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CLINICAL REVIEW

# MAMMARY TUMOURS IN THE CAT
# Size matters, so early intervention saves lives

**Joanna Morris**

**Practical relevance:** Mammary tumours are among the most common neoplasms in both cats and dogs, but the prevalence of malignant histological types is far higher in cats (ratio of malignant:benign is at least 4:1).

**Clinical challenges:** The more aggressive nature of mammary neoplasia in cats poses challenges for management. Prognosis is affected by tumour size and, therefore, early recognition and treatment of mammary tumours is paramount. Although the primary tumour can be excised surgically, no studies have shown that chemotherapy significantly extends survival time; hence, metastatic spread remains an important clinical problem.

**Patient group:** Mammary tumours usually affect older female cats, mainly entire females. Siamese and Oriental breeds may be predisposed. Male cats can develop mammary neoplasia, but this is rare.

**Evidence base:** This review summarises the current literature relating to aetiology, pathology, presentation, diagnosis, staging, treatment and prognosis of feline mammary tumours.

## Epidemiology

Mammary neoplasia is the third most common tumour type affecting female cats after lymphoma and skin tumours, accounting for 17% of tumours.[1] Reported incidence is 25.4 per 100,000 female cats per year.[1] Although precise statistics are not available, the incidence of mammary tumours may vary globally depending on cultural acceptance of neutering policies. Neutering is less common in Scandinavia and some other parts of Europe than in the UK, for example.

**Signalment**

Mammary tumours occur in older female cats (mean age 10–12 years),[2–4] and usually those that are entire.[5,6] Mammary tumours are also reported in male cats (mean age 12.8 years),[7] but this is rare, accounting for 1–5% of mammary tumours. Siamese cats and other Oriental breeds may be more at risk,[6] with mammary tumours occurring at a younger age;[4,8] however, domestic shorthair cats, being probably the most common cat breed, are also very frequently affected.

## Aetiology

As in humans and dogs, hormonal fluctuations associated with repeated oestrous cycles may influence the development of mammary tumours in cats. This is supported by a case control study reporting that cats spayed before 1 year of age had a decreased risk of developing mammary cancer,[9] and that intact cats were seven times overrepresented in a population of cats with mammary tumours compared with a control group.[10] However, cats spayed at less than a year old do still develop mammary tumours so the effect of early neutering does not eliminate the risk of mammary tumours,[8] and early studies reporting more tumours in intact cats may possibly have reflected neutering practices at the time rather than a true increased risk.[11]

Other evidence to support a hormonal aetiology is that oestrogen and progesterone receptors are found in normal mammary tissues and benign tumours but are often lost in malignant tumours and metastases.[12–17] In addition, exogenous progesterone administration to prevent pregnancy, or for behavioural aggression, causes tumour development (benign and malignant) in both male[18] and female cats.[19] A possible dose-related effect may occur, with increased risk of mammary carcinoma if given regularly rather than intermittently.[10]

There is no definitive evidence for a viral aetiology for mammary tumours in cats, although this was proposed in early literature, and obesity has not been implicated, unlike in dogs.

**Early neutering does not completely eliminate the risk of mammary tumours in cats.**

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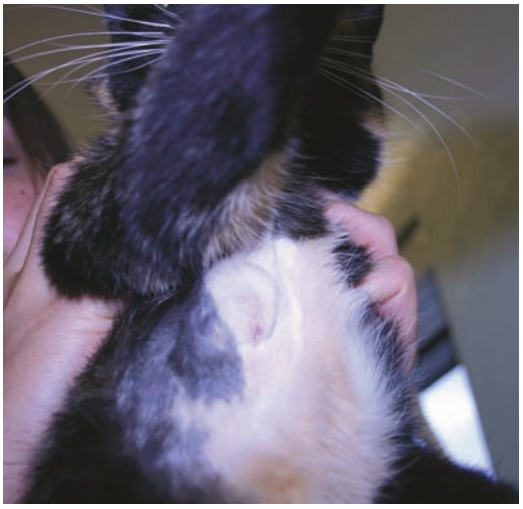


Figure 1 Mammary mass in the thoracic glands of an 11-year-old female entire (FE) domestic shorthair (DSH) cat

Figure 2 Mammary mass in the thoracic glands and axillary lymph node of an 8-year-old FE DSH cat

## Presentation

Cats have four pairs of mammary glands (two thoracic and two abdominal) and, although any gland may be affected, some studies have reported a predisposition for mammary tumours in the caudal glands.[11,20] Mammary tumours present as a single subcutaneous nodule or mass within the mammary glands (Figures 1 and 2), which may be discrete and mobile, or attached to underlying tissues and possibly ulcerated in appearance (Figure 3). A few may appear cystic. It is difficult to distinguish benign from malignant nodules in cats, so all should be treated as potentially malignant. Multiple mammary masses within several glands are common (usually ipsilateral but occasionally bilateral) (Figure 4) and were reported in 60% of cats in one study.[8] Sometimes, the true extent of the disease cannot be appreciated without clipping the fur. Drainage lymph nodes (inguinal or axillary) may also be visibly or palpably enlarged.

In particularly aggressive inflammatory carcinomas with extensive lymphatic involvement, the glands may be swollen, hot and painful.[4] This presentation may be difficult to differentiate from fibroadenomatous hyperplasia (fibroepithelial hypertrophy, feline mammary hypertrophy), although the latter more commonly affects young cats.[21]

Figure 3 Ulcerated mammary mass in the second abdominal gland of a 21-year-old male neutered DSH cat

**Differential diagnosis**

Numerous non-neoplastic hyperplasias and dysplasias can occur in the mammary gland, and although these are much less frequent in cats than in dogs, all may be mistaken for mammary tumours. These include ductal hyperplasia, duct ectasia (dilation), cysts, and lobular hyperplasia, all of which may show associated focal fibrosis. Extensive, bilateral gland distension and swelling of the mammary glands may also occur in fibroadenomatous hyperplasia, a type of lobular hyperplasia that may follow prolonged metoestrus, pseudopregnancy or pregnancy, or use of exogenous progesterone.[11,21]

## Diagnosis

If a mammary mass is palpated, confirmation that it is neoplastic requires biopsy of tissue or a fine needle aspirate (FNA) for cytology. Since most feline mammary tumours are malignant, FNAs are more reliable than in dogs and are useful to confirm the diagnosis (Figure 5).

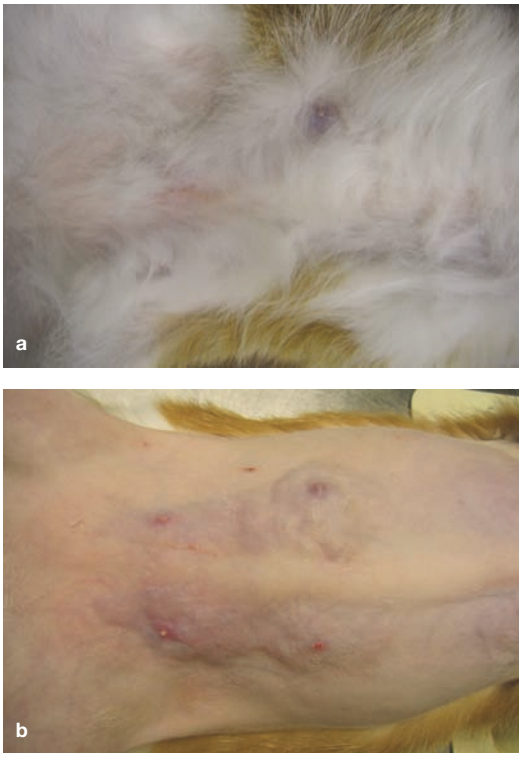



Figure 4 Bilateral mammary masses before (a) and after (b) clipping

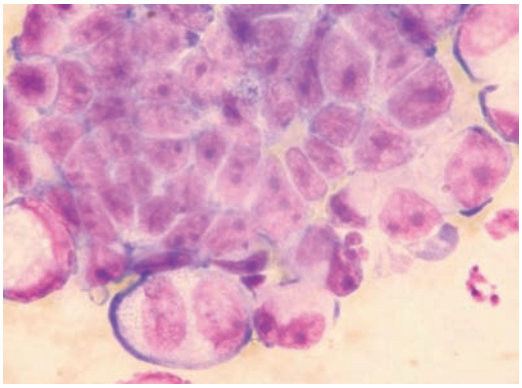


**Figure 5** Cytology of feline mammary carcinoma, showing a raft of polygonal neoplastic epithelial cells with anisocytosis and anisokaryosis, some multinucleate cells and prominent nucleoli, often several per nucleus. *Courtesy of Elizabeth Villiers*

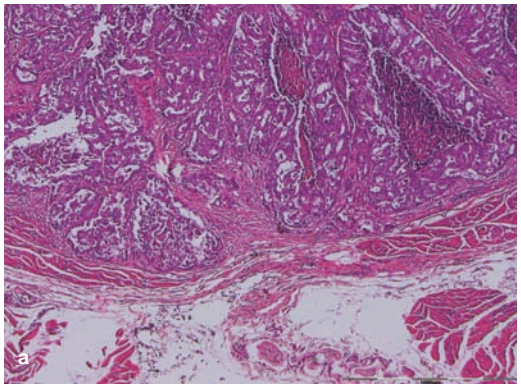
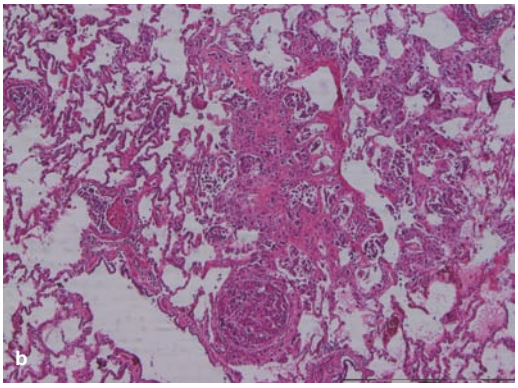



**Figure 6** Histology of feline mammary simple adenocarcinoma. Low power views showing primary tumour invading muscle (a), and pulmonary metastasis (b) with tumour cells in blood vessels and lung tissue. *Courtesy of Tim Scase*




**The main histological type of mammary tumour in the cat is simple adenocarcinoma.**

Most feline mammary tumours derive from glandular epithelium and all strictly are adenomas or adenocarcinomas, although the latter are often loosely referred to as carcinomas. Benign tumours are uncommon but, of these, fibroadenoma is most frequently reported, with simple adenoma or duct papilloma rarely seen. The main histological type of mammary tumour in the cat is simple adenocarcinoma derived from the luminal epithelium of the mammary ducts and alveoli (Figure 6). Complex or mixed tumours involving both luminal and myoepithelial cells are extremely infrequent in cats compared with dogs, although they may be associated with a better prognosis.[22,23] In cats, carcinomas may be tubulopapillary, solid, cribriform or mucinous, although squamous cell carcinoma and mixed carcinosarcoma are also reported.[24]

Inflammatory mammary carcinoma, which has a particularly poor prognosis owing to an additional inflammatory component blocking the lymphatics and affecting lymph drainage and causing swollen, painful glands, has been reported in three cats with underlying highly malignant, papillary mammary carcinomas.[25]

## Staging

If a mammary tumour is suspected or confirmed, investigations should be carried out to determine the local extent and degree of spread throughout the body prior to surgical excision. As so few mammary masses are benign, and gross appearance alone is an unreliable basis on which to distinguish benign from malignant tumours, complete staging should be routine for all mammary masses. The WHO staging system is usually applied (Table 1);[26] however, with many tumours being noticed earlier and in less advanced stages, fewer larger tumours over 5 cm diameter are being reported. Measurement of the primary tumour with calipers is important since the size of the tumour influences the prognosis: those <3 cm diameter being associated with better survival rates than those >3 cm (see later).

**As so few mammary masses are benign, complete staging should be routine for all.**

Staging of confirmed tumours should include palpation and aspiration of local drainage lymph nodes, since more than a quarter of cats have regional metastasis at the time of diagnosis.[27] Involvement of multiple axillary lymph nodes is commonly detected by lymphangiography (58–75% cases) but a single inguinal lymph node predominates (84–94% cats).[28] Although the axillary and inguinal lymph nodes are those mainly reported as being affected in feline mammary neoplasia (80% cats), the sternal lymph node may also be involved (30% cats).[27]

**Table 1** TNM and clinical staging system for feline mammary tumours

| Clinical stage | Tumour diameter (T) | Regional lymph node (N) | Distant metastasis (M) |
|---|---|---|---|
| I | <2 cm ($T_1$) | Negative ($N_0$) | Negative ($M_0$) |
| II | 2–3 cm ($T_2$) | Negative ($N_0$) | Negative ($M_0$) |
| III | >3 cm ($T_3$)<br>≤3 cm ($T_1$–$T_2$) | Negative or positive ($N_0$ or $N_1$)<br>Positive ($N_1$) | Negative ($M_0$)<br>Negative ($M_0$) |
| IV | Any T | Any N | Positive ($M_1$) |

Adapted from Owen[26]

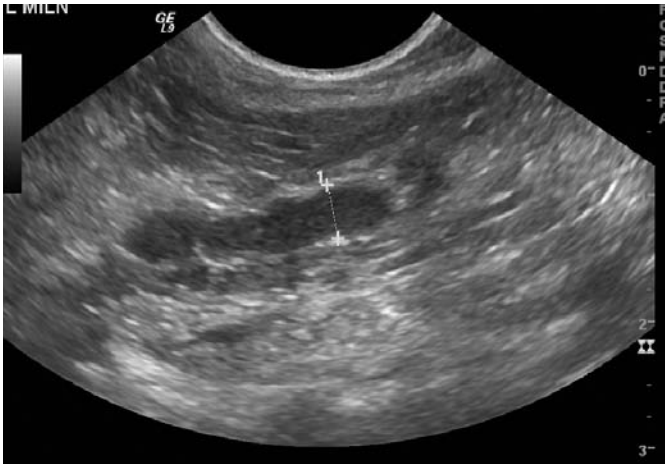


**Figure 7** Enlarged left medial iliac lymph node chain with surrounding hyperechoic fat detected by abdominal ultrasound at routine staging of an 11-year-old female neutered (FN) Abyssinian with mammary carcinomas of the left caudal abdominal and right cranial thoracic glands

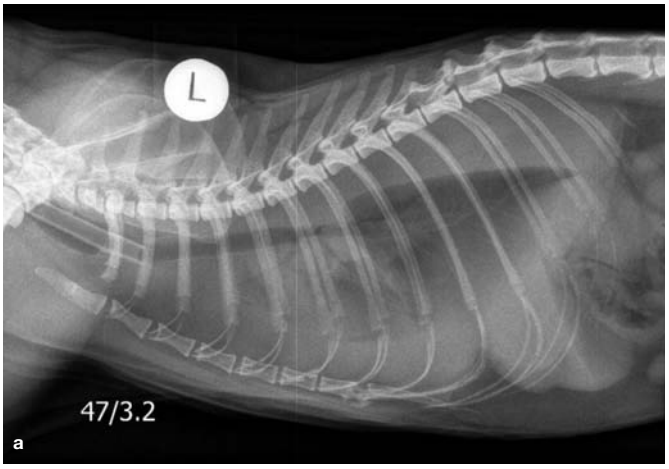
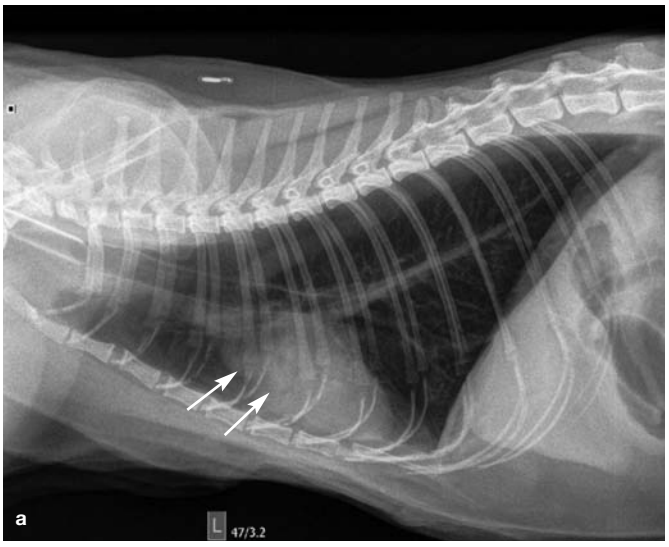



**Figure 8** Left lateral (a) and dorsoventral (b) radiographs of the thorax of the cat imaged in Figure 7. These views show general increased opacity within the thoracic cavity, with severe retraction of the lung fields from the dorsal wall and effacement of the cardiac silhouette and diaphragm, consistent with pleural effusion


For more distant spread, three-view chest radiography (preferably performed under anaesthesia with inflated lungs) and abdominal ultrasonography should be carried out, since the most common sites of metastasis are the lungs, medial iliac lymph nodes and abdominal organs (Figure 7). Pulmonary metastases usually appear as a miliary pattern on thoracic radiographs, but pleural surfaces can also be affected and in some cases metastatic lung disease can cause pleural effusion (Figure 8). More uncommonly, metastasis to bone can be detected.

Advanced imaging (ie, computed tomography [CT]) of the lungs provides more accurate assessment of metastases (see 'case notes'), and should be used where there is any concern about the radiographic appearance of the lungs (Figure 9).

**More than a quarter of cats have regional metastasis at the time of diagnosis.**



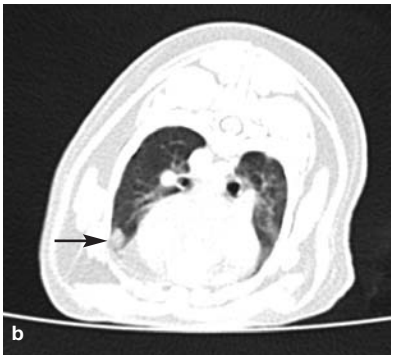




**Figure 9** Left lateral radiograph (a) of a 12-year-old FN DSH cat with a mammary carcinoma of the second abdominal gland. A couple of faint, ill-defined soft tissue opacities superimposed on the cardiac silhouette, and suspicious for metastasis, were noted on this view (arrows) but not the right lateral view. CT of the chest confirmed the presence of a 2–3 mm hyperattenuating nodule in the middle right lung lobe and (b) a 4.8 mm hyperattenuating nodule in the caudal part of the left lung lobe (arrow)

Since most affected cats are elderly, haematology, biochemistry and urinalysis should also be performed to assess for concurrent disease. Paraneoplastic conditions are rarely reported with mammary tumours, and feline leukaemia virus and feline immunodeficiency virus are not implicated in the aetiology. However, if further treatment, including chemotherapy is being considered, it is important to evaluate viral status since viral immunosuppression may influence whether treatment goes ahead.

## Surgical treatment

The mainstay of treatment for mammary tumours is still surgical resection. The extent of surgery is influenced by the lymphatic drainage in the feline mammary gland (see box), as tumour cells spread readily beyond the primary site and complete excision should encompass all known drainage pathways.

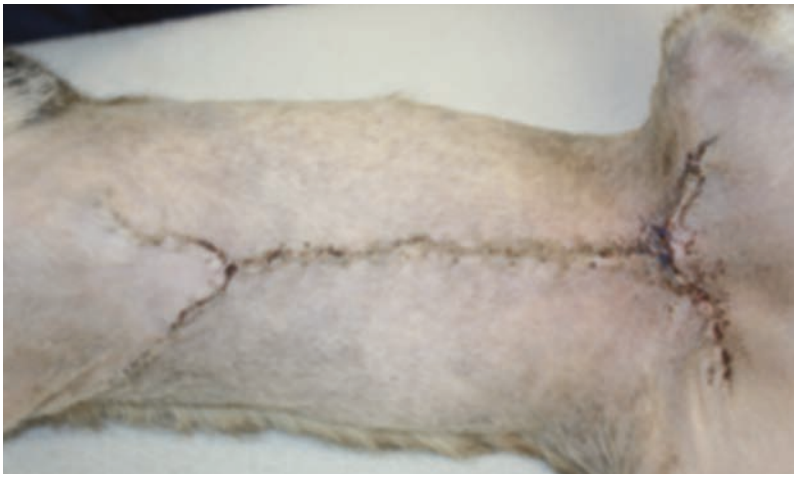
### Recommended approach

The recommendation based on drainage studies is to perform unilateral or bilateral mammary strips because of possible contact between individual glands and between left and right sides. While radiological imaging studies would suggest that this may not be necessary in every case, additional prognostic analyses do support the use of unilateral or bilateral mammary strips since the extent of surgery appears to make a significant difference to local recurrence/disease-free interval (DFI)[33] and survival time.[34] For bilateral strips a 2-week interval is recommended between surgeries although simultaneous bilateral mastectomy can also be performed (Figure 10). Tumour fixation to skin or abdominal fascia necessitates removal of these structures en bloc.[35]

✣ **Excision of lymph nodes** The inguinal lymph node is embedded in the caudal mammary gland and is therefore removed along with the gland as part of a mammary strip. The axillary lymph node should be removed if enlarged or positive for tumour spread on FNA or biopsy, but there is no evidence that prophylactic removal extends survival.

✣ **Concurrent ovariohysterectomy** There is no evidence that ovariohysterectomy at the time of mastectomy has any benefit on survival or tumour recurrence,[8] or effect on development of new tumours or carcinoma progression.[10] It might, however, reduce the need for progestin therapy, which may be beneficial.

**Figure 10** Bilateral mammary strip in a cat with mammary carcinoma. *Courtesy of Kathryn Pratschke*



### Lymphatic drainage

Lymphatic drainage has been studied by injection of dyes and anatomical dissection of cadavers,[29,30] and by radiological methods in live healthy cats;[28] the latter may be more accurate since dynamic blood pressure influences the direction of natural lymphatic flow. Most studies agree that the first and second (thoracic) glands drain cranially into the axillary lymph nodes; although cadaver dissections have shown that the second gland may drain caudally to the inguinal lymph node,[29,30] this has not been seen by radiological methods. The third (abdominal) gland drains both cranially to axillary and caudally to inguinal lymph nodes, and the fourth gland drains just caudally to the inguinal lymph node. Direct drainage from the third and fourth abdominal glands to the medial iliac lymph node was reported in one case each;[28] however, direct drainage of the first, second and third glands to the sternal gland has not been confirmed in the cat.[28,30]

Although connections between mammary glands and between left and right sides have been previously proposed, live imaging does not support this in the healthy cat.[28] Drainage may vary between normal glands and glands with mammary tumours, making it difficult to know the precise drainage pathway,[31] and perhaps making a case for indirect lymphography for each patient to help define the drainage pattern and examine sentinel lymph nodes.[32] Potentially this might enable more conservative resections to be performed.

**As tumour cells spread readily beyond the primary site, complete excision should encompass all known drainage pathways.**

## Chemotherapy

There is some data to show that chemotherapy may be effective on mammary cell lines in vitro,[36–38] and that treatment of non-resectable disease in vivo with doxorubicin and cyclophosphamide may shrink tumour size in 50% cases and possibly increase survival (Table 2).[38–40] The benefit of using chemotherapy as an adjunct to surgical excision of mammary tumours in cats, however, is still not clear (Table 3).

A large, multicentre study of 67 cats receiving adjunctive doxorubicin reported a median survival time of 448 days.[41] Although there was no control group in the study, this survival time was deemed longer than historical controls and was similar to that in another study of 23 cats without a control group (460 days) combining adjunctive doxorubicin with the COX-2 inhibitor meloxicam.[42] A further study of 73 cats, which included a control group of 36 cats undergoing surgical excision only, reported increased survival time and DFI for the cats receiving postoperative doxorubicin and cyclophosphamide (1406 versus 848 days [survival time] and 676 versus 372 days [DFI]);[34] however, the difference was not statistically significant.

**Table 2** Effect of chemotherapy (doxorubicin) on mammary carcinomas (gross disease)

| Clinical stage | Number of cats | Treatment | Control group | Median survival (days) | Response | Reference |
|---|---|---|---|---|---|---|
| III or above | 14 | Doxorubicin (30 mg/m$^2$ IV q2 weeks) | No | 215 (30.8 weeks) | >50% response in 9/14 | Stolwijk et al[38] |
| III or above | 14 | Doxorubicin (20–30 mg/m$^2$ IV q3 weeks) + cyclophosphamide (100 mg/m$^2$ PO for 3 days q3 weeks) | No | 180 | >50% response in 5/14 | Jeglum et al[39] |
| III or above | 14 | Doxorubicin (25 mg/m$^2$ IV) + cyclophosphamide (50 mg/m$^2$ PO for 4 days q3 weeks) | No | 90 | >50% response in 7/14 | Mauldin et al[40] |

**Table 3** Effect of chemotherapy (doxorubicin) as an adjunct to surgical removal of mammary tumours

| Clinical stage | Number of cats | Treatment | Control group | Median survival (days) | Median DFI (days) | Reference |
|---|---|---|---|---|---|---|
| III or below | 67 | Surgery + doxorubicin* | Historical | 448 | 255 | Novosad et al[41] |
| III or below | 37 | Surgery alone | Surgery alone | 1406 | 372 | McNeill et al[34] |
| | 36 | Surgery + doxorubicin† + cyclophosphamide‡ | | 848 | 676 | |
| III or below | 23 | Surgery + doxorubicin§ + meloxicam¶ | Historical | 460 | 269 | Borrego et al[42] |

DFI = disease-free interval
*Doxorubicin 1 mg/kg IV q3 weeks
†Doxorubicin dose not given (four cases doxorubicin alone)
‡Cyclophosphamide dose not given
§Doxorubicin 1 mg/kg IV q3 weeks (one case had vincristine 0.7 mg/m$^2$ IV and 13 cases had cyclophosphamide 250 mg/m$^2$ IV, 1 week after doxorubicin)
¶Meloxicam 0.2 mg/kg PO on day of surgery, then 0.1 mg/kg q24h for 5 days, then 0.025 mg/kg

**The benefit of using chemotherapy as an adjunct to surgical excision of mammary tumours in cats is still not clear.**



It is possible that with greater numbers and more statistical power, a true benefit of aggressive chemotherapy may become apparent. Alternatively, a different approach with antiangiogenic metronomic (low dose) chemotherapy may prove effective, although low dose chemotherapy using vincristine, cyclophosphamide and methotrexate did not prevent recurrence or metastasis in one report.[8]

## Other therapies

Although immunomodulators such as bacillus calmette-Guerin (BCG),[43] *Corynebacterium parvum*,[44] liposome-encapsulated muramyl tripeptide phosphatidylethanolamine (L-MTP-PE)[45] and oral levamisole[46] have been tried as intratumoural injections (BCG) or adjuncts to surgical excision of feline mammary tumours, none have proved successful in extending survival time or altering recurrence rate. There are no reports of using antioestrogens such as tamoxifen in cats, probably since most malignant feline mammary tumours lack oestrogen receptors and expected benefits would, therefore, appear to be minimal.

The small molecule inhibitors that target receptor tyrosine kinases (receptor tyrosine kinase inhibitors or RTKIs) are effective in the management of some types of veterinary cancers, particularly those with altered TK activity.[47] Imatinib and masitinib are well tolerated in cats;[48–51] however, there is no information about their efficacy against feline mammary tumours. (Further discussion on the use of targeted therapies in cats, with a particular focus on the idiosyncracies of feline patients, is provided in an accompanying article in this special issue.)

**Table 4 Prognostic factors for feline mammary tumours**

| Factor | Details |
|---|---|
| Tumour size* | Diameter <3 cm – median survival 21–24 months<br>Diameter >3 cm – median survival 4–12 months |
| Clinical stage† | Stage I – median survival 29 months<br>Stage II – median survival 12.5 months<br>Stage III – median survival 9 months<br>Stage IV – median survival 1 month |
| Surgical extent | Radical surgery (mammary strip) reduces recurrence rate compared with more conservative mastectomy |
| Histopathological grade | Well differentiated – 100% survival at 1 year after surgery<br>Poorly differentiated – 0% survival at 1 year after surgery |
| Mitotic index | <2 mitotic figures per high power field give longer survival |

*MacEwen et al[33] and Viste et al.[52] †Ito et al[53]

## Prognosis

Prognosis is guarded for most cats with mammary tumours, with deaths mainly attributable to local recurrence or metastasis. The average time between detection and death is reported to be 10–12 months;[20,35] however, as already mentioned, several factors affect prognosis of feline mammary tumours (Table 4).

### Clinical parameters

Prognosis is very much related to the size of the tumour at initial presentation, with tumours of large volume (>27 $cm^3$) or diameter (>3 cm) being associated with shorter survival times (4–12 months).[8,52,53] The degree of spread at initial presentation (eg, regional lymph node metastasis) also dramatically affects prognosis,[20,33,53] as does the extent of surgery carried out. Radical mastectomy produces a significantly longer DFI,[33,53] and histological completeness of resection correlates with survival.[27] The cat's age may also influence prognosis,[27,33] although more recent studies dispute this.[53]

### Histological parameters

A wealth of literature exists on histological markers detected by pathologists,[54] some of which influence prognosis. However, few are routinely used in diagnostic laboratories to offer helpful information to clinicians.

The most useful assessment by pathologists is histological grading, which is significantly related to both overall survival and DFI in univariate and multivariate analyses.[55–57] Mitotic index also correlates with survival time,[58] but although other proliferation markers such as Ki67,[57,59] AgNOR[60] and PCNA[61] may help determine high histological grade, they have not been shown to be independent prognostic markers. Similarly, although expression of hormone receptors (ER and PR) has been examined in feline carcinomas, receptor status does not correlate with overall survival and is not routinely assessed.[14,15] The epidermal growth factor receptor 2 (Her2/neu) is variably overexpressed in feline carcinomas and, while one study has associated this with survival,[62] more recent data has not.[63] High COX-2 expression in mammary carcinomas has also been linked with poor prognosis,[64] but this association is complicated by the fact that it also correlates with expression of the angiogenic factor vascular endothelial growth factor (VEGF), which itself is significantly correlated with overall survival.[65] More recently, expression of the cytoplasmic protein kinase, AKT, which is activated by numerous receptor tyrosine kinases such as EGF or by loss of the tumour suppressor gene PTEN (phosphatase and tensin homologue), has been significantly associated with shorter DFI.[66]

**Table 5 Comparison of mammary tumours in cats and dogs**

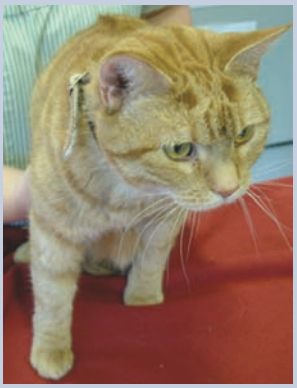
| | Cats | Dogs |
|---|---|---|
| Aetiology | Hormonal (oestrogen and progesterone) | Hormonal (oestrogen and progesterone)<br>Obesity at a young age |
| Signalment | Mean age 10–12 years<br>Siamese/Oriental and DSH cats most affected<br>Usually intact females<br>Rare in males – aggressive disease when seen | Mean age 6–10 years<br>Poodles, dachshunds and spaniels most affected<br>Usually intact females<br>Rare in males – more benign disease when seen |
| Staging | Often metastatic spread | Metastatic spread less frequent |
| Pathology | 80–90% malignant<br>Mainly simple adenocarcinomas | 50% benign<br>Complex/mixed benign tumours are common but carcinomas are usually of simple type |
| Treatment | Radical mastectomy (strips) advised | Depends on size and site (gland affected) but regional mastectomy or strip advised for most carcinomas |
| Chemotherapy | Several studies suggest at least some efficacy of doxorubicin against gross disease or metastasis | No conclusive evidence for efficacy of chemotherapy |
| Prognostic factors | Size of tumour<br>Clinical stage<br>Histological grade of tumour<br>Extent of surgery | Size of tumour<br>Clinical stage<br>Histological grade of tumour<br>Histological type of tumour |

**KEY POINTS**

- Mammary tumours in cats differ from those in dogs in terms of histological type and behaviour (Table 5).
- Early diagnosis is important for optimal management, as is a more aggressive surgical approach to treatment. In most cases adjuvant chemotherapy also needs to be considered.

Case notes

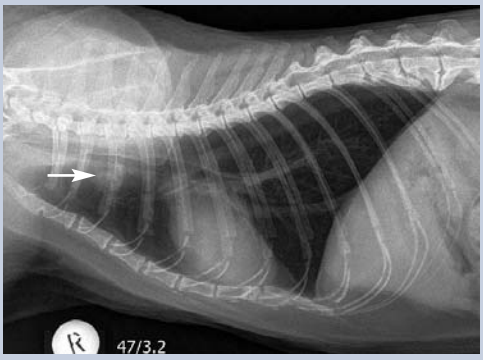
**Cleo, a 13-year-old FN DSH cat, presented with a 5 x 3 cm mammary mass in her right caudal abdominal gland. She had a short history of being pyrexic and inappetent before presentation, and had clinical signs of concurrent hyperthyroidism (palpable goitre) and an elevated heart rate (250 bpm).**



Cleo at presentation

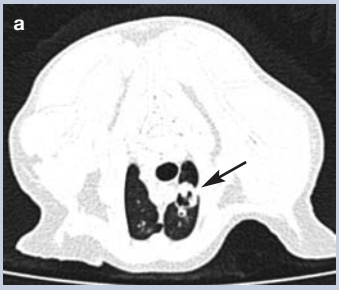
**Blood tests** Blood tests for haematology, biochemistry and glucose were all within normal limits. Thyroxine ($T_4$) was also normal (41 nmol/l), although perhaps higher than might be expected for a cat with other illness.

**Ultrasound and echocardiography** No significant abnormalities were detected on abdominal ultrasonography. Echocardiography detected mild changes of hypertrophic cardiomyopathy consistent with early primary disease or underlying hyperthyroidism.

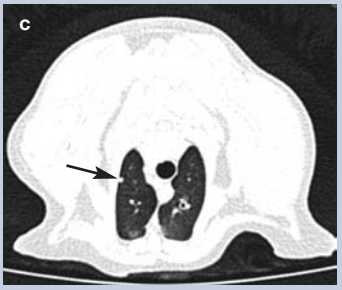



**Radiography** Inflated chest radiographs (see right) revealed a soft tissue opacity in the cranial lung field (right lung on dorsoventral view) at the level of the third rib, and bony changes were noted on the right scapula.

**Advanced imaging** CT of the chest was performed to further evaluate the nodule in the lung. A high resolution CT scan with lung field window confirmed the presence of an expansile, cystic lesion in the right lung field (see image a below). The waxing and waning pyrexia was thought to be linked to periodic necrosis within this expansile lung lesion. Metastatic nodules were noted at the dorsal periphery of the right lung lobe (b) and lateral margin of the left lung lobe (c). An expansile lytic lesion with areas of calcification was observed in the dorsal scapular border and scapular spine, consistent with metastatic spread (d and e).










**Treatment and outcome** Owing to the metastatic spread to lung and scapula, radical surgical excision of the mass was not performed. Cleo was managed with meloxicam and buprenorphine for a few weeks but sadly was then euthanased due to bone pain, weight loss and inappetence.

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## Conflict of interest

The author does not have any potential conflicts of interest to declare.

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