

## Mammary Gland Tumors

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### Canine Mammary Gland Tumors (MGT)

#### 1) Etiology and Risk Factors

Three main factors have been identified to play an important role in mammary tumor risks: age, hormonal exposure, and breed.

MGTs are rare in dogs younger than 5 years old. Tumor risk increases with age and risk becomes significant at 7-8 years of age. Risk continues to increase until age of 11-13 years. Malignant tumors are found more often in older dogs.

MGTs are the most common neoplasm in sexually intact female dogs (50-70% of all tumors in this subset of the population). Incidence is lower in Canada and United States than in Europe due to common practice of spaying at a young age. Risk of developing mammary tumors is 0.5% if spayed before 1<sup>st</sup> estrus, 8% if spayed before the 2<sup>nd</sup> estrus, and 26% if spayed after 2<sup>nd</sup> estrus. Protective effect of spaying is lost after 2<sup>nd</sup> estrus because sex steroid hormones have already had their primary effect on target cells. Products that contain medroxyprogesterone (progestin and estrogen combination) used for prevention of estrus and treating pseudopregnancy have also been associated with an increased incidence of mammary tumor.

About 1% of mammary gland tumors occur in male dogs and can be associated with hormonal abnormalities (estrogen secretion by a Sertoli cell tumor).

MGTs tend to be more common in smaller breeds: Maltese, Yorkshire terriers, Cocker spaniels, poodles, Chihuahuas, and dachshunds. Larger breeds also at increased risk include: English Springer, Brittany spaniels, English setter, German shepherds, Pointers, and Dobermans. Mammary tumors in small breed dogs are more likely to be benign than in large breed dogs.

Obesity at a young age and feeding homemade diets (high in red meat) are also risk factors. Mechanism linked to carcinogenesis is likely via effects on serum estrogen levels. Obesity is associated with decreased concentration of sex hormone-binding protein resulting in elevated serum free estrogen levels. Adipose tissue may also be a source of increased estrogen production via aromatase-mediated conversion of androgens. Being underweight during puberty (9-12 months of age) provides protective effects against MGTs development later in life.

#### 2) Pathology

Approximately 50% of canine MGTs are malignant, half of which will eventually develop metastatic disease. Metastatic sites can include lymph nodes, liver, lungs, and bones.

The entire mammary chains are exposed to growth factors (hormones, insulin-like growth factor 1) and sex hormones, resulting in a field carcinogenesis effect. Most dogs develop tumors in multiple glands. Histologic progression with increasing tumor size happens in dogs with multiple tumors. Areas of transition (carcinoma *in situ*) are seen in benign tumors. Benign and malignant mammary tumors are not separate entities. They develop initially from benign lesions and progress to invasive malignant lesions as part of a continuum influenced by hormonal field effects on mammary tissues.

#### *Histologic classification*

- Simple: Neoplasm composed of one cell type (either luminal epithelial or myoepithelial cells)
- Complex: Neoplasm composed of both cell types (luminal epithelial and myoepithelial cells)
- Mammary hyperplasia and dysplasia (precursor lesions of mammary neoplasms)
- Benign mammary neoplasia  
Adenoma, ductal adenoma, fibroadenoma, complex adenoma, and benign mixed tumors
- Malignant epithelial tumors  
Various types of carcinoma: *in situ*, adenocarcinoma, SCC  
Grading system (Elston and Ellis): Grade 1 is well-differentiated, grade 2 is moderately differentiated, and grade 3 is poorly differentiated. Tumor grade is a reliable prognostic factor.  
Vascular/lymphatic invasion also predict behavior.
- Malignant mesenchymal tumors  
Osteosarcoma, chondrosarcoma, fibrosarcoma, hemangiosarcoma, and carcinosarcoma (malignant mixed mammary tumor)  
Sarcomas are not graded according to Elston and Ellis system. The majority tend to be biologically aggressive tumors associated with a poor long-term survival.

### 3) Clinical Features

Mammary tumors are often incidental findings during wellness exam or may be discovered by their owners. Over half of the patients will present with multiple masses. This may represent simultaneous primary masses or a primary lesion with regional metastasis.

There are 5 pairs of mammary glands in dogs: 2 thoracic, 2 abdominal, and 1 inguinal. The 2 caudal pairs are more commonly affected (glands are naturally larger). Lymph node metastasis may occur to either axillary or inguinal lymph nodes. The two thoracic glands generally drain to axillary and sternal lymph nodes. The inguinal glands are drained by the inguinal lymph nodes. The 2 abdominal glands may drain to either site.

Tumor-induced lymphangiogenesis can cause unpredictable and erratic location of lymph node metastatic disease (can even happen in the contralateral gland).

Presence of lymph node enlargement, lymphedema, skin ulceration, and fixation to underlying tissues are suggestive of malignancy.

Inflammatory mammary carcinoma is a specific entity characterized by a rapid progression and poor prognosis. Dogs present with warm, erythematous mammary tissue, lymphedema, ulceration, and significant pain upon palpation. It can be mistaken for mastitis. The diagnosis may sometimes become apparent only after wound dehiscence. Most of these dogs also have distant metastasis and signs of systemic illness.

#### 4) Diagnostic Approach

Cytology is used to rule out nonmammary tumors (mast cell tumor, lipoma), but usually cannot differentiate between benign or malignant epithelial tumor.

Histology provides the definitive diagnosis. Benign and malignant tumors may occur concurrently. It is necessary to submit all excised masses for histopathology, rather than assume one mass is representative of all the tumors present.

#### *Staging*

Cytology of any palpable lymph node is recommended to assess preoperative extent of disease.

Three view thoracic radiographs are essential before surgery as pulmonary metastases warrant a poor prognosis and may affect a client's willingness to treat their pet.

Abdominal ultrasound is indicated in dogs with suspected regional lymph node involvement or changes on preoperative bloodwork suggesting abdominal disease (tumor- and nontumor-related).

#### Modified WHO Stage

Stage I: Tumor <3 cm

Stage II: Tumor 3-5 cm

Stage III: Tumor >5 cm

Stage IV: Regional lymph node metastasis

Stage V: Distant metastasis

#### 5) Treatment

##### *Surgery*

Surgery is indicated for most mammary tumors, with the exception of inflammatory mammary carcinomas and patients with distant metastasis. The type of surgery is not a

major prognostic factor for survival in dogs as long as complete excision is confirmed by histologic assessment of surgical margins. Surgical standard of care is minimal but adequate tumor excision via lumpectomy or partial mastectomy. Lumpectomy is reserved for dogs with tumors <0.5 cm. Wide excision has not been well defined, but for larger tumors, a general recommendation of 2-cm lateral margin seems appropriate (and may be modified according to patient size). The deep margin may need to include abdominal muscular fascia and/or portions of abdominal wall depending on size and fixation.

An exception to this surgical standard is unilateral radical mastectomy can be recommended for intact dogs at presentation due to the high rate of second tumor development in the remaining ipsilateral tissue (58% of intact intact dogs treated with regional mastectomy developed a second mammary mass, 75% of which were malignant). Disadvantage of this recommendation is that about 40% of dogs are treated with a larger "surgical dose" than needed.

Controversy exists as to whether or not to perform ovariohysterectomy (OHE) at the time of mammary tumor excision. Early reports suggested no benefit to OHE at the time of tumor excision. A more recent study showed that dogs undergoing OHE were more likely to survive at least 2 years than dogs that remained intact, which support the practice of OHE as an adjunct to complete tumor excision when a malignant gland tumor is suspected.

If OHE is performed simultaneously, penetration of the tumor prior to abdominal entry must be avoided to prevent direct spread of tumor cells. Tumor removal should follow abdominal closure.

The reported median survival after surgery is about 70 weeks for malignant tumors and 114 weeks for benign tumors.

### *Chemotherapy*

The role of chemotherapy has not yet been defined for canine mammary carcinoma. Various agents have been evaluated with variable outcomes: doxorubicin, carboplatin, 5-FU, cyclophosphamide, gemcitabine, and docetaxel.

Adjuvant chemotherapy is recommended for dogs with tumors at high risk of metastasis or recurrence. Dogs with large tumors, positive lymph nodes, and aggressive histology are not treated effectively with surgery alone.

### *Radiation Therapy*

Unlike for women with breast cancers, radiation therapy is rarely used in dogs (complete surgical removal easier in dogs). Anecdotal reports indicate this modality can be used for palliation for unresectable tumors or inflammatory carcinomas.

### *Hormonal Therapy*

Hormonal therapy has not been used as widely in dogs as in humans, in part because of difficulty of performing routine estrogen and progesterone assays on canine tissue. Ovariectomy is the most common form of hormonal ablation therapy performed in dogs.

Tamoxifen has both estrogenic and anti-estrogen effects and is indicated for estrogen receptor-positive breast cancer patients. Effects of this drug in dogs are equivocal (benign tumors are more likely to retain hormone receptors, hormone independence associated with a more aggressive histology and clinical behavior). Adverse effects include vaginal discharge, vulvar swelling, urinary incontinence, urinary tract infection, mental dullness, signs of estrus, partial alopecia, and pyometra (25%, stump pyometra if recent OHE).

### *Immunotherapy*

Various methods of nonspecific immunomodulation have been investigated with no clear clinical benefits (Immunocidin – mycobacterium cell wall).

### *Treatment of Inflammatory Mammary Carcinoma*

Surgery is contraindicated. Wound dehiscence, disseminated intravascular coagulation, and edema are common features. Pain control such as NSAIDs may help (tumors express high levels of COX-2). Palliative radiation therapy has been reported. Prognosis remains poor with short survival (about 1 month; although one report describes 6 month survival with the use of NSAIDs).

## 6) Prognosis

Negative prognostic factors include:

- Sarcoma, mixed malignant tumors, inflammatory carcinoma, and grade 3 carcinomas
- Vascular/lymphatic invasion
- Ulceration
- Fixed to adjacent tissue
- Advanced age
- German shepherd breed
- Tumor size >3 cm
- Nodal metastasis

## Feline Mammary Gland Tumor

### 1) Incidence and Risk Factors

Mammary tumors are the 3<sup>rd</sup> most common tumors in the feline species (lymphoma and skin tumors being the most common).

Three main risk factors have been identified: Age, breed, and hormonal influence.

Mammary neoplasia is seen predominantly in middle-aged to older cats. Mean age of diagnosis is between 10 and 12 years old. Risk increases with age and becomes significant at 7-9 years old. The risk continues to increase up until 12-14 years old.

Siamese cats are overrepresented when compared to other breeds. They are also younger when diagnosed with mammary tumors.

As in dogs, OHE at an early age lowers the risk of mammary tumor development. Cats spayed before 6 months of age have a 7-fold reduction in risk of mammary tumors. No benefit was found when cats are spayed after 2 years of age. Parity was not associated with risk of developing the disease.

### 2) Clinical Features

In contrast to the disease in dogs, the majority of feline mammary masses (85-95%) are malignant. Ulceration is common and suggestive of malignancy. Multiple lesions are present at the time of diagnosis in about 60% of cases. Larger tumors may become ulcerated, inflamed, and infected. Inflammatory mammary carcinomas are rare in cats, and clinical picture and outcome are similar to dogs.

### 3) Diagnostic Approach

CBC, serum biochemistry panel, and urinalysis should be evaluated in anticipation of anesthesia and surgery. Three view thoracic radiographs and regional lymph node palpation/FNA are important staging test, as metastatic rate is higher than 25% at presentation.

Histopathology is required to confirm the diagnosis. Biopsy samples are often obtained at the time of definitive surgery. Majority of mammary tumors in cats are diagnosed as adenocarcinomas.

#### Modified WHO Stage

Stage I: Tumor <2 cm

Stage II: Tumor 2-3 cm

Stage III: Tumor >3 cm and/or regional lymph node metastasis

Stage IV: Distant metastasis

#### 4) Treatment

##### *Surgery*

Unilateral (single tumor) or bilateral mastectomy (bilateral tumors) is generally considered the preferred surgical method in cats. The procedure significantly decreases the recurrence rate. Bilateral radical mastectomy may be done as a staged procedure (each side performed 2-6 weeks apart) or during a single surgical procedure (for cats with excessively loose mammary tissue if minimal postsurgical tension can be achieved, subjective more difficult recovery). Inguinal lymph node is removed with the caudal mammary gland. Axillary lymph node excision is recommended only if metastatic disease is suspected or confirmed.

##### *Chemotherapy*

Doxorubicin-based chemotherapy protocols have been evaluated most frequently. About 1/3 of cats with stage III or IV disease have measurable responses to the combination of doxorubicin and cyclophosphamide. Adjuvant doxorubicin (1 mg/kg IV every 3 weeks x 5) after surgery results in a median survival time of 15 months, with 1-year survival of 60% and 2-year survival of 35%. Literature suggest a role for adjuvant chemotherapy for advanced stage disease (2-year survival ~15% if surgery not followed by chemotherapy), while surgery only may be adequate for stage I tumors (<2 cm).

#### 5) Prognostic factors

Tumor size is the most reliable prognostic indicator. Median survival for tumors >3 cm is 6 months, for tumors 2-3 cm is about 2 years, and for tumors <2 cm is greater than 3 years.

Lymphatic invasion on histopathology is another negative prognostic factor.

Cats with lymph node metastasis tend to die within the first 9 months of diagnosis.

DSH cats have better outcomes than purebred cats.