



**UNIVERSITA' DEGLI STUDI DI PERUGIA – ITALY  
FACULTY OF VETERINARY MEDICINE**



## **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 which 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

“carcinoma” suffix EPITHELIAL

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

“sarcoma” suffix MESENCHIMAL

Grow slowly and without spread ...

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. Goldschmidt<sup>1</sup>, L. Peña<sup>2</sup>, R. Rasotto<sup>3</sup>, and V. Zappulli<sup>3</sup>

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**Table 1.** Histologic Classifications: 1974 and 1999

1974 HISTOLOGIC CLASSIFICATION <sup>7</sup>	1999 HISTOLOGIC CLASSIFICATION <sup>13</sup>
I. Carcinoma	I. Malignant tumors
A. Adenocarcinoma	1.1 Noninfiltrating (in situ) carcinoma
1. Tubular	1.2 Complex carcinoma
(a) Simple type	1.3 Simple carcinoma
(b) Complex type	1.3.1 Tubulopapillary carcinoma
2. Papillary	1.3.2 Solid carcinoma
(a) simple type	1.3.3 Anaplastic carcinoma
(b) complex type	1.4 Special type of carcinomas
3. Papillary cystic	1.4.1 Spindle cell carcinoma
(a) simple type	1.4.2 Squamous cell carcinoma
(b) complex type	1.4.3 Mucinous carcinoma
B. Solid carcinoma	1.4.4 Lipid-rich carcinoma
(a) simple type	1.5 Sarcoma
(b) complex type	1.5.1 Fibrosarcoma
C. Spindle cell carcinoma	1.5.2 Osteosarcoma
(a) simple type	1.5.3 Other sarcomas
(b) complex type	1.6 Carcinosarcoma
D. Anaplastic carcinoma	1.7 Carcinoma or sarcoma in benign tumor
E. Squamous cell carcinoma	2. Benign tumors
F. Mucinous carcinoma	2.1 Adenoma
II. Sarcoma	2.1.1 Simple adenoma
A. Osteosarcoma	2.1.2 Complex adenoma
B. Fibrosarcoma	2.1.3 Basaloid adenoma
C. Combined sarcoma	2.2 Fibroadenoma
D. Other sarcomas	2.2.1 Low-cellularity fibroadenoma
III. Carcinosarcoma (malignant mixed tumor)	2.2.2 High-cellularity fibroadenoma
IV. Benign	2.3 Benign mixed tumor
A. Adenoma	2.4 Duct papilloma
B. Papilloma	3. Unclassified Tumors
1. Duct papilloma	4. Mammary hyperplasia and dysplasia
2. Duct papillomatosis	4.1 Ductal hyperplasia
C. Fibroadenoma	4.2 Lobular hyperplasia
1. Pericanalicular	4.2.1 Epithelial hyperplasia
2. Intracanalicular	4.2.2 Adenosis
(a) noncellular type	4.3 Cysts
(b) cellular type	4.4 Duct ectasia
3. Benign mixed tumor	4.5 Focal fibrosis (fibrosclerosis)
4. Total fibroadenomatous change	4.6 Gynecomastia
D. Benign soft tissue tumor	
V. Unclassified Tumors	
VI. Dysplasias	
A. Cyst	
1. Nonpapillary	
2. Papillary	
B. Adenosis	
C. Epitheliosis	
D. Duct ectasia	
E. Fibrosclerosis	
F. Gynecomastia	
G. Other nonneoplastic proliferative lesions	
1. Noninflammatory lobular hyperplasia	
2. Inflammatory lobular hyperplasia	

Goldschmidt et al

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## 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<sup>9</sup>)

Ductal adenoma (basaloid adenoma<sup>9</sup>)

With squamous differentiation (keratohyaline granules)

Fibroadenoma

Myoepithelioma

Complex adenoma (adenomyoepithelioma)

Benign mixed tumor

### 6: Hyperplasia/Dysplasia

Duct ectasia

Lobular hyperplasia (adenosis)

Regular

With secretory activity (lactational)

With fibrosis—interlobular fibrous connective tissue

With atypia

Epitheliosis

Papillomatosis

Fibroadenomatous change

Gynecomastia

### 7: Neoplasms of the Nipple

Adenoma

Carcinoma

Carcinoma with epidermal infiltration (Paget-like disease)

### 8: Hyperplasia/Dysplasia of the Nipple

Melanosis of the skin of the nipple

### Criteria of Malignancy

A major problem in evaluating canine mammary neoplasms is identifying those neoplasms that are “truly” malignant. The presence of some cells, with enlarged nuclei and prominent nucleoli, often leads to the overdiagnosis of mammary carcinoma. The following are the most significant criteria for the diagnosis of malignant mammary tumors in the dog based on hematoxylin and eosin–stained sections:

- tumor type,
- significant nuclear and cellular pleomorphism,
- mitotic index,
- presence of randomly distributed areas of necrosis within the neoplasm,
- peritumoral and lymphatic invasion, and
- regional lymph node metastasis.

Tables 2 and 3 elaborate on some of these features.

### 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.

## What Vet. Pathologist must answer you ?

- 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 excission: 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 ?

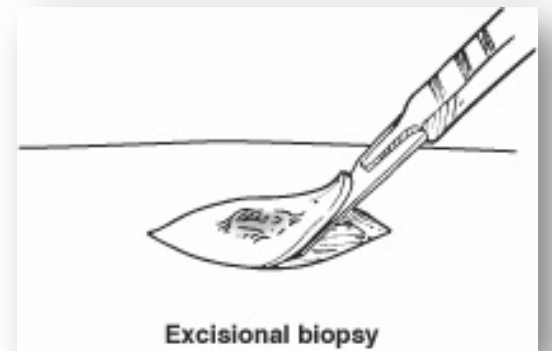
- When therapy is associated with significant collateral effects
- Nodular/ulcerative lesions that can hide a tumor
- Sudden, rapid, unusual developing injuries
- Lesions that appear during therapies (adverse reaction to drugs)
- During the active phase of the clinical disease and before it has established 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?

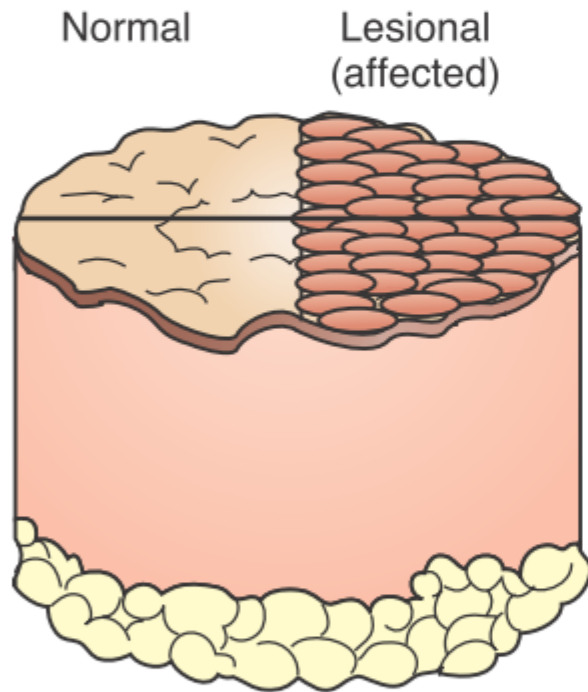
1. Have a clear idea about the type of material to be examined
2. Have clear ideas about how to send the material
3. Needs to know what information the pathologist to make a diagnosis
4. Knowing the language of the pathologist to understand the pathology report and be able to discuss with him/her.

# What type material send ?

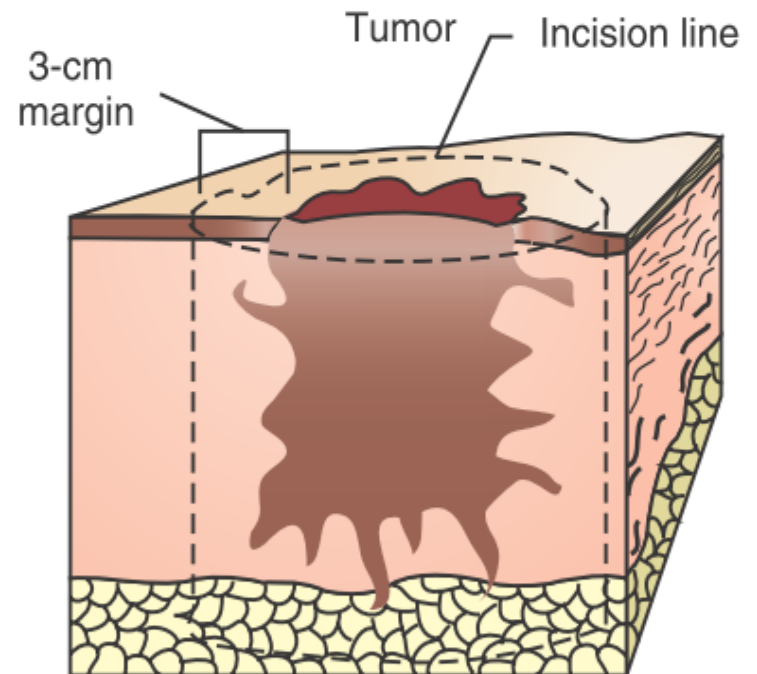
- Histological samples
  - Excisional biopsy (punch)
  - Needle's biopsy
  - Surgical samples
  - Freezing examination
  - Necropsy
- Citologycal samples
  - Fine-needle aspiration
  - Washing
  - Effusions
  - Sediments



## Non neoplastic lesions

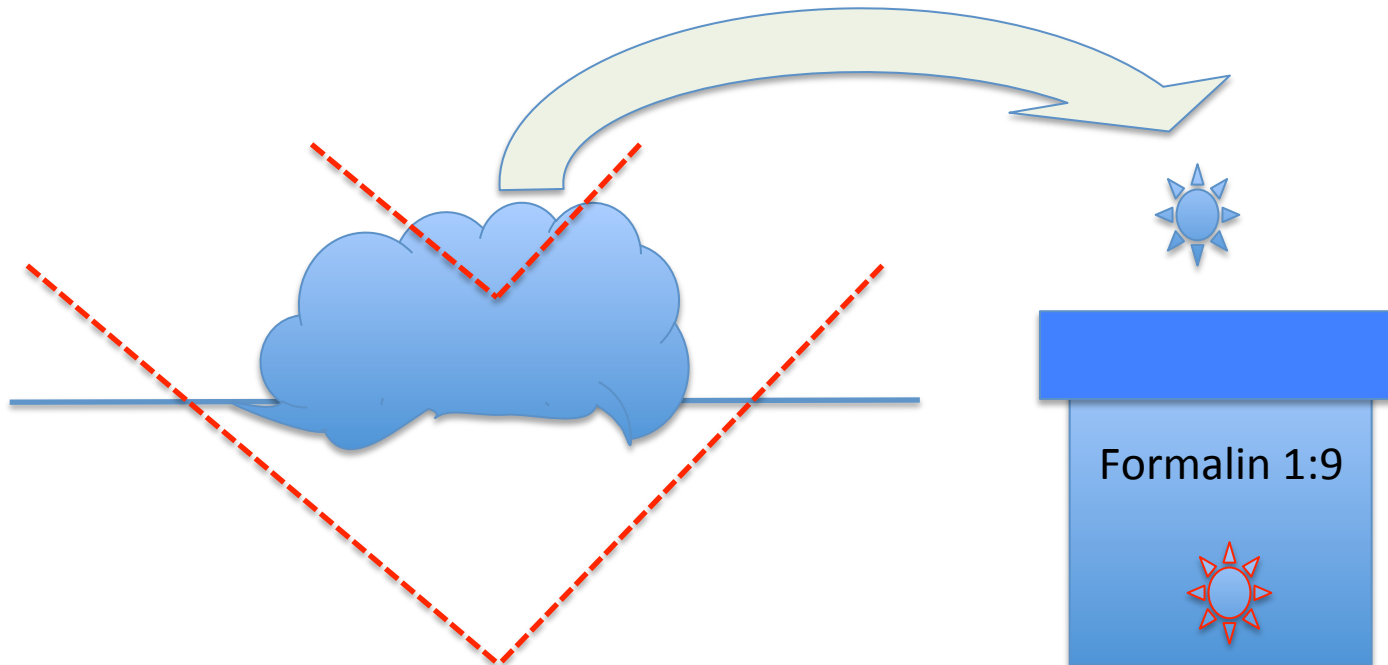


## Neoplastic lesions



## DIAGNOSTIC APPROACH TO MAMMARY AND SOFT TISSUES TUMORS

- 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

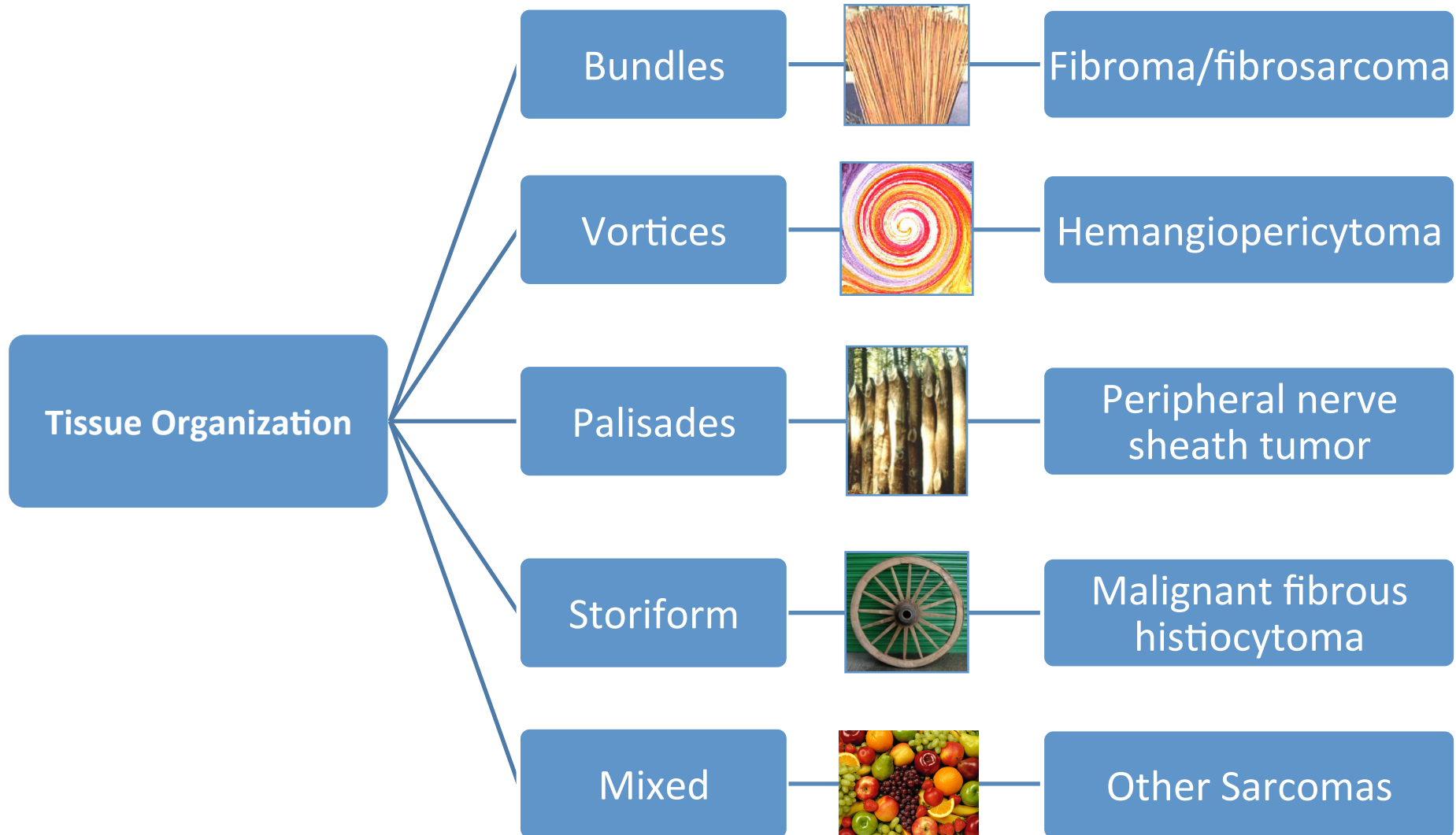
Tumors of Striated Muscle

Tumors of Vascular Tissue

Tumors of Peripheral Nerves

... others (Synovium, Mesothelium, Mast Cell Tumor, Histiocytic, ecc.)

# Pattern



# Stroma

- Hyaline
- 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 histogenesis 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. ...

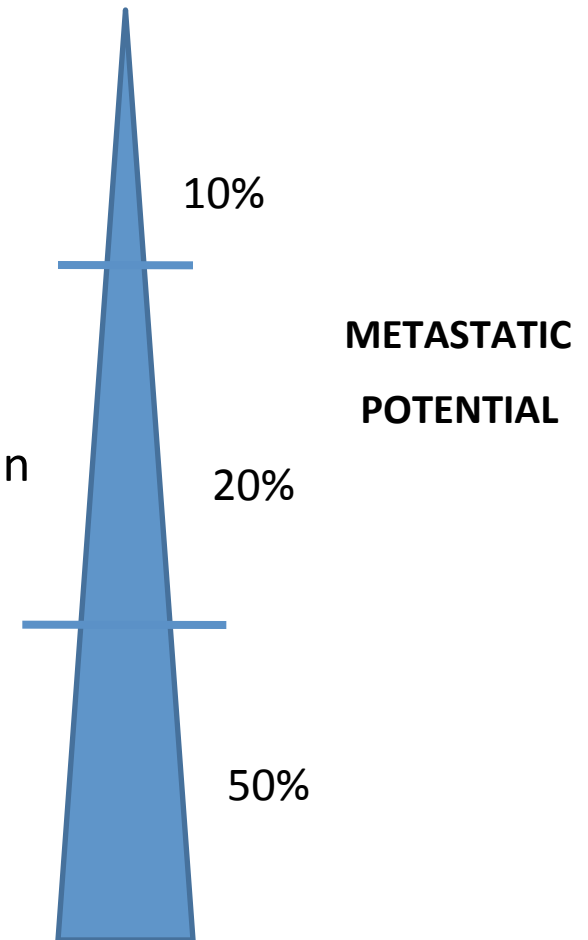
<b>Primary tumor (T)</b>				
T0		No evidence of primary tumor		
T1		Tumor <5 cm		
T2		Tumor >5 cm		
<b>Lymph nodes (N)</b>				
N0		No regional metastasis		
N1		Regional node metastasis		
<b>Distant metastasis (M)</b>				
M0		No distinct metastasis		
M1		Distant metastasis		
<b>Histopathologic grading (G)</b>				
G1		Well differentiated (low grade)		
G2		Moderately differentiated (intermediate grade)		
G3		Poorly differentiated (high grade)		
G4		Undifferentiated		
<b>Stage</b>				
IA	G1	T1	N0	M0
IB	G1	T2	N0	M0
IIA	G2	T1	N0	M0
IIB	G2	T2	N0	M0
IIIA	G3	T1	N0	M0
	G4	T1	N0	M0
IIIB	G3	T2	N0	M0
	G4	T2	N0	M0
IVA	Any G	Any T	N1	M0
IVB	Any G	Any T	Any N	M1

American Joint  
Committee on Cancer

AJCC of soft tissue  
sarcomas  
classification

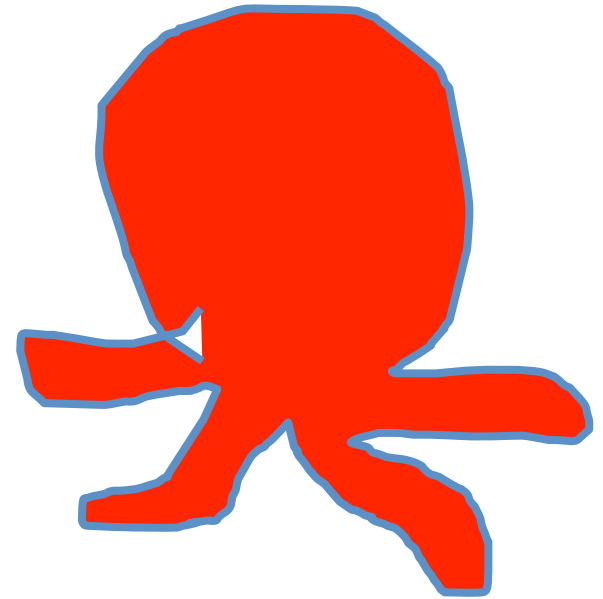
# Grading of STS in veterinary medicine

- **Grade I, low grade**
  - No necrosis
  - 0-9 mitosis per HPF
  - $\cong$  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

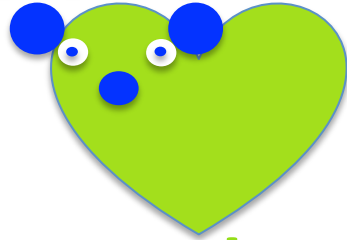


# PROGNOSTIC FACTORS

- Dimension (threshold: 5 cm)
- Localizzazione → completeness of surgical excision
- Histological grade
- Presence of metastasis



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