Mammary Gland Tumours

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Epidemiology mammary cancer in the dog

- Life-time risk up to 25% (?) in intact dogs
- Risk benign lesions 2-5 fold higher
- Risk male dogs <1% risk female dogs
- Breed predisposition?: spaniels, poodle, dachshund
- Median age 10-12 years, very rare in dogs <4 years
Mammary Cancer LIFE-TIME Risk
In the Western World

- Female 1 / 10
- Dog 1 / 40 to 1 / 4
- Cat 1 / 120 to 1 / 12

- Dog & cat: very rough estimates for intact animals (dependant on time, geographic place, progestin use!)

Multifocality of Mammary Tumours

<table>
<thead>
<tr>
<th>Species</th>
<th>Multiplicity</th>
<th>Type variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dog</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cat</td>
<td>+</td>
<td>±</td>
</tr>
</tbody>
</table>
Ovariectomy and Mammary Tumour Relative Risk (RR)

<table>
<thead>
<tr>
<th>Species</th>
<th>Mal. T RR</th>
<th>Benign T RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Dog</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cat</td>
<td>↓</td>
<td>=</td>
</tr>
</tbody>
</table>

Note: effect pronounced at young age
**Ovariohysterectomy and mammary cancer in the dog**

Ovariectomy protects against malignant tumours till approximately 2.5 year
- before 1\textsuperscript{st} estrus: RR= 0.08
- before 2\textsuperscript{nd} estrus: RR= 0.10
- before 2.5 year: RR= 0.26

RR= Relative Risk

---

**Estrus Prevention by Progestins and Mammary Tumour Risk (RR)**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Benign-T RR</th>
<th>Malignant-T RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>1.4 (\uparrow)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cat*</td>
<td>5.3 (\uparrow)</td>
<td>2.8 (\uparrow)</td>
</tr>
</tbody>
</table>

\*Cat: regular treatment with progestin or estrogen-progestin combination

Misdorp e.a. 1988, 1991
Early Pregnancy and Mammary Cancer Risk

- Human: RR decreased*
- Dog & cat: RR unaltered

Mammary Tumours in the Dog and Diets/Obesity

  - Lean dogs decreased risk
- Perez et al (JVIM 1998)
  Increased risk:
  - Diet high red meat
  - Obese young dogs
Mammary Tumours: Clinical Signs of Malignancy

- Rapid growth
- Non-circumscribed
- Fixation to skin or fascia
- Ulceration
- Nodal involvement
- Edema
- Dyspnea
Mammary Tumours: Clinical Signs of Malignancy

If present:
Probability of cancer is high, not absolute

If absent:
Possibility of cancer is still present

➢ “Wait till they grow is a killer”
Mammary Tumours: Mixed Conditions

- Mammary hyperplasia
- Pseudolactation
- Mastitis

Combined with:
- benign / malignant tumour

➢ Biopsy ⇒ treat additional condition ⇒ recheck

Mastitis Carcinomatosis
MASTITIS CARCINOMATOSA (INFLAMMATORY CARCINOMA)

- Massive swelling often 2-5 adjacent glands
- Erythema + pain
- Nipple retraction / edema
- Often recent exposure to sex steroids
- Rarely visible metastases at lung radiographs
- Often coagulopathy

CYTOLOGY OF MAMMARY TUMOURS

- Cat:
  - often conclusive
- Dog:
  - Only for experienced cytologists
  - Only clear benign and malignant diagnosis are reliable
  - Diagnosis of malignancy more reliable than absence of malignancy
  - Cytology of secretal fluid unreliable
  - Indicated to exclude other cutaneous and subcutaneous non-mammary lesions
  - Often mixed type of tumours
MAMMARY CARCINOMA
METASTASIS

1. Lymphatic
2. Hematogenous
   - lungs, pleura
   - liver/spleen/heart/kidney
   - brain
   - bone

Distant Organs Affected by Metastatic Mammary Cancer

- Lungs: 60-80%
- Pleura: 10-40%
- Liver: 10-20%
- Kidney: 10-20%
- Heart: 10-15%
- Bone: < 10%
Mammary Tumours: Clinical Examination Must Include:

1. Lymph node examination:
   (axillary, prescapulary, supramammary, iliac, popliteal): in any doubt: cytology
2. Thoracic examination:
   auscultation + percussion
   radiographs

MAMMARY GLANDS:
lymphatic connections
Lymphatic Drainage of the Normal and Neoplastic Mammary Gland in the Bitch.

Table 1. Lymphatic Drainage of the Normal and Neoplastic Mammary Gland in the Bitch

<table>
<thead>
<tr>
<th>Mammary Gland</th>
<th>Normal Lymphatic Drainage</th>
<th>Neoplastic Lymphatic Drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1, cranial thoracic</td>
<td>Axillary LN</td>
<td>Axillary LN, sternal LN</td>
</tr>
<tr>
<td>M2, caudal thoracic</td>
<td>Axillary LN</td>
<td>Axillary LN, sternal LN</td>
</tr>
<tr>
<td>M3, cranial abdominal</td>
<td>Axillary LN, superficial inguinal LN</td>
<td>Axillary LN, superficial inguinal LN, medial iliac LN</td>
</tr>
<tr>
<td>M4, caudal abdominal</td>
<td>Superficial inguinal LN</td>
<td>Superficial inguinal LN, axillary LN</td>
</tr>
<tr>
<td>M5, inguinal</td>
<td>Superficial inguinal LN</td>
<td>Superficial inguinal LN, popliteal LN, lymphatics—medial thigh</td>
</tr>
</tbody>
</table>

LN, lymph node.

Staging based on TNM system

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>V</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

T: primary tumor
- T1: <3 cm maximum diameter
- T2: 3-5 cm maximum diameter
- T3: >5 cm maximum diameter

N: regional lymph node status
- N0: no metastasis
- N1: metastasis

M: distant metastasis
- M0: No distant metastasis
- M1: Distant metastasis detected

Assessed by histology or cytology
Staging of course dependent on diagnostics used:

X-ray: negative

CT-scan: Positive
SURGERY OF MAMMARY TUMOURS

Each animal deserves an individual approach:
- number + location of glands involved
- possibility of malignancy
- lymphatic connections
- (lifetime-related) risk for new tumours

Always limit the risk of local recurrence:
“Think of surgery as your only weapon”

SURGERY OF MAMMARY TUMOURS
of possibly malignant nature (optimal)

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Excision</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 / M2</td>
<td>M1-3</td>
</tr>
<tr>
<td>M3</td>
<td>M1-5</td>
</tr>
<tr>
<td>M4 / M5</td>
<td>M3-5 (including RLN)</td>
</tr>
</tbody>
</table>

Notes
1. axillary node only removed if tumour-positive
2. extensive surgery only if life expectancy good
Mammary Tumour Recurrence in Bitches After Regional Mastectomy


- 99 bitches with single mammary tumour
- Regional mastectomy (one gland)
- 57 dogs (=58%) had new tumour in ipsilateral mammary chain
- Malignant primary tumours had higher risk for new malignant tumour

Try to be so aggressive as possible with surgery

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Mammary Tumours in the Bitch

“Do I need to perform ovariohysterectomy when operating an intact female dog with mammary tumours?”
Ovariohysterectomy?

- Ovariectomy protects against new benign tumours till approximately 7-8 year
- Ovariectomy protects against malignant tumours till approximately 2.5 year
  - Ovariectomy before 1st estrus: RR= 0.08, before 2nd estrus 0.10, before 2.5 year: RR= 0.26
- Ovariectomy does not inhibit recurrence (local/metastatic) of malignant tumours
  - Only 5% of metastases has steroid receptors

Endocrine Treatment of Mammary Cancer in the Dog and Cat

- Ovariectomy not proven effective against recurrent disease
- Anti-estrogen treatment often produces side effects, without firm proof of benefit
MAMMARY CANCER AND PROGNOSIS

VOLUME

NUMBER OF DAYS POST MASTECTOMY

MAMMARY CANCER AND PROGNOSIS

LYMPH NODES

NUMBER OF DAYS POST MASTECTOMY
MAMMARY CANCER HISTOLOGY

- Human: mostly epithelial tumours
- Cat: mostly epithelial tumours
- Dog: often epithelial tumours, in about 1/3 involvement of myoepithelium

- All: histologic grade related to prognosis

MAMMARY CANCER AND PROGNOSIS

[Graph showing cumulative percent disease-free over number of days post mastectomy for different histology grades (Grade 0, Grade I, Grade II).]
Mammary gland development

A. Nonpregnant
- inactive duct system

B. During pregnancy
- alveoli proliferate at the ends of the ducts

C. Lactating
- milk secretion and accumulation in alveolar lumen

Direction of growth

Early transit cells

Later transit cell of myoepithelial lineage

Differentiated luminal epithelial cell

Body cell undergoing apoptosis to generate lumen

Cap cell — the putative terminal-end-bud stem cell

Later transit cell of luminal epithelial lineage ['body cell']

Differentiated myoepithelial cell

Extracellular matrix

Symmetrical self-renewing cell division of cap cells
Asymmetrical cap-cell division to generate one new cap cell and one early transit cell
<table>
<thead>
<tr>
<th>Benign Non-Neoplastic Mammary Lesions in the Dog: Histologic diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ductal Hyperplasia</td>
</tr>
<tr>
<td>- Lobular Hyperplasia</td>
</tr>
<tr>
<td>- Epithelial hyperplasia</td>
</tr>
<tr>
<td>- Adenosis</td>
</tr>
<tr>
<td>- Cysts</td>
</tr>
<tr>
<td>- Ductectasia</td>
</tr>
<tr>
<td>- Focal Fibrosis</td>
</tr>
<tr>
<td>- Gynaecomasty</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign Mammary tumours in the Dog: Histologic diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Adenoma</td>
</tr>
<tr>
<td>- Simple adenoma</td>
</tr>
<tr>
<td>- Complex adenoma</td>
</tr>
<tr>
<td>- Fibroadenoma</td>
</tr>
<tr>
<td>- Benign mixed tumours (including foci of cartilage/bone)</td>
</tr>
<tr>
<td>- Duct papilloma</td>
</tr>
</tbody>
</table>
Malignant Mammary Tumours in the Dog:
Histologic diagnoses

- Non-infiltrating carcinoma (in situ)
- Complex carcinoma
- Carcinosarcoma
- Simple carcinoma
  - Tubular/papillar type
  - Solid type
  - Anaplastic type
- Sarcoma
  - Fibrosarcoma
  - Osteosarcoma
  - Other sarcomas
- Special carcinoma types
  - Spindle cell carcinoma
  - Carcinoma with squamous metaplasia
  - Mucinous carcinoma

HISTOLOGIC TYPE OF CANINE MAMMARY CANCER AND PROGNOSIS

Grade of malignancy:
I. relatively low:
   - complex carcinoma
   - tubular adenocarcinoma
   - papillary carcinoma
HISTOLOGIC TYPE OF CANINE MAMMARY CANCER AND PROGNOSIS

Grade of malignancy:
II. intermediate
   - simple (solid) carcinoma

HISTOLOGIC TYPE OF CANINE MAMMARY CANCER AND PROGNOSIS

Grade of malignancy:
III. relatively high:
   - anaplastic carcinoma
   - sarcoma
   - mastitis carcinomatosa
HISTOLOGY OF MAMMARY CANCER AND PROGNOSIS

- Completeness of excision
- Nodal involvement
- Mode of growth: infiltrative/intravascular
- Malignancy grade
  - cat: in majority high
  - dog: anaplastic > simple > complex carcinoma
    - sarcoma: high

Adjuvant therapy
CHEMOTHERAPY OF MAMMARY CANCER IN THE DOG AND CAT

- Dog: Sofar, no evidence in literature for beneficial effect of chemotherapy, either as primary or as adjuvant therapy.
- Cat: Doxorubicin (30mg/m²) may be palliative but often with side-effects

Multidrug resistance genes responsible for inadequate response to chemotherapy
_Honscha et al, Reprod Domest Anim, 2009_

- 103 canine mammary tumour probes were investigated for mRNA expression of seven ABC-transporters by RT-PCR. Almost all tumour samples expressed multidrug resistance-associated proteins (MRP1/3/5/6/7), Pgp and breast cancer resistance protein (BCRP).
- Doxorubicin not indicated for treatment of canine mammary tumours
IMMUNOTHERAPY OF MAMMARY CANCER IN THE DOG AND CAT

- Not effective:
  Dog: local/systemic BCG or CP
  - systemic levamisole
  - systemic liposome-encapsulated MTP
  Cat: systemic liposome-encapsulated MTP

COX-2 inhibition

- Carlos et al, Can Vet J 2009
- 7 dogs with inflammatory carcinoma (high grade carcinoma with dermal lymphatic invasion)
- Treated with Piroxicam
- Survival 128-223 days (median 185), which is relatively good response!
Feline Mammary Tumours

Histology

- 80% malignant tumours (changing?)
- Malignant tumours almost always of simple type
- Benign tumours:  - Fibroadenomatous hyperplasia
                   - Fibroadenoma (rare)
                   - Premalignant epitheliosis
Feline Mammary Tumours

Epidemiology

*Incidence:* 3rd most common tumour in the cat
*Breed predisposition:* Siamese RR 2 (vs other breeds)
*Age distribution:* Rarely <2 years, gradual increase >4 years
Peak 10-13 years
Exception: fibroadenomatous hyperplasia
Fibroadenomatous hyperplasia

Fibroadenomatous change:

- exposure to steroids: 1st to 2nd oestrus
  Pregnancy
  Progestin treatment
- rapid growth
- soft swellings
- ± circumscribed; sometimes massive
- single or multiple
- Mol&Rijnberk, 1997: associated with induction of GH mRNA, which stimulates local cell proliferation
Mammary tumours in the cat
Effects of ovariectomy I

Mammary tumours

<table>
<thead>
<tr>
<th></th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>0.35</td>
<td>0.86</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

(Misdorp, 1991)

RR = Relative Risk

Mammary tumours in the cat
Effects of ovariectomy II

- Cats spayed before 1-year of age have lower risk for mammary carcinoma
- Nevertheless mammary carcinoma can occur
- *(Overley et al, 2005)*
Progestin treatment of the cat: Effect on mammary tumour risk

Progestin: MPA/MA/Proligestone

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lesion</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>benign</td>
<td>5.3*</td>
</tr>
<tr>
<td></td>
<td>cancer</td>
<td>2.8*</td>
</tr>
<tr>
<td>Irregular</td>
<td>benign</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>cancer</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* P<0.001 (Misdorp, 1991)

Dog – Cat difference

- Progestins in dogs not related to higher incidence malignant tumours (benign!)
- Dog: estrus: always luteal (=progestin) phase of >60 days
- Dog 1-2 cycles per year
- Cat: induced ovulator
- Cat: 4-26 weeks cycling per year
Hormone receptors in the cat

- Benign proliferative mammary lesions in the cat are often ER+ and PR+
- ER and PR expression in malignant tumours is less frequent and at a reduced level
- Anti-hormonal treatment in mammary carcinomas in the cat (like tamoxifen) is not effective

Treatment of fibroadenomatous hyperplasia

- **Ovariectomy**
  - Regression of hyperplastic lesions 3-4 weeks
  - Addition of analgetics (not steroidal drugs!)

- **Discontinuation of medication**
  - In case of megestrol/medroxyprogesterone

- **Aglepristone (Alizine®) (=antiprogestin)**
  - 2 days 10mg/kg sc, followed by weekly injections until remission
  - Remission within 3-4 weeks
Feline mammary carcinoma

Adenocarcinoma
Feline Mammary Carcinoma Metastasis

- High rate distant metastasis (50-90%)
- Most frequent site: lungs (83%)
  mostly ill-defined interstitial/diffuse pulmonary pattern (Forrest & Graybush, 1998)
- Bone metastasis rare
  distal extremity more often than in dogs (Waters et al, 1998)

Diagnostic work-up

- general health status
- FNAB of mammary nodule
- regional lymph nodes (+ FNAB)
- X-ray lungs
- if present: cytology of pleural fluid
Carcinoma metastases in lymph node

FIG 1: (a) The four pairs of mammary glands in the cat, with their associated lymph nodes and lymphatic drainage. (b) Venous drainage of the mammary glands.
12 yr old DSH cat, mammary tumor

12 yr old DSH cat:
Mammary carcinoma
Thoracic fluid: Carcinoma metastases

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0/1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Feline Mammary Carcinoma
Survival fraction after surgery

<table>
<thead>
<tr>
<th>1 year</th>
<th>2 year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>30%</td>
<td>Weyer &amp; Hart, 1983</td>
</tr>
<tr>
<td>-</td>
<td>45%</td>
<td>MacEwen et al, 1984</td>
</tr>
<tr>
<td>31.8%</td>
<td>17.7%</td>
<td>Ito et al, 1996</td>
</tr>
<tr>
<td>47.3%</td>
<td>-</td>
<td>Castagnaro et al, 1998</td>
</tr>
</tbody>
</table>
Prognostic Factors

- Tumour size
- N-status
- Stage
- Mitotic index
- Necrosis
- Histologic grade
- Completeness of surgery
Influence of Stage on Survival in Feline Mammary Cancer after Surgery

<table>
<thead>
<tr>
<th>Stage</th>
<th>MacEwen et al, JAVMA 1984</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt; 36 months</td>
</tr>
<tr>
<td>II</td>
<td>24 months</td>
</tr>
<tr>
<td>III</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Prognostic effect Histologic Grade

Histological grading: 1-year survival:

- well differentiated (12.7%) 7/7
- moderately differentiated (60%) 19/33
- poorly differentiated (27.3%) 0/15
Surgery

- Unilateral or bilateral chain mastectomy
- Inguinal Ln always removed
- Axillary Ln only removed when enlarged
- Early vessel ligation essential
- Ovariohysterectomy?
Chemotherapy in feline mammary adenocarcinoma

- Mostly with doxorubicin
- Some partial remissions and stable diseases, seldom cures
- Beneficial in adjuvant to surgery?

Radiation therapy in feline mammary adenocarcinoma

To this date no reports on effectiveness
COX-2 and feline mammary cancer

- Different results COX-2 expression in literature => most likely high percentage COX-2 expression
- No studies known to date with COX-2 inhibitors in feline mammary cancer
- Results in other cancer types not promising despite COX-2 expression