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HOW I TREAT CANINE MAMMARY GLAND TUMORS

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INTRODUCTION

Mammary gland tumors (MGT) are the most common type of tumors in intact female dogs and rank second only to skin tumors in dogs of both genders. Approximately half of canine MGT are malignant and the remaining 50% are benign. All malignant MGT should be considered to have the potential for metastasis, but it is estimated that up to 50% can be well-controlled with local therapy only.1

DIAGNOSIS AND CLINICAL STAGING

Clinical evaluation of a patient with a mammary mass should include a CBC, chemistry profile, urinalysis and 3-view thoracic radiographs to check for metastatic disease. A surgical biopsy, typically an excisional biopsy, should be done as the initial diagnostic approach. Cytology of mammary masses is not considered reliable. Excisional biopsy may be therapeutic for dogs with benign tumors. Dogs with small, well-differentiated malignant tumors may be cured by excisional biopsy if the surgical margins are clean.

Status of the regional lymph node has a strong impact on survival so cytology or biopsy of the node should be evaluated in all dogs with malignant tumors. Palpation alone may be inaccurate to predict metastases since normal-feeling nodes may contain metastases. The 1st and 2nd glands drain to the axillary lymph node. Generally the axillary node cannot be aspirated unless it is grossly enlarged. The 4th and 5th glands drain to the inguinal node and the 3rd gland may drain to either node. The inguinal node should always be evaluated in dogs with tumors involving glands 3-5. If lymph node cytology is positive or questionable, a complete excision should be considered. It is controversial whether removing metastatic nodes significantly improves survival, but resection may improve local regional tumor control and prevent signs associated with progressive node enlargement.

SURGICAL TREATMENT OF CANINE MAMMARY GLAND TUMORS

Mammary Mass and Lymph Node Excision

Complete surgical excision is the single most effective modality for local control of canine MGT. The type of surgery does not necessarily influence survival as long as the entire tumor is removed with clean margins.2 Lumpectomy may be adequate for small tumors in any gland. For some tumors located in the 4th and 5th glands, a regional mastectomy with inguinal lymph node removal should be considered.

The decision to perform this procedure as opposed to a simple lumpectomy depends on the physical appearance of the mass and ability to evaluate the inguinal lymph node with cytology prior to surgery. If a caudally located mass is small (≤3-cm), well-circumscribed and cytology of the lymph node is normal, then lumpectomy would be indicated.

Inflammatory carcinomas are rare and present clinically as firm, hot, diffuse swellings in the mammary gland. Excisional biopsy is generally not recommended for these tumors, but instead an incisional biopsy should be done to confirm the diagnosis.

Ovariohysterectomy (OHE)

MGT in most intact female dogs contain estrogen receptors3 but most of the veterinary literature has not found a survival benefit in dogs with MGT that undergo OHE concurrent with tumor removal.4 The 2-year survival of dogs in one study that underwent OHE prior to mastectomy was 87% which was comparable to 88% for dogs that underwent OHE at the time of mastectomy or 88% for dogs that were left intact.2 One recent report, however, has shown a survival benefit. Dogs that underwent OHE concurrent or within 2 years before their mastectomy survived 45% longer (median, 755 days) than intact dogs (286 days) or dogs spayed more than 2 years before diagnosis (310 days).5 Since it may be an effective adjunct to mastectomy, OHE should be considered for intact dogs with MGT.

WHICH PATIENTS ARE CANDIDATES FOR ADJUVANT THERAPY?

Approximately 50% of canine MGT are benign and are cured with adequate surgical excision. The remaining tumors are malignant, but still, nearly half of these are cured with local surgery alone.1 When dogs with all types of malignant MGT are considered, the 2-year survival is estimated to be 75-90%.2,6

Histologic Features

Overall, approximately 36% of malignant epithelial tumors MGT may metastasize.1 11-32% of adenocarcinomas may metastasize1,7 while up to 57% of solid carcinomas and 46% of ductular carcinomas may metastasize.1 The decision to use adjuvant therapy should not be based solely on finding these histologic types. In contrast, other pathologic features such as vessel invasion and undifferentiated morphology or inflammatory carcinoma have all been associated with a guarded prognosis and would be indications for further therapies. In one study, the 2-year survival of dogs with tumors showing evidence of neoplastic emboli in vessels was only 60% compared to 90% for dogs without vessel invasion.6 In another study, dogs diagnosed with anaplastic carcinomas had a median survival of only 2.5 months.4

Inflammatory carcinomas are rare tumors and histologic evidence of dermal lymphatic invasion appears to be a hallmark. Palliative therapy with steroids or nonsteroidal anti-inflammatory drugs can be attempted but survival is generally less than 1 month.

Mammary gland carcinosarcomas and primary mammary gland sarcomas are rare and are associated with a high incidence of local recurrence and metastasis. The metastatic rate of carcinosarcomas may be as high as 100%1 and the median survival of dogs with mammary gland osteosarcomas may only be 90 days.

Metastatic Disease

Dogs with evidence of gross tumor metastases at diagnosis may have a median survival of only 5 months compared to 28 months in dogs without metastases.4

Tumor Size and Ulceration

Tumor size has been found to be an independent prognostic factor in many different studies.8 In one report, median survival was 22 months for dogs with tumors ≤3-cm compared to 14 months for dogs with tumors greater than 3-cm.4 Ulceration of the overlying skin has been associated with malignancy and has also been considered a negative factor. In a study by Pena, 54% of ulcerated MGT
metastasized while only 18% of non-ulcerated tumors metastasized. Tumor ulceration may be related to tumor size so this finding alone should not necessarily dictate the use of adjuvant therapy.

**WHAT TYPES OF ADJUVANT THERAPIES ARE AVAILABLE?**

**Chemotherapy**

There are a few reports evaluating various chemotherapy agents to treat malignant canine MGT. Doxorubicin, platinum drugs (cisplatin and carboplatin), 5-fluorouracil and cyclophosphamide have all been found to have either in vitro antitumor activity against a canine MGT cell line or in vivo efficacy when used to treat SCID mice transplanted with a canine MGT. Although clinical experience is limited, regression of non-resectable masses or metastatic lesions has been seen in some dogs. In the measurable disease setting, 2 consecutive cycles of single-agent chemotherapy are given. If no measurable response is observed, then a different chemotherapeutic should be considered. Response to therapy is determined by measurable reduction (at least 50%) in size or extent of disease.

There is only one trial evaluating the effectiveness of these drugs in the adjuvant setting. The 2-year survival of 8 dogs treated with surgery alone was 29% while that for 8 dogs treated with adjuvant 5-fluorouracil and cyclophosphamide was 100%. Other commonly used adjuvant protocols for dogs with MGT include single-agent doxorubicin, doxorubicin combined with cyclophosphamide or doxorubicin alternating with cisplatin.

**Anti-Estrogen Therapy**

In dogs, expression of estrogen receptors (ER) correlates with histologic differentiation so undifferentiated tumors that may benefit from adjuvant therapy are unlikely to be positive. Dogs with hormone receptor positive tumors are likely to benefit from anti-estrogen drugs such as Tamoxifen® but unfortunately commercially available assays to provide information of ER status in individuals are not readily available. Also, up to 25% of dogs experience adverse effects when treated with Tamoxifen® including vulvar swelling and pyometra.

**Radiation Therapy**

In a palliative setting, radiation therapy may help control local disease if a MGT is inoperable. Mammary gland sarcomas are rare, but may recur locally so adjuvant radiation should be considered if resection is incomplete.

**COX-2 Inhibition**

Up to 50% of malignant MGT may overexpress COX-2 so COX-2 inhibition with drugs such as Piroxicam® can be considered as an adjuvant therapy in some dogs. Clinical trials are not available and similar to most other approaches, multimodality therapy is likely to be of most benefit in dogs with aggressive tumors. Information about combining COX-2 inhibitors with conventional chemotherapeutics in dogs is limited and caution is advised.

**CONCLUSION**

Early surgical therapy to obtain clean margins remains the treatment of choice for most dogs with MGT. OHE at the time of MGT removal is of questionable benefit but may be a useful adjunct in select dogs. Based on limited clinical information, chemotherapy drugs may have a role in the treatment of dogs with malignant mammary tumors.

**REFERENCES**