Mammary tumours in dogs

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INTRODUCTION

Mammary tumours arise from the glandular epithelium of the mammary glands. Various histological forms are described. Other non-epithelial neoplasms can arise in the mammary region; these will not be discussed here.

The prevalence of mammary neoplasia varies remarkably between different countries. This variation is linked to cultural behaviour with respect to neutering practices. In Europe, incidence rates are generally higher in southern European and Scandinavian nations where neutering is less frequently performed (Perez-Alenza *et al.* 2000; Moe 2001). The incidence in entire bitches is approximately 71% (Benjamin *et al.* 1999). In countries where neutering is not routinely practised, this is easily the most significant neoplastic consideration affecting adult canines, despite the fact that the disease is almost never seen in adult males.

Mammary tumours can be benign or malignant (**Table 1**). Unfortunately, the distinction between the two can be considerably less clear-cut than one would like. Furthermore, to a non-pathologist the terminology is bewildering. The various canine epithelial mammary tumours are given in **Table 1**. Mammary tumours are classified first according to their tissue of origin and whether they are benign or malignant. Originating tissues include glandular (adenoma/adenocarcinoma), ductular (papilloma/carcinoma), myoepithelial and pluripotential (mixed) cells, though some uncertainty about the histogenetic origin of many mammary tumour types remains. In addition to the histogenetic and benign/malignant classification, additional descriptive terms can be used (**Table 2**). The distinction between tumours demonstrating tubular/papillary differentiation and those exhibiting solid/anaplastic histology is considered to be prognostically significant.

In entire bitches, the ratio of benign:malignant tumours is approximately 50:50. Neutering, however, appears to preferentially reduce the incidence of benign mammary neoplasia. Therefore, while the overall incidence of mammary cancer is considerably less in neutered bitches, the likelihood of malignancy is greater than 50 per cent.

AETIOLOGY

Physiological mammary development occurs under the

Table 1: Epithelial mammary tumours in the dog

	Tumour type	Histological features
Benign	Ductal papilloma	Simple or complex
	Adenoma	Simple or complex
	Benign mixed tumour	Epithelium plus mesenchymal tissue
	Fibroadenoma	
	Myoepithelioma	
Malignant	Adenocarcinoma	Solid, tubular or papillary Simple or complex
	Ductular carcinoma	Intra- or inter-lobular Simple or complex
	Spindle cell carcinoma	
	Anaplastic carcinoma	
	Squamous cell carcinoma	
	Mucinous carcinoma	
	Malignant myoepithelioma	
	Carcinoma or sarcoma in a mixed tumour	Epithelial and mesenchymal tissue, one is neoplastic
	Carcinosarcoma	Epithelial and mesenchymal tissue, both neoplastic

Table 2: Histological terms in canine mammary neoplasia

Histological term	Definition
Simple	Single (epithelial) tissue type present
Complex	Lesion with both epithelial and significant myoepithelial proliferation
Mixed	Contains both epithelial and/or myoepithelial tissue and a mesenchymal component such as fat, cartilage or bone
Solid	Solid sheets or cords of cells without evidence of tubular lumens
Anaplastic	No indication of cellular differentiation
Tubular	Tubular lumens present
Papillary	Frond-like epithelial projections

influence of the somatotrophic and gonadal hormones. Since cancer arises through subversion of some of these growth pathways, it makes biological sense that increased or prolonged exposure to growth promoting hormonal influences raises the risk of the development of neoplasia. The earliest study to recognise an increased risk of mammary neoplasia associated with remaining sexually entire was performed by Schneider *et al.* in 1969. This study yielded data that indicated that the relative risk of mammary neoplasia development was as low as 0.5% for bitches undergoing ovariohysterectomy before their first oestrus when compared to bitches that remained entire. While the original data from 1969 have not been superseded, it must be stated that the conclusions drawn are based upon remarkably few cases from the younger neutering age groups, as shown in **Table 3**. This study has led to early neutering practices in many countries, in particular the USA where it is commonplace to perform neutering surgery as early as 12 weeks of age. Intriguingly, bilateral oophorectomy has been shown to reduce the incidence of breast cancer among women carrying high-risk germline mutations in certain breast cancer susceptibility genes by up to 80% (Eisen *et al.* 2008).

Table 3: Age of neutering and relative risk of the development of mammary neoplasia in the bitch compared to intact individuals and number of cases from which statistics are derived. From Schneider et al. (1969)

Age at neutering	Relative risk of mammary neoplasia	n
Before 1st season	0.5%	1
Between 1st and 2nd seasons	8%	3
2 or more seasons	26%	20
2 or more seasons but <30months old	6%	2
2 or more seasons but >29 months old	40%	18

n: number of corresponding cases in study from which statistic is derived

Table 4: Proportion of canine mammary tumours exhibiting benign histology, cases separated according to tumour size

Tumour size (max diameter)	Benign cases (%)
<1 cm	98
1-1.9 cm	97
2-2.9 cm	85
3-3.9 cm	45
>4 cm	42

Subsequent veterinary studies have examined the impact of the timing of neutering on prognosis following diagnosis and management of mammary neoplasia. There are significant data indicating that neutering at the time of mammary resection affords no benefit to the patient. Over the last 10 years, multiple investigators have examined the possible role of aberrant hormone production and receptor expression. Immunohistochemical evaluations of oestrogen and progesterone receptor expression appear to indicate a loss of steroid dependency in tumour growth (Martin de las Mulas *et al.* 2005; Millanta *et al.* 2005). Mammary tumour tissue prolactin concentrations have been shown to be higher than normal mammary tissue (Queiroga *et al.* 2005) and, more recently, a marked correlation has been noted between mammary tumour tissue prolactin concentration and survival (Queiroga *et al.* 2008).

Sorenmo *et al.* (pers. comm. 2006) have proposed a model of canine mammary neoplasia development in which the malignant phenotype develops within an otherwise benign tumour. The proportion of tumours exhibiting characteristics of malignancy increased with increasing tumour size (**Table 4**). This model is derived from a prospective study of canine mammary tumours that is currently incomplete. The model is supported by other studies, which demonstrate a compelling association between the size of the primary tumour and overall survival (Philibert *et al.* 2003; Chang *et al.* 2005).

PRESENTATION

Mammary neoplasia can be presented as a solitary mammary mass or, frequently, as multiple lesions. A common scenario is the old dog, with multiple masses, which has finally been presented for veterinary attention because the largest of her mammary tumours now drags on the floor, or has spontaneously ulcerated due to its enormous size. In situations where previous advice may

Table 5: Histological 'stage' of canine mammary tumours and prognostic implications following appropriate surgery

Histological 'stage'	Features	Prognosis	Prognosis simplified
Stage 1	Lesions are non-infiltrative and resemble the tissue of origin. Tubular structures are evident	High probability of surgical cure	Curable
Stage 2	Loss of tubular lumen and/or invasion of the surrounding stroma but no evidence of vascular or lymphatic invasion	Median survival time 380 days	1 yr
Stage 3	Presence of lymphatic or vascular invasion	Median survival time 108 days	3 mths
Stage 4	Evidence of metastasis	Median survival time 108 days	3 mths

have been to simply monitor a mass because it had been behaviourally benign, or because an owner would simply not have accepted alternative management, it is important to remember that mammary tumour behaviour can change with the passage of time.

Mammary tumours primarily undergo metastasis to the regional lymph nodes or to the lungs. The primary lymph node beds (lymphocentra) are the superficial inguinal and the axillary sites. Examination of the lymph nodes is mandatory in the physical examination of a patient.

Inflammatory carcinoma is an unusual manifestation of mammary neoplasia typified by large erythematous and painful mammary swellings, frequently occupying all of the mammary tissues. Sometimes these lesions will spontaneously discharge a serous exudate. Patients are typically extremely depressed.

DIAGNOSIS

The use of cytology to diagnose mammary neoplasia presents a point of great controversy amongst veterinary oncologists. The principal reason for controversy is the marked heterogeneity that can be seen histologically within a single tumour. This variation represents more than histological pedantry. There is a subset of cases that present with an overtly benign tumour, for example a simple adenoma, with microscopic evidence of a malignant tumour in situ. These lesions exhibit malignant behaviour; survival times may correlate with the size of the malignant element.

Proponents of the use of diagnostic cytology in mammary neoplasia would therefore advocate the collection of at least four samples from distinct areas within the mass in question, with the ultimate diagnosis being determined by the sample that yields the most malignant cytological appearance.

Histological evaluation of an incisional or excisional biopsy remains the gold standard recommendation for mammary tumour diagnosis. A biopsy that includes the apparent junction between normal skin tissue and the mammary mass will give an indication of the degree of microscopic invasiveness. It is not practical to biopsy all mammary masses, particularly those that are less than 1 cm in diameter. For solitary small nodular masses, marginal (2 mm) excision will be diagnostic and may be curative. Importantly, the conservative margin obtained is unlikely to complicate a subsequent surgical procedure if one is indicated.

HISTOLOGICAL GRADE

Multiple strategies for assigning histological grade to canine mammary tumours have been presented (Gilbertson *et al.* 1983; Karayannopoulou *et al.* 2005). Features considered relevant to tumour grade include: Indicators of cellular differentiation; nuclear pleomorphism; and degree of invasiveness. A simplified system incorporating elements of histological grade and clinical stage is given in **Table 5**. It is important to note that the inflammatory carcinoma does not fit into other histological grading schemes and should be regarded as a separate entity in this context.

Table 6: T stage classification of canine mammary tumours. Other features of importance are recent rapid growth, clinical evidence of invasiveness and ulceration

T stage	Tumour size
T_{is}	Tumour in situ
T_1	<3cm diameter
T_2	3-5cm diameter
T_3	>5cm diameter

CLINICAL STAGE DETERMINATION

In oncology, definition of the clinical stage, or the anatomic extent of disease, is critical to good decision making. Since mammary tumours are recognised to be associated with metastasis in a number of cases, simple evaluations to define clinical stage are advised prior to performing invasive surgery. Therefore, close examination for multiple mammary masses and fine needle aspirates of enlarged regional lymph nodes must be performed. Thoracic radiography is recommended for all but the smallest lesions. Abdominal ultrasonography allows evaluation of the deep inguinal lymph nodes and the parenchyma of the abdominal viscera. For small lesions (<1 cm diameter) it would be hard to justify the expense of radiography or ultrasonography, as the likelihood of malignancy is so low.

Clinical stage also defines local invasiveness. Increasing tumour size is known to be associated with increasing probability of significant local invasion. In canine mammary tumours, the TNM classification separates tumours, where T relates to tumour size (**Table 6**) and whether it has invaded nearby tissue, N describes the involvement of regional lymph nodes and M describes metastasis. In a survey of 54 cases, two-year survival percentages were 62% for T1 tumours and 23% for T2 and T3 tumours (Kurzman & Gilbertson 1986).

MANAGEMENT

The mainstay of management for canine mammary tumours is surgery. Historically, recommendations

Figure 1a

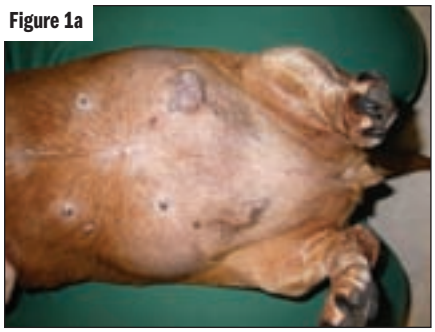


Figure 1b

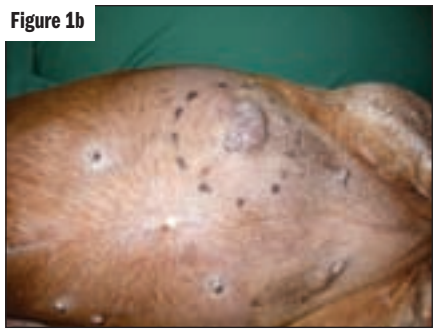
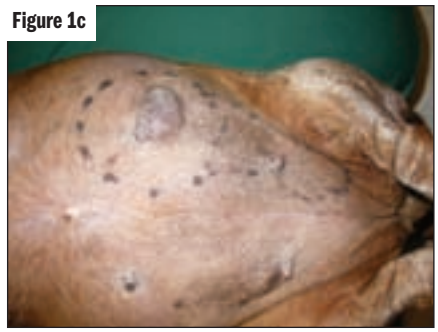


Figure 1c



Nodular mass arising in association with gland 4 on the left hand side in a miniature dachshund. This mass is mobile and slow-growing. Options for resection are indicated by marker pen in figures 1b and 1c. Figure 1b traces a 2 cm margin around the nodular mass. Figure 1c traces a 2 cm margin cranially and lateromedially but caudally the incision plan is extended to include the caudal mammary gland and the associated superficial inguinal lymph node. The second approach is likely to incur less morbidity because less mammary tissue is incised to achieve tumour removal.

have been made to perform surgery according to a notional distribution of lymphatic drainage. This is now recognised to be an oversimplification. Lymphatic drainage is anatomically considerably more variable than was previously thought. Instead, best management is now considered to be to perform the simplest surgery that allows the job to be done. For example, a small mass associated with a single mammary gland may, in theory, be removed by partial mammectomy (removal of part of a single gland) if a 1 cm margin were required. However, it would be considerably less traumatic to simply remove the entire gland than it would be to remove a part of a gland. If a superficial inguinal lymph node and gland four on the same side need to be removed, it would be less traumatic to remove glands four and five as well as the lymph node than it would be to attempt to dissect these structures free from the surrounding tissues (**Figure 1**).

Individual patients exhibit differing degrees of confluency between mammary glands and surgical plans should be individualised to accommodate this heterogeneity. This approach to surgical planning results in less traumatic surgery, less bleeding, quicker surgery and better recoveries.

For benign mammary tumours, marginal excision can be curative. For most malignant mammary tumours that resemble benign tumours a 1 cm margin will also be curative and in many surgical procedures, attempting to obtain a closer margin than this may introduce additional complication. Some lesions do not appear benign. Lesions fitting the following descriptors may exhibit a more sinister behaviour and should be treated as if they were known to be highly invasive and potentially metastatic: discolouration; irregular nodular instead of a solitary mass; presence of lymphadenopathy; and marked erythema.

Prophylactic surgery by means of a bilateral mammary strip can, of course, prevent mammary neoplasia developing in the future. This is, however, an extremely invasive surgical procedure with significant scope for the development of perioperative complications. These risks can be avoided by regular re-examination and prompt intervention in the event that a new mass is recognised. There are no data to suggest that a history of malignant mammary neoplasia exposes a bitch to a higher risk that subsequent de novo mammary masses will be malignant. Chemotherapy use has been described sporadically in the management of canine mammary neoplasia but the results have, historically, been disappointing. Drugs used

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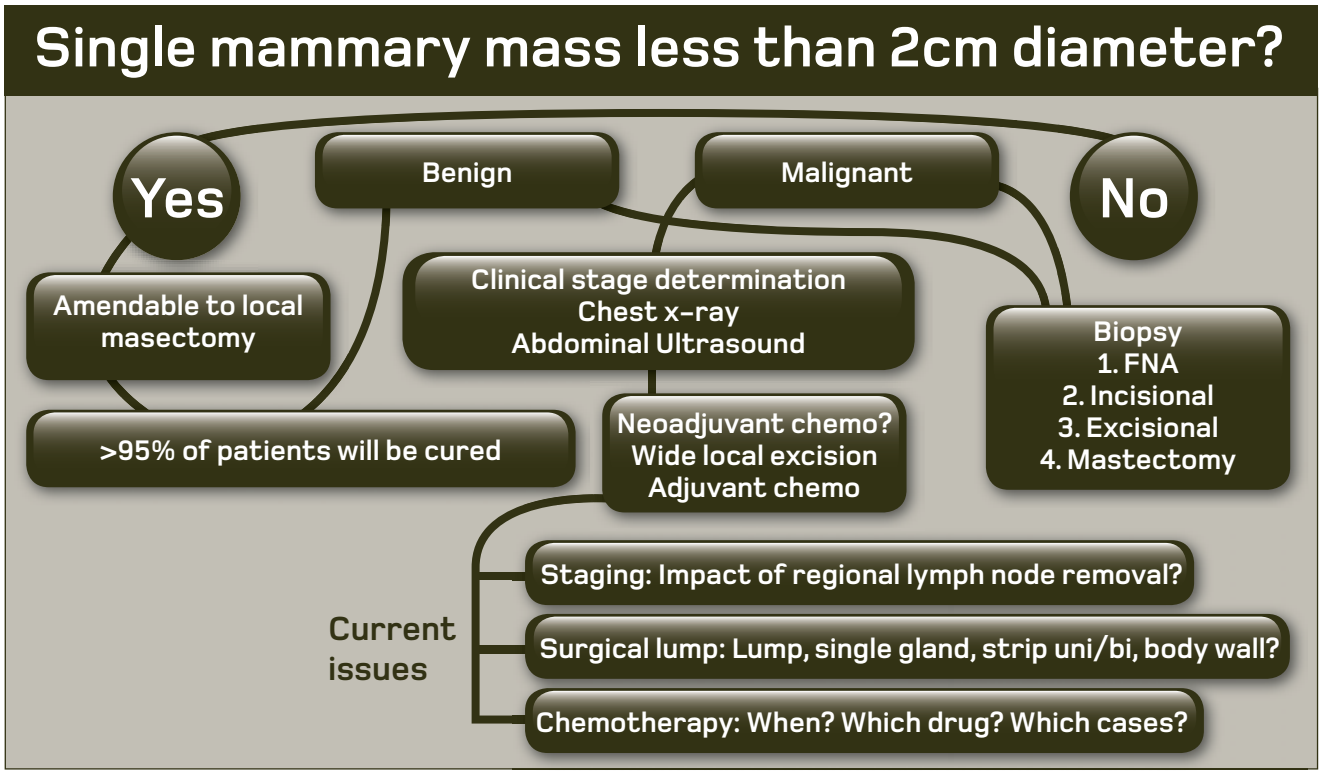

Figure 2: Flow chart indicating simplified approach to canine mammary tumours and highlighting current controversies and uncertainties.

include doxorubicin, epirubicin, cyclophosphamide and 5-fluorouracil (Karayannopoulou *et al.* 2001). A recent innovative formulation of paclitaxel has shown favourable responses in initial drug trials but this product is currently not available (Rivera *et al.* 2007). The author has used chemotherapy prior to definitive surgery (neoadjuvant therapy) with encouraging results. This allows determination of chemotherapy susceptibility in an individual case and enhances therapeutic decision-making.

A simple flow chart for management of canine mammary tumours is shown in **Figure 2**. While it is hoped that this is helpful, it must be acknowledged that there are numerous controversies and uncertainties in this field, as highlighted in the figure.

X-ray beam radiotherapy is contraindicated in mammary neoplasia due to the risk of radiation induced hepatic necrosis or gastrointestinal perforation.

Figure 3; Non-discrete mammary mass affecting the subcutaneous tissues associated with glands 3-5 on the right hand side in a giant Schnauzer. The tumour is infiltrating locally and causing spontaneous ulceration of the skin of the medial proximal thigh. This was a rapidly progressive and aggressive tumour. Speed of development, range of infiltration, fixed nature and ulceration were all clinical indicators of a very poor prognosis.

In human medical oncology, dramatic improvements have been achieved in outcomes for patients with breast cancer since the introduction of oestrogen receptor modulating agents such as tamoxifen. Limited studies have failed to demonstrate similar benefits in canine patients and have not been pursued further as the agonistic effects on oestrogen receptors induce unpleasant oestrus-like side effects.

PROGNOSIS

Benign mammary tumours should be cured by simple surgery. However, it is important to emphasise that histological evaluation of an excised specimen may not identify a microscopic nest of malignant cells within an otherwise benign nodule, resulting in a misdiagnosis.

For malignant mammary tumours, prognosis is related to histological grade and clinical stage (**Table 5**) as noted above. **Figure 3** shows an example of a malignant, rapidly progressive and aggressive tumour.

Histological 'stage 1' tumours are likely to be cured following complete surgical removal although cases that subsequently develop metastatic disease are recognised; in these cases it must be assumed that histological evaluation failed to reveal malignant tissue.

Histological 'stage 2' tumours have a median survival time of a year following surgery. In these cases, re-evaluations are recommended and consideration should be given to adjuvant chemotherapy or surgery in the event that progressive disease is recognised. Monitoring evaluations are suggested after six, 12 and 18 months.

For 'stage 3' tumours, further monitoring or therapy should

be considered on a quarterly basis if further intervention will be offered in the event that progressive disease is identified. With current knowledge and treatments, if adjuvant chemotherapy can be justified at all, it is for patients exhibiting stage 3 tumours.

Despite the poor prognosis described for patients with metastatic disease, occasionally those with regional lymph node metastases do still enjoy a prolonged period of a normal quality of life. Lymph node removal can be performed, but in nearly all cases the tumour has progressed beyond the limits of the lymph node capsule rendering simple lymphadenectomy useless; advanced surgical techniques are therefore required in this situation.

Inflammatory carcinoma carries a poor prognosis with most patients succumbing to their illness within four to eight weeks. Preliminary data have demonstrated improvements in clinical signs with the administration of COX inhibitors, in particular the COX-2 selective antagonist firocoxib (Queiroga FL, pers. comm. 2008).

FOLLOW–UP

After diagnosis of a malignant mammary tumour, consideration should be given to the indications or otherwise for further monitoring or therapy. Since chemotherapy has largely proved to be unrewarding, my recommendation instead is that patients that have been diagnosed with a high grade mammary tumour undergo serial monitoring by means of thoracic radiography and abdominal ultrasonography on a regular, initially quarterly, basis. Accurate recording of lymph node size and definition of the state of the hepatic and splenic parenchyma allow early changes due to the development of metastatic disease to be recognised.

At this time, surgery may be indicated. Alternatively, chemotherapy can be justified once the presence of gross disease has been confirmed, as response to therapy can then be quantified.

PITFALLS

As noted above, not all mammary tumours that are considered to be benign on the basis of histological evaluation subsequently demonstrate benign behaviour. The best histological service is obtained by providing your laboratory with all of the clinical detail that they might require. Remember that by the time a mass arrives at the laboratory, it bears little or no resemblance to the lesion as it appeared in situ. If you have concerns about the proximity of the tumour to a surgical margin, mark this margin in a manner that makes it clear to your histopathologist that you are concerned about this specific site. Similarly, if you feel that a part of the tumour appears more abnormal than the rest, mark this part and express your concerns in your detailed laboratory submission. There is no substitute for open communication between you and your histopathologist.

The surgical margins obtained are typically defined by the surrounding mammary anatomy rather than by oncological principles. Many mammary tumours would be appropriately managed by a skin incision reaching 1-2 cm from the apparent edge of the tumour. If you are presented with a mass that appears to require skin resection that reaches some distance from the anatomical limit of the mammae, then it may be best to assume that surgical removal has a high risk of proving incomplete. In this situation, it may be better to perform an incisional biopsy first and to discuss the case with an oncologist or a surgical specialist before proceeding with definitive mass removal.

The fibrous sheath of the rectus abdominis muscle presents a reasonably good barrier to deeper tumour invasion. Prior to embarking upon surgical resection of a mammary mass, the clinician should first ensure that there is no evidence of deep invasion of the underlying abdominal wall by grasping the mass and wobbling it (the ‘wobble test’). Masses exhibiting any degree of fixation to the underlying tissues will definitely not be completely removed by simple surgery and advanced imaging should be considered mandatory before a radical or compartmental surgical excision is considered. Some mammary masses exhibit intramuscular invasion despite a negative wobble test; this only becomes evident during surgery. In these cases, abdominal wall resection is required to achieve complete local tumour eradication as the first surgery will inevitably have introduced tumour into deeper tissue planes. This should be regarded as a specialist procedure that requires advanced imaging once again as part of treatment planning.

Tumours that appear superficial but affect a surprisingly broad area of tissue are often highly invasive and require wide and deep surgical margins to achieve a local cure. Once the underlying fascia has been disturbed, the magnitude of any subsequent surgery is significant and may, in fact, be prohibitive. It is, therefore, best not to disturb the fascia of the rectus abdominis when performing simple mammary surgery.

Histologically confirmed complete resection of canine mammary tumours should only be regarded to be likely to be predictive of clinical cure in cases of benign or histological stage 1 malignant cases. In all other cases, consideration should be given to embarking upon a course of subsequent monitoring and/or adjuvant therapy. There is little or no value in subsequent monitoring if no further action would be taken in the event that progression of disease (recurrence or metastasis) is recognised.

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