MAMMARY TUMOURS

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Parts in Italics are just for reading, not for studying

I. MAMMARY TUMOURS IN THE DOG

Mammary tumours are important in small animal veterinary practice. In the female dog the incidence of malignant mammary tumours is higher than that of any other cancer. In California the annual incidence rate in intact female dogs was estimated to be approximately 260/100,000 dogs. A rough extrapolation of this figure would lead to a life-time risk of about 2.5%. Yet, more recent studies indicated a life-time risk of up to 25% in intact female dogs. The risk for benign tumours is estimated to be 2 to 5-fold higher than that for malignant lesions. The incidence of both benign and malignant tumours in specific populations of dogs is correlated with life-expectancy and is strongly reduced by the practice of ovariectomy in young dogs, which is common in the US but forbidden in some European countries. The risk for tumours is increased by the use of injectable progestins for estrus prevention, for which the reverse is the case. The risk in male dogs is 1% or less of that in female dogs. The median age of tumour manifestation is between 10 and 11 years of age with rare occurrence in dogs less than four years of age. Several spaniel breeds and - according to some studies- the Poodle and Dachshund seem to be predisposed. About 20-40% of dogs with mammary tumours or dysplasias develop malignant neoplasms. It is often difficult to discriminate between benign and malignant mammary nodules by means of clinical criteria. Since some dogs with benign mammary tumours are at higher risk to develop malignant mammary tumours as well, the proper management of both types of disease is important.

Mammary tumours are rare before the age of 2 years, although fibroadenomatous lesions occasionally occur in dogs as young as one year. The incidence increases slowly after the age of 4 years, rises steeply between 6 and 10 years, and then the increase appears to lessen. There is ample evidence that both endogenous ovarian hormones and synthetic derivatives used in many countries to prevent estrus may stimulate mammary tumour development. In male dogs the incidence of mammary tumours is only about 1% of that in females.

Much is still unknown about the pathogenesis of mammary tumours and the factors that determine their biological behaviour. However, some important discoveries will be mentioned briefly in this chapter.

PATHOGENESIS

Endocrine factors

Mammary tumour development in the dog is inhibited by ovariectomy performed before 2½ years of age. If carried out later, it may still reduce the risk of benign tumours but will probably have little or no effect on the risk of malignant tumours. Furthermore, it has been demonstrated that administration of long-acting progestagens to prevent estrus causes a moderate increase in the risk of developing benign mammary tumours but not of malignant tumours. For prevention of estrus in dogs, ovariectomy before 2½ years of age is to be preferred over progestagen treatment with respect to the mammary tumour risk.
The role of endogenous hypophyseal hormones in mammary tumourigenesis in the bitch is still controversial. In bitches with mammary tumours neither growth hormone nor prolactin basal plasma levels were elevated when compared to age-matched controls in the same phase of the estrus cycle. On the other hand, both endogenous luteal phase progesterone and injected progestin induce growth hormone production in mammary epithelium in the dog. Differences in the length of time of exposure to progestins and consequently in exposure to growth hormone may be of importance in canine mammary tumourigenesis. Also some mammary neoplasms were found to express the GH gene, and it was indicated, that after malignant transformation this GH expression may become progesterone independent.

There is no convincing evidence that either parity or lactation significantly alters the mammary tumour risk, although the risk in female dogs used extensively for breeding from an early age onward may be somewhat lower.

Steroid and peptide hormones exert many of their actions in target cells by binding to specific high-affinity binding sites (receptors). Receptors for estrogens, progestins, and prolactin have been found in nearly all specimens of histologically normal mammary tissue of female dogs in which they were sought as well as in a high proportion of benign mammary tumours. They were present in only about half of the primary cancers and at lower concentrations than in non-malignant mammary tissues, indicating a loss of function of genes encoding for these receptors. This is consistent with the concept that deviations from normal control mechanisms develop progressively in malignant tumours.

It is still uncertain whether steroid hormones cause mutations, or whether they only enhance tumourigenesis by their growth-promoting effect. The available evidence indicates that steroid hormones act at an early stage in the development of tumours by increasing the number of susceptible cells. Growth may also be stimulated in cells that have undergone partial malignant transformation, but possibly to a lesser extent in fully malignant cells at a late stage of tumour development. Steroid receptor presence is infrequent in metastases of mammary cancers, which may indicate a more autonomous pattern of growth.

Genetic alterations

In experimental animals as well as in humans there is much evidence that genetic alterations are of major importance in the development and progression of tumours. Two types of alterations appear involved. The first includes an alteration of cellular proto-oncogenes in such a way that these become activated oncogenes. One example is that of a mutation of a gene coding for a hormone receptor that leads to the production of a truncated receptor, no longer able to bind its hormonal ligand. These truncated receptors may be constitutively active. Another example is that of a gene amplification leading to overexpression of, for example, a nuclear transcription factor such as c-myc. Of oncogenes expressing for the receptor of growth factors, overexpression of mRNA for c-erbB-2 (also called c-neu) has been detected in the majority of canine malignant - but not in benign - mammary tumours in one study.

The second type of alteration involves the loss or inactivation of a tumour-suppressor gene. Under normal circumstances such a gene may code for control of cell division or cellular senescence. Abrogation of this function may enhance tumourigenesis. The tumour suppressor p53 gene is the most frequently mutated gene in human cancer and recent studies in canine mammary cancer found 3 of 10 and 6 of 40 primary cancers, respectively, to contain p53 mutations, with one dog carrying a germ-line mutation. It appears that several of the genetic alterations described above, or others, are necessary before a cell turns into a tumour cell. Future research may reveal the extent to which the development and behaviour of canine mammary tumours are influenced by such genetic alterations.

Gross changes in nuclear DNA content can be determined by flow cytometry. An abnormal DNA content, or aneuploidy, has been observed in 50-60% of primary malignant
mammary tumours and found to be related with an adverse prognosis. Some benign proliferative lesions have also been found to contain aneuploid tumour cells. Perhaps this is related to the progression towards a malignant state occasionally observed in such histologically benign lesions. DNA flow cytometry also can be used to determine the number of proliferating cells. The fraction of cells in the S-phase of the cell cycle (SPF) has generally been found to be higher in malignant tumours than in benign lesions. In one study a high SPF was found to be associated with an unfavourable outcome after surgery of mammary tumours in dogs.

CLINICAL PRESENTATION AND DIAGNOSIS

Mammary tumours may present as a solitary mass or as multiple swellings. The caudal glands are more often affected than the cranial ones, probably because of their greater mass. Multiple lesions occur in more than half of the cases and in the majority of dogs they represent different primary lesions. Sometimes attentive owners will present a dog with multiple small nodules of only a few millimetres in size during metestrus or after a progestin injection. Once the steroid levels decrease such lesions may completely disappear. Purely cystic lesions also appear to be dependent upon hormonal stimulation.

Many other dogs are presented with firm nodules larger than just a few millimetres. Clinical signs of malignancy include rapid growth, non-circumscribed growth, fixation to skin and/or underlying tissues, and ulceration. The presence of more than one of these signs signifies a high risk for the presence of a malignant tumour, but their absence does not exclude malignancy. Large size may either be the result of rapid growth or merely the result of long delay before veterinary examination. Seemingly rapid growth can also occur in cystic lesions without necessarily being a grave sign. Rapid growth is also occasionally found in another condition. Although less common in the dog than in the cat, single or multiple soft circumscribed swellings may develop in young animals during metestrus or pregnancy or after treatment with progestagens. These are benign fibroadenomatous lesions which sometimes involve all mammary glands. They usually, but not always, disappear rapidly upon cessation of exposure to exogenous and endogenous sex steroids.

It is often impossible to differentiate between benign and malignant mammary tumours in the dog by physical examination. In some cases cytology of fine needle aspiration biopsies (preferably of a solid mass, not cystic fluids or secretions) may provide the diagnosis. The finding of several criteria of cellular malignancy by an experienced cytologist, will result in a diagnosis of malignancy with a high predictive value. However, many histologically and clinically malignant tumours lack clear cytological signs of malignancy and thus a conclusive cytological diagnosis cannot be made.

Lesions that remained indolent for a long time may suddenly change and the delay in treatment may turn an operable condition into an inoperable one due to local invasion or metastasis. If a tumour appears to be operable, possible sites of distant metastasis should be examined. These include distant lymph nodes, including the prescapular, sternal and deep inguinal nodes, and the lungs and other internal organs. Since metastases to other internal organs are infrequent without previous development of lung metastases, attempts to visualize these will rarely be productive if radiographic examination of the thorax does not reveal metastases in the lungs. Enlargement of deep inguinal nodes revealed by radiographic or ultrasound examination of the pelvic area may indicate the presence of metastasis. Such examinations, or lymphatic scintigraphy at highly specialised clinics, are particularly indicated in tumours with involvement of superficial inguinal nodes. Detectable distant metastases are unlikely with circumscribed loose-lying local tumours less than 1 cm in size and radiographic examination is debatable in such cases in view of its cost. In all other cases and also in dogs which have had previous surgery for a tumour it is a necessary pre-operative diagnostic procedure.

Mammary tumours may be found in a lactating mammary gland that sometimes also has signs of mastitis. These circumstances may hinder the definition of the extent of the
tumour. Cytologic examination of fine needle aspiration biopsies may help to exclude the differential diagnosis of inflammatory carcinoma (see below) and sometimes will reveal bacterial infection. Systemic antibiotic therapy is indicated for the latter and the lactation may be suppressed by bromocriptine, which inhibits prolactin secretion, in a dose of 10 µg/kg body weight, two times daily for 2-3 weeks. After this treatment it is usually easier to define whether the tumour can be excised.

**Inflammatory carcinoma**

The most aggressive neoplasm in the dog is the inflammatory type of carcinoma. This tumour often involves several adjacent mammary glands and sometimes the whole mammary chain or even both chains. At physical examination, the mass is warm, erythematous and painful. These signs are associated with the inflammatory reaction caused by massive invasive growth of tumour cells. Often the nipples are retracted in the oedematous tissue. Oedema may even involve the limbs at the side of the tumour. Nearly all cases of this type have been presented within 1-2 months after estrus or a progestin injection. Perhaps substances produced by the normal mammary epithelium have a growth-stimulatory effect on the tumour cells. Sometimes the cytological finding of highly anaplastic tumour cells in fine needle aspirates may help the clinician to differentiate inflammatory carcinoma from hyperplastic/inflammatory conditions. Systemic metastases are almost always present in dogs presented with inflammatory carcinoma. Due to the rapid infiltrative and invasive nature of this type of tumour, however, nodular type lung metastases are observed radiographically in only a minority of cases. Surgery cannot be expected to be beneficial. Responsiveness to systemic therapy, to be discussed later in this chapter, is very poor. Sometimes hemorrhagic diathesis develops due to disseminated intravascular coagulation (DIC). More frequently, the presence of DIC is recognized at laboratory blood examination by the finding of abnormal clotting times, split products and thrombocytopenia. However, DIC may also develop in dogs with or without previous surgery for tumours other than inflammatory carcinoma. Careful examination in such cases will often reveal metastases to regional lymph nodes if they are still in situ or to distant nodes. Lung metastases may be miliary, or, if larger, sometimes cannot clearly be recognized radiographically because of the obscuring effects of concurrent hemorrhage in the lungs.

**Clinical staging**

In order to provide a basis for predicting the prognosis of mammary cancers, a clinical staging system has been proposed by the WHO: The TNM-classification. Tumours are staged in different categories. T stands for tumour size and fixation, N for involvement of regional lymph nodes, and M for the presence or absence of distant metastasis, based upon, among other things, radiographic examination of the thorax. The TNM information leads to a division to four clinical stages, with local/loco-regional tumour extension progressing from stages I to III and distant metastasis being categorized as stage IV. The advanced stage III was found to be associated with a worse prognosis than earlier stages in one study using some modification of this staging system. A refinement of this staging system can probably be achieved by using results of cytological examination of needle biopsies of clinically abnormal lymph nodes, rather than by only using the finding of enlarged nodes. A firm consistency of lymph nodes may be as suggestive of metastasis as nodal enlargement, while the latter may also be caused by reactive lymphadenopathy.

In several studies the presence of regional lymph node metastasis has been found to be associated with an adverse prognosis, either when studying survival time or time until tumour recurrence. In a multivariate analysis, however, no additional prognostic value of nodal involvement was found after taking into account the strongly related factor of severe infiltrative growth. Since univariate analysis unequivocally indicates a prognostic effect of nodal involvement, it is a factor that easily can and should be determined by the clinician in order to present the owner with a more accurate assessment of the prognosis. This does not mean that surgery may not be of benefit in node-positive cancer. In many dogs removal of the
tumour en bloc with the tumorous node will result in at least local control and sometimes even in a complete cure.

Table 1  Histological Classification of Mammary Tumours of the Dog
(WHO, 1999)

<table>
<thead>
<tr>
<th>Malignant Tumours</th>
<th>Benign Tumours</th>
<th>Unclassified Tumours</th>
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<tbody>
<tr>
<td>1. Noninfiltrating (in situ) carcinoma</td>
<td>2.1 Adenoma</td>
<td>3. Unclassified Tumours</td>
</tr>
<tr>
<td>1.1 Noninfiltrating (in situ) carcinoma</td>
<td>2.1.1 Simple adenoma</td>
<td>3.1 Ductal hyperplasia</td>
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<tr>
<td>1.2 Complex carcinoma</td>
<td>2.1.2 Complex adenoma</td>
<td>3.1.1 Lobular hyperplasia</td>
</tr>
<tr>
<td>1.3 Simple carcinoma</td>
<td>2.1.3 Basaloid adenoma</td>
<td>3.1.2 Epithelial hyperplasia</td>
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<tr>
<td>1.3.1 Tubulopapillary carcinoma</td>
<td>2.2 Fibroadenoma</td>
<td>3.1.3 Adenosis</td>
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<td>1.3.2 Solid carcinoma</td>
<td>2.2.1 Low-cellularity fibroadenoma</td>
<td>3.1.4 Cysts</td>
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<td>1.3.3 Anaplastic carcinoma</td>
<td>2.2.2 High-cellularity fibroadenoma</td>
<td>3.1.5 Duct ectasia</td>
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<tr>
<td>1.4 Special types of carcinomas</td>
<td>2.3 Benign mixed tumour</td>
<td>3.1.6 Focal fibrosis (fibrosclerosis)</td>
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<td>1.4.1 Spindle cell carcinoma</td>
<td>2.4 Duct papilloma</td>
<td>3.1.7 Gynecomastia</td>
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<td>1.4.2 Squamous cell carcinoma</td>
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<td>1.4.3 Mucinous carcinoma</td>
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<td>1.4.4 Lipid-rich carcinoma</td>
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<tr>
<td>1.5 Sarcoma</td>
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<tr>
<td>1.5.1 Fibrosarcoma</td>
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<tr>
<td>1.5.2 Osteosarcoma</td>
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<tr>
<td>1.5.3 Other sarcomas</td>
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<tr>
<td>1.6 Carcinosarcoma</td>
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<td>1.7 Carcinoma or sarcoma in benign tumour</td>
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PATHOLOGY

Histopathologic examination may provide the clinician with information on the type of tumour and the type of growth. In addition, the completeness of removal may be assessed if the entire excised specimen is submitted for examination.

Benign proliferative lesions, including benign tumours and dysplasias, can be separated into those with and those without cellular atypia. In keeping with observations in humans, the finding in a dog of proliferative lesions with moderate cellular atypia was found to be associated with an elevated risk for development of infiltrative carcinoma in remaining mammary tissue. The term precancerous mastopathy was used for such atypical proliferative lesions.

If severe histological or nuclear atypia is found in a tumour without signs of infiltration through basal membranes in multiple sections, it is termed carcinoma in situ. Assuming that no tumour infiltration has occurred in other parts of the tumour that were not examined, this implies that the tumour cells had not yet acquired the capacity to infiltrate and metastasize.

Infiltrative adenocarcinomas can be divided into simple type (tumourous epithelium only) or complex type (tumourous epithelium and myoepithelium). A highly undifferentiated structural and cellular phenotype in which every sign of glandular organization is lost leads to
the diagnosis of anaplastic carcinoma. Malignant mesenchymal tumours include fibrosarcoma, osteosarcoma, osteochondrosarcoma or sarcoma of unspecified type. Sometimes tumours consist of both carcinomatous and sarcomatous components. Most sarcomas only spread by a haematogenous route, in contrast to carcinomas, which rarely develop haematogenous metastasis without lymphogenous spread. The risk of tumour recurrence ranks as follows: (carcino)sarcomas and anaplastic carcinomas > simple adenocarcinomas > complex adenocarcinomas. The type of growth (intraductal/infiltrative/invasion of vessels) is highly correlated with completeness of excision. The type of growth further is also important with regard to risk of distant metastasis and, together with completeness of excision, is important with regard to the risk of local recurrence.

TREATMENT

Surgery

As stated earlier, millimetre-sized nodules in dogs detected during a period of progestin exposure may sometimes disappear once this exposure ceases. Surgical excision of affected glands or, alternatively, removal of hormonal stimulation by ovariohysterectomy is undoubtedly unnecessary in many cases but it may prevent full neoplastic development in others.

Solid tumours or dysplasias larger than 0.5 cm are unlikely to be reversible upon cessation of hormonal stimulation. Surgery should be considered in dogs that are in good general condition. The tumours should not be fixed to underlying tissues and detectable distant metastases should be absent. Complete local excision must be deemed feasible at a safe distance from the tumour margins. A pre-operative biopsy in such cases is redundant and adds unnecessary expense. In other cases a conclusive cytological diagnosis or a histological diagnosis by examination of an incisional biopsy is needed before a decision can be made regarding the type of treatment.

Nodulectomy should be considered to be a diagnostic procedure rather than a possible cure. It is contraindicated in dogs with multiple lesions or a single lesion larger than 1 cm, or if any clinical sign of malignancy can be detected.

Based on the results from diagnostic procedures described above, the clinician should decide whether it is reasonable to aim for a complete cure by surgery, that is, in lesions without signs of malignancy, or in lesions of limited extension if malignancy is likely or certain. In early stage cancers or benign disease, radical surgery may be curative. In animals in which a long life expectancy is probable, tumour recurrence of present tumours or appearance of new primaries is best inhibited with total chain resection. If the other chain is free of detectable nodules, it is advised to include ovariohysterectomy prior to the chain resection in the same operation. This may reduce the growth of microscopic benign lesions and also will result in atrophy of remaining mammary tissue facilitating early detection of new tumours.

If a less radical approach is followed there is a high likelihood of development of new primary tumours, a risk which is less important in old animals. In addition, nodulectomy or simple mastectomy has an increased risk of a local recurrence as compared to chain resection or block dissection, if the tumour is malignant and invades lymph vessels. If a malignant tumour is present in either one of the two thoracic glands or in the caudal abdominal or inguinal gland, a block dissection does not completely eliminate the risk of a tumour recurrence in the remaining ipsilateral mammary glands or distant regional lymph nodes. In about 10% of dogs lymph drainage occurs from the two cranial glands to the caudal abdominal gland or vice versa. During resection of caudal mammary glands the superficial inguinal node is removed because of its intimate anatomic association with the mammary tissue. The axillary nodes are removed only if tumour involvement is likely or certain.

If lesions are poorly circumscribed or fixed to underlying tissues or if there is regional metastasis, the question to be weighed is whether surgery may achieve at least local control. If cytological or histological examination demonstrates that the tumour is malignant, local
control, by performing chain resection or at least block dissection, is probably the best that can be achieved, in view of the high probability of distant metastasis. Thus, in a dog with a large ulcerating mass with lymph node involvement in one mammary chain and small circumscribed lesions in the other mammary chain, removal of the latter often may be omitted. Follow up of such cases and of all other malignancies is advised at 1 month after surgery and then at 3-month intervals for the first year. Extreme extension in width or major fixation of the tumour to underlying tissues may make complete removal impossible resulting in the diagnosis of locally advanced, inoperable cancer.

Apart from tumour-related features, the type of surgery may be limited by advanced age and other factors that influence life-expectancy, but also the owners’ expectation of the result of the surgery. Malignant tumours without overt distant metastases will have developed micro-metastases in 50-70% of cases at the time of presentation. Tumour-related death after surgery reportedly occurs in 40-60% of dogs and in the majority of cases during the first two years.

Adjuvant treatment

In only 20-30% of human breast cancer patients, protocols using either hormonal or chemotherapy after surgery of primary disease delay recurrent disease, resulting in a significant improvement of the prognosis. Current investigations are concerned with whether very aggressive chemotherapy is more effective. The related toxicity will preclude the use of such high-dose regimens in canine mammary cancer treatment. In veterinary practice, major improvement in the management of mammary tumours in dogs instead should come from efforts at earlier treatment. Treatment delay at present is found to average from 6 months to over a year in many studies.

If pathological examination of malignant tumours indicates incomplete excision, the first consideration should be whether rapid re-operation may offer a beneficial perspective. If this is unlikely, radiotherapy using an equipment that delivers radiation of sufficient energy may help to prolong local control in some of such cases. If examination reveals extensive intravascular invasion by the tumour, there is not only a very high risk of local recurrence but also of distant metastasis. There is also a high risk of distant metastasis if there is regional lymph node involvement or if the tumour is of an aggressive histological type. In these cases only systemic therapy might interfere with the development of distant metastasis and only if effective against the tumour in question.

Ovariectomy and the administration of anti-estrogens has been found to be effective in preventing or delaying metastatic disease in about 50% of human patients with estrogen receptor positive breast cancer. In the few studies of the effect of ovariectomy in the dog, the development of distant metastasis was not found to be reduced. This is not surprising in view of the frequent absence of steroid receptors in mammary carcinoma metastases in the dog. Yet, adjuvant ovariectomy might reduce the subsequent development of tumours, in particular of benign tumours, in the remaining mammary tissue. I have used an anti-estrogens (Tamoxifen, 0.7 mg/kg q 24 h) for 4-8 weeks in 10 dogs with advanced mammary cancer but observed no measurable effect in any of these dogs.

The value of chemotherapy as an adjuvant to surgery is uncertain in canine mammary cancer, in either preventing local recurrence or distant metastasis. The efficacy in aggressive disease such as anaplastic carcinomas with severe infiltration or vascular invasion appears to be low. Perhaps some benefit can be gained in dogs undergoing surgery for simple carcinomas of clinical stages II-III. There have been isolated reports that drugs such as Adriamycin administered as single agent or in combination with other drugs may improve disease-free survival in such animals. Yet, a recent study of 31 dogs that did not (n=19) or did receive adjuvant chemotherapy (n = 12, doxorubicine or taxol) did not demonstrate any benefit related to disease-free or overall survival. Additional carefully conducted clinical trials are needed.

Management of inoperable disease
The major impediment to surgery is extensive fixation to underlying tissues. In such locally advanced mammary cancers some dogs may benefit from radiotherapy. If there is sufficient response, surgical excision of remaining tumour may be considered. It should be recognized, however, that many such patients also have systemic dissemination of tumour, that leads to symptoms in a short time.

No major improvement is to be expected from present chemotherapeutic treatment in dogs with established distant metastases. In isolated cases there may be tumour remission during chemotherapy.

A particularly life-threatening condition is pleural effusion due to metastatic carcinoma. Since this effusion is often partly enhanced by the inflammatory response to the cancer cells, basic supportive therapy may achieve short-term palliation. After drainage of as much as possible of the fluid, prednisolone (2 mg/kg body weight daily for 3 days, followed by 0.5-1 mg/kg) may be given. Care should be taken to avoid dehydration if antidiuretics are used. There are anecdotal data on the use of chemotherapy in pleural effusion.
II. MAMMARY TUMOURS IN THE CAT

When a cat with a mammary mass is presented, a malignancy must be considered. At least 80% of feline mammary tumours are malignant. Mammary tumours are known to be at least the third most frequently occurring tumour in the cat, following hematopoietic neoplasms and skin tumours and account for 17% of neoplasms in female cats.

There are indications that there is a breed-associated predilection for mammary tumours, with some investigators suggesting that domestic short-haired and Siamese cats have higher incidence rates than other breeds. Mammary neoplasia has been reported to occur in cats from nine months to 23 years of age, with a mean age of occurrence of 10 to 12.

Hormonal influences seem to be involved in the pathogenesis of mammary tumours in the cat. Ovariectomy at about puberty reduced the mammary cancer risk approximately seven-fold. No other studies have examined the effect of age of ovariectomy upon mammary tumour incidence. Considering that nowadays the majority of cats are spayed (if done) below 6 years of age, it is no suprise that more recent studies have also been able to show that oophoractomized cats have a 40-60% lower risk to develop mammary cancer than intact cats. The lack of a similar protective effect against development of benign tumours in one study, is puzzling and should be confirmed by other studies. A strong association has been documented between the prior use of drugs containing synthetic progestins or estrogen-progestin combinations and the development of benign or malignant mammary masses in cats, in both cases increased the risk more than 3-fold over that in untreated cats. A benign fibro-epithelial hyperplasia (also called fibroadenomatous change, see below) may be seen in some cats with recent exposure to sex steroids.

Evidence that sex steroids may interact with mammary cells and hence influence mammary tumourigenesis come from the observation that normal tissue as well as benign proliferative lesions frequently express low levels of ER and moderate levels of PR. The much less frequent expression of ER and PR in mammary carcinomas indicates frequent loss of steroid dependence during malignant progression. Androgen receptors have been detected in 5/5 unselected carcinomas and 2/9 carcinomas not containing remnant benign mammary tissue, the latter able to introduce false-positivity.

A role of GH in feline mammary tumourigenesis cannot be excluded. The progestin-related fibro-epithelial hyperplasias have been shown to locally express GH, as also some malignant tumours did, even without PR presence, indicating progression to autonomous GH expression in some malignancies. Still, the systemic increase in GH blood levels induced by progestins has not been observed in the cat.

PATHOLOGY AND NATURAL BEHAVIOR

Mammary Tumours and Dysplasias

Between 85-93% of the feline mammary tumours will be malignant, the great majority histologically classified as adenocarcinoma, and a minority as sarcoma. Many of the tumours, especially the large, more invasive neoplasms, adhere to the skin and are ulcerated. Lymphatic and lymph node invasion is frequently present and visible at necropsy. In several studies, more than 80% of the cats with a mammary malignancy had metastases to one or more of the following organs at the time of euthanasia; lymph nodes, lungs, pleura, liver, diaphragm, adrenal glands, and kidneys.

Some 20% of mammary masses are benign neoplasms or dysplasias, including simple/complex adenomas and fibroadenomas as well as duct papillomas. Hyperplasias also form part of this group, with sometimes major atypia, making a distinction with in situ carcinoma difficult. Hyperplastic lesions may be multifocal and occur in cats from 1-14 years of age with an average of 8 years. Most cats were intact females. One type of hyperplasia is worthy of separate discussion:
Fibroepithelial Hyperplasia:

This may occur in young cats shortly after a (silent) estrus from about six months of age, or during pregnancy, as well as in both male and female cats treated with progestins, the majority being less than 2 years old, but occasionally in older animals thus treated. One or more often several glands may be enlarged, and sometimes massive two-sided enlargement is seen, thought to result from hormonal stimulation of the glandular tissue. The mass may become erythematous and even lead to necrosis of the skin. Edema of skin and subcutis is common and occasionally may involve both rear legs. Necrosis and ulceration may be associated with bleeding and localized infection. Systemic infection and pulmonary embolism have been reported. The primary condition can be easily confused with an acute mastitis. Diuretics, corticosteroids and testosterone has been advocated but the results are variable. Regression has been seen after termination of pregnancy in some affected animals. Ovariohysterectomy was found effective in most cases with gradual regression of the masses. If an ovariohysterectomy is to be performed and the glands are still greatly enlarged, then a flank incision should be used. In animals experiencing the influence of long-acting injectable progestins, ovariohysterectomy will not have immediate effect, but the administration of anti-progestins was beneficial: Aglepristone (=antiprogestin), 2days 10mg/kg sc, followed by weekly injections until remission. Remission will occur usually within 3-4 weeks.

CLINICAL PRESENTATION AND DIAGNOSIS

Feline mammary cancers are often presented to the veterinarian at an average of five months after they are initially noted and therefore frequently in an advanced state of development. The neoplasm may adhere to the overlying skin, but infrequently is adhered to the underlying abdominal wall. The tumour is usually firm and nodular. At least one-quarter of affected patients have ulcerated masses. The nipple may be exudate a tan or yellow fluid. The tumour can involve any or all mammary glands. More than half of the affected cats have multiple gland involvement. Metastatic lung and thorax involvement may be extensive and may cause respiratory insufficiency due to a pleural carcinomatosis with an effusion, often containing malignant cells.

Before any diagnostic or therapeutic steps are taken, the health status of the cat must be fully assessed. A serum chemical profile, urinalysis, and a complete blood count may be done to identify any presurgical abnormalities. The number, site and size of primary tumours should be recorded, together with possible signs of fixation. Alterations in size and consistency of lymph nodes should be assessed and any suspected node should be biopsied, preferably by FNAB. Thoracic radiographs in both the right and left lateral and ventrodorsal planes should be made to search for pulmonary, lymph node and pleural metastases. Mammary tumour pulmonary metastases appear radiographically as interstitial densities. They range from those that are faintly seen, to those that are several centimeters in diameter, to miliary pleural lesions than can produce significant effusion. Sternal lymphadenopathy is occasionally seen. Aging changes in the lungs and pleura, as well as inactive inflammatory lesions, may simulate metastatic disease. Treatment should not be withheld because of equivocal radiographic findings. Bronchoscopy and cytology of alveloar lavage may help in the differential diagnosis, as may a lungbiopsy, albeit at greater risk of complications

Because of the high frequency of malignancy, an aggressive approach should be taken to confirm the diagnosis. With the exception of cases in which fibro-epithelial hyperplasia is suspected based on history and clinical signs, a preliminary biopsy is usually not recommended because 80-85% of the masses in a mammary gland will be malignant. However, cytology may be helpful to rule out possible skin or subcutaneous non-mammary malignancies. Tissue for histopathology is taken at the time of mastectomy. If pleural fluid is removed from a cat with a mammary gland lesion, cytology should be done on the fluid to search for malignant cells.
Clinical Staging

The most important features of staging of malignant tumours are to evaluate a) the primary tumour(s) (T); b) the regional lymph nodes (N); and c) identify any distant metastatic sites (M). Size and clinical evidence of invasiveness (fixation to skin or fascia) of the primary tumour lead to the proper T-category. Regional lymph nodes should be examined carefully and fine needle aspiration or surgical removal may be necessary to determine metastasis and help to categorize the N-status. Any sign of distant metastasis leads to a M1 status. This includes involved distant lymph nodes, pleural effusion proven to contain tumour cells or radiographic signs of metastatic disease in the lungs or radiographic/ultrasonographic signs of lymph node involvement in thorax or abdomen.

Table 2  TNM Classification Feline Mammary Tumours WHO’80

<table>
<thead>
<tr>
<th>T: tumour size</th>
<th>N: Reg. Ln involvement</th>
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<tr>
<td>T0</td>
<td>N0 no involvement</td>
</tr>
<tr>
<td>T1 &lt;1cm</td>
<td>N1 homolateral involvement</td>
</tr>
<tr>
<td>T2 1-3 cm</td>
<td>N2 heterolateral involvement</td>
</tr>
<tr>
<td>T3 &gt;3 cm</td>
<td>M0 no distant metastasis</td>
</tr>
<tr>
<td>a: no fixation</td>
<td>M1 distant metastasis</td>
</tr>
<tr>
<td>b: fixation to skin</td>
<td>M0 no distant metastasis</td>
</tr>
<tr>
<td>c: fixed to muscle/fascia</td>
<td>M1 distant metastasis</td>
</tr>
</tbody>
</table>

Table 3  Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T: tumour size</th>
<th>N: Reg. Ln involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0 M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0/1 M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N M1</td>
</tr>
</tbody>
</table>

TREATMENT

Mammary neoplasms in the cat have been treated in a variety of ways. Surgery is the most widely used treatment. It may be used alone or in combination with chemotherapy or other modes of cancer therapy.

Surgery

The success of surgery is hindered by the invasive nature of the disease and its tendency for early metastasis. Radical mastectomy (i.e., removal of all glands on the affected side) is the surgical method of choice because it significantly reduces the chance of local tumour recurrence. With very large malignant tumours, the poor prognosis may lead to consider a surgical removal aiming to obtain just local control.

The surgeon's knowledge of the anatomy of the area is critical for local control of the tumour. The cat, unlike the dog, usually has four pairs of mammary glands. The cranial two glands on each side have a common lymphatic system and drain into the axillary lymph nodes and then to sternal nodes. The caudal two glands drain to inguinal lymph nodes. Tumour fixation to skin or abdominal fascia necessitates en bloc removal of these structures. Complete unilateral mastectomy is usually performed if the tumour(s) is confined to one side. Staged mastectomy, (two weeks apart) or simultaneous bilateral mastectomy is done when tumours are bilateral. The inguinal lymph node is virtually always removed with gland 4, while the axillary...
lymph nodes are only removed if enlarged and cytologically positive for tumour. Aggressive or prophylactic removal of axillary nodes probably has little therapeutic benefit.

Although ovariohysterectomy has been shown not to decrease the incidence of recurrence, some believe that it is warranted, in particular in relation to the need to stop progestin treatment (if applied). If the mammary mass is due to a benign condition such as fibroepithelial hyperplasia, ovariohysterectomy often results in regression of the hyperplastic tissue (see above). As an alternative, injectable antiprogestins proved effective in bringing fibroepithelial hyperplasia into regression.

**Chemotherapy**

In contrast to the dog there might be some better indication for chemotherapy in the feline mammary cancer, although the results are still not very good. Chemotherapy using doxorubicin (30 mg/m$^2$ iv slowly) alone or the combination of doxorubicin (25-30 mg/m$^2$ IV slowly) and cyclophosphamide (50-100 mg/m$^2$ per os Day 3, 4, 5, and 6 following doxorubicin) has been shown to induce short term responses in about half of cats with metastatic or nonresectable local disease. Partial responses (>50% regression) to doxorubicine alone or in combination with cyclophosphamide were noticed in 9/14 and 7/14 cats, respectively. The median survival time in these studies for those cats responding were 8 or 5 months, respectively, versus 6 and 2.5 months, respectively, for the 5 and 7 cats that did not respond. The chemotherapy protocol can be repeated every 3-4 weeks. Prospective studies using combined adjuvant chemotherapy and mastectomy in the cat have yet to be performed.

**Other treatment modalities**

To date radiotherapy has not proven to be effective in feline mammary tumours. Anti-hormonal treatment in mammary carcinomas in the cat has also not proven to be effective. This was expected as the more malignant tumours and also the metastases appear to have less PR and ER receptors than the benign lesions. Most tumours do express COX-2. Nevertheless, no studies are known to date with COX-2 inhibitors in feline mammary cancer. Results in other cancer types are not promising despite COX-2 expression.

**PROGNOSIS**

In the last 20 years, little progress has been made in extending the survival time of feline mammary tumour patients. Because stromal invasion is almost always present and metastases are frequently present at the time of surgery, a guarded-to-poor prognosis should always be given. With conservative surgery, 66% of the cats that have had their tumours surgically excised have a recurrence at the surgical site. Most studies state that the time from tumour detection to the death of the cat is 10 to 12 months.

The most significant prognostic factors affecting recurrence and survival for feline malignant mammary tumours are tumour size, extent of surgery, and histologic grading. Tumour size is the single most important prognostic factor for malignant feline mammary tumours. Cats with a tumour size of greater than 3 cm in diameter will have a median survival time of 4 to 6 months. Cats with a tumour size of 2-3 cm in diameter will have a significantly better survival time with a median of about two years, and cats with less than a 2 cm diameter tumour will have a median survival time of over three years. Thus, both the owner and the practitioner should realize that early diagnosis and treatment is a very important prognostic factor for malignant feline mammary tumours.

Few studies have reported the significance of lymph node metastasis in prognosis. In one study, 22 (49%) of 45 tumour-bearing cats had metastasis to the regional lymph node(s). Lymph nodes were clinically palpable in only 10 (21%) of these cats. This provides further rationale to perform a radical mastectomy, including regional (inguinal) lymph node removal, in all cats. Due to the location, the axillary lymph node should only be removed if enlarged or cytologically positive for tumour cells.

Very few studies have been performed to evaluate the effectiveness of the extent of
local therapy in malignant feline mammary tumours. One study did show that a radical mastectomy would reduce the - troublesome - development of local recurrence but did not increase overall survival time. A further prognostic factor for malignant mammary tumours is the degree of nuclear differentiation. Well differentiated tumours with few mitotic figures - indicative of low proliferation rate - have been shown to have increased survival times but, unfortunately, are rare compared to the more undifferentiated forms. In addition, a high proliferation index assessed by measurement of Ki-67 positive cells, appeared related with reduced survival in cats operated for mammary carcinoma.