

O – Oncology

ADVANCES IN THE TREATMENT OF MAMMARY NEOPLASIA

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MALIGNANT MAMMARY TUMORS IN CATS

Mammary epithelial tumors are the most common type of feline mammary tumor, with adenocarcinomas and solid carcinomas predominating. Mixed mammary tumors and mammary sarcomas are rare, and sarcomas appear to be slow to metastasize.

Mammary carcinomas are seen in older cats with a median age of 10 to 12 years. The risk for a female cat developing mammary carcinoma increases steadily with age especially if intact. The effect of neutering on development of mammary carcinoma in cats is less clear than it is for dogs however there is evidence to suggest that neutering may prevent mammary tumor development. In one study, the relative risk for a spayed female developing mammary carcinoma was approximately half that of an intact cat.

While domestic shorthaired and longhaired cats are most commonly reported with mammary carcinoma, only tricolored cats have been shown to be about twice the risk for developing the disease. Even more striking is the increased incidence of mammary carcinoma in the Siamese breed accounting for >25% of patients.

The signalment factors shown to be prognostic for survival after surgical resection of mammary carcinoma are breed (domestic shorthaired cats had longer survival times in one study), and age (older cats having worse survival rates).

Clinical Presentation and History

Mammary carcinomas in cats may remain undetected by an owner until they become quite large or ulcerative, even if a previous mass was detected. Thus, mammary carcinoma is often advanced by the time a veterinarian is consulted. Feline mammary carcinoma is an invasive and often rapidly metastatic tumor. A standard staging

protocol involves at least a minimum database (CBC, biochemical profile, urinalysis, T4 and FeLV/FIV) and thoracic radiographs. Careful visual and digital assessments of the extent of the primary and metastatic tumors are also essential. Multiple gland involvement may be seen and in some cats the entire mammary chain is affected either unilaterally or bilaterally, which probably indicates lymphatic spread rather than multiple synchronous primaries. There is frequent anastomosis between the thoracic and abdominal lymph drainage in cats, although there does not appear to be lymphatic anastomosis across the midline. The most frequently involved regional lymph nodes are the axillary or inguinal lymph nodes, although the sternal lymph node may be enlarged in some cats. In one study, 27% of cats had histologic evidence of mammary carcinoma metastases to the lymph nodes.

Pulmonary metastases occur more frequently than regional lymph node metastases. Pulmonary metastases usually appear as a miliary pattern on thoracic radiographs, and may obliterate normal lung. The clinical factors shown to be independent predictors of survival for cats after surgery for mammary carcinoma are; tumor diameter, with a worse prognosis for larger tumors; cats with small tumors had both longer remission after surgery and longer survival times.

Additionally, the finding of lymph node metastasis at diagnosis was highly associated with poor survival following surgery. Similarly the finding of distant metastases was a poor prognostic factor. Staging of cats according to WHO (World Health Organization) criteria takes into account the size of the tumor as well as the presence of lymph node or distant metastases. WHO staging in one study also found the presence of metastases to be a poor prognostic sign for survival after surgery.

Staging and Prognosis

WHO Stage	Median Survival (Months)	Description
I	29	T < 1 cm, no N
II	12.5	T < 1 cm and N or T = 1-3 cm + N
III	9	T > 3 cm, or T < 3 cm + fixed N
IV	1	Any T or N with M

Histologic grading systems rely on subjective appraisal of nuclear variation, mitotic figures, differentiation of epithelial elements, invasion of lymphatics or surrounding stroma, lymphoid

cellular reaction and ductular development. When used to classify tumors as well, moderately or poorly differentiated, there appeared to be prognostic value to this system.

Histologic grade and prognosis

Grade	Number of cats	%of total	Percent alive 12 months after surgery
Well-differentiated	7	12.7%	100%
Moderately differentiated	33	60%	54.5%
Poorly differentiated	15	27.3%	0

In another study, the presence of necrosis within the tumor, and an increasing number of mitotic figures were associated with shorter survival.

In summary, the clinician should take histologic findings of mitotic count, nuclear and cellular pleomorphism into account when looking for prognostic factors. These criteria when combined with staging information gained from thoracic radiographs, abdominal ultrasonography and the presence or absence of lymph node metastases, together with tumor size should allow the veterinarian to assess the prognosis for an individual cat with mammary carcinoma.

Treatment

Feline mammary carcinomas are invasive and the high rate of lymphatic involvement mandates aggressive treatment. The entire affected mammary chain should be removed with wide surgical margins, however the efficacy of this treatment is less clear than would be desired. Surgical excision alone is unlikely to result in a cure due to metastatic spread, however, the extent of surgery appears to play a role in reducing local recurrence and survival times. Studies that looked at the effect of conservative surgery (the affected gland and adjacent tissue) compared to radical surgery (unilateral or bilateral mastectomy) found there was no difference in survival between the two groups. However; the *histologic completeness* of resection appears to correlate with survival.

Due to the high metastatic potential of mammary carcinoma, chemotherapy would appear to be the most likely treatment modality to improve survival as an adjuvant to surgery. At the present time, doxorubicin appears to be the adjuvant chemotherapy drug of choice.

Radiation therapy has not been extensively used in the treatment of mammary carcinoma however, it may be effective in preventing local recurrence.

Supportive Care

Analgesia is essential during and after surgical removal of any mammary tumor. Antiemetics can be helpful at reducing the adverse effects of chemotherapy, and supplemental feeding methods and appetite stimulants must be considered in all patients to facilitate healing and prevent weight loss during therapy. In addition, treatment of underlying secondary problems such as renal or heart disease is important.

PROGNOSTIC FACTORS FOR DOGS WITH MAMMARY CARCINOMA

Somewhat surprisingly, the prognosis for dogs with mammary cancer is not influenced by either tumor location or number of tumors. Other factors that are not prognostic are number of pregnancies, age at first pregnancy and occurrence of pseudopregnancies. The following are prognostic factors that have been shown in studies to predict survival or disease-free interval.

Stage

Dogs with stage 1 tumors were more likely to survive longer than dogs with any other stage

tumor. This effect of tumor stage was similar in other studies and is detailed in the two Tables below.

Effect of tumor stage on survival.

Stage	Percent alive 1 year after surgery	Percent alive 2 years after surgery
1	97.9	97.9
3	75.8	66.4
4	13.6	13.6

Effect of tumor stage on survival.

Stage	Number of dogs	Median Survival Time (months)
1	8	17
2	7	14
3	14	7
4	6	3

Tumor Size

This is probably one of the most important prognostic factors for a dog with a mammary mass. Dogs with mammary tumors less than 3 cm in diameter have a significantly better prognosis than dogs with larger tumors, Tumor size is also a factor in the staging of mammary tumors, and stage is also an important prognostic factor.

high fat diet (> 39%), there was no difference in survival for the different intake levels of dietary protein. Dogs that have a mammary carcinoma may benefit from a low fat, high protein diet after surgery. These studies do not account for the type of fat consumed (eg: n-3 vs n-6 long chain fatty acid content) or for the carbohydrate content of the diet, all of which may influence outcome.

Metastasis

Metastases to regional lymph nodes has been associated with an increased risk for tumor recurrence and for decreased overall survival. Tumor stage, and specifically the presence of distant metastases, were found to be prognostically important in other studies. Those dogs with no metastases were more than 3 times as likely to survive one year from diagnosis.

Degree of Invasion and Ulceration

Dogs with tumors that ulcerate overlying skin have a worse prognosis (shorter overall survival times) than dogs with tumors without ulceration. Rapid and invasive growth correlates with a worse prognosis, which may be recognized as fixation of the tumor to the underlying skin. Vascular or lymphatic invasion is a poor prognostic factor; dogs with histologic evidence of invasion have a shorter median survival.

Age

Older dogs have a worse prognosis in some studies. It is unclear if this is due to tumor related factors or competing risks.

Histopathology

Important factors include histologic classification, degree of nuclear differentiation, and the presence of lymphoid accumulation. In general, the more highly differentiated the tumor, the better the prognosis. Dogs that have mammary cancer but no evidence of lymphoid cellular reactivity at the time of initial mastectomy have a threefold increased risk of developing recurrence within two years compared to those with such reactivity. Dogs with precancerous lesions have a nine-fold increased risk of developing mammary cancer in the future. Thus, precancerous lesions should not be dismissed as benign.

Diet and Body Weight

In one study, the effect of diet in the year prior to diagnosis on survival after surgery showed that dietary fat and dietary protein together influenced outcome. When dogs were categorized by the percent of total calories they derived from fat and protein, the median survival time for dogs fed a low fat diet (< 39%) with protein greater than 27%, 23-27%, and less than 23% was 3 years, 1.2 years, and 6 months, respectively. One-year survival for dogs on a low fat diet with 15%, 25%, and 35% of total calories derived from protein was 17%, 69%, and 93%, respectively. For dogs fed a

Dogs that have evidence of infiltration into adjacent tissue, or had permeation into lymphatics or blood vessels had a worse prognosis.

When reviewing a histopathology report, the clinician should look for information regarding completeness of the surgical excision; invasion into lymphatics or blood vessels, and differentiation of the tumor.

Hormone-Receptor Activity

Dogs with tumors that are estrogen- and/or progesterone-receptor positive have a better prognosis than dogs with tumors that do not have receptors, with longer disease-free and overall survival times. Receptor-positive tumors are likely to be benign.

Proliferative Activity

Dogs with tumors that showed a high proportion of Ki-67 staining (which is an immunohistochemical marker for cellular proliferation) were more likely to develop metastases in three studies. Additionally Ki-67 staining was inversely related to survival time.

Ovariectomy Status

In one study dogs that were intact at the time of surgery for a mammary carcinoma survived a shorter time (median survival 9.5 months)

compared to dogs ovariectomized within the 2 years before surgery (median survival 25 months). Dogs ovariectomized more than 2 years before mammary tumor surgery did not benefit to the same extent. In addition, dogs that were intact had a higher proportion of solid and anaplastic carcinomas than either group of ovariectomized dogs (80% solid carcinomas in intact dogs compared to 20% (<2 years) and 7% (> 2 years)). In contrast ovariohysterectomy at the time of tumor removal had no effect on survival in another study with approximately 60% of dogs with malignant tumors dying within 2 years of surgery whether they were spayed at the time or not.

Extent of Surgery

The extent of surgery influences neither survival nor disease-free interval but rather the histologic completeness of surgical margins as assessed by histopathology has been shown to be prognostic for survival so the best surgery to achieve complete margins is the surgery that should be offered.