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

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Histological features</th>
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<tbody>
<tr>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Ductal papilloma</td>
<td>Simple or complex</td>
</tr>
<tr>
<td>Adenoma</td>
<td>Simple or complex</td>
</tr>
<tr>
<td>Benign mixed tumour</td>
<td>Epithelium plus mesenchymal tissue</td>
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<tr>
<td>Fibroadenoma</td>
<td></td>
</tr>
<tr>
<td>Myoepithelioma</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Solid, tubular or papillary</td>
</tr>
<tr>
<td>Ductular carcinoma</td>
<td>Intra- or inter-lobular</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td></td>
</tr>
<tr>
<td>Malignant myoepithelioma</td>
<td></td>
</tr>
<tr>
<td>Carcinoma or sarcoma in a mixed tumour</td>
<td>Epithelial and mesenchymal tissue, one is neoplastic</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>Epithelial and mesenchymal tissue, both neoplastic</td>
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</tbody>
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Table 2: Histological terms in canine mammary neoplasia

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

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 not have been superseded, it must be stated that the conclusions drawn are based upon remarkably few cases from 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).
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.

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
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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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.

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.

**REFERENCES**


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