A MULTIDISCIPLINARY APPROACH TO MAMMARY AND SOFT TISSUES TUMORS IN DOMESTIC ANIMALS

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WHAT IS A TUMOR?

Tumor is a “NEW GROWTH” generally composed by abnormal mass of tissue, that have undergone heritable genetic changes, the growth of whiches exceeds and is uncoordinated with that of normal tissues and persists in the same excessive manner after cessation of the stimulus which evoked the change.
Nomenclature and Classification:

Tumor: mass or tissue swelling    Cancer: should be reserved for reference to a malignant neoplasm

Tumors can be **BENIGN** (non cancerous)    or    **MALIGNANT** (cancerous)

“oma” suffix (e.g. papilloma) **EPITHELIAL**

“oma” suffix (e.g. osteoma) **MESENCHIMAL**

Grow slowly and without spread ...

“carcinoma” suffix **EPITHELIAL**

“sarcoma” suffix **MESENCHIMAL**

Grows rapidly, invade and destroy normal tissues ... spread throughout the body ...
How tumor could be and how it can behave?

Locally invasive or metastatic

Primary or metastatic (blood or lymphatic system)

Named by the part of the body (tissue) where it first originated ... in different case its are called “mixed tumors”

Essentially five broad category:

1. Carcinoma
2. Sarcoma
3. Lymphoma
4. Leukemia
5. Myeloma (Plasmacytoma)
Classification and Grading of Canine Mammary Tumors

M. Goldschmidt¹, L. Peña², R. Rasotto³, and V. Zappulli²

Table 1. Histologic Classifications: 1974 and 1999

1974 HISTOLOGIC CLASSIFICATION¹ 1999 HISTOLOGIC CLASSIFICATION¹³

I. Carcinoma
A. Adenocarcinoma
1. Tubular (a) Simple type (b) Complex type
2. Papillary (a) Simple type (b) Complex type
3. Papillary cystic (a) Simple type (b) Complex type
B. Solid carcinoma (a) Simple type (b) Complex type
C. Spindle cell carcinoma (a) Simple type (b) Complex type
D. Anaplastic carcinoma
E. Squamous cell carcinoma
F. Mucinous carcinoma
II. Sarcoma
A. Osteosarcoma
B. Fibrosarcoma
C. Combined sarcoma
D. Other sarcomas
III. Carcinosarcoma (malignant mixed tumor)
IV. Benign
A. Adenoma
B. Papilloma
1. Duct papilloma
2. Duct papillomatosis
C. Fibroadenoma
1. Pericanalicular
2. Intracanalicular (a) noncellular type (b) cellular type
3. Benign mixed tumor
4. Total fibroadenomatous change
D. Benign soft tissue tumor
V. Unclassified Tumors
VI. Dysplasias
A. Cyst
1. Nonpapillary
2. Papillary
B. Adenosis
C. Epitheliosis
D. Duct ectasia
E. Fibrosis
F. Gynecomastia
G. Other nonneoplastic proliferative lesions
1. Noninflammatory lobular hyperplasia
2. Inflammatory lobular hyperplasia

Proposed Histologic Classification: 2010

1: Malignant Epithelial Neoplasms
Carcinoma—in situ
Carcinoma—simple
a. Tubular
b. Tubulopapillary
c. Cystic-papillary
d. Cribriform
Carcinoma—micropapillary invasive
Carcinoma—solid
Comedocarcinoma
Carcinoma—anaplastic
Carcinoma arising in a complex adenoma/mixed tumor
—The benign counterpart is still detectable in the section.
Carcinoma—complex type
—The epithelial component is malignant, and the myoepithelium is benign.
Carcinoma and malignant myoepithelioma
—The epithelial and myoepithelial components are malignant.
Carcinoma—mixed type
—The epithelial component is malignant; the myoepithelial mesenchymal component is benign; and the mesenchymal component is cartilage or bone.
Ductal carcinoma—malignant counterpart of ductal adenoma
Intraductal papillary carcinoma—malignant counterpart of intraductal papillary adenoma

2: Malignant Epithelial Neoplasms—Special Types
Squamous cell carcinoma
Adenosquamous carcinoma
Mucinous carcinoma
Lipid-rich (secretory) carcinoma
Spindle cell carcinomas
Malignant myoepithelioma
Squamous cell carcinoma—spindle cell variant
Carcinoma—spindle cell variant
Inflammatory carcinoma (see Inflammatory Carcinoma section)

3: Malignant Mesenchymal Neoplasms—Sarcomas
Osteosarcoma
Chondrosarcoma
Fibrosarcoma
Hemangiosarcoma
Other sarcomas

4: Carcinosarcoma—Malignant Mixed Mammary Tumor

5: Benign Neoplasms
Adenoma—simple
Intraductal papillary adenoma (duct papilloma)
Ductal adenoma (basaloid adenoma)

Descriptions
The following are descriptions pertaining to the above classification.
what to do when we are faced with a suspected tumor?

YES, I DID HAVE MY MAMMOGRAM TODAY... WHY DO YOU ASK?
Clinical and Gross Evaluation:

Shape, dimensions, color, type of growth (exophytic or endophytic), margins, number of tumors, mobility, involvement of LN and or other organs (nipple for mammary tumors), consistency (calcifications), exudate/transudate, ulcerations, cysts, necrosis, effusions, haemorrhage, ecc.
MORPHOLOGICAL CHARACTERISTICS: Gross Pathology

Grossly tumor is an abnormal mass of tissue and a large variety of terms are used to describe the gross appearance of neoplasms, including papillary, sessile, pedunculated, ulcerative, circumscribed, multicentric, annular, ecc. but most tumors cannot be definitively diagnosed grossly.
• Is tumor or other type of lesions?
• If tumor: benign, malignant, locally aggressive, ecc.
• If tumor: primitive or metastatic?
• What kind of tumor?
  Identification of specific histotype!
• Margins of excision: sufficient or insufficient?
• Is possible identify prognostic histological criteria (grading?)
It is really always useful perform citology?
Cytology and malignancy in tumors:

- The only sure data to make a diagnosis of tumor in cytology is to find foreign and atypical cells in a tissue where its are normally absent (ex: melanocytes or mast cells in a lymph node, ecc.)
- Other criteria: evaluation of every single case ...
Cytological malignancy
Nuclear malignancy
Cytoplasmic malignancy
# Morphological pattern of the cells

## Cytoplasm
- **Staining affinity:**
  - Eosinophilic:
    - Smooth muscle, myofibroblast, fibrohistiocytic
  - Basophilic:
    - Fibroblastic origin, nervous cells
- **Cytoplasmic vacuoles:**
  - Intracytoplasmatic,
  - With well-defined nuclear indentation: lipoblasts
- **Cytoplasmic inclusions:**
  - Materiale PAS positivo

## Nuclei
- **Shape**
  - Cigar shape
    - Smooth muscle tumors
  - Waiving with pointed ends
    - Nervous tumors
  - Spindly with pointed ends
    - Fibroblasts
- **Chromatin:**
  - Hyperchromic
    - Nervous and lipidic tumors
Other patterns for complete evaluation:

• Mitotic index
• Giant Cells
• Inflammatory infiltrations
• Periphery of the tumor
  – Type of growth (expansive or infiltrative)
  – Margins of excision (1-2 cm)
• other
  – Multicentric growth
  – Necrosis
  – Vascular invasion
When perform a biopsy?

- When therapy is associated with significant collateral effects
- Nodular/ulcerative lesions that can hide a tumor
- Sudden, rapid, unusual developing injuries
- Lesions that appear during therapies (adverse reaction to drugs)
- During the active phase of the clinical disease and before it has established a therapy that could alter the histological appearance
- In case of multiple differential diagnoses
What the clinician should know that you want to ask the pathologist?

1. Have a clear idea about the type of material to be examined
2. Have clear ideas about how to send the material
3. Needs to know what information the pathologist to make a diagnosis
4. Knowing the language of the pathologist to understand the pathology report and be able to discuss with him/her.
What type material send?

- Histological samples
  - Excisional biopsy (punch)
  - Needle’s biopsy
  - Surgical samples
  - Freezing examination
  - Necropsy

- Citological samples
  - Fine-needle aspiration
  - Washing
  - Effusions
  - Sediments
Non neoplastic lesions

Neoplastic lesions

McGavin: Pathologic Basis of Veterinary Disease, 2007
Preoperative Biopsy: benign or malignant tumor

FNA or trucut: Pathologist with good experience
  – Be careful with your collection (necrosis, inflammation, ecc.)

Excisional biopsy: look “your” margins

Incisional biopsy: …
Histopathology:
Histopathology:
DIAGNOSTIC APPROACH TO MAMMARY AND SOFT TISSUES TUMORS

• FNAB
  – Not exfoliative
  – Allows to exclude other types of tumors: mast cell tumors, lipoma, ecc.
  – Allows to exclude inflammation (with correct execution)
• In other cases traditional biopsy
  – Incisional
  – Excisional (look at margins !)
• Hematology, radiology (osseous invasion of torax, ecc.), FNA regional LN, CT or MRI.
Coloration of margins

• Colorazione margini
  – Ink
  – tempera paints or acrylics
  – On fresh or fixed tissues
Processing of sample

• To obtain representative sections for:
  – Tumor
    • One section every centimeter of maximum diameter of tumor
  – Margins
  – Tissue at the border of necrotic areas
  – Tumor and adjacent tissue
  – Every unusual macroscopic aspect of tissues involved
WHO Histological classification of Mesenchymal Tumors of Skin and Soft Tissues of Domestic Animals - 1998

- Tumors of Fibrous Tissue
- Tumors of Adipose Tissue
- Tumors of Smooth Muscle
- Tumors of Striated Muscle
- Tumors of Vascular Tissue
- Tumors of Peripheral Nerves

... others (Synovium, Mesothelium, Mast Cell Tumor, Histiocytic, etc.)
Pattern

Tissue Organization

- Bundles
  - Fibroma/fibrosarcoma
- Vortices
  - Hemangiopericytoma
- Palisades
  - Peripheral nerve sheath tumor
- Storiform
  - Malignant fibrous histiocytoma
- Mixed
  - Other Sarcomas
Stroma

- Hyalinous
- Fibrous
- Myxoid
- Osteocartilaginous
Approach to the pathology report of soft tissue tumors

• Pathologist must answer at these questions:
  – Tumor or not?
  – If tumor:
    • Benign, locally aggressive, malignant
  – If malignant tumor:
    • Primitive or metastatic?
  – What kind of tumor is it? Histotype?
  – Excision margin evaluation
  – There are histological criteria of prognostic importance (GRADING)?
Similarities in the biological behavior of soft tissue tumors

- Pseudocapsule but infiltrative growth along fascial planes
- Frequent local recurrence after conservative surgery
- Hematogenous metastases (20% cases) (except synovial sarcoma)
- Histological grade predictive for metastasis
- Poor response to chemo-and radiotherapy for tumors of size > 5 cm
Problems of classification

• In human medicine, the proposed classification system is based on or histogenetic origin of the tumor (Weiss SW, Goldblum JR (2001) Enzinger and Weiss's soft tissue tumours 4th edition. Mosby: St Louis)

• Problems:
  1) Difficulty in having similar opinions between different pathologists about histogenesys of many of these tumors. Some sarcomas have, in different areas of the tumor, different cell types
  2) Some tumors appear strongly undifferentiated as to make impossible a sub-classification in original histotype, despite the aid of laboratory investigations (EM, IHC)
  3) The biggest problem is that it does not take into right account the degree (malignant index, f.e.) of the tumor and its implication for prognosis
Problems of classification

• Once determined the right histotype, the tumor is "classified" with grades 1 to 4, in relation to the degree of differentiation (similarity with the tissue of origin)

• Most of histological types is low grade, intermediate, or high (grade 1, 2, or 3, respectively). However, some STS as well-differentiated liposarcomas and liposarcomas mixoid are always low-grade, while others such as rhabdomyosarcomas, synovial sarcomas, and tumors of mesenchymal chondrosarcoma and Ewing extraskeletal osteosarcomas are always high-grade

• The American Joint Committee on Cancer (AJCC) has developed a clinicopathological staging system that takes into account primarily the extent and size of the tumor. ...
<table>
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<th>Primary tumor (T)</th>
<th>No evidence of primary tumor</th>
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<tbody>
<tr>
<td>T0</td>
<td>Tumor &lt;5 cm</td>
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<tr>
<td>T1</td>
<td>Tumor &gt;5 cm</td>
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<th>Lymph nodes (N)</th>
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<th>Distant metastasis (M)</th>
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<td>M0</td>
<td>Distant metastasis</td>
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<th>Histopathologic grading (G)</th>
<th>Well differentiated (low grade)</th>
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<tr>
<td>G1</td>
<td>Moderately differentiated (intermediate grade)</td>
</tr>
<tr>
<td>G2</td>
<td>Poorly differentiated (high grade)</td>
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<tr>
<td>G3</td>
<td>Undifferentiated</td>
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Grading of STS in veterinary medicine

- **Grade I, low grade**
  - No necrosis
  - 0-9 mitosis per HPF
  - ≅ histotype

- **Grade II, medium grade**
  - < 50% necrosis
  - 10-19 mitosis per HPF
  - Recognizable characters of histological origin
  - **Grade III, high grade, poorly differentiated**
  - > 50% necrosis
  - > 20 mitosis per HPF
  - Histological type of origin can not be recognized

Erhart N. et al., JAAHA, 2005 and Morello E., Atti SCIVAC Rimini, 2006
PROGNOSTIC FACTORS

• Dimension (threshold: 5 cm)

• Localizzazione $\rightarrow$ completeness of surgical excision

• Histological grade

• Presence of metastasis
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