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## TREATMENT OF MAMMARY GLAND TUMORS AND PERIANAL NEOPLASIA

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### CANINE MAMMARY GLAND TUMORS

Mammary gland tumors (MGT) are common in the bitch especially in countries where spaying is not commonly practiced, such as Scandinavia. The incidence of MGT also appears to be greater in bitches treated with injectable progestins for estrus prevention. Female dogs are less likely to develop MGT if they are spayed early in life. The risk of MGT in male dogs is less than 1% of that in female dogs. The median age for dogs with MGT is between 10 and 11 years and it is extremely rare for dogs younger than 4 years old to develop this cancer. Some pure breed dogs may be predisposed with the spaniel breeds, poodles and dachshunds over represented in some studies.

Half of dogs presented with MGT have single masses. The other half has multiple masses developing simultaneously or subsequently in the mammary tissue. Masses may be associated with the nipple or, more commonly, associated with the gland itself. About 70% of canine MGT develop in the caudal mammae (4 and 5).

### ETIOPATHOGENESIS

It is clear that the disease has a hormonal dependant etiology. The risk for malignant tumor development in dogs spayed before the first estrus is 0.5%. Dogs spayed after the first estrus have an 8% risk and this increases to 26% if the dog is spayed after the second estrus compared to the risk in intact dogs. Risk reduction or the protective effect of spaying for the development of malignant MGT is lost if the animal is spayed late in life (after 2-3 years of age). A protective effect of early pregnancy seen in women has not been demonstrated in dogs.

Ovarian steroid hormones (estrogen and progesterone) are mitogenic for mammary cells due to binding to the rich estrogen and progesterone receptors (ER and PR) on these cells. Malignant canine MGT have ER and PR in less than 50% of cases with far less metastatic lesions displaying these receptors. So there appears to be a loss of the receptors as tumors become more undifferentiated and presumably this corresponds to a decrease in the steroid dependency of these cells for their growth. There may be over expression of a growth hormone (GH) gene in some MGT cells that may be progesterone induced. This GH gene possibly results in GH having local effects via induction of insulin-like growth factor-I (IGF-I) expressed by mammary stromal cells. As well as an increase in GH production induced by progestins, a rise in blood levels of IGF-I and IGF-II occurs, which may stimulate mammary cell proliferation. GH effects on differentiation and the interplay between other growth factors and their receptors complicate the whole process.

Genes play a role in the transmission of growth signals from the cell surface to the nucleus. There has been no evidence that the *ras* genes are over expressed in canine MGT but there is evidence (from mRNA studies) that *c-erbB-2* (or *c-neu*) is an oncogene over expressed in some canine MGT. The tumor suppressor gene p53 is mutated in some canine MGT. Alterations in a second tumor suppressor gene,

*BRCA1*, occur in some tumors studied in dogs. The whole story of gene alterations in the etiopathogenesis of canine MGT still needs to be told and work continues.

Another factor in the pathogenesis and prognosis of MGT studied is nuclear DNA content abnormalities studied by flow cytometry. About half of canine malignant MGT had abnormalities (DNA aneuploidy). This reflects genetic instability and can be seen in some benign MGT too, possibly reflecting a potential for malignant transformation.

Obesity at an early age appears to be a risk factor in dogs. It is a known risk factor in women and rodents. So nutrition plays some role in tumor development and it appears from one study that homemade meals were associated with an increase risk of MGT compared to commercial diets.

### TUMOR BEHAVIOUR

Classically, this disease in dogs has been called a "50:50 cancer." That is, about half of the dogs presented to veterinarians with mammary masses have malignant disease and half have benign lumps. Half of those dogs with malignant tumors will be cured by appropriate excisional surgery.

Most MGT are epithelial (carcinoma). Pure sarcomas (fibrosarcoma, osteosarcoma, etc.) are rare. Similarly, a rare diagnosis is a tumor with both malignant cells from epithelial and connective tissue lineage, carcinosarcoma. The latest revision of the WHO classification attempts to divide tumors into groups with prognostic implication. It appears from one study that ductular carcinomas make up about 20% of the malignant tumors of the canine mammary gland and adenocarcinomas of other histiogenic origin made up the majority of the remaining tumors. Ductular carcinomas were 8 times more likely to be fatal than the adenocarcinomas. All the carcinosarcomas caused the death of the host. In another study, a pathological staging system was used and the degree of differentiation and invasiveness were predictive of tumor aggressiveness.

Carcinomas generally metastasize via the lymphatic route. Carcinoma that metastasizes to the inguinal lymph nodes may enter the pudendal lymphatics and spread to the internal iliac nodes. Other common metastatic sites include lung, liver, kidney and bone.

### INFLAMMATORY CARCINOMA

Inflammatory carcinoma of the breast is considered a separate entity with respect to biological behaviour. These MGT grow extremely rapidly invading lymphatics readily causing oedema and inflammation for the skin and adjacent tissue. All or part of the mammary chain may be involved with a diffusely swollen and poorly demarcated, red, often pruritic lesion resembling an acute dermatological infection ("hot spot") or mastitis. Cytological evaluation of aspirates or impression smears has been useful in diagnosing this entity.

These dogs may develop disseminated intravascular coagulation and a coagulation profile may be indicated as part of the work-up for these dogs. Metastasis is common.

Surgery is not indicated as a treatment for this. Most of these cannot be resected, and if they are resected, they tend to recur within weeks to a month after surgery. Short-term benefits of radiation therapy have been reported but cures are elusive. In our clinical experience, response to chemotherapy has been poor. Overall the outlook for these dogs is very bleak.

**WORK-UP**

The aim of the clinical work-up is to establish staging. This is the TNM classification:

1. **Tumor (T)** – the most important features to note with the primary tumor are growth characteristics (recent rapid growth vs. long stable history), size, clinical evidence of invasiveness (fixation to adjacent structures), ulceration and evidence of inflammatory carcinoma.
2. **Lymph nodes (N)** – evaluate for extension to regional lymph nodes (inguinal, axillary, presternal, internal iliac, and prescapular nodes).
3. **Metastases (M)** – lung and bone (lumbar vertebrae especially)

Other components of the work-up pertain to general health evaluation and starts with a detailed history taking and physical exam. Ancillary tests include CBC, serum biochemistry, routine urinalysis and coagulation profile if indicated (see inflammatory carcinoma). Thoracic radiography in both lateral projections and dorsoventral or ventrodorsal projections is used to detect lung involvement. Abdominal radiograph is useful to detect bone metastases to the lumbar vertebrae and abdominal ultrasonography can help detect enlarged retroperitoneal nodes.

Cytology of the primary tumor rarely helps in the diagnosis but may rule out diseases masquerading as MGT such as mast cell tumors. Evaluation of a fine needle aspirate or impression smear may also help prompt diagnosis of inflammatory carcinoma.

Pre-operative biopsy is generally not indicated and the definitive diagnosis is usually made on histological evaluation of an excisional biopsy.

**TREATMENT**

Surgery is the mainstay for treating MGT in dogs where there is not clinical evidence of metastatic disease. Half of the dogs with malignant MGT will be cured with surgery alone. The technique used largely depends on the size and extent of the tumor. In dogs, MGT should be removed with the lowest “dose” of surgery able to completely remove the cancer. Once the specimen is removed we recommend “inking” the surgical margins and fixing it and the regional lymph node where this has been removed in 10% neutral buffered formalin. The excised tumor must be evaluated for tumor type and grade as well as completeness of resection (margins). The node should be evaluated for extension of disease. Other tests such as flow cytometry, AgNORs, S-phase fraction, steroid receptor assays are rarely performed on excised tumor tissue from dogs at routine diagnostic laboratories.

**SURGERY**

Mammary cancer in the dog should be removed by the simplest procedure that will remove all known cancer in the mammary gland. That is not to say that incomplete resection or debulking surgery is acceptable.

**Lumpectomy**

Here the surgeon makes an incision over the skin and removal of a nodule (<5 mm) from the breast with a small rim of normal tissue. This is only suitable for benign nodules. Further surgery is indicated if the biopsied nodule is malignant.

**Mamectomy**

This is the removal of one mammary gland where the mass (> 10 mm) is located in the substance of the gland and is displaying some fixation to the skin or fascia. The involved skin or fascia must be removed with the mass. It is often easier to remove glands 4 and 5 together due to their close anatomical relationship.

**Regional Mastectomy**

This was proposed some time ago based on the complex relationship of the mammary gland lymphatic drainage in the dog. Based on the premise of lymphatic drainage, tumors involving glands 1, 2, or 3 should be removed en bloc. Similarly, tumors involving 4 or 5 should be removed en bloc. Basically, however, it is more important to remove the entire known tumor by the simplest procedure rather than going through the semantics of determining the lymph drainage pattern of the affected gland.

**Unilateral or Bilateral Mastectomy**

Glands 1 to 5 can be removed as a unit if multiple tumors or several large tumors preclude rapid and wide removal by lesser procedures.

Simultaneous bilateral mastectomy can rarely be performed in dogs in my experience except for those individuals with very pendulous mammary glands. It is the preferred technique for cats, however. If both sides need to be removed from dogs, then a staged unilateral mastectomy (two unilateral mastectomies 2-3 weeks apart) is the preferred technique.

**Lymph Node Removal**

The inguinal node is removed when glands 4 and 5 are removed and should be dissected from the specimen after surgery and submitted separately to complete the staging. If the axillary or inguinal nodes are large or cytologically positive for cancer they must be removed. Removing positive nodes does not influence survival outcome other than helping staging and predicting outcome.

**CHEMOTHERAPY**

The role of adjuvant chemotherapy has not been established in dogs although some workers report promising results with Doxorubicin and Cyclophosphamide. For dogs with high-grade lesions or node positive disease, adjuvant chemotherapy may offer some benefit. This still has to be substantiated in proper, controlled clinical trials.

**RADIATION THERAPY**

As with chemotherapy, no reliable information on the value of radiation is yet available.

**BIOLOGICAL RESPONSE MODIFIERS**

Studies have been completed using levamisole, *Corynebacterium parvum*, Bacillus Calmette-Guérin (BCG), and liposome muramyl-tripeptide phosphatidylethanolamine (L-MTP). No validated, clinically applicable immunomodulating approach is available that can be considered to have proven therapeutic effectiveness.

**HORMONAL THERAPY**

It still appears that spaying dogs at the time of treatment (surgery) for their malignant MGT does not influence prognosis. This is still hotly debated in many circles despite years of argument, evaluation of retrospective data and

laboratory investigations. There has not been any well-designed prospective study to clearly address the issue of ovariectomy as an adjunct treatment for dogs with malignant mammary tumors.

Tamoxifen (antioestrogen) does not appear to have any beneficial effects for dogs with MGT and can produce moderate to severe side effects.

#### SUMMARY OF CANINE MGT PROGNOSTIC FACTORS

Good	Poor	Indifferent
<3cm	>3cm	Age
Well circumscribed	Invasive	Breed
Lymph node (-)	Lymph node (+)	OHE status
Lymphoid cellular reactivity (+)	Lymphoid cellular reactivity (-)	Weight
	Inflammatory carcinoma	Type of Sx (simple vs. radical)
ER or PR (+)	Ulceration	
Carcinoma	Sarcomas	
Well differentiated	ER (-)	Number of tumors
Complex	Carcinoma	Gland(s) involved
Tubular/Papillary	Poorly differentiated	
AgNOR count – low	Simple Solid, anaplastic AgNOR count - high	

#### FELINE MAMMARY GLAND TUMORS

Where about half of the dogs presented with mammary masses have malignant tumors, over 90% of cats with mammary nodules have malignant disease. Mammary gland tumors are the third most common cancer of cats following hemopoietic cancers and skin tumors. Domestic shorthaired cats and Siamese cats may have higher incidence rates than other cats. Siamese cats may have twice the risk of any other breed of developing MGT.

The disease has been reported in cats as young as 9 months old and as old as 23 years with a mean age of 10 years old. Cats spayed at 6 months had approximately 7-fold reduced risk of MGT compared to intact cats. Cats receiving drugs containing synthetic progestins or estrogen-progestin combinations have a 3-fold greater risk of developing mammary masses (benign and malignant) compared to untreated cats.

Many of the tumors, especially the larger ones, are invasive, adhere to the skin and are ulcerated. Lymphatic and lymph node invasion is common. More than 80% of cats with malignant MGT in several studies had metastases at the time of euthanasia.

Histology is usually adenocarcinoma (80%). Sarcomas, squamous cell carcinomas, and mucinous carcinomas are less common.

Mammary tumor pulmonary metastases appear radiographically as interstitial (milliary) densities. Sternal lymphadenomegaly is sometimes present. Biopsy is recommended of feline mammary masses. Radical mastectomy is the treatment of choice as it significantly reduces the chance of local tumor recurrence. The inguinal nodes are removed and evaluated for tumor extension. Axillary nodes are only removed if enlarged or cytologically positive for tumor extension.

Chemotherapy with doxorubicin or doxorubicin and cyclophosphamide has been recommended although trials are underway and results demonstrating efficacy are pending.

The prognosis for cats with MGT is usually guarded. Two thirds of cats where their tumors were removed by conservative surgery developed local tumor recurrence. The most significant prognostic factors affecting recurrence and survival for cats with MGT are tumor size, extent of surgery and histological grading. Tumor size is the single most important factor. Cats with a tumor size of greater than 3 cm in diameter will have a median survival time of 4 to 6 months. Cats with a tumor size of 2 to 3 cm in diameter will have a median survival time of 2 years, and cats with tumors less than a 2 cm diameter will have a median survival time over 3 years.

#### PERIANAL TUMORS

Almost any tumor can occasionally affect the perineum and perianal region. Mast cell tumors, soft tissue sarcomas, other skin tumors, lymphoma and so on are examples but the most common are those of the sebaceous glands; the perianal tumors (often called circumanal or hepatoid tumors).

Perianal tumors are common in the male dog and rare in the female dog or the cat. Perianal adenomas are the most common making up over 80% of perianal tumors in the intact male dog.

Perianal adenomas commonly occur in older, intact male dogs and are thought to be androgen dependant where as perianal adenocarcinomas (the evil cousins) occur in castrated and intact male dogs and are not thought to rely on a source of androgen for their growth. Perianal adenomas in females appear to be largely restricted to spayed animals. In rare occasions, testosterone secretion from the adrenal gland may stimulate the development of perianal adenomas. Dogs with Cushing's disease may be prone to developing these lesions and it may warrant investigation particularly when adenomas occur in females.

Perianal adenomas and adenocarcinomas derive from sebaceous glands. Apocrine gland carcinomas develop from the apocrine glands lining the anal sacs and older, spayed female dogs are over represented in most studies of this cancer in dogs. A true hormonal dependence for apocrine gland carcinoma has not been shown. Apocrine gland adenocarcinoma is very rare in the cat.

#### PRESENTATION

Dogs with benign lesions generally present with a perianal mass that has been growing slowly over months to years. The lesions usually cause no obvious pain or discomfort and may be single or multiple. Most occur on the hairless regions around the anus, although they may extend into haired adjacent skin and may even occur on the tail base, scrotum

and prepuce. Despite their benign behaviour they can look aggressive with areas of ulceration and fixation to deeper structures.

The malignant form, perianal adenocarcinoma, usually has a more rapid growth history but can look grossly very similar to perianal adenoma. Characteristically they are firmer; more commonly ulcerated and frequently adhere to adjacent structures such as the rectum and even the pelvis. These tumors can become quite large. Difficulty with defecation leading to obstipation is a late clinical sign. A perianal mass in a castrated male dog must be considered suspicious for adenocarcinoma.

Dogs with anal sac adenocarcinoma (apocrine gland carcinoma) may not present because of signs directly referable to the primary tumor, which may be small (5 – 10 mm). These dogs may have hypercalcemia and the presenting complaint by the owner may be that the dog is polydipsic, polyuric, anorexic, has vomiting and so on. Also it is not uncommon for these dogs to be straining to defecate due to pelvic canal obstruction from palpably enlarged internal iliac (sub lumbar) lymph nodes. The primary tumor can usually be palpated on rectal examination as a nodule in one of the two anal sacs located ventrolaterally on either side of the anal sphincter.

#### WORK-UP

The intact male presenting with a perianal mass to our clinic receives a complete physical examination and a detailed history is taken from the owners. Once it is established that the dog is otherwise healthy, (minimum data base blood work and urinalysis are usually evaluated) and adenoma or adenocarcinoma is suspected then the dog is taken to surgery and the lesion is usually excised and the dog castrated. Preoperative biopsy is considered if the lesion is large and cannot be excised easily. Fine needle aspiration cytology is useful to rule out other cancers, such as mast cell tumors, but cannot be relied upon to differentiate perianal adenoma from perianal adenocarcinoma. If the histopathology is consistent with adenoma then no more treatment is necessary. If the disease is adenocarcinoma then abdominal ultrasonography to evaluate lymph nodes and liver is performed and thoracic radiography is done for staging. Further surgery is usually necessary to obtain clean margins and adjuvant chemotherapy is considered.

A perianal mass in the castrated dog or if there is recurrence of the mass in the recently castrated dog previously diagnosed with adenoma always necessitates biopsy. Adenocarcinoma must be suspected in this scenario.

Dogs with tumors of the anal sac receive the same physical examination and history evaluation. Large caudal abdominal nodes are frequently palpated via abdominal palpation or rectal exam or both. These dogs are often suffering from the effects of hypercalcemia and require prompt laboratory evaluation and attention. Abdominal radiography and ultrasonography are performed. Thoracic radiography is also recommended. Renal complications from hypercalcemia can occur in these dogs and renal parameters need to be carefully scrutinized from blood work and urinalysis. Biopsy of the anal sac mass establishes the definitive diagnosis however these dogs have a characteristic presentation and rarely require a tissue biopsy before treatment.

#### TREATMENT

Castration and tumor removal or cryosurgery is usually all that is required to cure dogs with perianal adenoma. Perianal adenocarcinomas are locally invasive and do not respond to castration. Wide surgical margins need to be obtained. It is possible to remove over 50% of the anal sphincter and regain continence after a short period of temporary fecal incontinence. Regional node metastases can often be resected. Lymphadenectomy is generally performed by ventral midline laparotomy although I have performed a dorsal approach to the rectum to remove sub sacral nodes on occasion. Following subtotal lymphadenectomy, external beam radiation therapy can help prevent disease progression although we have experienced good results with doxorubicin based chemotherapy protocols.

Treatment of anal sac apocrine gland carcinomas requires wide resection of the primary with lymphadenectomy in most cases. Radiation of the nodes and primary site follows. We have treated dogs with excision of the primary and lymphadenectomy followed by doxorubicin at 30 mg/m<sup>2</sup> every 21 days for 5 treatments with quite good results. Hypercalcemia usually resolves within days of surgery.

#### PROGNOSIS

Generally, intact male dogs with perianal adenoma treated with castration and excision have an excellent prognosis with over 90% cured.

Sebaceous gland adenocarcinoma in the male dog is difficult to cure but dogs with early stage disease can do well after wide surgical excision. Tumors less than 5 cm in diameter (T2NoMo or less) had survivals in excess of 70% at 2 years with wide surgical excision.

Anal sac carcinomas carry the worst prognosis with approximately 50% 1-year survivals even with surgery, lymphadenectomy and adjuvant therapy. Metastasis at diagnosis and hypercalcemia appear to be poor prognostic indicators.

More work needs to be done to determine the roll of adjuvant radiation and chemotherapy in the management of this disease although preliminary data looks encouraging.