapy; and group 3 (n = 10) cats treated with toceranib phosphate. The study endpoints were time to progression (TTP) and tumour-specific survival (TSS). Treatment-related toxicity was evaluated according to the Veterinary Co-operative Oncology Group's Common Terminology Criteria for Adverse Events version 1.1 (VCOG-CTCAE).

Results Overall mean TTP and TSS were 23 and 44 days, respectively. Cats with clinical signs at the time of diagnosis had a lower TSS (14 days) than asymptomatic cats (120 days; $P < 0.001$). Cats with pleural effusion had a lower TSS (16 days) than cats without ($P < 0.001$). Median TSS was 58, 75 and 63 in groups 1, 2 and 3, respectively ($P = 0.197$). Toxicity was observed in 66.7%, 20% and 30% of cats in groups 1, 2 and 3, respectively.

Conclusions and relevance To the best of our knowledge, this study includes the highest number of patients with metastatic FMC assessed. Despite the overall poor prognosis, some cats survived >6 months, indicating that adjuvant treatment may be an option to consider in metastatic disease. More studies are warranted for better understanding and management of stage IV patients.

Keywords: Metastatic mammary tumour; meloxicam; metronomic chemotherapy; toceranib phosphate; de novo metastatic

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Introduction

Feline mammary carcinomas (FMCs) are the third most common tumour type in cats.[1–3] They are characterised by their clinical and histological aggressiveness and consequent systemic progression.[4,5] Reported metastatic rates range from 50% to 90%, with the most commonly affected sites being the lungs, lymph nodes, liver and pleura.[6]

Cats with distant metastasis are classified according to World Health Organization (WHO) modified staging system as stage IV, with an associated poor prognosis as metastatic disease is the leading cause of death in these animals.[1,7] Described clinical manifestations of patients with thoracic metastasis are related to the development of respiratory impairment, such as dyspnoea and/or cough, inappetence and weight loss.[3,8] In some cases, metastatic disease can also cause pleural effusion.[3] The reported median survival time for cats with stage IV disease is approximately 1 month.[9]

FMCs are a useful comparative model for human breast cancer as both diseases share some similarities in carcinogenesis and clinical behaviour.[10,11] In human breast cancer there is a subpopulation of patients who already have metastatic disease at the initial diagnosis, designated as de novo metastatic breast cancer.[12] Treatment for human metastatic breast cancer depends on several factors, namely biological markers (hormone receptors and human epidermal growth factor type 2 [HER2] expression), number and site of metastases, previous treatments, and the need for rapid disease and control of clinical signs.[13] For these reasons, both single agent or a multidrug combination of high-dose chemotherapy, tyrosine kinase inhibitors and/or metronomic chemotherapy (MC) are recommended.[13,14]

There are several pitfalls of managing a feline patient with metastatic mammary disease. Some authors have described the use of doxorubicin and cyclophosphamide, in both gross disease and advanced metastatic FMC, but these studies combine patients in different WHO stages and the clinical benefit remains unclear.[15,16] For cats with pleural effusion secondary to FMC, systemic chemotherapy with docetaxel, with or without doxorubicin, may promote a better response than intrapleural cyclophosphamide.[8] To the best of our knowledge, these are the only studies evaluating the treatment of metastatic FMC.

Owing to the small number of publications on the subject, this retrospective study aimed to investigate the outcome, treatment-related toxicity and clinical prognostic factors in stage IV cats with or without adjuvant chemotherapy treatment.

Materials and methods

Case selection

A retrospective multicentre study was performed in four veterinary institutions (Onevet Hospital Veterinário do Porto, Onevet Hospital Veterinário Berna, Centro Hospitalar Veterinário and Hospital Escolar Veterinário). Records were searched between January 2012 and December 2019 to identify cats with stage IV mammary carcinoma according to the WHO modified clinical staging system.[17]

Only cats with a complete medical record were included in the study. For inclusion, cats with a previous history of mammary tumour must have had a histopathological diagnosis of mammary carcinoma. In cats with de novo metastatic disease, mammary nodules were confirmed as malignant tumours by cytology or histopathology. Cats were excluded if they had a history of other cancers besides mammary carcinomas. Stage IV (measurable metastases) were detected either on clinical examination, three-view thoracic radiographs and/or abdominal ultrasound and/or a total body CT. Metastatic disease was confirmed by cytology and/or histopathology. Some cats with pulmonary nodules were assumed to have lung metastases based only on imaging studies.

Cats receiving adjuvant chemotherapy treatment, after detection of metastatic disease, were divided into three treatment groups: group 1 consisted of cats treated with maximum tolerated dose (MTD) chemotherapy; group 2 included cats treated with MC; and group 3 consisted of cats treated with toceranib phosphate (TP) (Palladia; Zoetis). MTD chemotherapy was defined as the administration of chemotherapy agents at the MTD, with interrupted drug-free periods. MC was defined as the continuous oral administration of chemotherapy agents at a low dose, without treatment discontinuation.[18] In cats receiving adjuvant chemotherapy treatment, related adverse events (AEs) were accessed and registered according to the Veterinary Co-operative Oncology Group's Common Terminology Criteria for Adverse Events version 1.1 (VCOG-CTAE).[19] Clinical response and evolution were assessed at follow-up visits, registered and defined according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0) criteria.[20]

All cats (including non-treated cats) were submitted to at least one control follow-up, which consisted of a complete physical evaluation and thoracic radiography and/or abdominal ultrasound. Owing to the study's retrospective nature, follow-ups were performed based on the clinician's assessment but performed at least every 3 weeks in the first 12 weeks after stage IV diagnosis. Cats without clinical follow-up or incomplete records were excluded.

Additional information collected and included in the study consisted of signalment, history of previous administration of contraceptives, previous history of mammary tumours and treatment procedures, clinical signs at presentation, staging imaging procedure, site of metastasis, presence/absence of effusion, concomitant mammary disease, palliative mammary surgery excision, follow-up staging results, time to progression (TTP) and tumour-specific survival (TSS). TTP was defined as the time between the diagnosis of stage IV and the first documentation of

progression. Progressive disease (PD) and stable disease (SD) were defined according to RECIST (version 1.0) criteria.[20] TSS was defined as the interval between stage IV diagnosis and tumour-related death.

Statistical analysis

Descriptive statistics were used in the analysis of clinical variables and histopathological data. Continuous data were tested for normality with the Shapiro–Wilk test. To assess differences and to evaluate the distribution of features between groups the χ^2 test was applied. The Kaplan–Meier product-limit method was used to access progression, survival and 6 month survival rate, and the differences were evaluated by the log-rank test. Results are shown as median days with the corresponding 95% confidence intervals (CIs). *P* values <0.05 were considered significant. Cats were censored if they were lost for follow-up, alive at the end of the study or had no documented PD at the end of the study.

Results

Cat and tumour characteristics

Eighty-four cats were considered for inclusion. Five cats were excluded owing to absent mammary cytology or histopathological confirmation. Three cats were excluded owing to incomplete data. Two cats were excluded because they had presumptive hepatic metastases that were not confirmed histologically or cytologically, and one cat was excluded because it had a history of another tumour (sarcoma) and had no cytology or histopathology to confirm metastatic disease.

Seventy-three cats met the inclusion criteria and were included in the study. The mean age of the study cats was 12.28 ± 2.86 years (range 6–20 years) and and the predominant breed was domestic shorthair (n = 62 [84.9%]), followed by Persian (n = 6 [8.2%]) and other breeds (Abyssinian, Siamese and Norwegian Forest Cat) (n = 5 [6.8%]). Fifty-five (75.3%) were spayed females and 18 (24.7%) were intact females at the time of presentation. Twenty-four (32.9%) had a history of previous oral contraceptive administration (information was unknown for 10 cats). Fifty-five (75.3%) cats were previously submitted to mammary surgery (15 cats [27.3%] had a partial mastectomy, 37 [67.3%] had a unilateral mastectomy and three [5.5%] had a bilateral mastectomy) and developed metastatic disease, 18 (24.7%) were diagnosed for the first time with mammary carcinoma and had distant metastasis (de novo metastatic FMC).

Before stage IV diagnosis, 19/55 cats previously submitted to surgery received chemotherapy treatment. Eleven cats were treated with MC (cyclophosphamide 15 mg/m^2 PO q24h with meloxicam for 6 months or until disease progression) and eight with doxorubicin (1 mg/kg every 3 weeks, for four cycles).

Regarding all cats in the study (n = 73), at the time of detection of metastatic disease, 39 (53.4%) cats were symptomatic. Reported clinical signs included: dyspnoea/cough (n = 17 [43.6%]), anorexia (n = 12 [30.8%]), weight loss (n = 5 [12.8%]) and a combination of these signs (n = 5 [12.8%]). Table 1 summarises some of the clinical characteristics for the cats included in the study.

Regarding the detection of metastatic disease, 64 (87.7%) cats underwent thoracic radiography and abdomen ultrasonography and nine (12.3%) had a total body CT. Nineteen (26%) cats underwent biopsy and 28 (38.4%) cats had cytology of suspicious lesions to confirm metastatic disease (confirmed in all cases). Twenty-six (35.6%)

Table 1 Baseline characteristics of cats with metastatic mammary carcinoma according to adjuvant chemotherapy treatment

Variable	Total cases (n = 73)	No treatment (n = 39)	Group 1 (n = 9)	Group 2 (n = 15)	Group 3 (n = 10)	*P* value
Metastatic disease						0.255
Metastatic	55	27	9	12	7	
De novo metastatic	18	12	0	3	3	
Presence of clinical signs						0.020
Symptomatic	39	27	4	6	2	
Asymptomatic	34	12	5	9	8	
Duration of signs (days)*						0.924
>5	18	13	2	2	1	
⩽5	21	14	2	4	1	
Concomitant mammary disease						0.419
Yes	42	22	5	7	8	
No	31	17	4	8	2	
Pleural effusion						0.749
Yes	25	15	3	5	2	
No	48	24	6	10	8	

Group 1 received the maximum tolerated dose; group 2 received metronomic chemotherapy; and group 3 received toceranib phosphate
*Median set as cut-off value; n = 39

Table 2 Adverse events (AEs) recorded in cats with metastatic mammary carcinomas, according to chemotherapy treatment groups

	Group 1 (n = 9) MTD	Group 2 (n = 15) MC	Group 3 (n = 10) TP
Number of cats with AEs	6 (66.7)	3 (20.0)	3 (30.0)
AEs recorded for each cat (number of episodes/cat)	Case 1: Anorexia grade 2 (3) Case 2: Anorexia grade 2 (3) Case 3: GI grade 3 (3) Case 4: Anorexia grade 3 (1), GI grade 3 (1) Case 5: GI grade 2 (2) Case 6: GI grade 1 (5)	Case 1: Renal grade 2 (1), GI grade 1 (2) Case 2: Anorexia grade 1 (3) Case 3: Renal grade 2 (1), GI grade 2 (3)	Case 1: Anorexia grade 2 (3), GI grade 2 (2) Case 2: Anorexia grade 1 (1) Case 3: BM grade 1 (4)
Dose decrease	3 (33.3%)	1 (6.7%)	1 (10%)
Hospitalisation	1 (11.1%)	0 (0%)	0 (0%)

Data are n (%) unless otherwise indicated
AEs, adverse events; BM, bone marrow; GI, gastrointestinal; MTD, maximum-tolerated dose; MC, metronomic chemotherapy; TP, toceranib phosphate

cats were assumed to have lung metastasis based only on radiographs or CT scan. Sixty-three (86.3%) cats had pulmonary metastases, four (5.5%) had hepatic metastasis, four (5.5%) metastases in multiple sites (one hepatic and renal, two hepatic and spleen, and one pulmonary, skin and rib) and two (2.7%) had skin metastasis. Nine (12.3%) cats were submitted to palliative surgery for local mammary tumour cytoreduction.

Adjuvant treatment groups

Group 1 (MTD) included nine (12.3%) cats; group 2 (MC) included 15 (20.5%) cats and group 3 (TP) included 10 (13.7%) cats. Thirty-nine (53.4%) cats were not submitted to adjuvant chemotherapy treatment. All groups were well balanced and without any significant differences between clinical variables except for the presence of signs at diagnosis ($P = 0.020$; more symptomatic animals in non-treated cases) (Table 1). Considering only treatment groups (groups 1, 2 and 3), no statistical differences were observed ($P > 0.05$).

Of the group 1 (MTD) cats, seven (77.8%) cats were treated with doxorubicin as a single agent (1 mg/kg every 3 weeks) and two (22.2%) cats with carboplatin (250 mg/m^2 every 3 weeks). The median number of treatments were two (range 1–4). Of the group 2 (MC) cats, 11 (73.3%) cats received cyclophosphamide (15 mg/m^2 PO q24h) and four (26.7%) received chlorambucil (range 0.4–0.6 mg/kg every other day [EOD]). The median duration of MC treatment was 60 days (range 8–400 days). Of the group 3 (TP) cats, 10 (100%) received TP (range 2.4–3.3 mg/kg EOD). The median duration of treatment was 55 days (range 35–300 days). All cats (treated and not treated) included in the study, received supportive analgesic therapy according to clinical evaluation (meloxicam, buprenorphine and/or gabapentin).

Toxicity

The AEs in each group of treatment are given in Table 2. In group 1, one cat needed hospitalisation (severe anorexia and gastrointestinal signs) and stopped treatment, and three other cats needed a 25% dose decrease owing to moderated anorexia and gastrointestinal signs. In group 2, one cat needed a dose decrease (cyclophosphamide 10 mg/m^2 EOD) owing to moderate gastrointestinal signs, and in group 3 one cat stopped treatment administration for 1 week owing to slight gastrointestinal signs but continued with treatment thereafter.

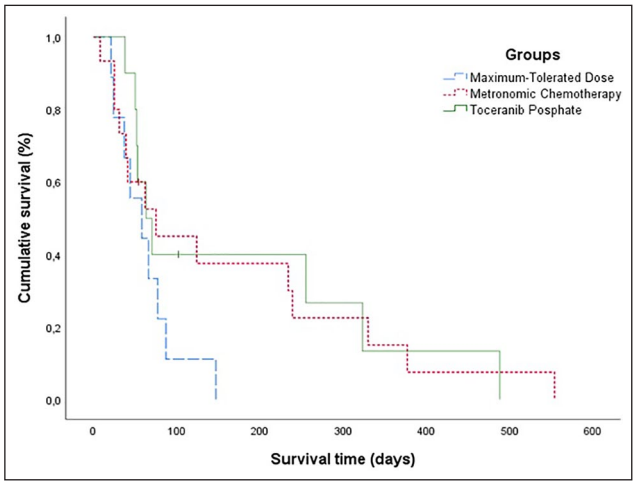

Figure 1 Kaplan–Meier survival curve for tumour-specific survival (TSS) of cats with metastatic mammary tumours, according to treatment groups. Median TSS was 58 days, 75 days and 63 days for groups 1 (maximum tolerated dose), 2 (metronomic chemotherapy) and 3 (toceranib phosphate), respectively. Differences were not statistically significant ($P = 0.197$). Censored cats are indicated by tick marks

Outcome and prognosis

Overall, median TTP was 23 days (range 0–342 days; 95% CI 7–39) and median TSS was 44 days (range 0–554 days; 95% CI 28–60). Cumulative survival at 6 months was 19.4%. TTP and TSS according to treatment groups are presented in Figure 1. For cats receiving adjuvant treatment, TTP was 50 days (95% CI 27–73) and TSS was 63 days (95% CI 46–79). Prognostic factors for TSS are given in Table 3. Kaplan–Meier curves associated with the

presence of signs and of pleural effusion are presented in Figures 2 and 3, respectively.

Overall, 19 (26%) cats had SD, while 54 (74%) had PD. After stage IV diagnosis, nine (12.3%) cats developed new tumours in the mammary gland. At the end of the study, 66 (90.4%) cats died of cancer-related causes, six (8.2%) were alive and one (1.4%) was lost to follow-up.

Table 3 Median tumour-specific survival (TSS) time for clinical characteristics in 73 cats with metastatic mammary carcinomas

Variable	n = 73	Median TSS (days)	95% CI	Six month cumulative survival (%)	*P* value*
Metastatic disease					
Metastatic	55	39	26–52	13.8	0.048
De novo metastatic	18	128	9–246	30.5	
Presence of clinical signs					
Symptomatic	39	14	5–23	2.7	<0.001
Asymptomatic	36	128	25–231	55.6	
Duration of signs (days)					
>5	18	8	0–30	0	0.595
⩽5	21	14	0–28	0.05	
Pleural effusion					
Yes	25	16	1–30	4	<0.001
No	48	64	46–81	22.7	
Location of metastasis					
Lungs	63	58	41–75	22.6	0.001
Hepatic	4	21	4–38	0	
Multiple	4	1	0–3	0	
Skin	2	37	36–38	0	
Mastectomy after stage IV†					
Yes	9	323	105–540	51	0.012
No	64	37	21–53	15	

**P* value for log-rank test (median TSS)
†Partial mastectomy after stage IV diagnosis with a palliative intent

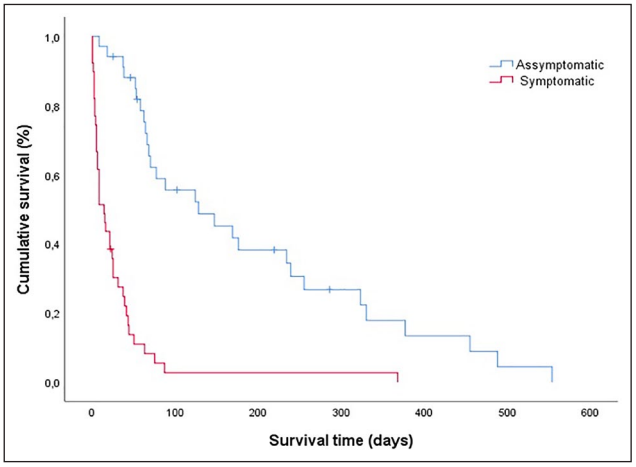

Figure 2 Kaplan–Meier survival curve for tumour-specific survival (TSS) of cats with metastatic mammary tumours, according to the presence of signs at diagnosis. Median TSS was 14 days for symptomatic cats and 128 days for asymptomatic cats. Differences were statistically significant ($P < 0.001$). Censored cats are indicated by tick marks

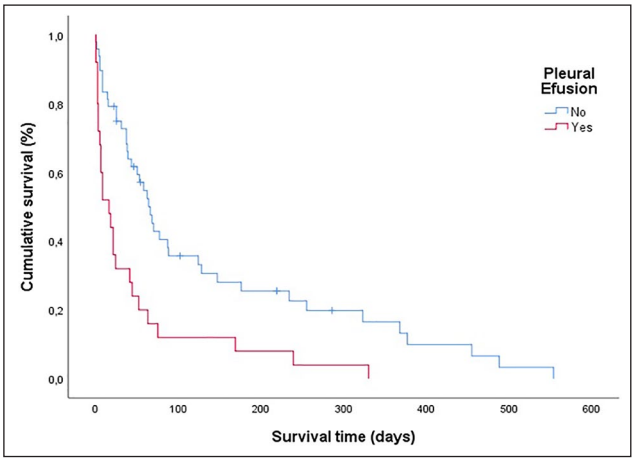

Figure 3 Kaplan–Meier survival curve for tumour-specific survival (TSS) of cats with metastatic mammary tumours, according to presence of pleural effusion at diagnosis. Median TSS was 16 days for cats with pleural effusion and 64 days for cats without pleural effusion. Differences were statistically significant ($P < 0.001$). Censored cats are indicated by tick marks

Discussion

Mammary carcinomas are one of the leading causes of cancer-related deaths in middle-aged and older cats.[7,21] The poor prognosis associated with this disease, mainly attributed to the high metastatic rate, makes it undeniable that most FMCs will be incurable.[1,3] As such, managing patients with metastatic disease, achieving disease control and improving quality of life will be, at some point, the main goals of treatment. In past years, several reports have been published on feline mammary tumours, but only a few have addressed patients with metastatic disease.

Based on the results obtained in the present study, metastatic FMC has a poor prognosis associated with an overall median survival time of 44 days. These results are similar to previous studies, which report survival times ranging from 1 to 3 months.[9,16] Itoh et al[9] describe that all 29 cats in their study with metastasis and without treatment died within 5 months of diagnosis. Nonetheless, according to our results, survival ranged from 0 to 554 days, which supports the heterogeneity of metastatic FMC and also suggests that survival may change according to several factors.

Regarding treatment options, no significant differences in progression and survival were found between treatment groups. However, we need to be aware that the present study has a relatively small number of animals and that additional studies with a high number of cases will be needed to confirm our results. The current literature describes doxorubicin protocols as a therapeutic option for palliative treatment.[8,15,16] However, as previously stated, the majority of these published studies included cats in different WHO stages, which makes it difficult to validate the real benefit of treatment in metastatic disease. In contrast to published reports, here MTD did not improve survival when compared with other treatments and was associated with a high number of AEs, often requiring dose reduction and supportive care.

However, MC has been proposed for treatment in several aggressive cancers in dogs.[22,23] In women with metastatic breast cancer, MC is an alternative to conventionally scheduled MTD treatment and an attractive approach to improving outcomes in aggressive breast cancers.[14,24] Owing to the similarities shared in mammary cancers between cats and humans, we had hypothesised the same benefit, which was not proved.[11,25] The fact that MC did not improve survival in the present study could be related to the rapid progression of the tumour not giving us enough time to prove efficacy, as reported by other authors.[26]

Likewise, TP has been previously described as a possible treatment option in some tumours in cats as it is a tyrosine kinase inhibitor, with an antiangiogenic and antitumoral effect.[27–30] In humans, small-molecule inhibitors are used in advanced breast cancer as a first-line treatment or when conventional treatment fails.[13,31] As tumour angiogenesis plays a vital role in tumour growth and metastases in a variety of cancers, the inhibition of vascular endothelial growth factor receptor could offer some clinical benefit in FMC.[32,33]

Regarding toxicity assessment, the results were in line with previous studies comparing MTD with MC.[26] Toxicity associated with MC or TP was low in these cats, as reported in other studies evaluating these therapies.[27,34] In humans, the aims of intervention in metastatic breast cancer are to relieve symptoms, prolong life and an adequate quality of life, with minimal adverse effects.[35] Applying the same principles to metastatic FMC, MC or TP appear to be more reasonable choices than MTD.

Furthermore, according to the present study, several clinical manifestations can be considered useful negative prognostic factors. The presence of signs at diagnosis and pleural effusion appear to be the more significant and important negative prognostic factors. These have also been described for cats with primary lung cancer.[36] Yet, asymptomatic cats with primary lung carcinoma appear to have longer overall survival times. Despite the same location, the prognosis and evolution of primary lung carcinoma and metastatic FMC do not appear to be the same. Pleural effusion is also a main concern in cats with primary or secondary lung neoplasia and is associated with a poor prognosis. In contrast to the results in the present study, Yakunina and Treshalina[8] suggest the use of doxorubicin combined with docetaxel and describe a median survival of 2.8 months for cats with pleural effusion secondary to FMC.

It is noteworthy that these prognostic factors may help predict outcome and guide decision-making. In this study, nine cats with de novo metastatic stage IV were submitted to palliative mammary surgery with a median survival time of 322 days. Resection of the primary tumour appears to influence the prognosis and improve outcome in metastatic breast cancer. Several mechanisms have been proposed to explain this benefit, such as the disruption of self-seeding of the primary tumour, cancer stem cell elimination and overall reduction tumour burden.[37–40] Tumour manipulation can also lead to tumour cell destruction and releasing tumour-associated antigens into circulation, improving immune response by an abscopal effect.[41] As 57.5% of cats had local mammary disease at diagnosis and 12% of cats developed new mammary tumours and/or local metastatic disease after the diagnosis, local resection may be suggested and necessary to improve the quality of life, especially in ulcerated and aggressive local disease. However, possible negative prognostic factors and the clinical score of the patient, namely anaesthetic risk and quality of life, should be considered.

This study has some limitations mainly due to its retrospective nature. As there were only medical records available, quality of life during treatment may not be accurately captured, so only AEs were reported. Imaging

examinations for the detection of metastatic disease were not standard and could influence survival as CT scans are more sensitive in the detection of metastatic burden, namely pulmonary nodules.[42] Additionally, as the decision of adjuvant treatment was left for the owners, there were a superior number of symptomatic cats that did not receive adjuvant treatment, which might reflect a selection bias. Prospective randomised clinical trials are necessary to clarify the role of adjuvant treatment in cats with metastatic disease.

Nevertheless, to the best of our knowledge, this is the largest study on metastatic FMC. In the past decade, the introduction of screening programmes and advancements in treatments decreased human breast cancer mortality by 25–38%.[12] In a few years, we hope to achieve the same reduction in FMC-associated mortality. New studies addressing the treatment of FMC at different stages will hopefully allow us to treat our patients better.

Conclusions

Metastatic FMC has a poor prognosis and the role of adjuvant therapy is yet to be confirmed. Asymptomatic cats appear to have superior survival times. In order to improve the quality of life, palliative local surgery may be performed. More studies are warranted to improve prognosis.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animals described in this work (either experimental or non-experimental animals) for the procedures undertaken (either prospective or retrospective studies). No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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