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Effect of perioperative desmopressin in cats with mammary carcinoma treated with bilateral mastectomy

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Abstract

Perioperative administration of desmopressin has shown to significantly decrease rates of local recurrence and metastasis, and increase survival times in dogs with grade II and III mammary carcinomas. The objective of this study was to compare the oncologic outcome of cats with mammary carcinoma treated with bilateral mastectomy with or without perioperative administration of desmopressin. Medical records from nine veterinary institutions were searched to identify cats diagnosed with mammary carcinoma treated with bilateral mastectomy. Sixty cats treated with single-session or staged bilateral mastectomy were included. There were no significant differences in oncologic outcomes found between cats treated and not treated with desmopressin. No adverse effects were seen in any of the cats treated with perioperative desmopressin. Postoperative complications occurred in 18 cats (38.3%) treated with single-session bilateral mastectomy and in three cats (23.1%) treated with staged bilateral mastectomy (P = .48). Histologic grade and a modification of a proposed five-stage histologic staging system were both prognostic for disease-free interval. Incomplete histologic excision was associated with significantly increased rates of metastasis and tumour progression, and a shorter median survival time (MST). Cats that developed local recurrence also had a significantly shorter MST. The results of this study do not support the use of perioperative desmopressin to improve outcome when performing bilateral mastectomy for the treatment of mammary carcinoma in cats.

KEYWORDS

bilateral mastectomy, cats, desmopressin, mammary carcinoma

1 | INTRODUCTION

Mammary tumours are one of the most commonly diagnosed tumours in cats and malignant mammary tumours comprise more than 80% of all feline mammary gland masses.[1] Treatment options for mammary carcinoma include surgery, chemotherapy, radiation therapy, immunotherapy, and combinations of these modalities.[2] Surgery is the preferred first-line therapy.[2-4] The aggressiveness of surgical excision has a significant impact on outcome as median survival times (MSTs) are significantly better for cats treated with bilateral mastectomy (917 days) compared with either unilateral mastectomy (566 days) or local mastectomy (217 days).[2] More recently, a large multi-institutional study examined the outcomes of cats with mammary

Cell Line Validation Statement: Cell line validation was not conducted because cell lines were not used in this retrospective study.

carcinoma treated with either unilateral or bilateral mastectomy; bilateral mastectomy was an independent prognostic factor for survival with MSTs of 1140 and 473 days for cats treated with bilateral and unilateral mastectomy, respectively.[4] Complications associated with the various surgical approaches for treatment of mammary carcinoma have demonstrated a significant difference between cats treated with unilateral and bilateral mastectomy. A higher complication rate was reported for cats treated with single-session bilateral mastectomy (40.6%) than unilateral or staged bilateral mastectomy (21.3% and 35.7%, respectively); however, this difference was not significant.[4]

In addition to treatment with bilateral mastectomy; histologic grade, lymphovascular invasion (LVI), and lymph node metastasis are independent prognostic factors for cats with mammary carcinoma.[2,5,6] Other prognostic factors include tumour size, ulceration, presence of distant metastatic disease, tumour subtype, and proliferation status (as defined by the immunohistochemical markers Ki67 and AgNOR).[2,3,6-9]

Conflicting evidence exists regarding the benefit of chemotherapy in the adjuvant treatment of cats with mammary carcinoma. In one study, adjuvant doxorubicin-based chemotherapy resulted in a survival benefit for cats treated with unilateral mastectomy, but not with other mastectomy procedures.[10] In other studies, adjuvant chemotherapy resulted in a significant improvement in oncologic outcomes in cats treated with various mastectomy procedures; however, the impact of chemotherapy was not assessed between the different types of mastectomies performed.[2,4]

Desmopressin (1-deamino-8-D-arginine vasopressin or DDAVP) is a synthetic analog of anti-diuretic hormone (ADH, vasopressin). Desmopressin has traditionally been used in the management of diabetes insipidus and the prophylactic treatment of various bleeding disorders prior to surgical procedures because of its ability to stimulate the release of factor VIII and von Willebrand factor.[11,12] More recently, desmopressin has been studied as an adjuvant in the surgical management of oncologic cases.[13,14] The proposed mechanism of desmopressin for improving outcome in cancer patients is because of limiting the formation of tumour emboli and modulating tissue interaction at target organs.[15-18] Desmopressin increases intravascular fibrinolysis possibly by modulating secretion of urokinase, a profibrinolytic, allowing breakdown of the protective fibrin shell of circulating tumour cells and reducing subsequent trapping of tumour cells in target organs.[15-18] It is also thought to limit attachment of tumour cells by altering P-selectin expression on endothelial cells and platelets.[15,19]

Desmopressin has been shown to decrease the progression of breast cancer in both experimental murine and clinical canine studies.[15,20] Administration of desmopressin reduced the lung colonisation of murine mammary cancer lines,[15] and decreased lymph node and pulmonary metastases in murine mammary carcinoma models.[20] One study showed that desmopressin, administered at 1 μg/kg intravenously 30 minutes preoperatively and 24 hours postoperatively, resulted in significantly decreased rates of local recurrence and metastasis, and increased survival times in dogs with grade II and III mammary carcinomas; no major adverse effects were noted.[14] Additionally, application of desmopressin at a concentration of 1000 nM to canine mammary cancer cells resulted in a decrease in cell proliferation by 22%.[21] However, to the authors' knowledge, there are no studies examining the efficacy or safety of desmopressin usage in cats.

The primary objective of the present study was to retrospectively compare the outcome of cats with mammary carcinoma treated with bilateral mastectomy with or without perioperative administration of desmopressin. Our primary hypothesis was that cats receiving perioperative desmopressin would have significantly greater survival than cats not treated with perioperative desmopressin. Our secondary hypothesis was that cats receiving perioperative desmopressin would not have an increased rate of complications. The secondary objective was to examine postoperative complication rates in cats treated with single-session and staged bilateral mastectomies.

2 | MATERIALS AND METHODS

2.1 | Patients

Medical records from nine veterinary institutions were searched from 16th September 1991 to 31st December 2017 to identify cats diagnosed with mammary carcinoma and treated with bilateral mastectomy. The majority of these cats were included in a previously published retrospective study.[4] Medical records were reviewed, and owners and referring veterinarians were contacted when required to assess long-term outcome.

2.2 | Criteria for selection of cases

Cats with histologically confirmed mammary carcinoma treated with single-session or staged bilateral mastectomy were eligible for inclusion in the study. Informed consent was given by owners of cats that received perioperative desmopressin.

2.3 | Medical records review

Medical records were reviewed and the following information was recorded: age and bodyweight at time of surgery, gender (including neuter status if known), breed, history of prior treatment with progestins, history of previous gestation, and duration of clinical signs prior to examination by a veterinarian. The number, location, maximum dimension of the largest mammary mass, presence of ulceration, and presence of lymphadenomegaly were recorded. Preoperative imaging information included abdominal ultrasound and thoracic abnormalities.

Surgical data abstracted included whether desmopressin was administered perioperatively, whether bilateral mastectomy was performed as a single-session or staged procedure, if lymphadenectomy was performed, and intraoperative and postoperative complications.

Desmopressin was administered at 1 μg/kg intravenously 30 min preoperatively and 1 μg/kg intravenously 24 hours postoperatively. Intra- and post-operative complications were recorded. The pathology report was reviewed for completeness of excision, the Elston and Ellis (EE) histologic grade, presence or absence of LVI, and presence or absence of lymph node metastasis.

Cats were assigned a clinical stage according to the modified World Health Organization (WHO) tumour-node-metastasis (TNM) classification system described for feline mammary tumours (Table 1).[10] In this study, nodal status was largely determined following surgical resection, relying on histologic examination of the regional lymph node.

Tumours were also staged according to a modification of a proposed five-stage histologic staging system previously described in cats with mammary carcinoma (Table 2).[22] In this system, carcinomas were scored according to four criteria: local invasiveness, pathologic tumour size (pT), pathologic nodal stage (pN), and LVI. Briefly, local invasiveness was assessed using immunohistochemical staining of myoepithelial cells to enable distinction between mammary carcinomas *in situ* from invasive mammary carcinomas. pT (ie, the largest diameter measured on histologic slides) replaced clinically measured tumour size (T), excluding not only the skin but potential areas of mammary hyperplasia. For the purposes of this study, clinical tumour size was used because pT was not consistently reported in the histopathology reports. pN replaced clinical nodal stage, relying on histologic examination of the regional lymph node. Finally, LVI, the presence of tumour emboli within lymph and/or blood vessels, was used to complement lymph node evaluation in order to define the regional spread as a high proportion of their cases were of unknown pN.

For cats that received adjuvant chemotherapy, the agent used, the dosage, the number of doses, and whether the prescribed protocol was completed were recorded.

Outcome measures examined included local tumour recurrence, regional or distant metastasis, and survival. Tumour progression was defined as the diagnosis of local recurrence, nodal metastasis, or distant metastasis. The disease-free interval (DFI) was defined as the interval between the first mastectomy and tumour progression. Local recurrence was defined as a cytologically or histologically confirmed mammary carcinoma at or close to the previous resection site. If metastasis was suspected or confirmed based on physical exam, imaging, necropsy, cytology, or histopathology, the site of metastasis was recorded. Overall survival time was calculated from the date of mastectomy. The cause of death was noted when available. Tumour-related death was defined as death or euthanasia as a result of local recurrence, de novo tumour development, or regional or distant metastasis. Death because of an unknown cause was considered tumour related.

2.4 | Statistical analysis

Descriptive statistics were calculated for continuous variables. Continuous variables were tested for normality using skewness, kurtosis and Shapiro Wilk tests. The continuous variables were non-normally distributed so median and range were used to describe the variables. Frequencies and percentages were used to describe categorical variables.

Fisher's exact tests or Wilcoxon rank sum tests were used to assess for differences in characteristics of mammary masses and extent of disease between cats that received desmopressin and those that did not. Fisher's exact tests were performed to assess for associations between the procedure (single-session or staged bilateral mastectomy) and the development of postoperative complications, wound complications, or respiratory complications. Fisher's exact tests were also performed to assess for associations between the administration of desmopressin and the development of wound complications, requirement of revision surgery, development of respiratory distress, local recurrence, or development of regional or distant metastases.

Kaplan-Meier methodology was used to calculate the median DFI, MST, and 1- and 2-year survival rates. Cats were censored in the DFI analysis if they were disease-free at date of last follow-up or dead. Cats were censored in the survival analysis if they were lost to follow-up or alive at last follow-up. Log rank tests of Cox proportional hazard analysis were used for assessment of association of categorical variables (use of perioperative desmopressin and adjuvant chemotherapy administration) with DFI or survival time. Cox proportional hazards regression analysis was performed to assess for variable associations with time to tumour recurrence or metastasis, and

TABLE 1 Modified World Health Organization (WHO) clinical staging system for feline mammary tumours[10]

Stage	T—primary tumour size		N—regional lymph nodes		M—distant metastasis	
I	T1	<2 cm maximum diameter	N0	No histologic or cytologic evidence of metastasis	M0	No evidence of distant metastasis
II	T2	2–3 cm maximum diameter	N0		M0	
III	T1 or T2		N1	Histologic or cytologic evidence of metastasis	M0	
	T3	> 3 cm maximum diameter	N0 or N1		M0	
IV	Any T		Any N		M1	Evidence of distant metastasis

TABLE 2 Modified histologic staging system of feline mammary tumours[22]

Stage	T—primary tumour size	pN—nodal stage	LVI—lymphovascular invasion
I	T1 ≤ 20 mm	pN0 or pNX	LVI–
II	T2 > 20 mm	pN0 or pNX	LVI–
IIIA	T1 ≤ 20 mm	pN+	LVI+
IIIB	T2 > 20 mm	pN+	LVI+

Abbreviations: pN0, absence of nodal metastasis; pN+, presence of nodal metastasis; pNX, nodal stage unknown; LVI–, absence of lymphovascular invasion; LVI+, presence of lymphovascular invasion.

TABLE 3 Characteristics of mammary masses and extent of disease in 60 cats with mammary carcinoma treated with bilateral mastectomy that were administered (n = 15) and not administered (45) perioperative desmopressin

Category	Desmopressin	No desmopressin	*P* value
Number of tumours present	2 (1–4)	2 (1-4)	.55
Location of tumours (chain)[a]			.31
Right	5 (33.3)	9 (28.1)	
Left	8 (53.3)	12 (37.5)	
Bilateral	2 (13.3)	11 (34.4)	
Location of tumour (gland)[b]			
First (axillary)	3 (20.0)	14 (34.1)	.52
Second (thoracic)	8 (53.3)	11 (26.8)	.06
Third (abdominal)	7 (46.7)	15 (36.6)	.37
Fourth (inguinal)	5 (33.3)	24 (58.5)	.43
Largest tumour diameter (cm)[c]	1.6 (0.5-5.4)	2.0 (0.3-5.0)	.28
Ulcerated Tumour[d]	1 (6.7)	5 (12.5)	1.0
Modified TNM staging[c]			.28
Stage I	7 (50.0)	11 (28.2)	
Stage II	1 (7.1)	7 (17.9)	
Stage III	6 (42.9)	21 (53.8)	
Stage IV	0 (0.0)	0 (0.0)	
Modified histologic stage[c]			.26
Stage I	3 (21.4)	14 (35.9)	
Stage II	0 (0.0)	5 (12.8)	
Stage IIIA	8 (57.1)	10 (25.6)	
Stage IIIB	3 (21.4)	10 (25.6)	
Histologic grade[e]			.13
Grade I	0 (0.0)	6 (24.0)	
Grade II	4 (33.3)	9 (36.0)	
Grade III	8 (66.6)	10 (40.0)	

Note: Continuous data are given as median (range); categorical data are given as number (%).
[a]Data were missing for 13 cats that were not treated with perioperative desmopressin.
[b]Data were missing for four cats that were not treated with perioperative desmopressin.
[c]Data were missing for one cat treated with perioperative desmopressin and six cats that were not treated with perioperative desmopressin.
[d]Data were missing for four cats that were not treated with perioperative desmopressin.
[e]Data were missing for three cats treated with perioperative desmopressin and 20 cats that were not treated with perioperative desmopressin.

associations between the administration of desmopressin on survival time for histologic grade, and modified WHO TNM and histologic stage.

Statistical analysis was performed using commercially available software (SAS version 9.4, SAS Institute Inc., Cary, NC, USA.). A *P* value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Sixty cats treated with bilateral mastectomy met the inclusion criteria. The median age and body weight were 12 years (range 3-18 years) and 4.0 kg (range 2.7-7.9 kg). At the time of initial presentation there were 54 spayed females (90.0%), five intact females (8.3%), and one neutered male (1.7%). Parturition history was recorded for 34 cats; six cats (17.6%) had at least one litter and 28 cats (82.4%) were known to be nulliparous. One cat (1.7%) had previously been treated with progestins, 22 cats (36.7%) had not previously been treated with progestins, and previous treatment of progestins was unknown in the remaining 37 cats (61.7%). Breeds included 36 domestic short-hair cats, seven domestic long-hair cats, four Siamese, three each of domestic medium-hair and Persian cats, two each of exotic short-hair and Ragdoll cats, and one each of Birman, Himalayan and Turkish Angora cats. There was no significant difference in age, sex and neuter status, breed, body weight, parturition history, and previous treatment of progestins between cats treated and not treated with perioperative desmopressin.

Tumour location was reported in 56 cats. The first (axillary) glands were involved in 17 (30.4%), the second (thoracic) glands were involved in 19 (33.9%), the third (abdominal) glands were involved in 22 (39.3%), and the fourth (inguinal) glands were involved in 29 cats (51.8%). Tumours were located in more than one mammary gland in 35 cats (58.3%). The number of mammary masses, location of mammary masses (right, left, or bilateral) and which specific glands were affected, the maximum dimension of the largest mammary mass, and the presence or absence of ulceration, along with histologic grade, and assigned modified WHO TNM and modified histologic stage for cats treated and not treated with perioperative desmopressin are presented in Table 3.

Three-view thoracic radiographs were performed in 56 cats (93.3%) and abdominal ultrasonography was performed in 18 cats (30.0%). Pulmonary or intra-abdominal metastasis was not evident in any cat. Fine-needle aspirates of regional lymph nodes were performed in five cats and metastasis was diagnosed in two of these cats.

3.2 | Treatment and histologic results

Of the 60 cats, 47 (78.3%) were treated with a single-session bilateral mastectomy and 13 (21.7%) were treated with staged bilateral mastectomies. Perioperative desmopressin was administered to 15 cats, all from a single hospital, and 14 of these cats treated with single-session bilateral mastectomy (Figure 1).

Surgical time was reported for 54 cats (90.0%). The median surgical time was 65.0 minutes (range 33-180 minutes) for the 47 cats that underwent single-session bilateral mastectomy and 67.5 minutes (range 41-115 minutes) for both first and second unilateral mastectomies for seven cats treated with staged bilateral mastectomies. The median time between the first and second unilateral mastectomies in cats treated with staged bilateral mastectomies was 5.0 weeks (range 2.5-54 weeks). In one cat, a unilateral mastectomy was performed and a staged unilateral mastectomy was carried out 54 weeks later for treatment of a second mammary carcinoma in the contralateral mammary chain. This cat met the inclusion criteria for the study and hence was not excluded from analysis.

Regional lymph nodes (axillary or inguinal) were extirpated in 42 cats during single-session bilateral mastectomies. Seven cats treated with staged bilateral mastectomy had lymph node extirpation performed; six cats had lymph nodes extirpated during both their first

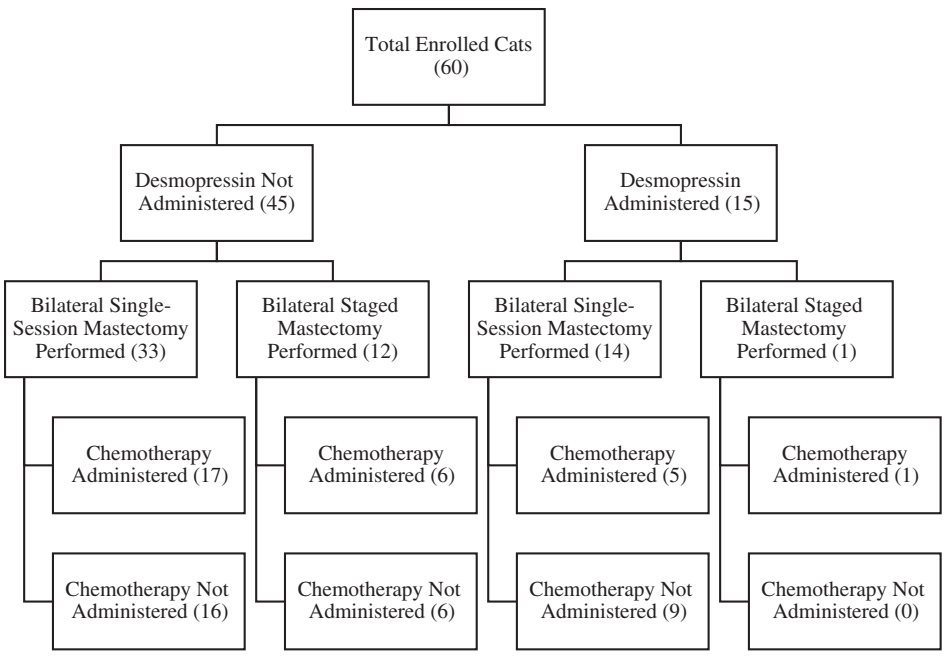

FIGURE 1 Breakdown of treatments in 60 cats with mammary carcinoma treated with bilateral mastectomy. A total of 47 cats were treated with single-session bilateral mastectomy and 13 cats were treated with staged bilateral mastectomy. A total of 29 cats received adjuvant chemotherapy, but drug therapies were not standardized across patients; some cats received more than one round of chemotherapy

and second unilateral mastectomies, and one cat during her second unilateral mastectomy.

Postoperative complications were noted in 18 cats (38.3%) treated with single-session bilateral mastectomy and in three cats (23.1%) treated with staged bilateral mastectomy. One cat treated with a staged bilateral mastectomy had postoperative complications following both surgeries. There was no significant difference in postoperative complications between cats treated with either single-session or staged bilateral mastectomies (P = .48). Wound complications were the most common postoperative complication in cats treated with single session (n = 17, 94.4%) and staged (3, 100.0%) bilateral mastectomies; there was no significant difference in the rate of wound complications between the two groups (P = .57). Of cats with wound complications, revision surgeries were performed in five cats (29.4%) treated with single-session bilateral mastectomies and one cat (33.3%) treated with staged bilateral mastectomy. Respiratory complications were noted in the postoperative period in two cats (11.1%) treated with single-session bilateral mastectomy. One cat developed respiratory distress because of the tension of the closure, and was treated with releasing incisions and opening the cranial aspect of the incision. This patient failed to respond to management and was euthanized. The second cat had a previous history of asthma and arrested in hospital; post-mortem results revealed subacute pneumonitis and alveolar thrombosis suggestive of toxic insult (oxygen toxicity) or an allergic immune response. No cat treated with staged bilateral mastectomy developed respiratory complications. There was no significant difference in respiratory complications between the two surgical groups (P = .72). Postoperative complications for cats treated and not treated with perioperative desmopressin are presented in Table 4. Clinically, no adverse effects were attributed to administration of desmopressin.

All 60 cats were confirmed with mammary carcinoma. Histologic grade was recorded in 37 cats: grade I (n = 6), grade II (n = 13) and grade III (n = 18). Completeness of excision was documented in 55 cats with complete histologic excision in 53 cats (96.4%, five cats with <2 mm and 48 cats with ≥2 mm histologic tumour-free margins) and incomplete histologic excision in two cats (3.6%). Lymphatic invasion was present in 23 cats (38.3%) and vascular invasion in seven cats (11.7%). Two cats (3.6%) had both lymphatic and vascular invasion; a total of 28 cats (46.7%) had LVI. Regional lymph nodes were assessed in 49 cats and lymph node metastasis was diagnosed in 19 of these cats (38.8%).

Twenty-nine cats were treated with adjuvant chemotherapy (Figure 1). Twenty-six cats were treated with a protocol where the main drug was either doxorubicin or epirubicin. Of these, 16 cats were treated with either doxorubicin or epirubicin alone, three cats each were treated concurrently with cyclophosphamide and carboplatin, two cats were treated concurrently with another chemotherapy drug, and one cat each was treated concurrently with another chemotherapy drug and carboplatin, and a combination carboplatin, cyclophosphamide and another chemotherapy drug. The remaining three cats received other chemotherapy drugs. Eighteen cats (62.1%) treated with adjuvant chemotherapy completed their course. Of these, nine cats were treated with either doxorubicin or epirubicin alone, three cats were treated concurrently with cyclophosphamide, one cat each was treated concurrently with carboplatin, carboplatin and another chemotherapy drug, and carboplatin, cyclophosphamide and another chemotherapy drug. No cats treated with either doxorubicin or epirubicin in combination with other chemotherapy drugs completed their chemotherapy course. All cats treated with other chemotherapy drugs alone completed their course. Of the 11 cats that did not complete their chemotherapy course, treatment was stopped in four cats because of progressive disease, three cats because of non-tumour related deaths, and one cat each for a delayed postoperative complication, extravasation of doxorubicin, and persistent gastrointestinal toxicity. One cat was being treated with chemotherapy at the time of data collection.

3.3 | Outcome

Seven cats (13.2%) were diagnosed with local recurrence. Median time to local recurrence was 342 days (range 32-1070 days). Five of these cats were treated with subsequent surgery and one cat was also treated with an alternating course of carboplatin and vincristine-cyclophosphamide chemotherapy. Incomplete histologic excision was significantly associated with tumour progression (hazard ratio [HR]: 31.8; 95% confidence interval [CI]: 1.9-524.6; P = .02). The disease progression rates were 30.2% and 100.0% in cats with complete and incomplete histologic excision, respectively.

Regional or distant metastasis was diagnosed in 16 cats (32.7%). Median time to metastasis was 269 days (range 55-966 days). Metastatic sites included the lungs (n = 13, 26.5%), regional lymph nodes (3, 6.1%), and other distant sites (3, 6.1%) including the spleen, brain, and peritoneal space. Incomplete histologic excision was also significantly associated with metastasis (HR: 21.1; 95% CI: 2.9-152.5; P = .02). The overall metastatic rates were 24.5% and 100.0% in cats with complete and incomplete histologic excision, respectively. Both local recurrence and distant metastasis were recorded in two cats, both were not treated with perioperative desmopressin. Local tumour

TABLE 4 Postoperative complications in 57 cats with mammary carcinoma treated with bilateral mastectomy that were administered (n = 15) and not administered (42) perioperative desmopressin

Complication	Desmopressin	No desmopressin	*P* value
Infection or dehiscence	7 (46.7)	13 (31.0)	.34
Revision surgery needed	1 (6.7)	5 (11.9)	.36
Respiratory distress	0 (0)	2 (4.8)	1.0

Note: Data are given as number (%).

recurrence, nodal metastasis, distant metastasis, and site of metastasis for cats treated and not treated with perioperative desmopressin are presented in Table 5.

Overall, the median DFI was 966 days (95% CI, 513 days; upper limit could not be calculated). The median DFI for cats treated and not treated with perioperative desmopressin was not reached and 966 days, respectively (P = .9). The lower 95% CI limit for cats treated and not treated with perioperative desmopressin was 266 and 344 days, respectively. The upper 95% CI limits could not be calculated for both groups. There were no significant differences in DFI between cats treated and not treated with desmopressin with respect to histologic grade or histologic or clinical stage. Overall, there was no significant difference in DFI for the modified WHO TNM staging scheme; however, there were significant differences in DFI when using the modified histologic staging scheme and histologic grade (P = .03 and .04, respectively). A summary of DFI and 1- and 2-year disease-free rates for the modified histologic staging scheme and histologic grades is presented in Table 6. There were no statistically significant associations between DFI and the number of tumours present, location of the tumour (chain and gland), maximum tumour dimension, ulceration of the tumour, LVI, lymph node metastasis, and adjunctive chemotherapy treatment.

At the time of completion of the present study, 16 cats were still alive, 15 cats had died or had been euthanised because of tumour-related reasons, 13 cats had died because of unrelated causes, and 16 cats were lost to follow-up. Median follow-up time of cats censored in the survival analysis was 383 days (range 3-3145 days). Of the 15 cats that had died or had been euthanized because of tumour-related reasons, 13 were euthanised because of distant metastasis, 11 of which were to the lungs, and one cat each died because of local recurrence and as a result of a postoperative complication. Of the 13 cats who died as a result of unrelated causes, six cats were euthanised following development of congestive heart failure, three cats were euthanised for poor quality of life unrelated to their mammary carcinoma, one cat arrested because of suspected oxygen toxicity (based on necropsy findings of subacute pneumonitis and alveolar thrombosis), and one cat each was euthanised following an undiagnosed intestinal mass, kidney failure and suspected bacterial cholangitis.

The MST for all cats and cats not treated with perioperative desmopressin was 3145 days (95% CI, 536-3145 days). The MST was not reached for cats treated with perioperative desmopressin, but this was not statistically significant (P = .9). There were no significant differences in survival time between cats treated and not treated with desmopressin with respect to histologic grade or histologic or clinical stage. Overall, the 1- and 2-year disease-specific survival rates were 66.8% at both time intervals for cats treated with perioperative desmopressin, and 81.6% and 61.7%, respectively, for cats not treated with perioperative desmopressin. Incomplete histologic excision and local tumour recurrence were associated with a significantly decreased MST (HR: 28.9; 95% CI: 4.0-210.2; P < .0001 and HR: 3.3; 95% CI: 1.0-10.4; P = .03, respectively). In the seven cats that developed local tumour recurrence, the MST for those that were treated with subsequent surgery was not reached. The MST for cats that developed local tumour recurrence and were not treated was 316 days (95% CI, 96-536 days); however, this was not significant (P = .06). A summary of MSTs and 1- and 2-year disease-specific survival rates for prognostic factors is presented in Table 7. There were no statistically significant associations between survival time and the number of tumours present, location of the tumour (chain and gland), maximum tumour dimension, ulceration of the tumour, LVI, lymph node metastasis, modified WHO TNM stage, modified histologic stage, histologic grade, and adjunctive chemotherapy treatment.

4 | DISCUSSION

This multi-institutional, retrospective study did not find a significantly improved outcome following perioperative administration of desmopressin in cats with mammary carcinoma treated with bilateral mastectomy. It has been well documented that surgical manipulation enhances the release of tumour cells into circulation, as demonstrated by reverse transcription polymerase chain reaction studies.[23,24] At the same time, surgery, perioperative factors (anaesthesia, blood transfusions, hypothermia, and postoperative infections), and the subsequent wound-healing response may permit tumour growth and metastasis by upregulating inflammation in the surgical bed allowing tumour cell adherence, causing systemic immunosuppression, and unleashing dormant metastases.[25,26] But there are also suggestions for new therapeutic approaches that may help reduce these risks.[25,26] Thus, when performing oncologic surgery, investigation of therapies that mitigate

TABLE 5 Disease-related events in 60 cats with mammary carcinoma treated with bilateral mastectomy that were administered (n = 15) and not administered (45) perioperative desmopressin

Variable	Desmopressin	No desmopressin	P value
Local recurrence[a]	2 (14.3)	5 (12.8)	1.0
Regional or distant metastasis[b]	3 (21.4)	13 (37.1)	.33
Lymph node	0 (0.0)	3 (8.6)	
Lungs	3 (21.4)	10 (28.6)	
Other distant site	1 (7.1)	2 (5.7)	

Note: Data are given as number (%).
[a]Data were missing for 1 cat treated with perioperative desmopressin and 6 cats that were not treated with perioperative desmopressin.
[b]Data were missing for 1 cat treated with perioperative desmopressin and 10 cats that were not treated with perioperative desmopressin.

TABLE 6 Disease-free interval (DFI) and 1- and 2-year disease-free rates in cats with mammary carcinoma treated with bilateral mastectomy with respect to histological stage and grade; CI: Confidence interval; Ref: Referent category for Cox proportional hazards analysis

Category	Median DFI	Hazard ratio (95% CI)	Disease-free Rate		*P* value[a]
			1-year	2-year	
Modified histologic stage					.03
Stage I	966	Ref.	78.6%	78.6%	
Stage II[b]	-	0.4 (0.0-3.9)	-	-	
Stage IIIA	518	1.8 (0.5-6.2)	66.1%	39.7%	
Stage IIIB	343	5.2 (1.4-19.2)	36.4%	0.0%	
Histologic grade					.04
Grade I	Not reached	-	75.0%	75.0%	
Grade II	802	1.6 (0.2-15.3)	74.0%	74.0%	
Grade III	518	3.4 (0.4-30.1)	55.0%	27.5%	

[a]*P* value for log-rank tests.
[b]The median DFI for cats with histologic stage II mammary carcinoma could not be calculated as only one cat was diagnosed with local tumour recurrence at 1022 days postoperatively.

TABLE 7 Disease-specific survival time and 1- and 2-year survival rates in cats with mammary carcinoma treated with bilateral mastectomy for statistically significant factors for median survival time

Category	Survival time		Survival rate		*P* value
	Median	95% CI	1-year	2-year	
Histologic excision					<.0001
Complete	3145 days	706-3145 days	81.8%	65.4%	
Incomplete	94 days	91-96 days	0.0%	0.0%	
Local recurrence					.03
Yes[a]	536 days	96 days	71.4%	42.9%	
No	3145 days	706-3145 days	83.4%	70.4%	

[a]The upper 95% CI limit could not be calculated.

the perioperative risk of cancer spread, such as administration of desmopressin to animals with mammary carcinoma, is appropriate. Previous studies performed in experimental mice models and spontaneously occurring mammary carcinomas in dogs have shown promising improvement in outcomes with the use of perioperative desmopressin.[13,14,20] This is the first study to investigate efficacy of desmopressin administration to cats with mammary carcinoma, which is particularly important as feline mammary carcinoma has been proposed as a model for invasive breast cancer in women.[27,28]

In this study, the perioperative administration of desmopressin at high doses was adopted from pilot and extended clinical trial in dogs with stage III or IV mammary carcinoma.[13,14] The original protocol described the administration of desmopressin at a clinically relevant dose recommended for dogs with von Willebrand's disease (vWD) 30 to 60 minutes prior to surgery.[13,29] Previous pharmacodynamic studies of desmopressin in normal dogs showed repeat administration of desmopressin within 24 hours was associated with a significantly diminished response.[30] A phase II dose-escalation trial found this protocol of perioperative desmopressin to be safe in women with breast carcinoma undergoing surgery as first treatment.[31] The therapeutic dose of desmopressin for human patients with type I vWD is 0.3 μg/kg IV.[32] Doses of 0.3 to 0.4 μg/kg have been found to induce maximal elevation of factor VIII activities in healthy human patients.[33-35] A progressively increased response in factor VIII was obtained in dogs with doses of 0.2 to 0.6 μg/kg, suggesting a greater dose of desmopressin is required in dogs to produce comparable haemostatic effects reported in women.[30] vWD is rarely recognized in cats and is limited in the literature to two single case reports, both diagnosed with type III vWD.[36,37] To the authors' knowledge, there are no studies investigating the effects of desmopressin on haemostatic parameters in cats. It is therefore possible that the protocol reported in dogs and used in the present study was either the incorrect dose or interval to achieve the desired haemostatic effects to reduce intraoperative tumour dissemination and improve outcomes.

Desmopressin is well-tolerated in dogs.[13,14] While the compound has few side effects, it may lead to fluid retention and hyponatraemia after repeated administration.[38] The evidence for elevated vWF levels as a risk factor for venous thromboembolism is weak, but some studies have demonstrated an association in patients with known cardiovascular disease.[38,39] Clinically, no specific intra- or postoperative complications were attributed to the administration of desmopressin in this study. Thus, based on this study, perioperative use of desmopressin at 1 μg/kg before and after surgery appears to be safe at this dose in cats. In the authors' experience, cats may have a short,

transient episode of mild hypotension after administration of the preoperative dose of desmopressin, but this resolves without additional intervention.

In previous studies, 28% and 36% of dogs with mammary carcinoma treated with perioperative desmopressin developed either local tumour recurrence or lung metastasis.[13,14] There are marked differences in the recommended dose of surgery between cats and dogs with mammary carcinomas. In dogs, there is no significant improvement in outcome with more aggressive mastectomy procedures.[40] In comparison, cats have a significant survival benefit with more aggressive mastectomy procedures and bilateral mastectomy is an independent prognostic factor for survival.[2] Moreover, cats treated with unilateral mastectomy have significantly higher local recurrence and regional and distant metastatic rates than cats treated with bilateral mastectomy.[4] Hence, cats treated with unilateral mastectomy may be more likely to benefit from perioperative desmopressin in comparison to cats treated with bilateral mastectomy. A similar finding was reported in a study of mammary carcinomas in cats where adjuvant doxorubicin-based chemotherapy protocols only provided a significant survival benefit in cats that underwent unilateral mastectomy and not other mastectomy procedures, including bilateral mastectomy.[10]

The EE method of histologic grading is an independent prognostic factor in feline mammary carcinoma and also represents the gold standard in assessment of invasive human breast cancer.[6,41-43] In other studies, the EE grading system has shown to have significant prognostic value for postsurgical survival in cats with mammary carcinoma.[5,44] Despite significant differences in DFI between histologic grades, a recent study supports the findings reported herein where histologic grading using the EE grading system was not significantly associated with survival time.[45] A limitation of the EE grading system is that tumour classification is heavily skewed toward grade II or III carcinomas.[6,45] In the present study, 35.1% and 48.6% of tumours evaluated were grade II and III, respectively. Interestingly, the 1- and 2-year disease-free rates for cats with grade I and II carcinomas were nearly identical in our study population, supporting the finding of other investigators that a grade II designation lacked prognostic value.[5] Modifications of both the EE grading system and histologic adaptation of the TNM clinical staging system have been proposed for feline mammary carcinomas with the aim of a more discriminating grading and staging method, respectively.[22,45] The modified WHO TNM staging scheme was not prognostic in this study; however, our results further validated the five-stage histologic staging system as a strong prognostic factor for DFI.[22] Similar to previously reported findings, this staging system identifies a very high-risk group (stage IIIB) of cats.

Improved outcome associated with bilateral mastectomy for the treatment of mammary carcinoma in cats has been suggested to be, in part, a function of the ability to achieve adequate local resection.[4] However, while the incomplete excision rate is higher in cats treated with unilateral mastectomy, it should be noted that significant differences have not been found between surgical procedures and margin status.[4,22] In this study, incomplete histologic excision was reported in 3.6% of cats. This is comparable to the previously reported incomplete histologic excision rate of 2.4% in cats treated with bilateral mastectomy.[4] Our results support those of previous studies where incomplete histologic excision has shown to be significantly associated with a higher rate of tumour progression and shorter MST.[4,22,46]

The development of local tumour recurrence was also a significant predictive factor for survival. Further surgical resection is warranted for cats with local tumour recurrence. While not significant (P = .06), the MST of cats treated with surgical resection of their recurrent disease was not reached, whereas the MST for untreated cats was only 316 days.

A common misconception is that single-session bilateral mastectomy is associated with a significantly higher complication rate than staged bilateral mastectomy.[4] In a recently published large retrospective study of cats with mammary carcinomas, a significant difference in complication rates was found between cats treated with unilateral and bilateral mastectomy, but not between cats treated with single-session and staged bilateral mastectomy.[4] Despite a higher complication rate in cats treated with single-session bilateral mastectomy,[4] this difference was not significant and the complications rates of single-session (40.6%) and staged bilateral mastectomies (35.7%) were numerically similar. One of the aims of this study was to explore the complication rate in more detail. Similar to the aforementioned study, there was a higher complication rate in cats treated with single-session bilateral mastectomy (38.3%) than cats treated with staged bilateral mastectomies (23.1%), but this was not significant. For single-session bilateral mastectomy, the complications in most cases were minor and consisted of wound dehiscence or surgical site infection. These were often managed conservatively with less than a third of cats requiring surgical intervention to address these postoperative wound complications. The cost of managing these minor complications and the recovery following surgical revisions, if required, would presumably be substantially less compared to the added cost and recovery time associated with a second unilateral mastectomy for cats treated with staged bilateral mastectomies. Single-session bilateral mastectomy is, however, associated with subjectively greater wound tension following primary closure of the defect, particularly over the costal arch and in the inguinal region.[47] This increased wound tension may decrease chest wall expansion, reduce lung volume, and lead to respiratory distress and death. Respiratory-related death was reported in one cat treated with a single-session bilateral mastectomy in the present study. In the experience of two of the authors (JL and MC), this complication is more likely in overweight and obese cats. To minimize the risk of this complication, the lateral margins of the planned bilateral mastectomy are marked after the cat has been anaesthetised and clipped, and the degree of wound tension is assessed by digitally opposing the marked lateral margins. If wound tension is subjectively determined to be mild, then a single-session bilateral mastectomy is performed; however, if wound tension is moderate to high, then a staged bilateral mastectomy is recommended. Thus, the surgeon should discuss with the client the risks of complications relative to costs and total recovery time of one vs two procedures, and additional anaesthesia and surgery with staged bilateral mastectomies.

Limitations include the retrospective nature of this study and the distribution and number of cats treated with perioperative

desmopressin. Only 15 cats were treated with perioperative desmopressin and all of these were treated at a single hospital and the majority of these cases were treated with single-session bilateral mastectomy. Full medical records were required for inclusion in the study, but treatments and postoperative staging were not standardised between doctors, institutions, and data contributors, which could contribute to error, bias, or confounding. As a result of the challenges of retrospectively classifying location of recurrence, there was no objective measure used to define "close" in regard to distance from previous resection site and this was subject to interpretation during data collection at each institution. Furthermore, 26.7% of cats were lost to follow-up and the outcome of these cats may have had an impact on the results of this study.

In conclusion, perioperative desmopressin appears to be safe in cats when administered at 1 μg/kg 30 minutes prior to and 24 hours after surgery; however, at this dose and schedule, perioperative desmopressin did not improve oncologic outcomes in cats with mammary carcinoma when treated with bilateral mastectomy. There was no difference in the postoperative complication rate between single-session and staged bilateral mastectomies, and the majority of these complications were mild and often able to be managed conservatively.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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