



Retrospective Study on Survival Time of Cats with Mammary Carcinomas Undergoing Surgery Alone or with Adjuvant Chemotherapy

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ABSTRACT

This retrospective study was carried out to evaluate disease free interval (DFI) and survival time of cats with mammary carcinomas that underwent mastectomy (RM) and adjuvant chemotherapy (RMAC) in 35 cats to remove the neoplastic mammary chain and regional inguinal lymphadenectomy. According to performed treatment, the cats were divided into two groups. The RM group (21 cats) received no adjuvant therapy, and the RMAC group (14 cats) received chemotherapy with mitoxantrone or doxorubicin. Histopathological margins were considered complete in all cases. Eight cats had histologically confirmed lymph node involvement at the time of surgery. Three cases were classified as stage I, 21 cases as II and eight cases as III. Nine cats had tumor recurrence (four cats of RM group and five cats of RMAC group) and 12 cats had distant metastasis to the lungs (six cats of each group). Mean and median survival times were 1625 and 2404 days in the RM group, while mean DFI was 815 days. In RMAC group, mean and median survival times were 719 and 690 days, while mean DFI was 549 days. Surgery remains the main treatment and more studies are necessary to evaluate the benefit of adjuvant chemotherapy.

Key words: Feline, Mammary carcinoma, Oncology, Surgery, Chemotherapy

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INTRODUCTION

Mammary tumors are usually malignant in cats, with high metastatic rate. Distant metastasis can occur to the lungs, pleura, liver, diaphragm, adrenal gland, spleen, kidney, uterus and ovary (Macewen et al., 1984; Ito et al., 1996; Castagnaro et al., 1998; Viste et al., 2002; Borrego et al., 2009; Gimenez et al., 2010; Matos et al., 2012; Morris, 2013; Mills et al., 2015; Campos et al., 2016). Neutered animals are less likely to develop tumors than intact cats (Misdorp et al., 1992).

Surgery is the main treatment for mammary tumors in cats. Complete surgical intervention may be adequate for treatment of small tumors. However, for cats with larger tumors, postoperative survival is reported to be <1 year and many of these cats die from metastatic disease. Adjuvant chemotherapy postoperatively may increase survival time in these cases (Mcneill et al., 2009).

Tumor size, extent of surgery, histologic grade, lymph node involvement, lymphovascular invasion, tumor size and tumor grade have been described as prognostic factors. Other factors that influence disease-free interval and survival are clinical staging, histologic subtype, molecular subtyping, overexpression of Her2, mitotic index, development of metastatic disease and location of metastatic disease (Macewen et al., 1984; Ito et al., 1996; Castagnaro et al., 1998; Viste et al., 2002; Gimenez et al., 2010; Matos et al., 2012; Morris, 2013; Mills et al., 2015; Campos et al., 2016; Marques et al., 2016; Soares et al., 2016).

The objective of this study was to investigate disease free interval (DFI) and survival time (ST) of cats with mammary carcinomas that underwent radical unilateral mastectomy (RM) or radical unilateral mastectomy with adjuvant chemotherapy (RMAC).

MATERIALS AND METHODS

A retrospective study evaluated 35 cats diagnosed with mammary carcinoma from August 2013 to August 2016, regardless of breed, age or reproductive status, were studied. Cats with distant metastasis at diagnosis and / or unresectable tumors were excluded of the study.

All cats underwent tumor staging before surgery including complete history, physical examination, measurement of tumors, Complete Blood Count (CBC), serum biochemistry profile, three view thoracic radiographs and abdominal ultrasound. The animal's reproductive status were classified as early spayed (ovariohysterectomy was performed less than 1 year old), late spayed (more than 1 year old) or intact. Oncologic examination included palpation of mammary nodules, gland localization, mass measurement and regional lymph node palpation.

An aggressive treatment (radical unilateral mastectomy or radical bilateral mastectomy in steps) was performed in all cases, and no aspiration or biopsies were performed prior to surgery. All cats underwent radical unilateral mastectomy. If tumors were present at both chains, staged bilateral mastectomy was performed (the other mammary chain was removed 4-8 weeks after the first surgery). A three-centimeter margin was obtained around tumors. For staging purposes, regional inguinal lymphadenectomy was performed in all cases. Axillary lymphadenectomy was performed if the lymph node was enlarged or visible during surgery. After histopathology, cats were classified according to the WHO TNM staging system (Owen, 1980).

The animals were divided in two groups, according to treatment. The RM group received no adjuvant therapy. The RMAC group received chemotherapy starting at the time of suture removal (15-30 days after surgery). The chemotherapy regimen consisted of four doses of doxorubicin (ADRIPLASTINA; Pfizer, Rio de Janeiro) administered at a dose of 20 mg/m², as a slow intravenous (IV) injection, once every 3 weeks. Mitoxantrone (EVOMIXAN; Evolabis, São Paulo) was administered at a dose of 6 mg/m², as a slow intravenous (IV) injection, once every 3 weeks in cats with evidence of renal disease. Ondansetron (VONAU; Biolab, Rio de Janeiro) was administered to all cats, at a dose of 0.5 mg/kg q 12 h, orally in the first seven days after chemotherapy, in order to prevent nausea.

Local recurrence was defined as the presence of a mass in the site of surgery (removed mammary chain) and new tumor was defined as presence of a mass in the other mammary chain, and these were determined by physical examination. Thoracic radiographs were performed every three months, or when there was clinical evidence of metastasis (dyspnea and/or cough). Cats that developed local recurrence or new tumors after treatment were offered surgery and those in which distant metastasis were found were advised for euthanasia when there was poor life quality.

All cases were included in the statistical analysis. The DFI was defined as the time from surgery until the development of local recurrence or metastatic disease. Survival was defined as the time from the original surgery until death from any cause. Median DFI and ST were determined by the use of the Kaplan–Meier product-limit method. Results shown are median number of days with 95% confidence intervals. The effect on survival and DFI of both groups, tumor size and regional metastasis were examined using Kaplan–Meier survival analysis with logrank and Wilcoxon tests.

Ethical Approval

This project was approved by CEUA (Comitê de Ética no Uso de Animais) of Fluminense Federal University, Brazil with the protocol n. 548.

RESULTS

Thirty-five cats with histologically confirmed mammary carcinoma were studied from August 2013 to August 2016. All cats were female and age ranged from 5 to 14 years old (mean 10 years). Twenty-five cats (71%) were mixed breed, six (17%) were Siamese, three (9%) were Persian and one (3%) was British shorthair. Mean weight was 4.32 kg. Nine cats (26%) were intact, four cats (11 %) were early spayed, 14 cats (40%) were late spayed and eight cats (23%) were spayed at unknown date.

Twenty-eight cats had a single tumor and seven cats had multiple tumors. Nodules were located in the caudal glands in 26 cases, in the cranial glands in eight cases and were multiple and poorly circumscribed in four cases. Eight cats (23%) had histologically confirmed lymph node involvement at the time of surgery. Three cases (9%) were histologically classified as stage I, 24 cases (69%) as stage II and eight cases (22%) as stage III.

None of the cats had prior surgeries for mammary tumors. Twenty-seven cats underwent unilateral mastectomy (77%) and eight cats underwent bilateral mastectomies performed in different surgeries (23%). Ovariohysterectomy was performed in all intact cats at the time of surgery prior to tumor removal. Histopathological margins were considered complete in all cases.

Ten cats had evidence of renal disease at the time of diagnosis based on sonographic abnormalities or evaluation of urinalysis, but only three cats had azotemia. These cats received subcutaneous fluid therapy (150 mL three times a week) during chemotherapy. Mitoxantrone was used instead of doxorubicin in these cats. Twenty-one cats were included in the RM group and 14 cats were included in the RMAC group. Two cats (14%) received doxorubicin chemotherapy and 12 cats (86%) received mitoxantrone chemotherapy. The most frequent adverse events of chemotherapy were azotemia (seven cases), leukopenia (four cases), anorexia (two cases) and vomiting (one case).

Nine cats (26%) had tumor recurrence (four cats of RM group and five cats of RMAC group) and 12 cats (24%) had distant metastasis to the lungs (six cats of each group). Seventeen cats of the study are dead, 13 because of disease progression or distant metastasis. The other four cats died due to unrelated causes (renal disease, hepatic lipidosis, soft tissue sarcoma and unknown cause). Eighteen (18/35) cats are still alive and being monitored, most of them free of disease. Mean and median survival times were 1625 and 2404 days in the RM group, while mean DFI was 815 days (Table 1). In the RMAC group, mean and median survival times were 719 and 690 days, while mean DFI was 549 days (Table 2 and Figure 1).

High grade tumors had significantly lower survival times and DFI. Grade III tumors had mean ST and DFI of 637 and 471 days, respectively, whereas grade II tumors 1405 and 756 days. Regional metastasis was also correlated to ST and DFI, as cats with metastasis to lymph node at the time of surgery had lower survival times, but there were no statistical significance (Figure 2). Tumor size was not correlated to prognosis.

Table 1. Age, breed, reproductive status, affected gland, histopathology, histological grade, regional metastasis, disease free interval, survival time and evolution of cats with mammary carcinoma treated with surgery alone (RM)

| Cat | Age | Breed | Reproductive status | Gland | Histopathology | Grade | LN | DFI | ST | Status |
|-----|-----|-------------------|---------------------|----------|-------------------|-------|----------------|------|------|----------------|
| 1 | - | Persian | Unknown spayed | A | Adenocarcinoma | I | N ₀ | 620 | 620 | Alive |
| 2 | - | Mixed | Early spayed | I | Adenocarcinoma | II | N ₀ | 568 | 568 | Alive |
| 3 | 9 | Mixed | Intact | I | Adenocarcinoma | II | N ₀ | 630 | 630 | Alive |
| 4 | 12 | Mixed | Early spayed | I | Adenocarcinoma | II | N ₀ | - | 1080 | Dead (Sarcoma) |
| 5 | 13 | Mixed | Unknown spayed | I | Adenocarcinoma | II | N ₀ | 960 | 960 | Alive |
| 6 | - | Mixed | Unknown spayed | I | Adenocarcinoma | II | N ₀ | 781 | 781 | Alive |
| 7 | 12 | Persian | Late spayed | I | Carcinoma in situ | I | N ₀ | 911 | 911 | Alive |
| 8 | - | Siamese | Unknown spayed | I | Adenocarcinoma | II | N ₀ | 633 | 633 | Alive |
| 9 | 10 | Mixed | Intact | A | Adenocarcinoma | II | N ₀ | 596 | 596 | Alive |
| 10 | 13 | Mixed | Intact | A | Adenocarcinoma | II | N ₀ | 473 | 473 | Alive |
| 11 | 11 | Mixed | Late spayed | I | Adenocarcinoma | III | N ₁ | 291 | 291 | Alive |
| 12 | - | Mixed | Unknown spayed | I | Adenocarcinoma | II | N ₀ | 120 | 120 | Dead (D) |
| 13 | 8 | Mixed | Intact | T, I | Adenocarcinoma | III | N ₁ | 360 | 360 | Dead (D) |
| 14 | 11 | Mixed | Late spayed | T | Adenocarcinoma | II | N ₀ | - | 7 | Dead (U) |
| 15 | 13 | British shorthair | Late spayed | T, A | Adenocarcinoma | II | N ₀ | 120 | 120 | Dead (D) |
| 16 | 14 | Siamese | Late spayed | A | Adenocarcinoma | II | N ₀ | 480 | 2404 | Dead (D) |
| 17 | 7 | Mixed | Late spayed | Multiple | Adenocarcinoma | II | N ₀ | 570 | 570 | Dead (D) |
| 18 | 5 | Persian | Early spayed | I | Adenocarcinoma | II | N ₀ | 1800 | 1800 | Alive |
| 19 | 8 | Mixed | Unknown spayed | I | Adenocarcinoma | I | N ₀ | 935 | 935 | Alive |
| 20 | 9 | Mixed | Intact | I | Adenocarcinoma | II | N ₀ | 990 | 1140 | Dead (D) |
| 21 | 12 | Mixed | Intact | Multiple | Adenocarcinoma | II | N ₀ | 999 | 999 | Alive |

*A: Abdominal gland; I: Inguinal gland; T: Thoracic gland; LN: Lymph node metastasis; D: Died from disease progression or metastasis; U: Died from unknown cause.

Table 2. Age, breed, reproductive status, affected gland, histopathology, histologic grade, regional metastasis, disease free interval, survival time and evolution of cats with mammary carcinoma treated with surgery and chemotherapy (Group RMAC).

| Cat | Age | Breed | Reproductive status | Gland | Histopathology | Grade | LN | Chemotherapy | DFI | ST | Status |
|-----|-----|---------|---------------------|----------|-------------------------|-------|----------------|--------------|-----|------|------------|
| 1 | 13 | Mixed | Early spayed | T | Adenocarcinoma | III | N ₀ | Mitoxantrone | 270 | 450 | Dead (D) |
| 2 | 11 | Siamese | Intact | A | Adenocarcinoma | II | N ₁ | Mitoxantrone | 700 | 700 | Dead (D) |
| 3 | 10 | Mixed | Late spayed | T, A | Adenocarcinoma | II | N ₀ | Doxorubicin | 70 | 180 | Dead (D) |
| 4 | 14 | Mixed | Intact | I | Adenosquamous carcinoma | III | N ₁ | Mitoxantrone | 570 | 630 | Dead (D) |
| 5 | 11 | Siamese | Late spayed | T | Adenocarcinoma | III | N ₀ | Mitoxantrone | 420 | 420 | Dead (CRF) |
| 6 | 12 | Mixed | Late spayed | T | Adenocarcinoma | II | N ₀ | Mitoxantrone | 379 | 379 | Alive |
| 7 | 10 | Mixed | Late spayed | I | Adenocarcinoma | III | N ₀ | Mitoxantrone | 398 | 398 | Alive |
| 8 | 10 | Siamese | Unknown spayed | I | Adenocarcinoma | II | N ₁ | Mitoxantrone | 743 | 743 | Alive |
| 9 | 13 | Mixed | Late spayed | T | Adenocarcinoma | III | N ₁ | Mitoxantrone | 360 | 690 | Dead (D) |
| 10 | 13 | Siamese | Late spayed | A | Adenocarcinoma | II | N ₀ | Mitoxantrone | 340 | 340 | Dead (D) |
| 11 | 10 | Mixed | Late spayed | I | Adenocarcinoma | III | N ₁ | Mitoxantrone | 720 | 1230 | Dead (D) |
| 12 | 7 | Mixed | Unknown spayed | Multiple | Adenocarcinoma | II | N ₀ | Mitoxantrone | 770 | 770 | Dead (HL) |
| 13 | 13 | Mixed | Late spayed | A | Adenocarcinoma | II | N ₁ | Doxorubicin | 886 | 886 | Alive |
| 14 | 10 | Mixed | Intact | Multiple | Adenocarcinoma | II | N ₀ | Mitoxantrone | 226 | 226 | Alive |

*A: Abdominal gland; I: Inguinal gland; T: Thoracic gland; LN: Lymph node metastasis; D: Died from disease progression or metastasis; CRF: Died from chronic renal failure; HL: Died from hepatic lipidosis

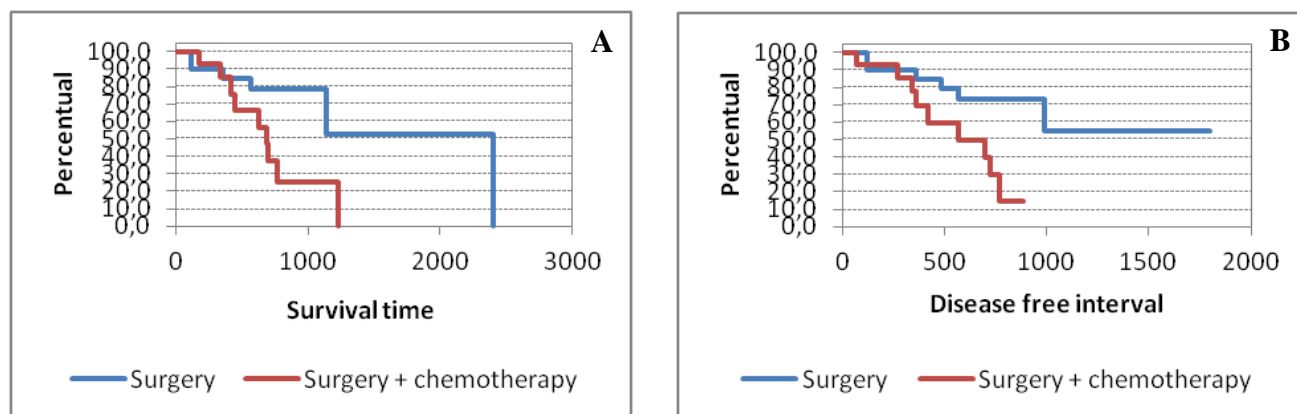


Figure 1. Kaplan-Meier survival plot of cats with mammary carcinoma according to treatment group (surgery or surgery and chemotherapy). A: Survival time in both groups. B: Disease free interval in both groups

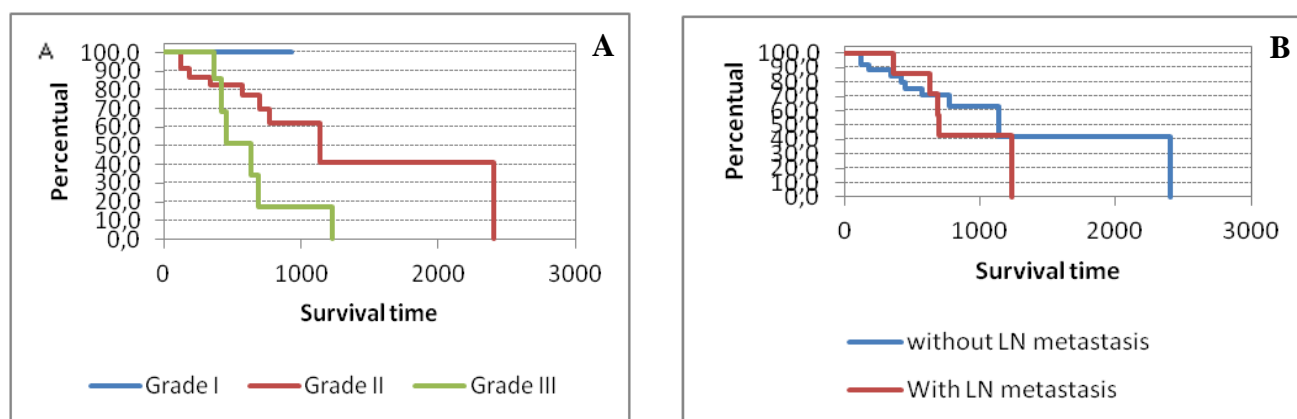


Figure 2. Kaplan-Meier survival plot of cats with mammary carcinoma according to tumor histologic grade (A) and presence of lymph node metastasis at surgery (B)

DISCUSSION

The mean age of cats in this study is similar to that reported in other studies (Borrego et al., 2009; Cunha et al., 2015). Intact or late spayed cats were the majority of cases in this study, suggesting that early ovariohysterectomy reduces the risk of developing a mammary tumor in cats (Misdorp et al., 1992; Overley et al., 2003).

Adjuvant chemotherapy is commonly recommended for the treatment of feline mammary tumors. However, few studies have evaluated the benefit of adjuvant chemotherapy (Jeglum et al., 1985; Novosad et al., 2006; Borrego et al., 2009; Mcneill et al., 2009; Campos et al., 2014; Cunha et al., 2015). The mean survival time of cats with mammary tumors undergoing surgery alone is only 10–14 months, with the vast majority of cats dying of metastatic disease (Castagnaro et al., 1998). Cats subjected to radical surgery plus doxorubicin had median survival times and median disease free interval of 448 and 255 days respectively in one study (Novosad et al., 2006) and disease free interval and survival time were 269 and 460 respectively when a cox-2 inhibitor was added (Borrego et al., 2009). In the present study, mean and median survival times were 1625 and 2404 days in RM group, with mean DFI of 815 days. In RMAC group, mean and median survival times were 719 and 690 days, with mean DFI of 549 days. There was no benefit in ST and DFI of cats that received adjuvant chemotherapy. A possible hypothesis is that the RMAC group had 42,8% mammary carcinomas staged as grade III, while the RM group had only 9,5% grade III tumors. High grade tumors would have a poorer prognosis despite adjuvant treatment (Seixas et al., 2011).

High grade tumors had significantly lower survival times and DFI, as previously reported (Preziosi et al., 2002; Seixas et al., 2011; Mills et al., 2015). Grade III tumors had mean ST and DFI of 637 and 471 days, respectively, whereas grade II tumors 1405 and 756 days. Most of cats with grade III tumors also had lymph node metastasis and were therefore submitted to adjuvant chemotherapy. Chemotherapy might have improved ST in these cases (Campos et al., 2014), but this data can't be analyzed in this study as only two cats with grade III tumors did not receive chemotherapy and ST couldn't be compared.

Eight cats (23%) had histologically confirmed lymph node involvement at the time of surgery. Three cases (9%) were histologically classified as stage I, 24 cases (69%) as stage II and eight cases (22%) as stage III. Cats with metastasis to lymph node at the time of surgery had lower survival times, but there was no statistical significance. The presence of lymph node metastases also showed statistically significant negative correlation with survival in previous studies (Mills et al., 2015). Tumor size was not correlated to prognosis in this study, which differs from Viste et al., 2002.

Cats with evidence of renal disease are not good candidates for doxorubicin chemotherapy because of its nephrotoxicity properties (O'Keefe et al., 1993). An alternative option for these cases is mitoxantrone (Cunha et al., 2015). Nevertheless, some cats (six cats) developed azotemia. Mitoxantrone should be administered with caution, especially in cats with renal disease. In conclusion, surgery remains the main treatment and adjuvant chemotherapy has not been proven to be of benefit. It may have a role in grade III tumors and/or cats with lymph node metastasis, yet to be defined.

Competing Interests

The authors have no competing interests to declare.

Author's contribution

The authors Simone Cunha, Katia Corgozinho and Heloisa Souza were responsible for the clinical, oncological, surgical and chemotherapeutic treatment of the cats, as well as the article writing. The authors Kassia Silva, Juliana Leite, Marcela Mello and Ana Ferreira performed the histopathology, and review of the manuscript.

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