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Canine mammary tumors: treatment, prognostic factors and outcome

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Abstract

Surgery represents the most important treatment modality in canine mammary tumors. The goal of surgery is to remove all current tumors +/- prevent new tumors in the mammary glands. Dogs with negative clinical or histopathological prognostic factors are not treated effectively with surgery alone. Systemic therapy, including OHE and/or chemotherapy may be considered for these dogs.

Surgical Treatment

Surgery is the mainstay of treatment in canine mammary tumors and can be curative in patients with benign tumors, low grade histology or early stage disease (small tumors). According to a large prospective randomized trial, there is no benefit to performing radical mastectomy compared to simple mastectomy, i.e. removing only the affected gland(s) in dogs with mammary tumors¹. No difference was found between remission and survival in dogs treated with radical versus simple mastectomy. Based on these findings, a standard surgical approach to mammary tumors has been adapted by many: Depending on the size, location and numbers of tumors, the surgery may include simple mastectomy, regional mastectomy radical mastectomy or a combination of these procedures. The goal of the surgery is to remove all current tumors with complete surgical margins. Prophylactic mastectomy of normal mammary glands is not indicated according to these guidelines. However, other publications have reported a very high incidence (50-95%) of new mammary tumors in dogs with a prior history of malignant tumors²,³,⁴. One of these studies included only dogs with one mammary tumor and concluded that an ipsilateral mastectomy should be performed in such patients based on the high incidence of new tumors in the same chain⁴. Another study included dogs with multiple tumors (70%), both sides were equally affected and new tumors developed in 50 % of dogs with prior malignant tumors³. These observations may suggest that prophylactic mastectomies may indeed have a role in selected high risk patients. However, there are currently no studies or guidelines to appropriately identify the dogs in which prophylactic mastectomy should be performed. Alternatively, owners should be advised that new tumors are common, further surgeries may be needed and therefore continued monitoring is important. However, some owners may be reluctant to subject their dogs to a second surgery. Unfortunately, an untreated new primary tumor and subsequent metastasis is, according to the
author’s experience, not an uncommon cause of death in some of these dogs. A simple mastectomy, i.e. removal of the entire affected gland rather than a smaller procedure such as a lumpectomy may also be considered in patients with small tumors; studies have found a high incidence of high grade pre-neoplastic lesions adjacent to malignant lesions. A simple mastectomy will prevent progression and subsequent new tumors developing from such lesions. Canine mammary tumors represent a wide range of clinical presentations and biological behaviors; it is therefore not likely that one standard surgical guideline is appropriate for all cases. Further research is needed to better identify cases that benefit from prophylactic mastectomy so that the recommendations can be tailored to a patient’s specific risk profile.

Prognostic Factors

Several prognostic factors have been identified in dogs with mammary gland tumors. These factors help identify patients that are not treated effectively with surgery alone and require systemic therapy. The most important clinical prognostic factors include tumor size, lymph node status and WHO stage. The histological prognostic factors include tumor type, histological grade and vascular invasion.

Clinical prognostic factors: Tumor size has been found to be prognostic according to many independent investigators. Three different size categories are described in both staging systems: T1: < 3 cm, T2: 3-5 cm, and T3: > 5 cm. There is general agreement that size have prognostic significance, and these size categories capture crucial changes in prognosis based on tumor size alone. In reality there is likely a gradual change in prognosis with increasing tumor size, but the current size categories provide reliable prognostic information.

Lymph node status is also important for prognosis. Metastasis to the local lymph node confirms a metastatic phenotype and implies metastasis beyond the affected lymph node. Several studies have confirmed that dogs with positive regional lymph nodes have a significantly worse prognosis than dogs with negative lymph nodes. In fact, tumor size becomes irrelevant if the local lymph nodes are involved. A positive local lymph node constitutes stage IV disease as indicated by the revised staging system, and is a clear indication for systemic therapy.

WHO stage (both original and revised) has been shown to have prognostic significance. Information regarding tumor size and lymph node status are incorporated into the staging systems and since both of these factors carry prognostic significance by themselves, it is therefore not surprising that WHO stage also is prognostic. Several studies have shown that dogs with lower stage disease have a significantly better prognosis than dogs with advanced stage disease.

Histopathological prognostic factors: Primary malignant mesenchymal mammary tumors (sarcomas) are associated with a guarded prognosis. Osteosarcomas are the most common primary mammary gland sarcomas and are characterized by aggressive biological behavior, similar osteosarcomas in other sites. The WHO staging system used for epithelial tumors does not apply here; and it is important to note that sarcomas usually do not metastasis via the local lymph node but rather via the hematogenous route; therefore dogs with primary mammary gland osteosarcomas have a poor prognosis despite the absence of lymph node metastasis. Tumor grade is also predictive of outcome in dogs with epithelial tumors. The presence or absence of tubule formation, nuclear pleomorphism, and number of mitosis per 10HPF are evaluated and scored. Tumors are graded as grade I: well differentiated, grade II: intermediate, and grade III: undifferentiated. Despite subtle differences these grading systems are nevertheless useful in identifying dogs with aggressive tumors. Dogs with simple carcinomas have a worse prognosis than dogs with other carcinomas, and the presence of histological and
vascular invasion is associated with a worse prognosis, and should therefore be considered when making decision regarding systemic therapy.8

Systemic Treatment and outcome

Dogs with large tumors, lymph node metastasis or unfavorable histology are not treated effectively with local therapy alone. Dogs with distant metastasis are not likely to benefit from surgery, but may be palliated with chemotherapy. The options for systemic treatment in canine mammary tumors include hormonal therapy in the form of surgical ovarian hormonal ablation, i.e. ovariohysterectomy and/or chemotherapy.

Hormonal therapy: The goal of hormonal therapy is to prevent carcinoma cells from receiving stimulation from hormones. This can be achieved through ovariohysterectomy (OHE) or medical means, such as specific estrogen receptor modulators (SERMS), suppression of estrogen synthesis by aromatase inhibitors or LHRH agonists. Tamoxifen, an estrogen receptor antagonist, commonly used in women with ER positive breast cancer, has also been evaluated in dogs, but due to the side effects, this is not a feasible option in dogs. OHE is a practical solution. The use of hormonal therapy in canine mammary tumors is based on the documentation of these tumors hormone dependence as well as the lessons learned from human breast cancer therapy where hormonal therapy has been found to significantly reduce recurrence and prolong survival in hormone receptor positive breast cancers. The results from the canine studies, all retrospective and non-randomized, however, are conflicting.9,10,11. Only a high powered prospective randomized trial where the effect of OHE stratified and analyzed in context of hormone receptor status can determine whether hormonal therapy has a role in dogs with mammary tumors.

Chemotherapy: Similar to hormonal therapy, there are no prospective randomized trials on the effect of chemotherapy in dogs with high risk tumors. Nevertheless, chemotherapy is often used in dogs with negative prognostic factors. A prospective non-randomized study showed a significant survival benefit in dogs with high risk tumors (WHO stage III) treated with a combination of cyclophosphamide and 5-fluorouracil12. Many oncologists also add doxorubicin to the above protocol. This is based on the fact that this is one of the most effective agents in high risk human breast cancer. No studies have confirmed its activity in dogs however. Primary mammary gland Osteosarcoma is highly aggressive and associated with a poor prognosis; similar protocols to those used for appendicular osteosarcomas may be useful in these cases. Case examples will be presented illustrating the use of systemic therapy and outcome in dogs with mammary tumors.
References


