In The Name Of God

Dr. Fatemeh Namazi

Associate Professor of Pathology

School of Veterinary Medicine

Shiraz University

Principles of Classification and Diagnostic Criteria in the Pathology of Tumors in Small Animals

- **Tumor classification and nomenclature**
- **Pathological Criteria of malignancy**
- **Tumor grading and staging**
- **Common tumors in small animals**

General Nomenclature

- **Neoplasia**

Neoplasia is a process of “new growth” in which normal cells undergo:

✓ Irreversible genetic changes

✓ Unresponsive to ordinary controls on growth

- **Tumor** (“swelling”) or **cancer** (“crab”)

Describe the clinical appearance or infiltrative behavior of these abnormal growths

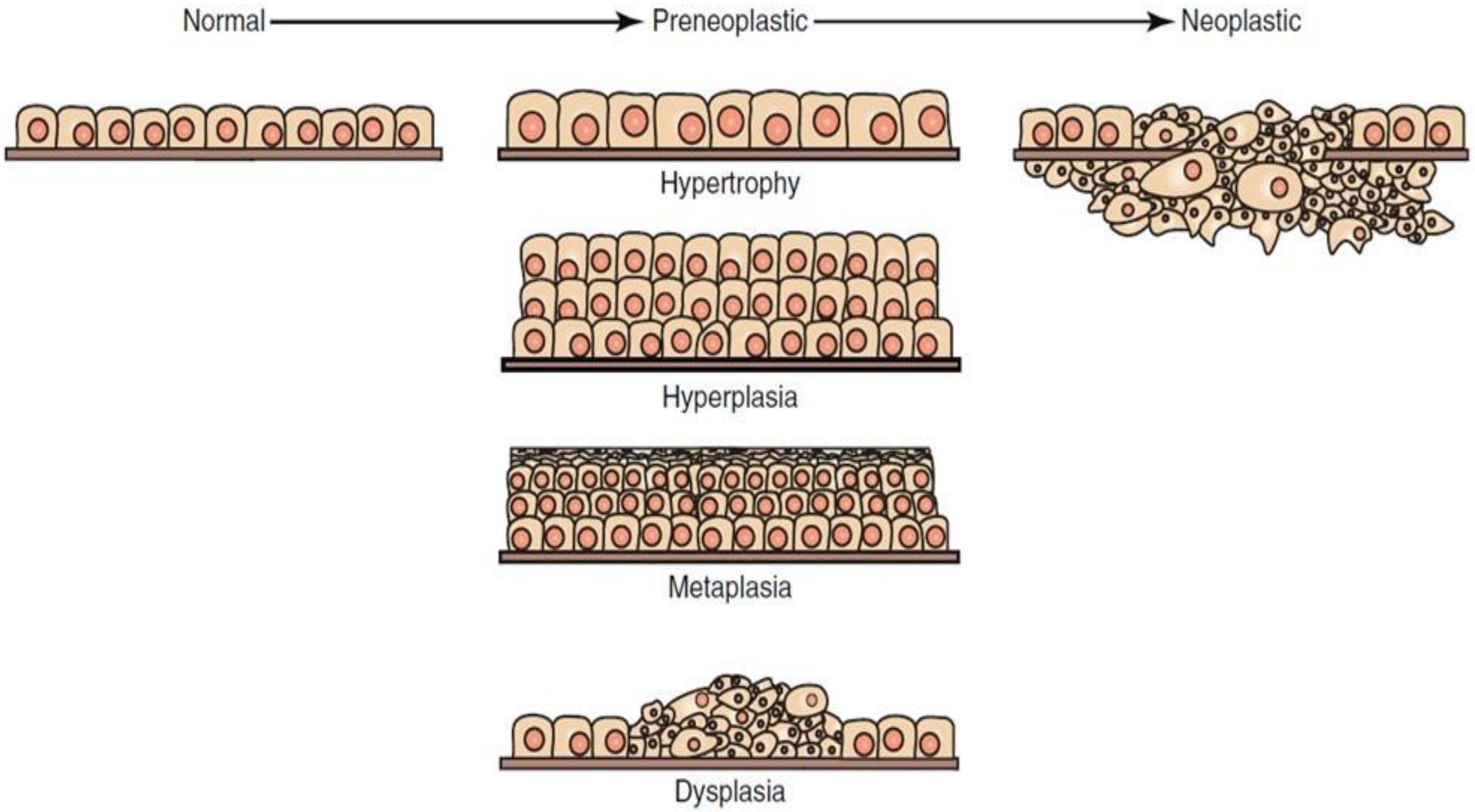
- The terms neoplasm and tumor may refer to either benign or malignant growths
- The term cancer always denotes a malignant growth

- Benign tumors do not invade surrounding tissue or spread to new anatomic locations

- Malignant tumors, if left untreated, invade locally, spread by metastasis

- Nervous system tumors are often localized and very rarely metastasize → clinical signs and death by interrupting important neurologic pathways

Preneoplastic Changes



Tumor Types: Cell of Origin

Microscopically, most tumors consist of a single cell type, either mesenchymal or epithelial

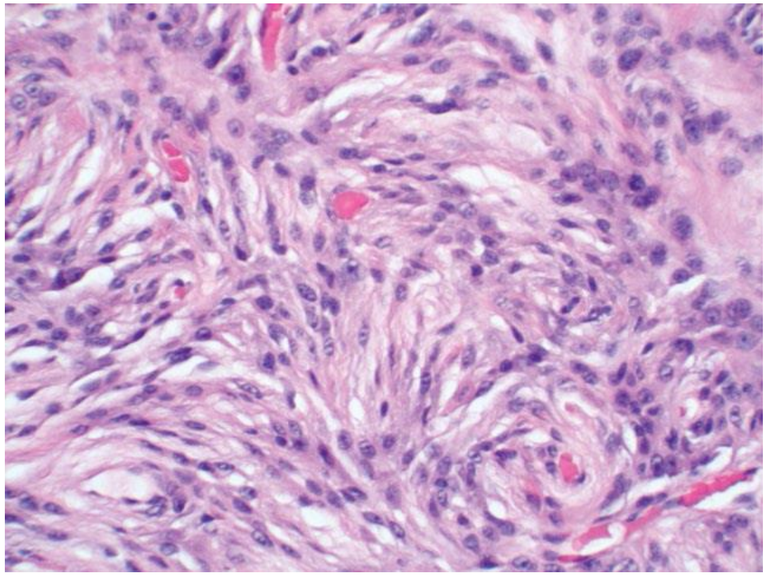
Neuroectodermal tumors and tumors that have lost significant features of cellular differentiation may be more difficult to classify

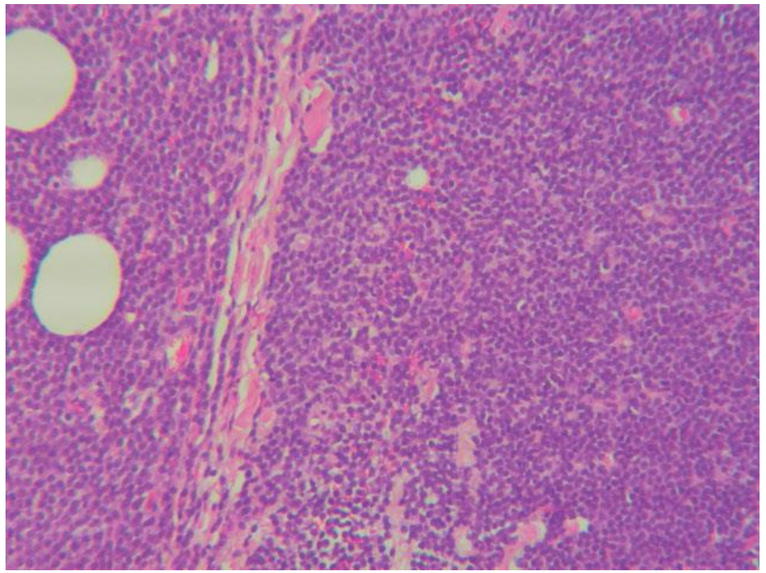
Mesenchymal Tumors

Mesenchymal tumors arise from cells of embryonic mesodermal origin

These tumors are generally composed of:

- **Spindle cells arranged in streams and bundles**
- **Round cells arranged in solid sheets**





Mesenchymal Tumors

Benign tumors → the suffix -**oma** to the name of the cell of origin

Lipo~~cyte~~ + oma → Lipoma

Fibro~~blast~~ + oma → Fibroma

Osteo~~blast~~ + oma → Osteoma

Malignant tumor → **Sarcoma**. A prefix or modifier indicates the tissue of origin

Liposarcoma, Fibrosarcoma, Osteosarcoma

Malignancies arising from Hematopoietic system → **Leukemia**

Characterized by large numbers of neoplastic cells in the peripheral blood or bone marrow

Epithelial Tumors

All three embryonic cell layers can give rise to epithelial tissues:

- ✓ Ectoderm
- ✓ Mesoderm
- ✓ Endoderm

- ➢ Benign tumors → the suffix **-oma**
- ➢ The terms **papilloma**, **adenoma**, and **polyp** ⇒ benign epithelial tumors
- ➢ The term papilloma ⇒ a benign growth arising from a cutaneous or mucocutaneous surface

Epithelial Tumors

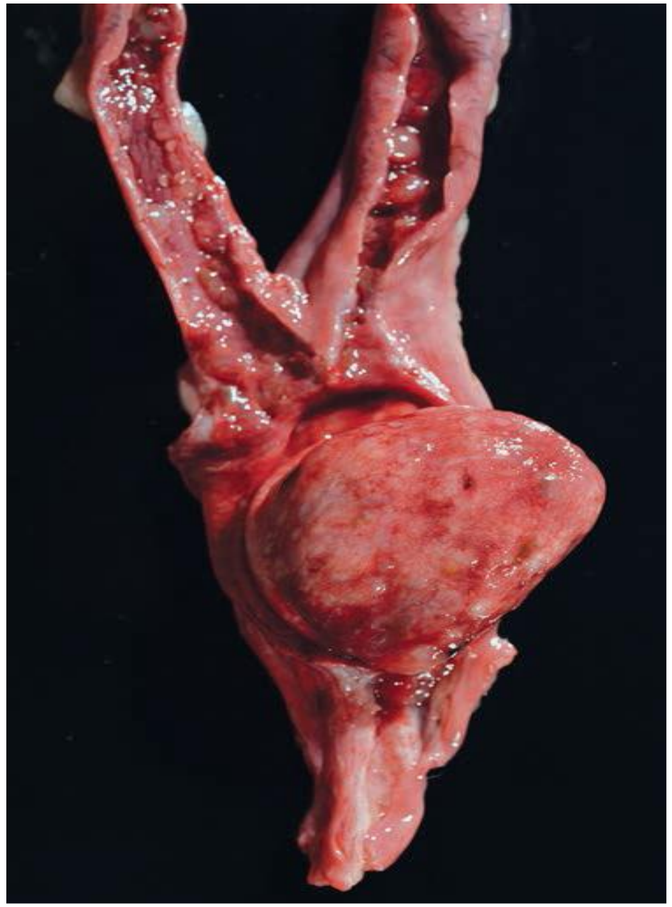
- Adenoma denotes:

- Tumor arising from glandular epithelium → mammary epithelium

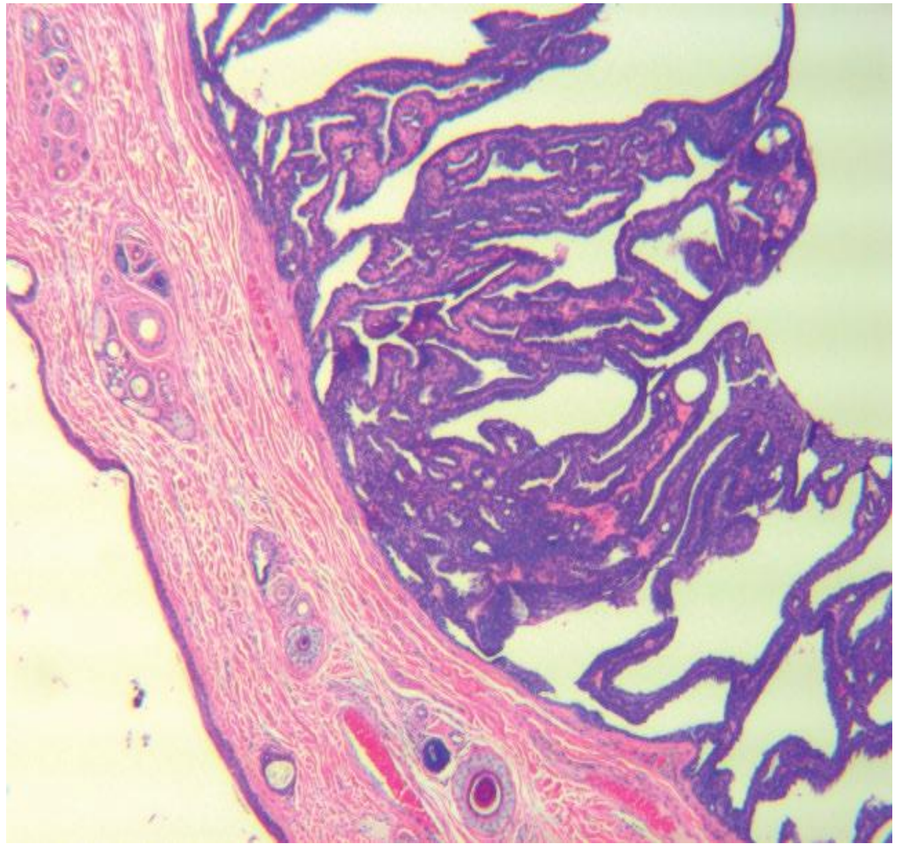
- Tumor derived from nonglandular epithelial tissue that exhibits a tubular pattern microscopically → renal tubular adenoma

- A polyp is a grossly visible, benign epithelial tumor projecting from a mucosal surface that does not invade underlying tissue

Endometrial Polyp



Apocrine gland adenoma



Epithelial Tumors

- All malignant tumors → **Carcinoma**
- Carcinomas → nests, cords, or islands of neoplastic epithelial cells
- **Adenocarcinoma** → glandular growth pattern
- Carcinoma in situ → preinvasive form of carcinoma that remains within the epithelial structure and does not penetrate the basement membrane or invade underlying stroma

Epithelial Tumors

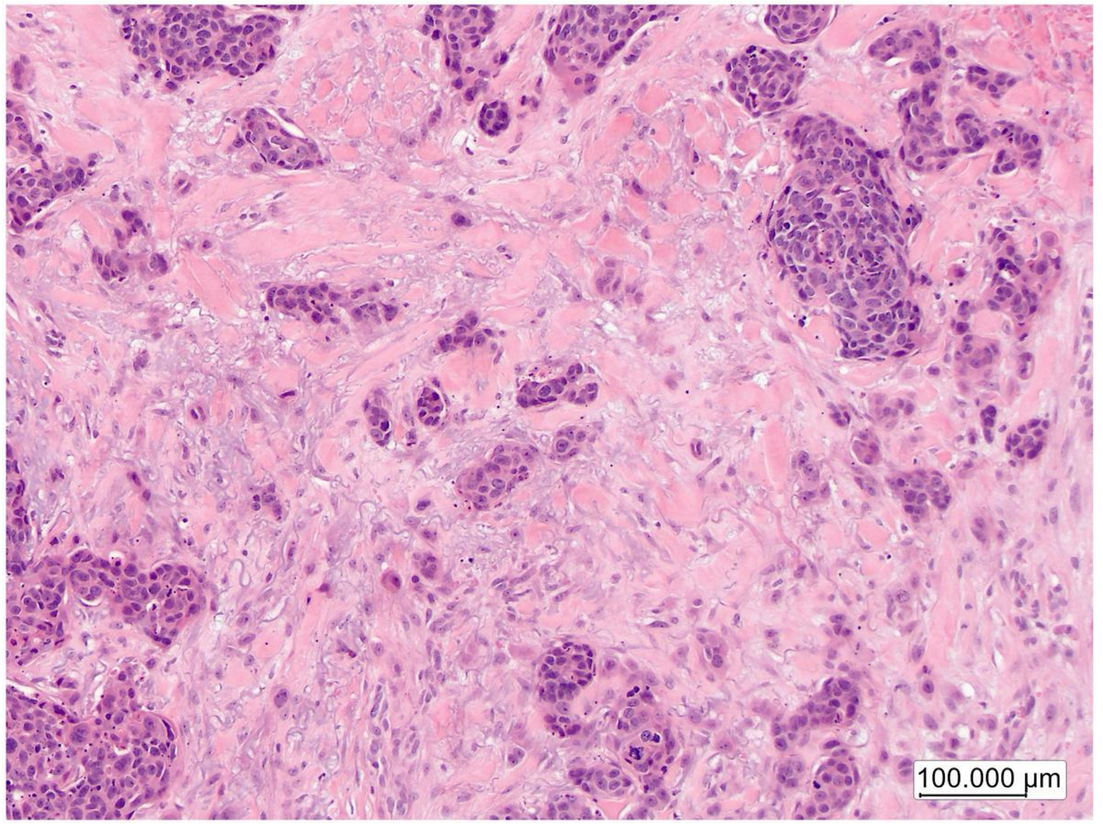
- The neoplastic epithelial cells of mucinous adenocarcinomas produce abundant mucin

- Carcinomas that stimulate significant desmoplasia → Scirrhous

- Melanocytes:

- Benign tumor → is termed a “benign melanoma” or “melanocytoma”
- Malignant → malignant melanoma

Carcinomas with desmoplasia



TUMORS OF NEURAL CREST CELLS

- Neural crest cells arise embryologically when the neuroectoderm separates from the overlying ectoderm
- The neuroectoderm become the central nervous system and Neural crest cells give rise to a variety of cell types, including:

  - ✓ Schwann cells
  - ✓ Melanocytes
  - ✓ Adrenal medullary cells
  - ✓ Ganglion cells

TUMORS OF NEURAL CREST CELLS

- Since cells of neural crest origin are neither truly mesenchymal nor epithelial, the word "**malignant**" and the suffix **"–oma"** are used

- For example, tumors arising from the adrenal medulla are called:

✓ Benign → pheochromocytomas

✓ Malignancy → malignant pheochromocytoma

TUMORS OF UNCERTAIN ORIGIN

- Neoplastic cell populations of uncertain origin that have lost characteristic features of differentiation → undifferentiated neoplasms

MIXED TUMORS

- A tumor containing multiple cell types is called a mixed tumor

- Mixed tumors are believed to arise from a single pluripotent or totipotent stem cell capable of differentiating into a variety of more mature cell types

MIXED TUMORS

- The benign mixed mammary gland tumor of dogs

✓ Mixture of neoplastic elements, fibrous connective tissue, cartilage, and bone

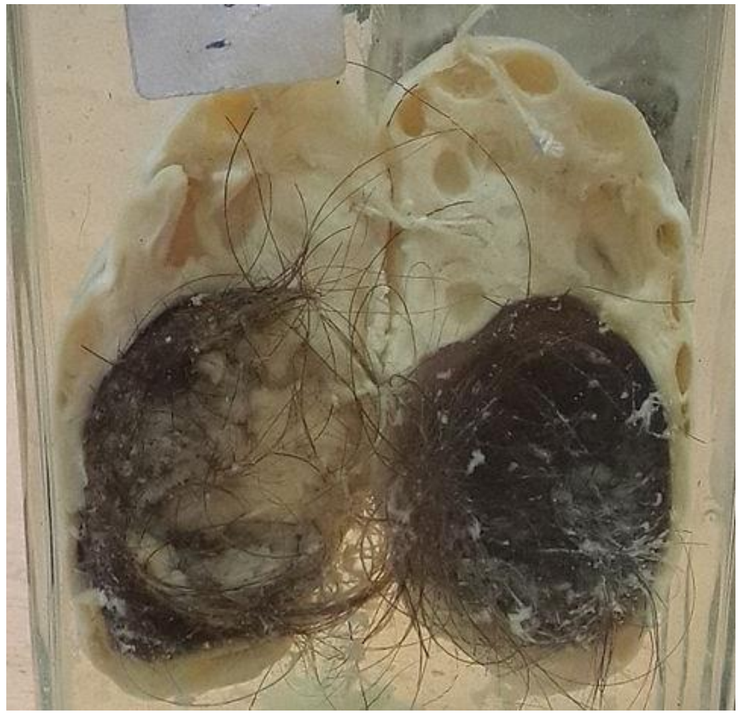
- Teratomas and teratocarcinomas, which arise from totipotential germ cells

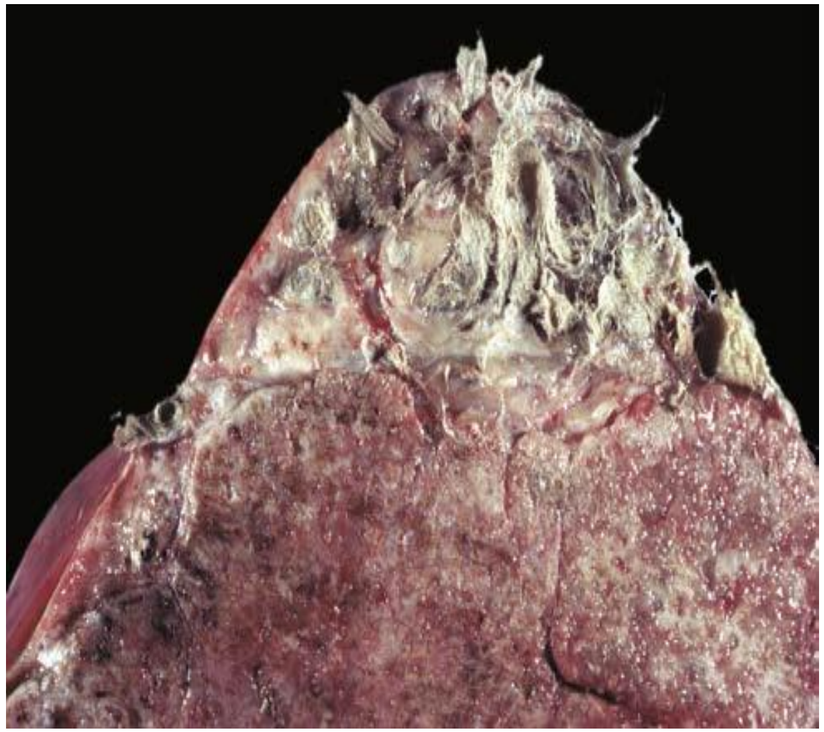
✓ Contain tissues normally derived from all three embryonic cell layers

✓ Composed of a bizarre mixture of adult and embryonic tissue types

Ovarian teratoma

- The most common tissues seen macroscopically are hair, cartilage, and bone





TUMOR-LIKE LESIONS

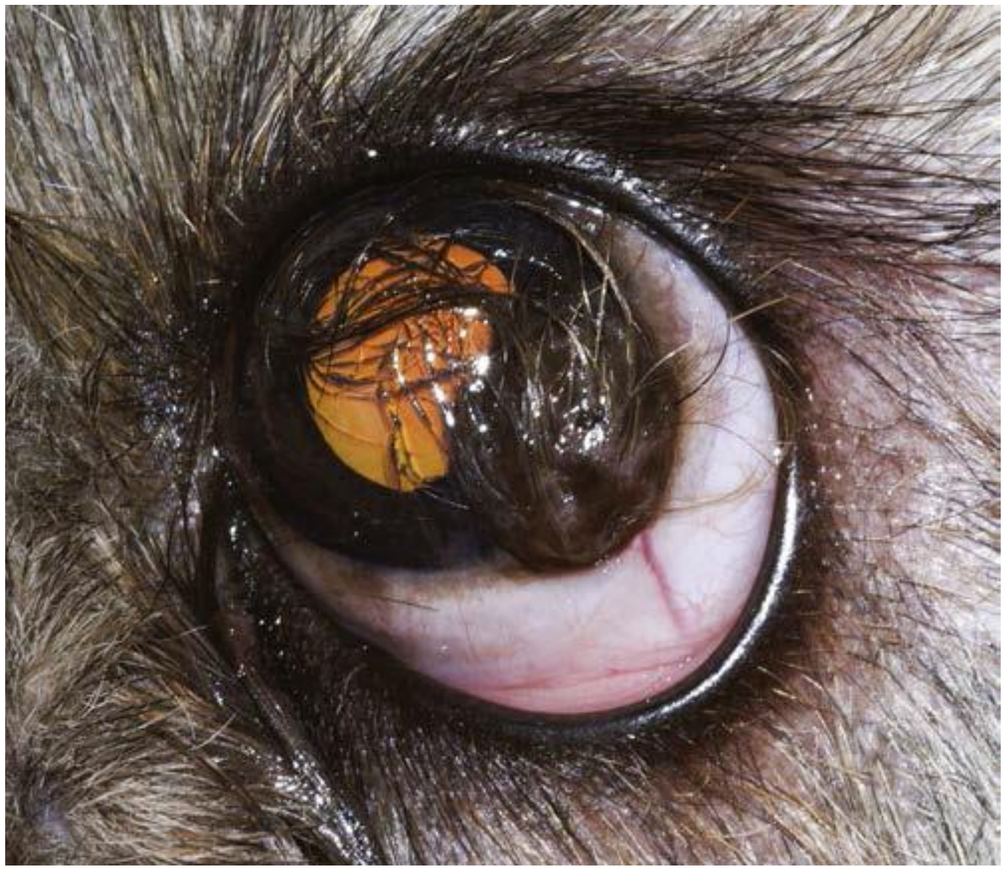
➢ Nonneoplastic growths

- Hamartomas → disorganized but mature mesenchymal or epithelial tissues found in their normal anatomic location

- Choristomas → normal mature tissue located at an ectopic site

✓ Dermoid

Dermoid



Origin	Cell origin	Benign	Malignant
MESENCHYMAL	Fibroblast	Fibroma	Fibrosarcoma
	Lipocyte	Lipoma	Liposarcoma
	Chondrocyte	Chondroma	Chondrosarcoma
	Osteoblast	Osteoma	Osteosarcoma
	Vascular endothelium	Hemangioma	Hemangiosarcoma
	Lymphocyte	Lymphoma	Lymphosarcoma
	Leukocyte & Erythrocyte	*	Leukemia
	Mast cell	Mast cell tumor	Mast cell tumor
	Smooth muscle cell	Leiomyoma	Leiomyosarcoma
	Skeletal muscle cell	Rhabdomyoma	Rhabdomyosarcoma

Origin	Cell origin	Benign	Malignant
EPITHELIAL	Squamous epithelial cell	Papilloma	Squamous cell carcinoma
	Melanocyte	Benign melanoma (melanocytoma)	Malignant melanoma
	Lower alimentary tract Columnar epithelium	Adenoma	Adenocarcinoma
	Upper alimentary tract Squamous epithelial cell	Papilloma	Carcinoma
	Transitional epithelium	Papilloma	Transitional cell carcinoma

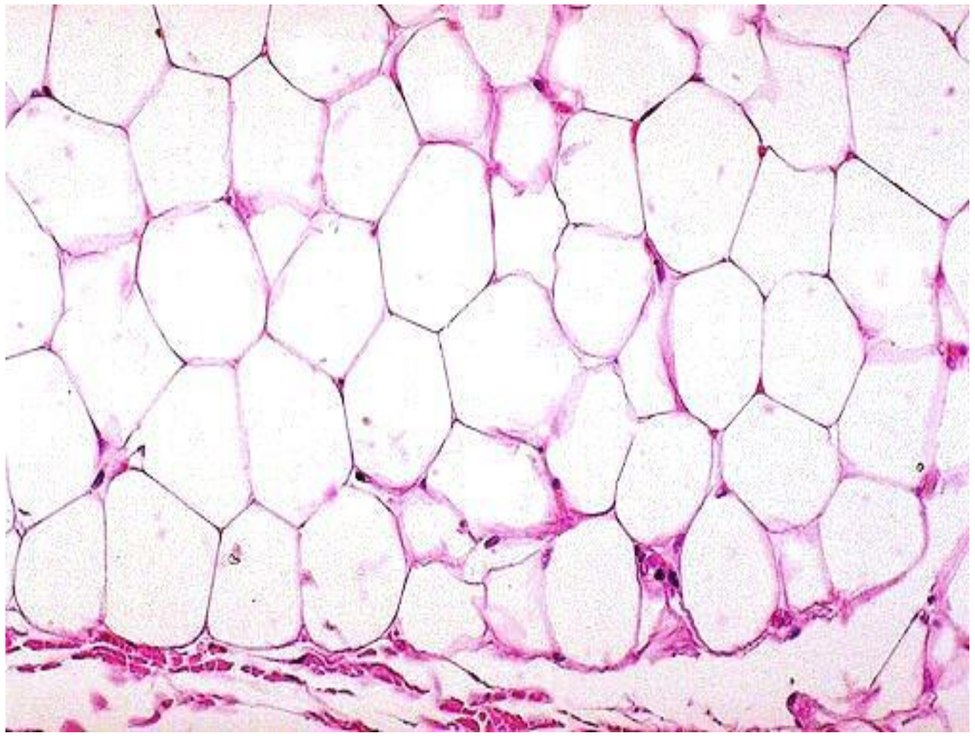
Origin	Cell origin	Benign	Malignant
Solid epithelial organs	Hepatocyte	Adenoma	Hepatocellular carcinoma
	Renal tubular cell	Adenoma	Carcinoma
	Germ cell	seminoma	Malignant seminoma
	Sertoli cell	Sertoli cell tumor	Malignant Sertoli cell tumor
	Germ cell	Dysgerminoma	Dysgerminoma
	Stromal cell	Granulosa cell tumor Luteoma	* *

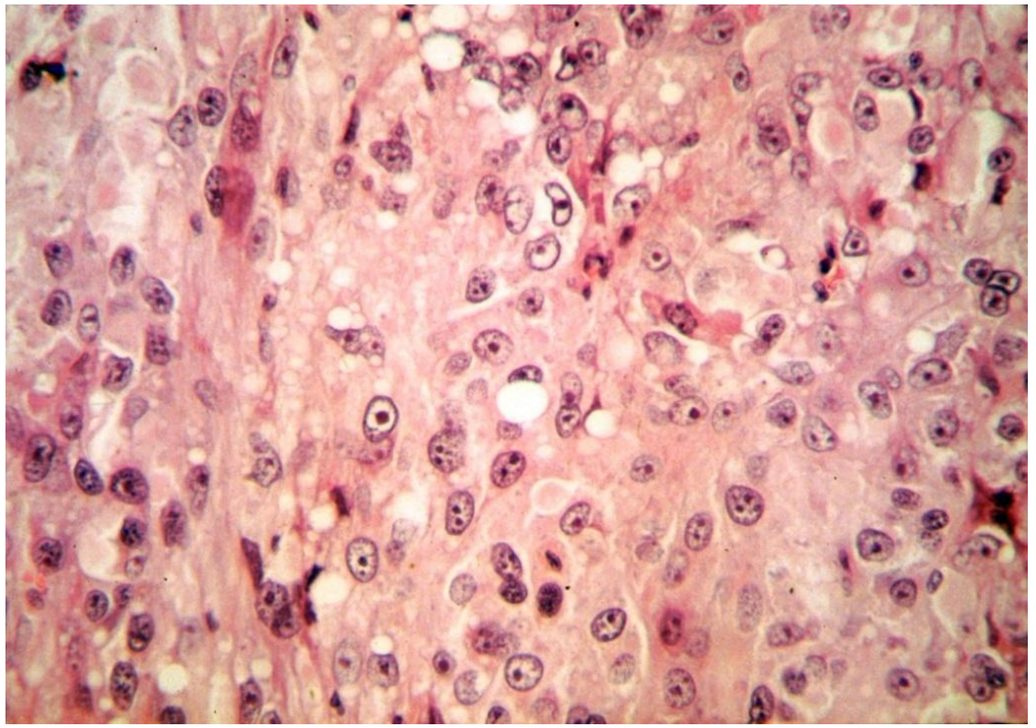
Origin	Cell origin	Benign	Malignant
NERVOUS TISSUE	Astrocyte	*	Astrocytoma Glioblastoma
	Oligodendrocyte	*	Oligodendroglioma
	Schwann cell	Schwannoma	Malignant peripheral nerve sheath tumor (malignant schwannoma)
	Neuron	Ganglioneuroma	*
MIXED TUMORS		Benign mixed mammary tumor (dog)	Malignant mixed mammary tumor (dog)
	Germ cell	Teratoma	Teratocarcinoma

Comparisons between Benign and Malignant Tumors

Characteristic	Benign	Malignant
Differentiation	Well-differentiated Structure similar to tissue of origin	Poorly differentiated Tissue of origin sometimes unclear Variable degrees of anaplasia
Growth rate	Slow growth Rare mitotic figures Normal mitotic figures	Rapid growth Frequent mitotic figures Abnormal mitotic figures
Local invasion	No invasion Cohesive and expansile growth Capsule often present	Local invasion Infiltrative growth Capsule often absent
Metastasis	No metastasis	Metastasis sometimes present

Comparisons between Benign and Malignant Tumors



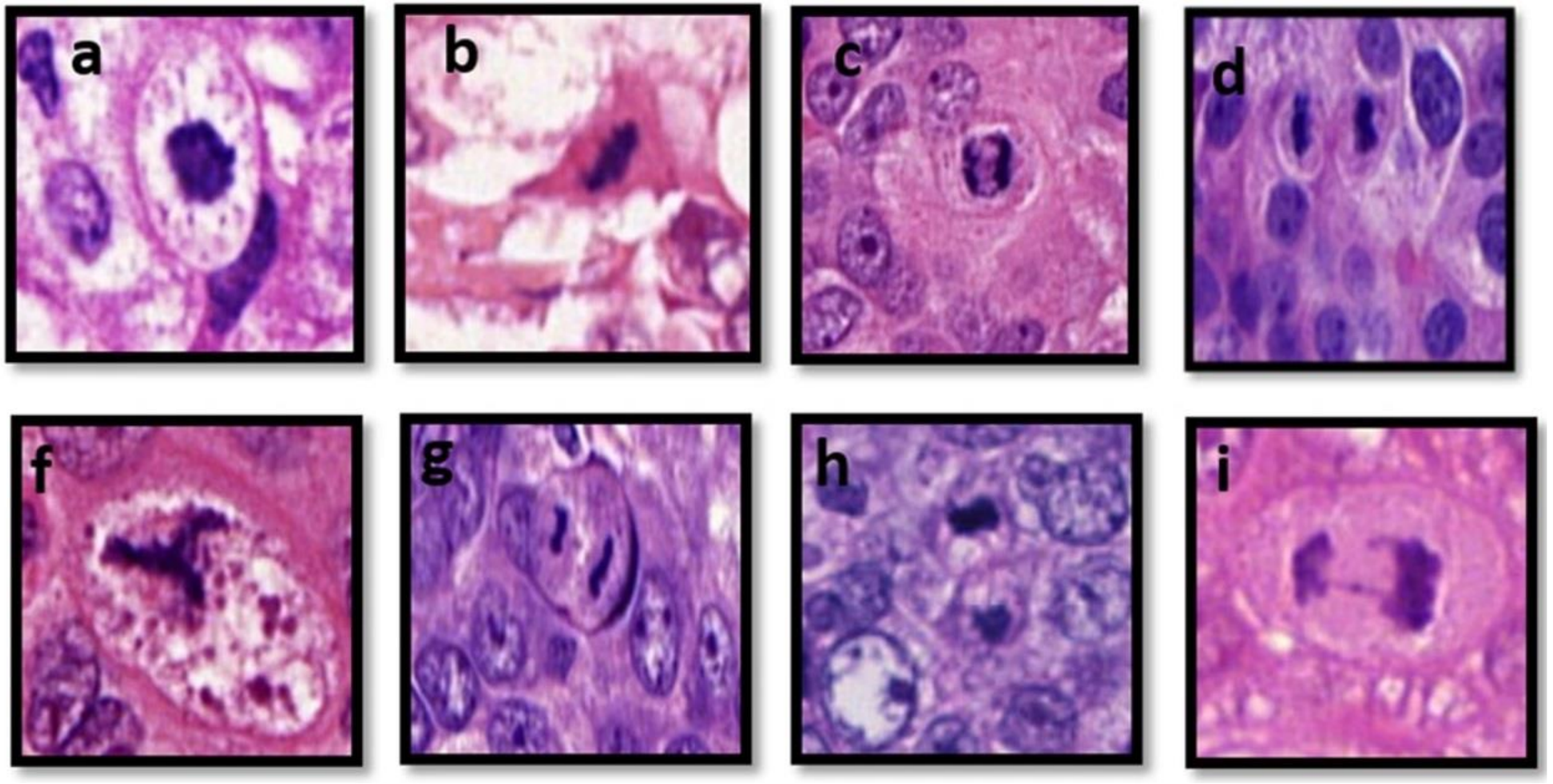


Prophase

Metaphase

Anaphase

Telophase



Tripolar

Polar asymmetry

Non-uniform separated cells

Anaphase bridge

DIFFERENTIATION OF TUMORS

- Each normal, fully differentiated, mature tissue type has a characteristic gross and microscopic appearance that varies little from individual to individual of an animal species

- To a variable extent, neoplastic tissues lose these mature differentiated features of cellular morphology and organization

  - Well differentiated
  - Poorly differentiated
  - Undifferentiated

GROSS PATTERNS OF TUMOR GROWTH

- Careful observation of the gross appearance, anatomic localization, and distribution of tumors during clinical examination, surgery, or necropsy can aid in determination of the tissue of origin and biologic behavior of the tumor if a neoplastic process is present

- Grossly, neoplasms most commonly appear as one or more raised nodules extending above or displacing tissue within a body structure

GROSS PATTERNS OF TUMOR GROWTH

- Most carcinomas and sarcomas → firm nodules

- As exceptions, hepatocellular carcinomas are typically soft

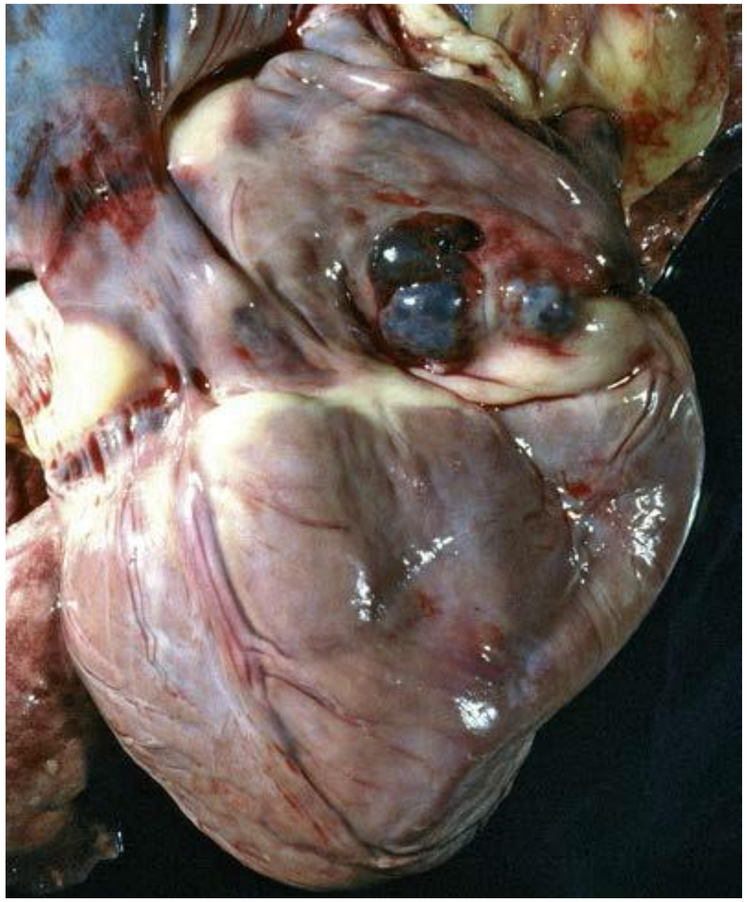
- osteosarcomas → hard

- lipoma and liposarcomas → fatty or greasy appearance

- Hemangiosarcomas → red and blood filled

- Interestingly, hemangiosarcoma metastases may sometimes be flat or depressed, instead of raised

Hemangiosarcoma



Metastasis of hemangiosarcoma

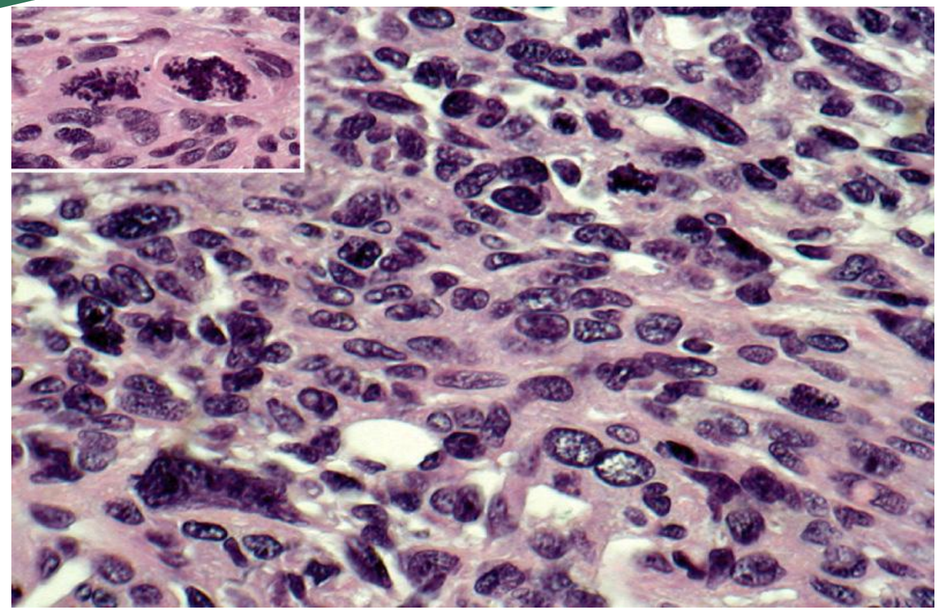
MICROSCOPIC TUMOR MORPHOLOGY

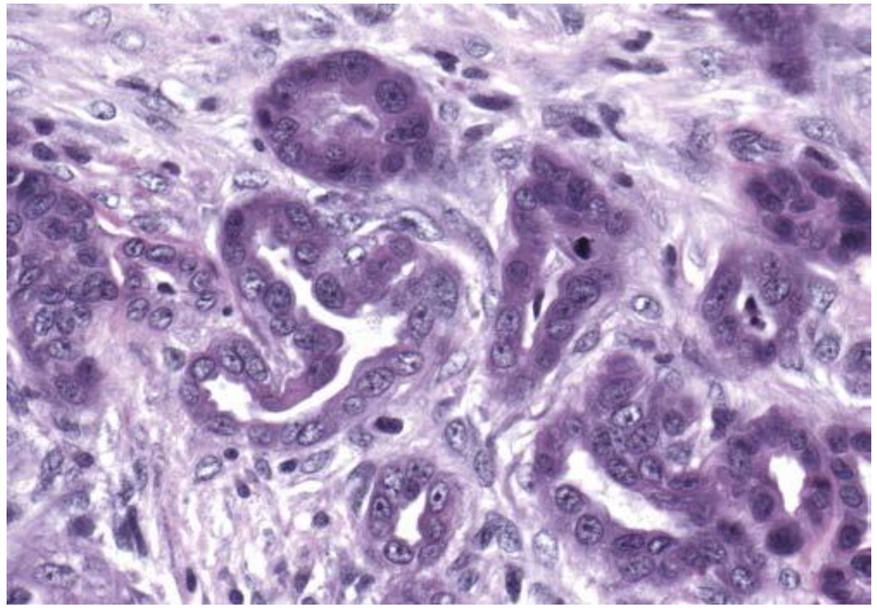
- In general, malignant tumors are less differentiated than benign tumors
- Anaplastic malignancies are poorly differentiated cells with:

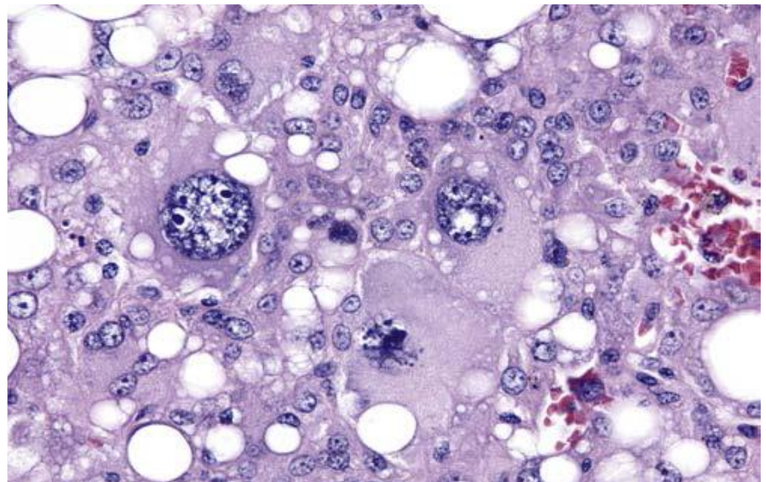
  - Wide variation in cell size (anisocytosis) and shape (pleomorphism)
  - Variability in nuclear size (anisokaryosis), shape
  - Prominent or multiple nucleoli

MICROSCOPIC TUMOR MORPHOLOGY

- Bizarre cells with very large nuclei
- Hyperchromatic nuclei
- Increased nuclear to cytoplasmic ratio
- Numerous mitotic figures







May lose characteristic cytoplasmic features such as cilia or pigment

- AMELANOTIC MELANOMAS

✓ Positive immunohistochemical reactivity for Melan-A

HALLMARK OF MALIGNANCY:

Anaplasia

Metastasis

TUMOR CELL FUNCTION

- Loss of specialized function frequently accompanies loss of differentiated morphologic features in tumors
- Thyroid adenomas → hyperthyroidism

PARANEOPLASTIC EFFECTS

- In addition to the direct effects, tumors may cause a variety of systemic clinical signs → paraneoplastic syndromes
- Approximately 75% of human cancer patients develop paraneoplastic syndromes
- The incidence in veterinary cancer patients is unknown

Recognition of paraneoplastic syndromes is important:

1. These syndromes may facilitate early tumor diagnosis if they arise in the initial stages of tumor development

2. Treatment of metabolic abnormalities associated with paraneoplastic syndromes may be required to ensure effective cancer management

3. The severity of paraneoplastic abnormalities may reflect the tumor burden

4. Monitoring such abnormalities may be useful in determining tumor response to therapy and identifying tumor recurrence or spread

➢ **Cachexia**

- Notable weight loss

- In cancer cachexia → lost both muscle and fat
- Simple starvation → preferentially lost fat

- Consumption of extra calories will not prevent or reverse the catabolic state of cancer cachexia

- Anorexia, impaired digestion, nutritional demands of tumor, nutrient loss in effusions or exudates

✓ Cytokines (TNF-α, IL-6, IL-1)

➢ **Endocrinopathies**

Endocrine Tumors

- A functioning endocrine tumor produces the hormonal products of the tissue of origin

- Thyroid adenoma → thyroid hormone → hyperthyroidism

➢ Insulinoma (tumors of β-cells) → hyperinsulinemia → hypoglycemia

✓ Dependence of nervous system on glucose → lethargy, muscle weakness, seizures

✓ Hypoglycemia of unknown origin may also occur with other tumor types

Nonendocrine Tumors

- Ectopic hormone production
- Identical to the normal hormone, modified form, a similar protein

➢ Parathyroid hormone–related peptide → hypercalcemia of malignancy

- Dogs:

✓ Adenocarcinoma of the anal sac (≈90% of cases)
✓ lymphoma (≈20% of cases),
✓ Multiple myeloma (≈15% of cases)

- Muscle weakness, cardiac arrhythmia, anorexia, vomiting, renal failure

- Metastasis to bone → hypercalcemia → not a true paraneoplastic disorder

➢ Skeletal Syndromes

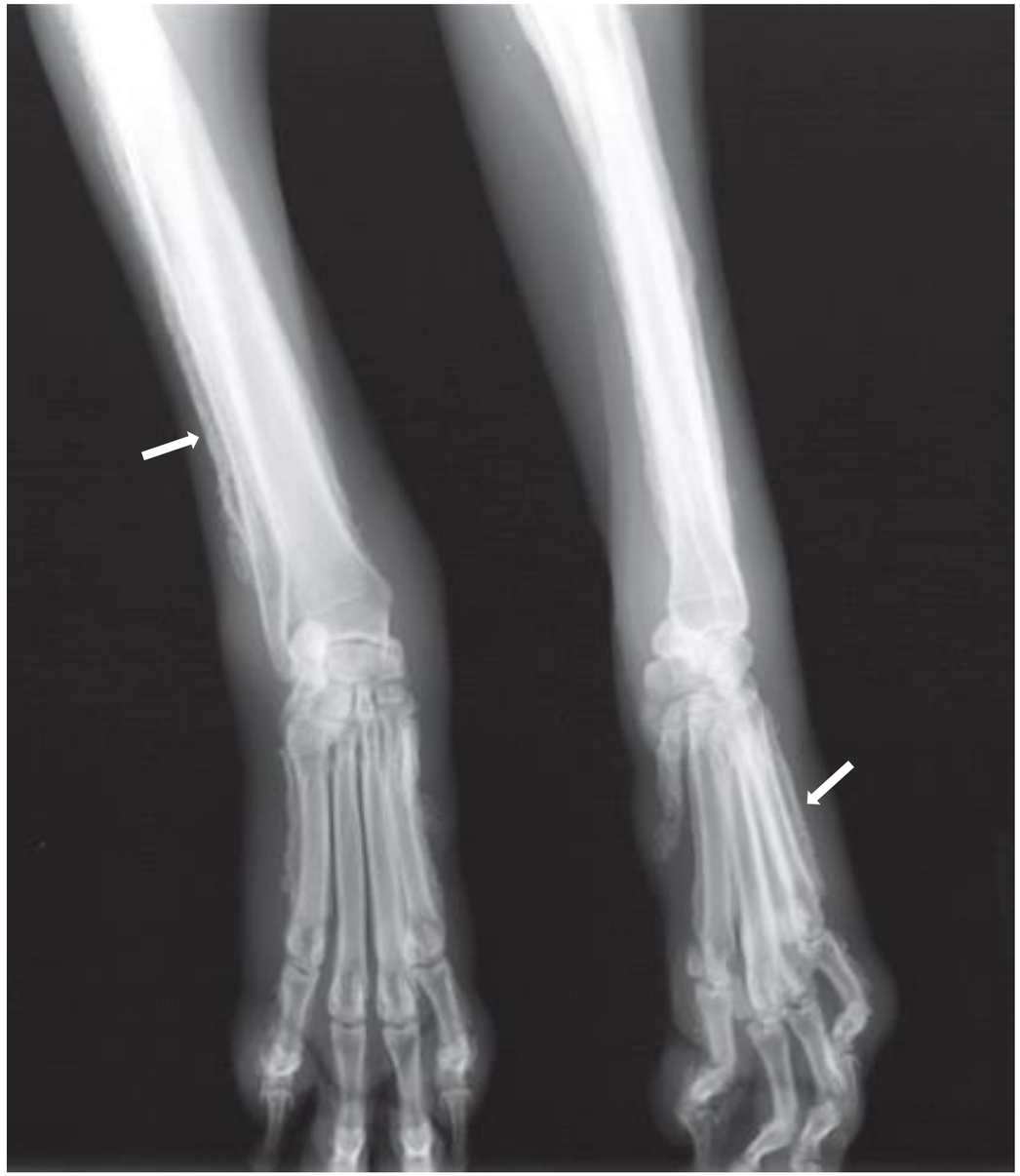
Hypertrophic osteopathy

- Extensive periosteal new bone growth
- Symmetric lameness
- Unknown cause → abnormalities of growth hormone production

Myelofibrosis

- Overgrowth of nonneoplastic fibroblasts in the bone marrow
- Impairs normal hematopoiesis → cytopenias
- Unknown cause

Hypertrophic osteopathy



➢ Vascular and Hematologic Syndromes

- Nonhematopoietic cancer → eosinophilia and neutrophilia → unknown cause → alterations in circulating cytokines
- Anemia → inflammation, bone marrow effacement, myelofibrosis
- Polycythemia → ectopic production of erythropoietin
- Thrombocytopenia → decreased platelet production, increased consumption
- Hemangiosarcoma → DIC → thrombocytopenia and anemia

➢ Cutaneous Syndromes

- A few reports in dogs and cats
- Flushing, alopecia, necrolytic dermatitis

Syndrome of nodular dermatofibrosis

- German shepherd dogs

✓ Multiple benign-appearing fibrous nodules in the skin

✓ Bilateral renal cystadenocarcinomas

➢ Miscellaneous Syndromes

- Mast cell tumors are very common in dogs
- Release of excess histamine → gastrointestinal ulceration, hemorrhage
- Gastrin-secreting tumors in dogs and cats → gastroduodenal ulceration, abdominal pain, vomiting, blood loss

✓ Gastrinoma → malignant neuroendocrine neoplasia (pancreas)

GRADING

- Tumor’s biologic behavior
- Grading schemes vary depending on the species and tumor type
- All grading schemes evaluate the degree of differentiation of tumor cells

Well differentiated (very similar to normal cells)

Moderately differentiated” (somewhat similar to normal cells)

“Poorly differentiated” (highly anaplastic, few features of normal cells)

- **Low grade or grade I**
- **Medium grade or grade II**
- **High grade or grade III**

Other criteria that may be included in grading schemes include:

- The mitotic count (number of mitotic figures per ten 400× fields)
- The extent of tumor necrosis
- Tumor invasiveness
- Overall tumor cellularity

STAGING

- Tumor staging gives an indication of the extent of tumor growth and spread in the animal

- In general, staging is determined by the clinician through compilation of clinical examination, imaging, and pathology findings

- Staging guides the therapeutic plan and provides prognostic information

➢ One of the most widely used schemes is the TNM system:

- **The size of the primary tumor (T)**
- **Degree of lymph node involvement (N)**
- **Extent of metastasis (M)**

- T0 is given to in situ tumor, whereas T1 to T4 indicate increasing size of the primary tumor

- N0 indicates the absence of detectable lymph node involvement, whereas N1 to N3 indicate progressive involvement

- M0 signifies no detectable metastasis, whereas M1 and M2 indicate metastasis to one and two organs, respectively

There is some variability in tumor staging at different institutions. This variability often reflects the:

- Availability of more sophisticated imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI)

- More sensitive techniques of histologic detection, such as immunohistochemistry for cytokeratin to detect micrometastases in lymph nodes of carcinoma patients

Stage	Definition
T0	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Metastasis to one organ
M2	Metastasis to two organs

TUMOR DIAGNOSIS

- Cytologic examination
- Histopathologic examination
- Immunohistochemical staining
- Flow cytometry

CYTOLOGIC TUMOR DIAGNOSIS

- Rule out nonneoplastic inflammatory conditions
- Better evaluation of fine nuclear and cellular details
- Evaluating bone marrow, in which fine cellular detail is required to determine cell lineage and stage of maturation
- Sample collection is quick and easy and requires no special equipment

FINE-NEEDLE TECHNIQUES

- Clean glass microscope slides, 20- to 22-gauge needle and a 6- to 12-ml syringe are typically used

- The sampling site must only be cleaned as for an injection, such as with an antiseptic wipe

- If the mass is suspected to have fluid filled or necrotic areas, then it is best to avoid these areas

✓ Collect cytology sample from more solid areas

LIMITATIONS OF CYTOLOGY

- Maybe not definitive diagnosis
- Not always representative of the entire lesion
- Does not contain tumor cells, such as an area of inflammation, hemorrhage, or reactive fibroplasia
- Does not allow evaluation of tissue architecture

HISTOPATHOLOGIC TUMOR DIAGNOSIS

- A definitive diagnosis of cancer is frequently obtained by standard histologic evaluation

- The margins of excisional biopsy specimens are commonly evaluated for evidence of extension or invasion of the neoplastic cells to the edge of the surgical site as an indicator of completeness of surgical excision

SAMPLE COLLECTION FOR HISTOPATHOLOGIC TUMOR EVALUATION

- Regions of inflammation, hemorrhage, necrosis, or reactive fibrosis should be avoided

- 10% neutral buffered formalin
- 10:1 ratio of formalin to tissue

- Unless special cryopreservatives are used to embed and flash freeze tissues under laboratory conditions, diagnostic tissues should never be frozen before submission

- Minimize specimen handling and manipulation with forceps or digital pressure
- Surgical margins can be delineated using special tissue dyes or suture patterns
- For the best results, the pathologist must be provided with detailed information regarding clinical history, anatomic location, gross lesion appearance, and any surgical intervention attempted

HISTOPATHOLOGIC EVALUATION OF TUMORS

- Ultimately a 3- to 5-μ thick section
- Stained with H&E

DETERMINATION OF NEOPLASIA

- Evaluating the cells for features of malignancy:
  - Abnormal morphologic features
  - High mitotic count
  - High nuclear to cytoplasmic ratio
  - Evidence of invasion or metastasis

HISTOCHEMICAL STAINS

- The granules in a poorly differentiated canine mast cells

✓ Toluidine blue stain

- Fibrosarcoma

✓ Masson’s trichrome

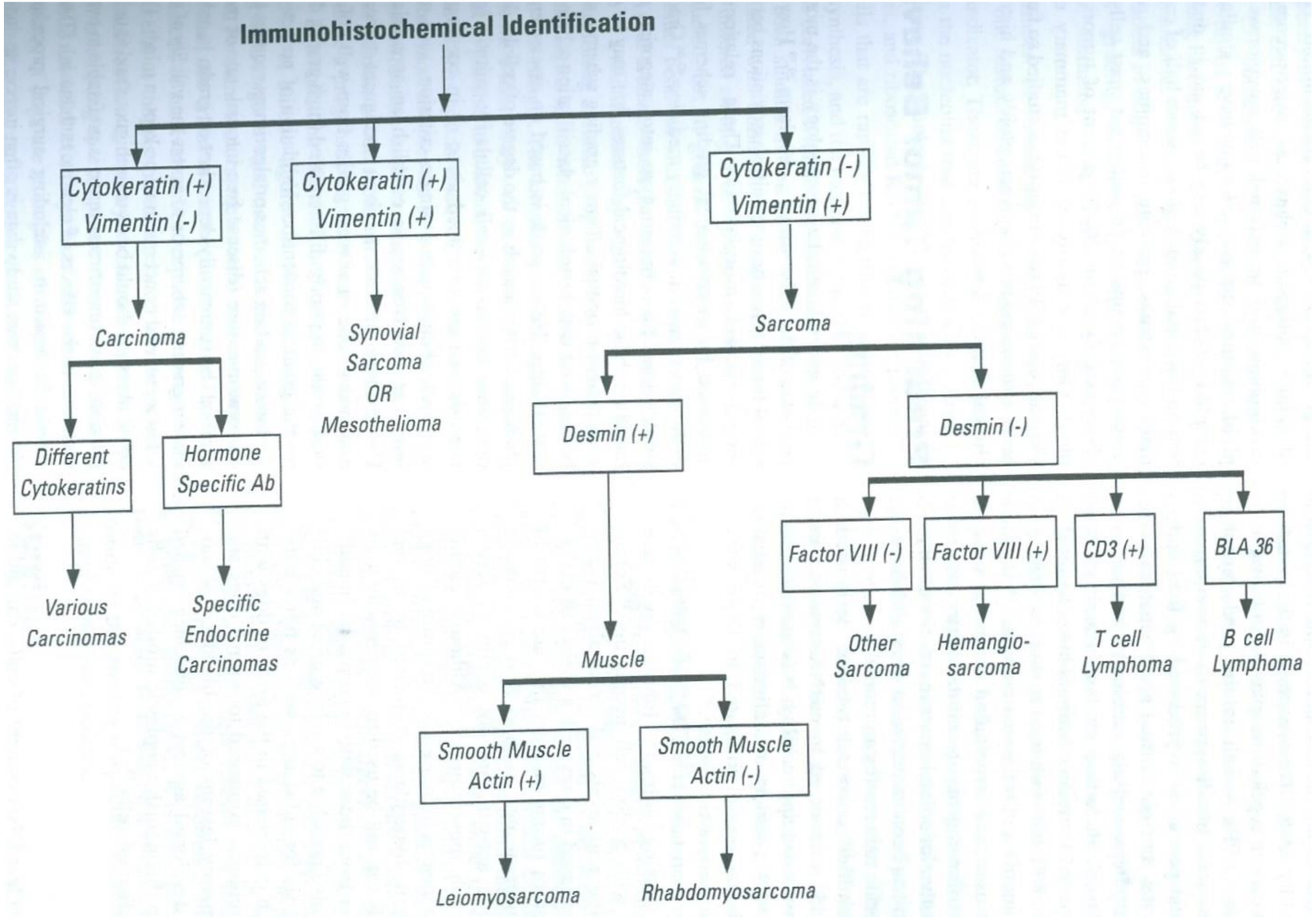
IMMUNOHISTOCHEMISTRY

- When tumor type or origin is not directly apparent, immunohistochemistry for specific cell markers may be used

✓ Undifferentiated neoplasms

✓ Hemangiosarcoma may lack clear vascular channels and resemble a fibrosarcoma

✓ Lymphoma originates from B or T lymphocytes


Immunohistochemical Identification
Cytokeratin (+) Vimentin (-)
Cytokeratin (+) Vimentin (+)
Cytokeratin (-) Vimentin (+)
Carcinoma
Synovial Sarcoma OR Mesothelioma
Sarcoma
Different Cytokeratins
Hormone Specific Ab
Desmin (+)
Desmin (-)
Various Carcinomas
Specific Endocrine Carcinomas
Factor VIII (-)
Factor VIII (+)
CD3 (+)
BLA 36
Muscle
Other Sarcoma
Hemangio-sarcoma
T cell Lymphoma
B cell Lymphoma
Smooth Muscle Actin (+)
Smooth Muscle Actin (-)
Leiomyosarcoma
Rhabdomyosarcoma

CHALLENGES IN FIXATION

Overfixation

- Can lead to excessive cross-linking → false negatives

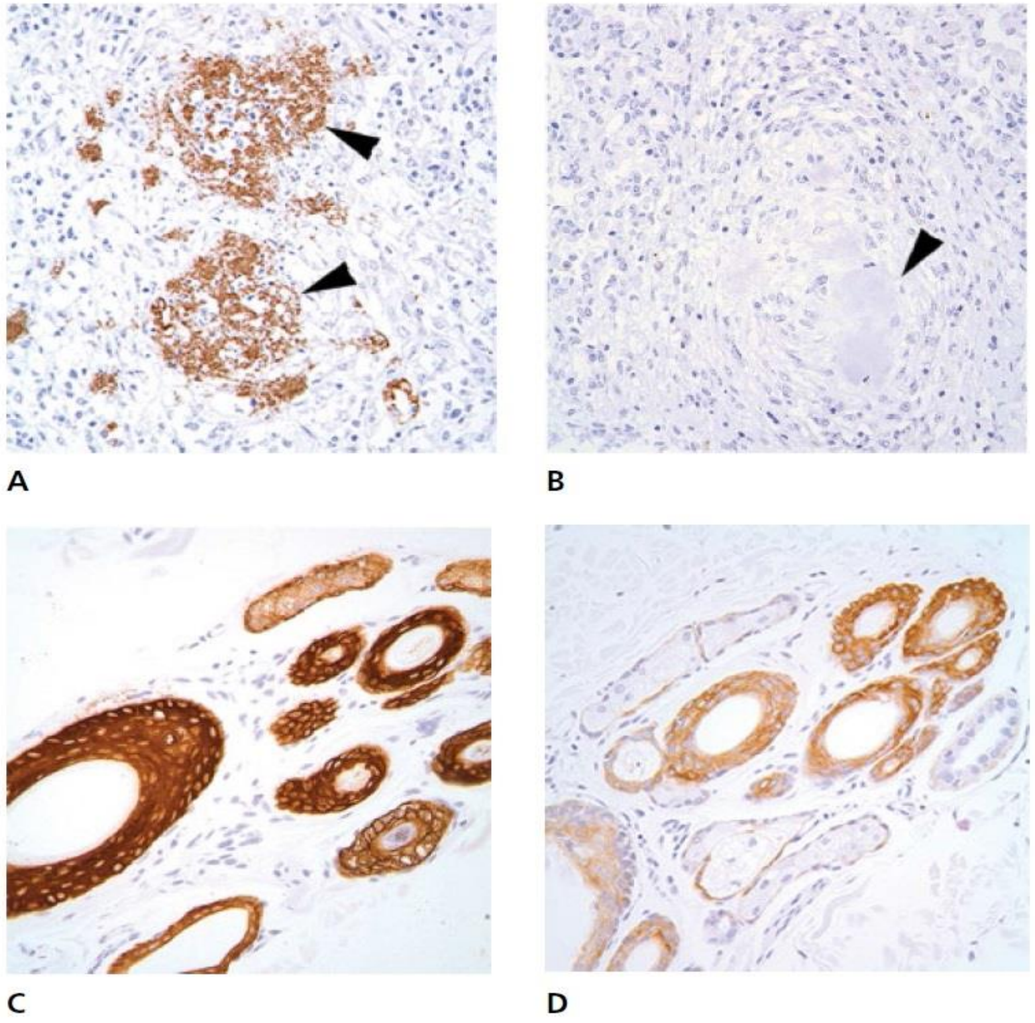
Underfixation

- More common and problematic, it can leave the core of large samples unfixed → inconsistent staining and unreliable results

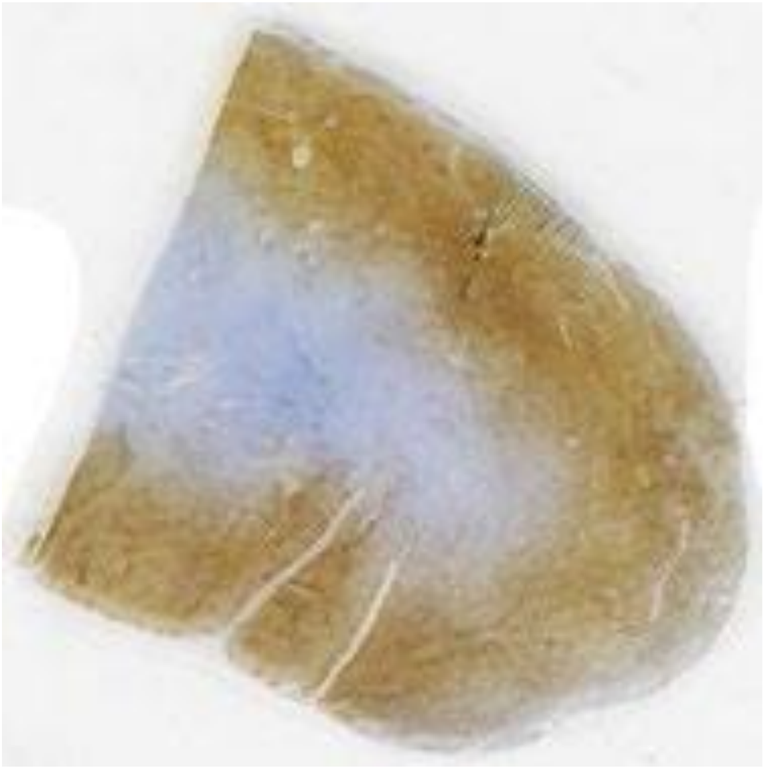
Delayed fixation

- Affects certain markers, especially in enzyme-rich tissues → rapid autolysis and potential background staining issues

Overfixation



Underfixation



DECALCIFICATION PROCESS

Weak Acids

- Solutions like formic acid diluted in formalin are recommended for decalcification to preserve immunoreactivity

Strong Acids

- The use of strong acid decalcifying solutions can negatively affect the immunoreactivity of certain antigens

IHC INTERPRETATION OVERVIEW

Cellular Location

- Identifying where the antigen is located (cytoplasmic, membrane, or nuclear)

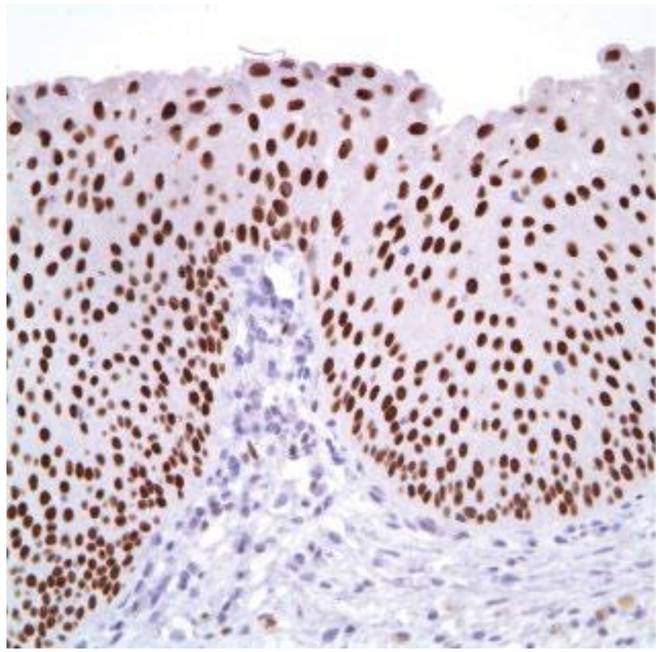
✓ Cytokeratin and vimentin should appear cytoplasmic

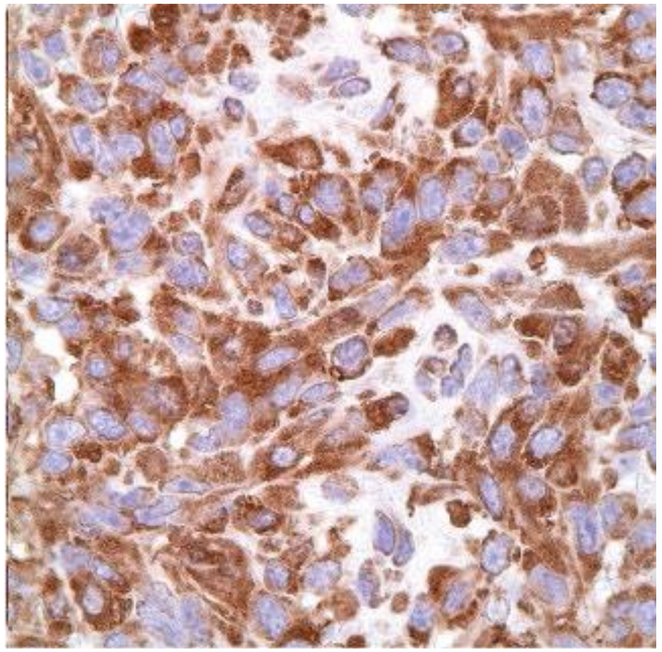
✓ Thyroid transcription factor 1 (TTF-1) should be nuclear

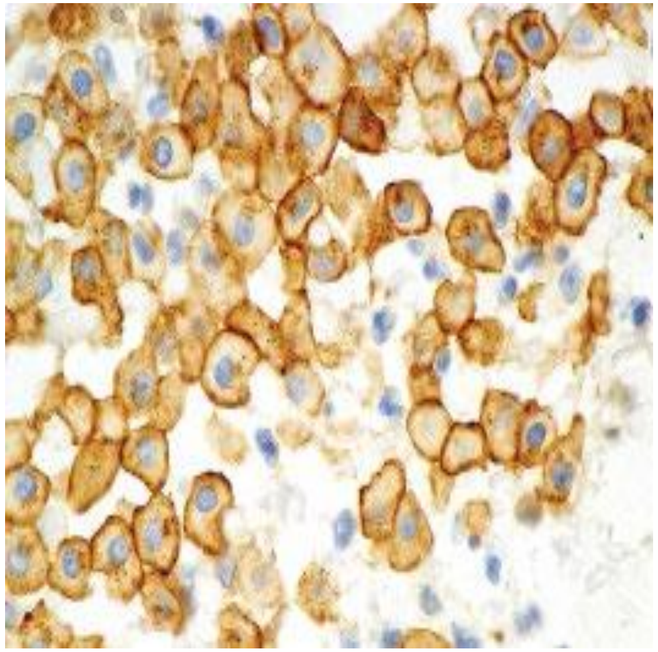
Distribution and Intensity

- Describing how the antigen is distributed within the tissue and the intensity of the labeling, alongside the percentage of positive cells

Cellular location: nuclear, cytoplasmic, and membranous, respectively







Positive Results

- A cut-off of “10%” positive cells → considering an IHC test positive
- Variable depending on the antigen and tumor type

True vs. False Positivity

- Distinguishing true positive from false positive is crucial
- True positives display cell-to-cell heterogeneity in labeling

- False positives often show homogeneous labeling without background reactivity in surrounding stroma

Background Staining in Immunohistochemistry

- Proper controls help differentiate between background staining and true positive results
- Background staining can arise from various sources:

1

Endogenous Enzyme Activity:

- Peroxidase → RBCs and some leukocytes. It can be inactivated using

✓ Hydrogen peroxide

✓ Formalin-fixed tissues generally exhibit lower endogenous enzyme activity compared to unfixed tissues

- Alkaline Phosphatase → intestine, bone → calcium chloride or manganese sulfate

2 Endogenous Avidin-Biotin Activity (EABA):

- A frequent issue with avidin-biotin detection systems
- Endogenous biotin is abundant → liver, kidney, brain → false-positive

- Blocking methods → using powdered milk, egg white → non-avidin-biotin systems may provide a more effective solution

3 Endogenous Pigments:

- In heavily melanotic tissues: melanin can mimic the color of the DAB reaction, complicating evaluations. Strategies to address this include:

✓ Counterstaining with Azure B: Melanin turns green while DAB remains brown

✓ Bleaching Slides: To reduce melanin interference

4 Other Causes of Background Staining:

- Poorly Fixed or Necrotic Tissue → variable background intensity
- Partially Detached Sections → May trap reagents, increasing background staining
- Suboptimal Antibody Concentration or Inadequate Antigen Retrieval → increased background
- Excessive Chromogen Incubation → background staining

FLOW CYTOMETRY

- Flow cytometry is used to assess the expression of cell surface proteins (cluster of differentiation [CD] markers)
- Appropriate samples for use in flow cytometry include blood and body fluids
- Flow cytometry can also be performed on samples from solid tissues that are aspirated as for a fine-needle cytology
- Samples should have sufficient cells

- Should be free of clots and contaminants

- Should be fresh and 48 hours is generally considered the maximal storage time for retaining adequate viability and antigen expression

- Cell viability may be prolonged by storage in:

✓ Cold tissue culture media / in buffers containing EDTA and a protein source such as fetal bovine serum

- Samples from neoplastic tissues with high cell turnover, such as some types of lymphoma should probably be analyzed within 24 hours of collection

- Commercially available antibodies → dog and cat samples

✓ T cell markers (CD3, CD5, CD4, CD8)

✓ B cell markers (CD21, CD79a)

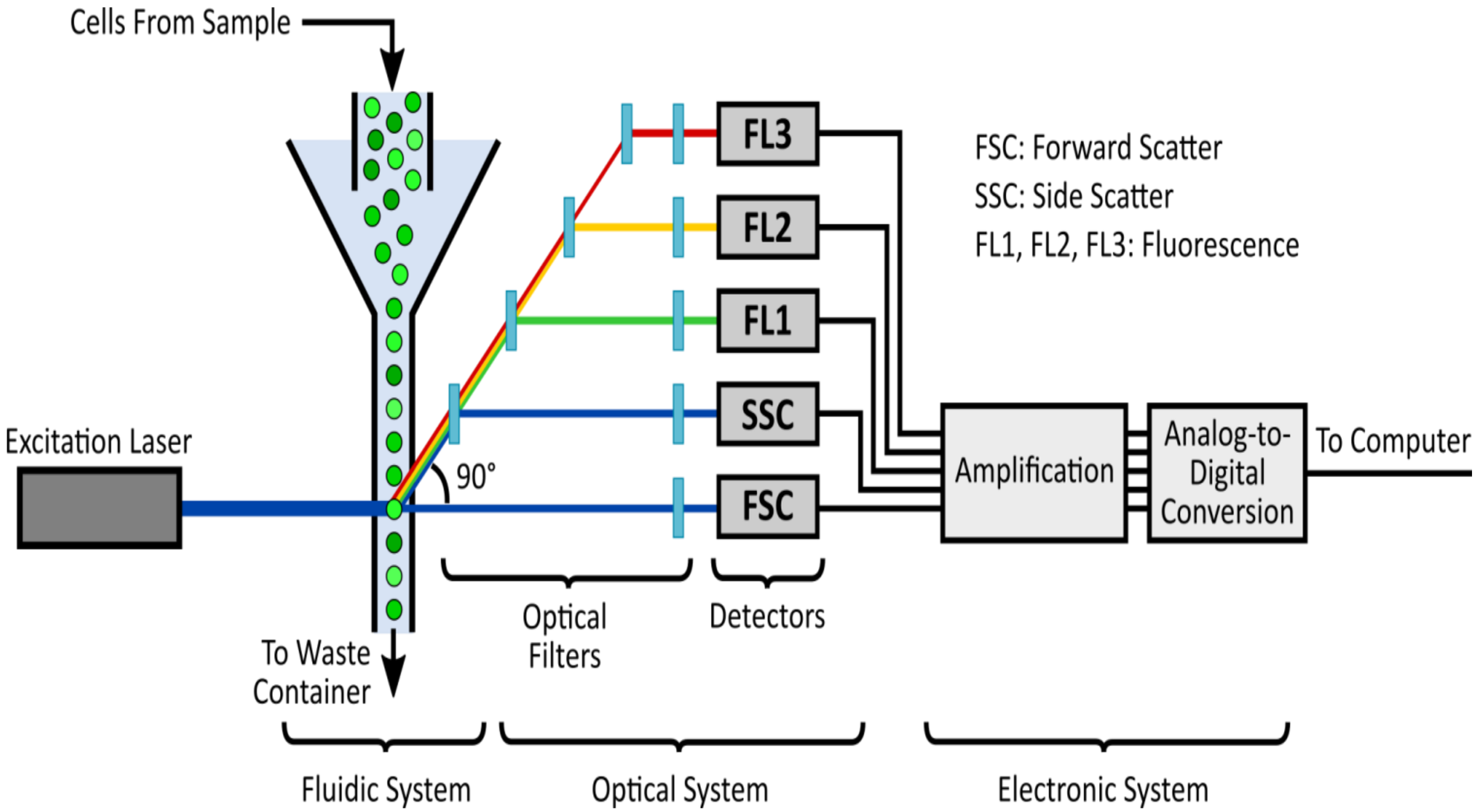
✓ Neutrophil and monocyte markers (CD11c, CD11d)

➢ Leukemia

➢ Lymphomas

Cell counting/sorting, Diagnosis, Prognosis

✓ Some lymphomas have much longer median survival time compared with other types

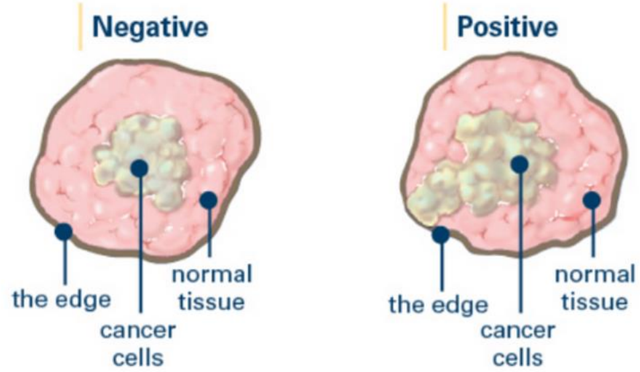

Cells From Sample
FL3
FL2
FL1
SSC
FSC
FSC: Forward Scatter
SSC: Side Scatter
FL1, FL2, FL3: Fluorescence
Excitation Laser
90°
Amplification
Analog-to-Digital Conversion
To Computer
To Waste Container
Optical Filters
Detectors
Fluidic System
Optical System
Electronic System

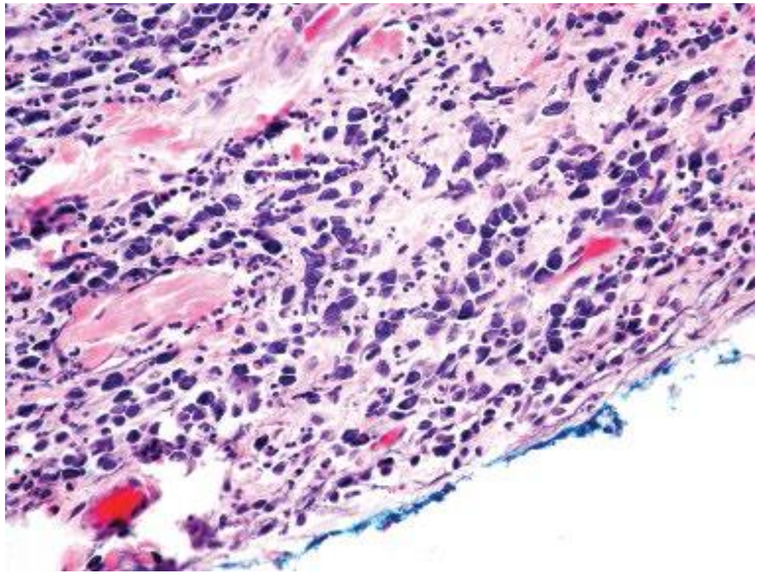
SURGICAL MARGIN EVALUATION

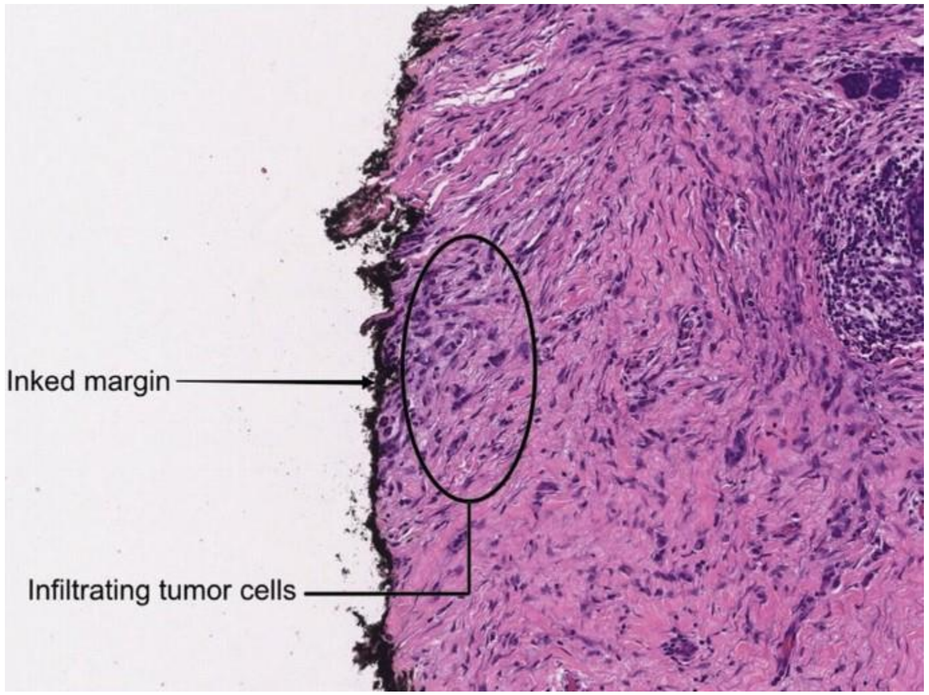
- Microscopic evaluation of surgical margins is a valuable to determine if a tumor has been completely excised
- Importantly, having clean (tumor-free) surgical margins on a histologic slide does not guarantee that the patient is free of tumor
- The appropriateness of the tumor-free margin size depends on the tumor type

- **Incomplete excision (or dirty margins):** when tumor cells are present along the surgical margin
- **Narrow (or close) excision:** when tumor cells are less than 2 mm from the surgical margin
- **Complete excision (or clean margins):** when tumor cells are more than 2 mm from the surgical margin
- Submission of regional lymph nodes → determining tumor spread
- Metastases can skip regional nodes → absence of tumor in regional nodes does not necessarily guarantee the patient is free of metastatic disease

SURGICAL MARGIN EVALUATION







Common TUMORS In Small Animals

TUMORS OF THE MAMMARY GLAND

Epidemiology

- Mammary neoplasms are very common in dogs, cats
- Tumors are much more common in intact females and rare in males
- The incidence rate is directly related to ovariectomy and the age at which this is undertaken
- In those countries where ovariectomy is commonly performed on dogs, there is a lower overall incidence of mammary neoplasms but a higher incidence of malignant mammary neoplasms
- In cats, the overall incidence of mammary tumors is low compared to dogs

Risk factors

Age

- Most mammary neoplasms occur in middle age to older dogs

Diet and obesity

- A diet high in red meat and dogs were obese at 1 year of age → increased risk of neoplasms
- There was a suggested association of longer survival times following removal of malignant mammary tumors in dogs fed a low-fat, high-protein diet

Clinical presentation

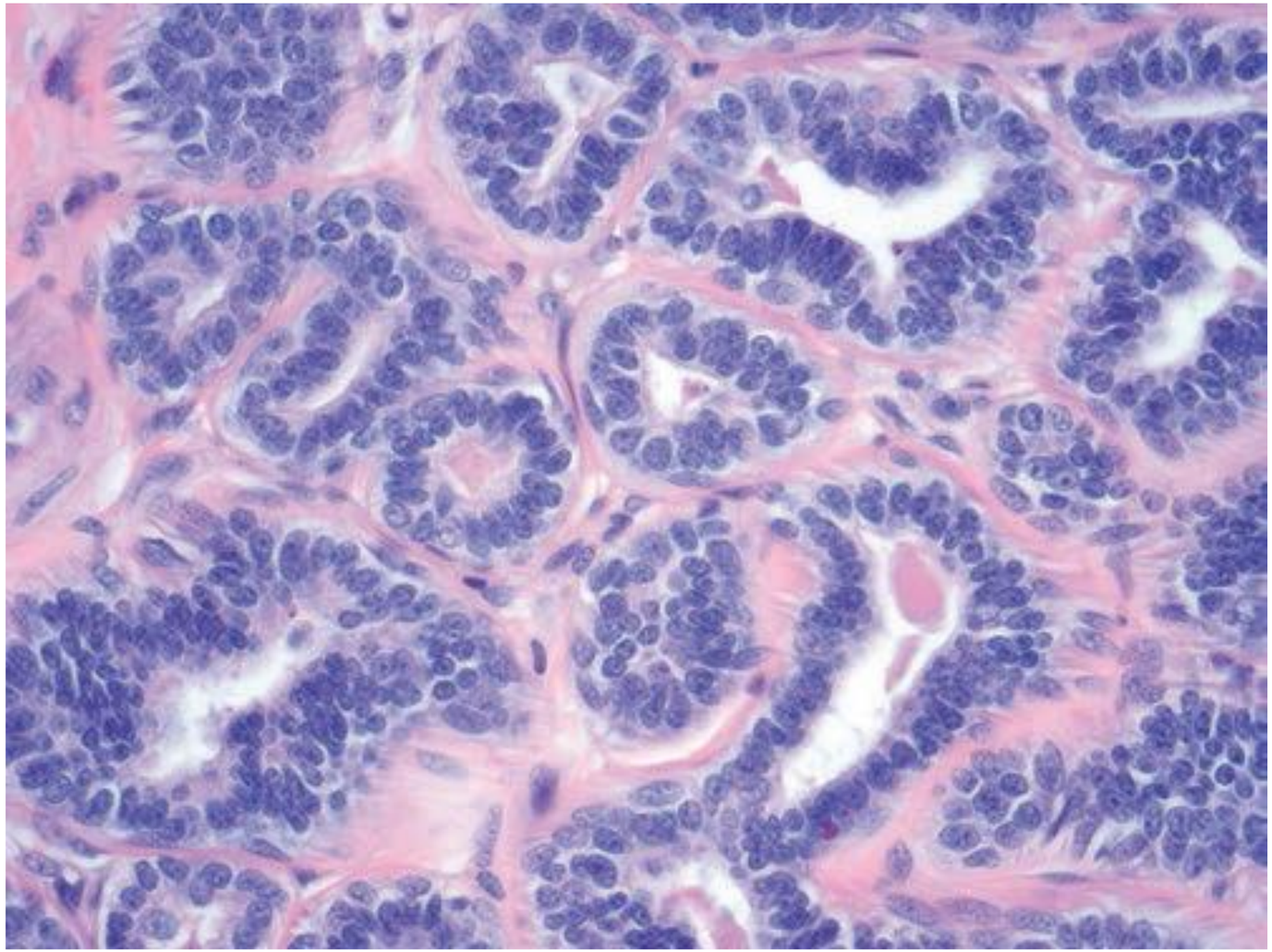
- The caudal mammary glands are most frequently affected
- Most dogs with neoplasms do not present with any signs of systemic illness
- If the tumors metastasize → cachexia and difficult respirations terminally

BENIGN TUMORS

ADENOMA

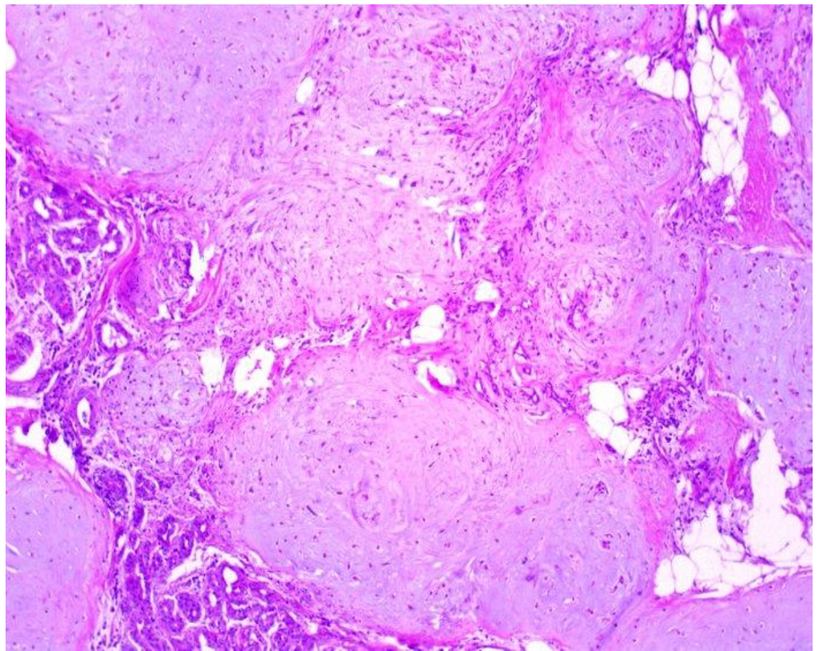
- The tubules are lined by a single layer of cuboidal to columnar cells
- Moderate amount of eosinophilic cytoplasm
- Nuclei are central, round to oval, and a small central nucleolus
- Fibrovascular stroma is scant to moderate
- Mitotic count is low

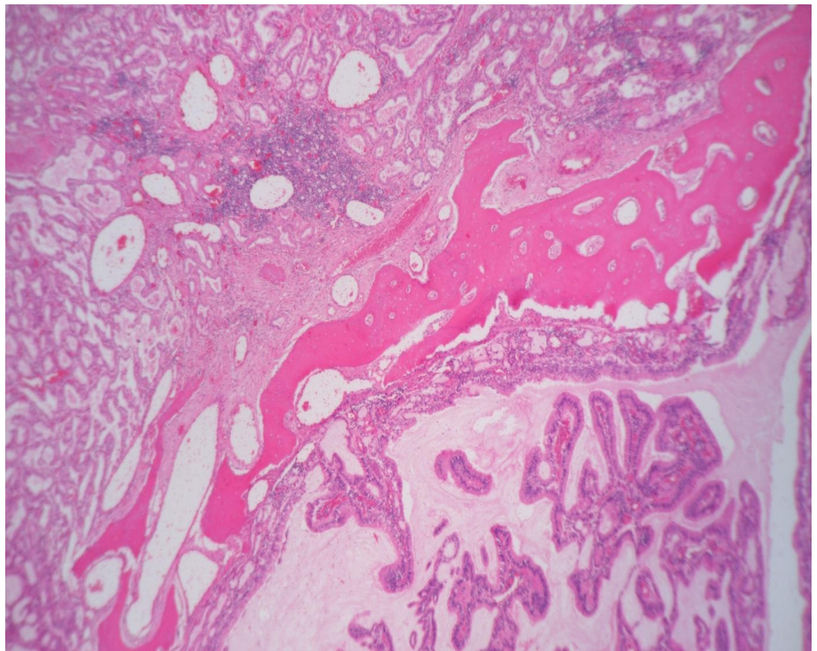
Mammary gland Adenoma



BENIGN MIXED TUMOR

- These neoplasms are always benign
- This neoplasm has both epithelial and myoepithelial proliferation
- Foci of cartilage and/or bone, and variable amounts of fibrous stroma



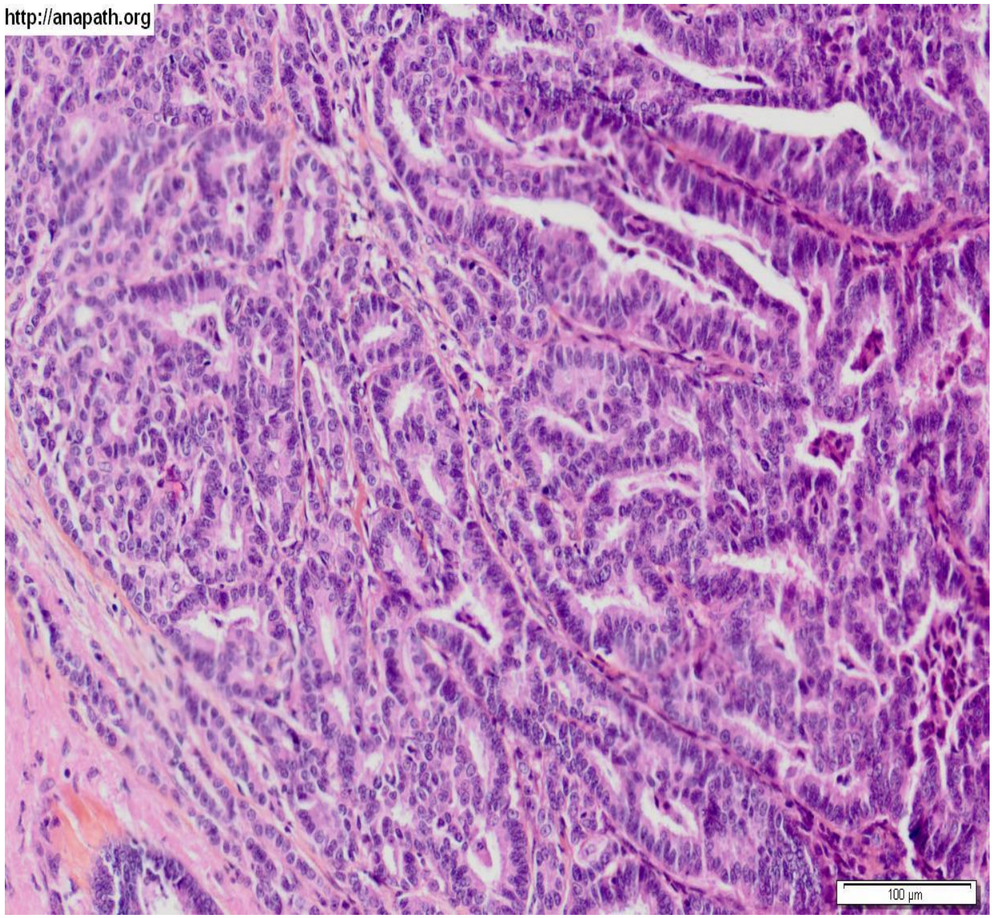


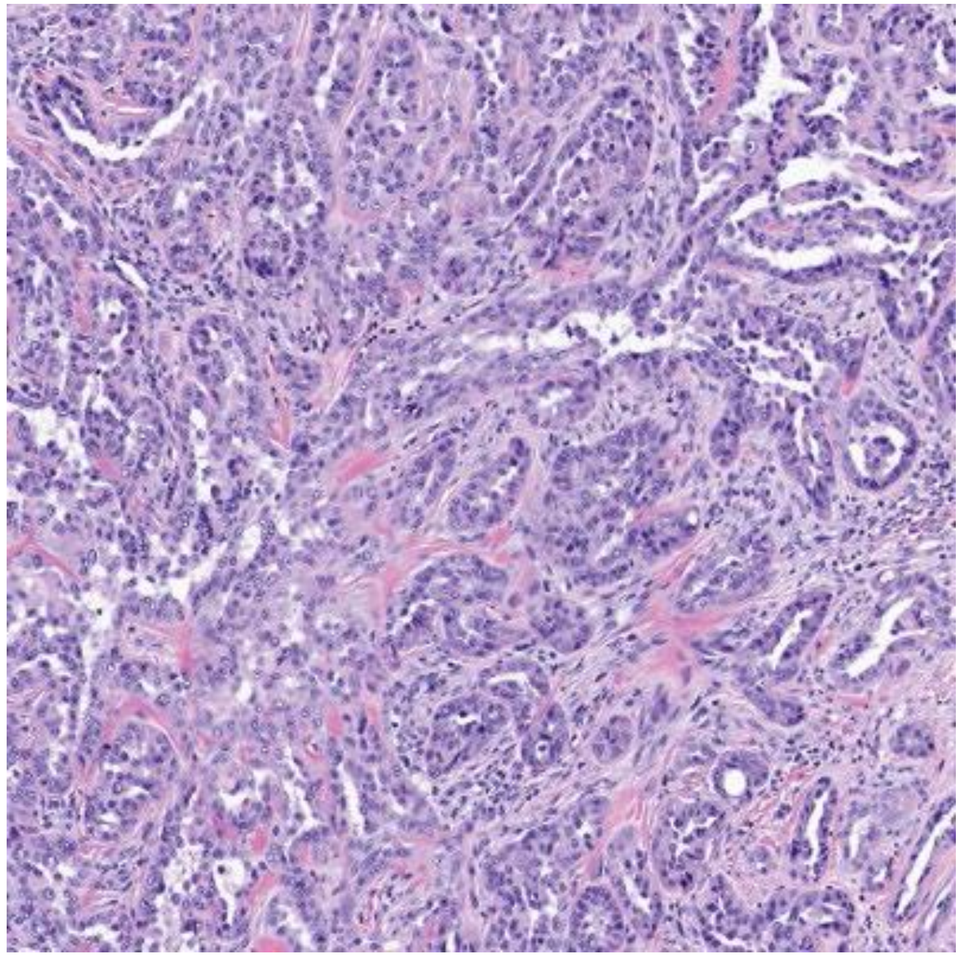
MALIGNANT TUMORS

A. TUBULAR CARCINOMA

- Common mammary carcinomas in dogs
- The cells are arranged predominantly as tubular or gland-like structures
- Nuclear pleomorphism is variable and nuclei may be hypochromatic
- Nucleoli may be single and very large or multiple and small
- Cells often have an eosinophilic cytoplasm and cell margins are relatively distinct

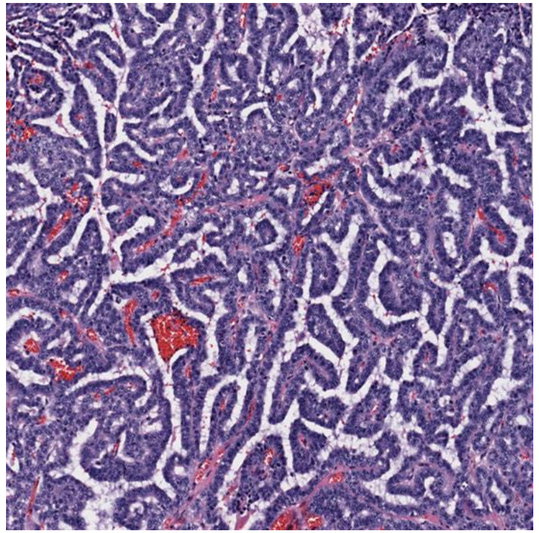
TUBULAR CARCINOMA





B. TUBULOPAPILLARY CARCINOMA

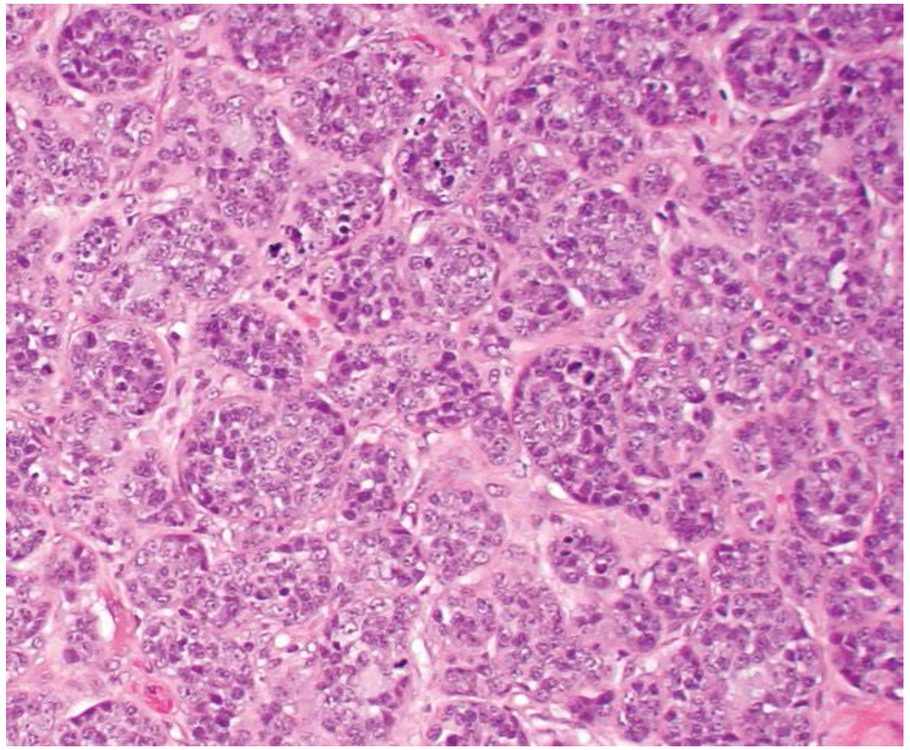
- There are papillae extending into tubular lumina and the papillary structures are predominant
- The remaining features are described above under tubular carcinoma
- Tubulopapillary carcinomas are more malignant than tubular carcinomas

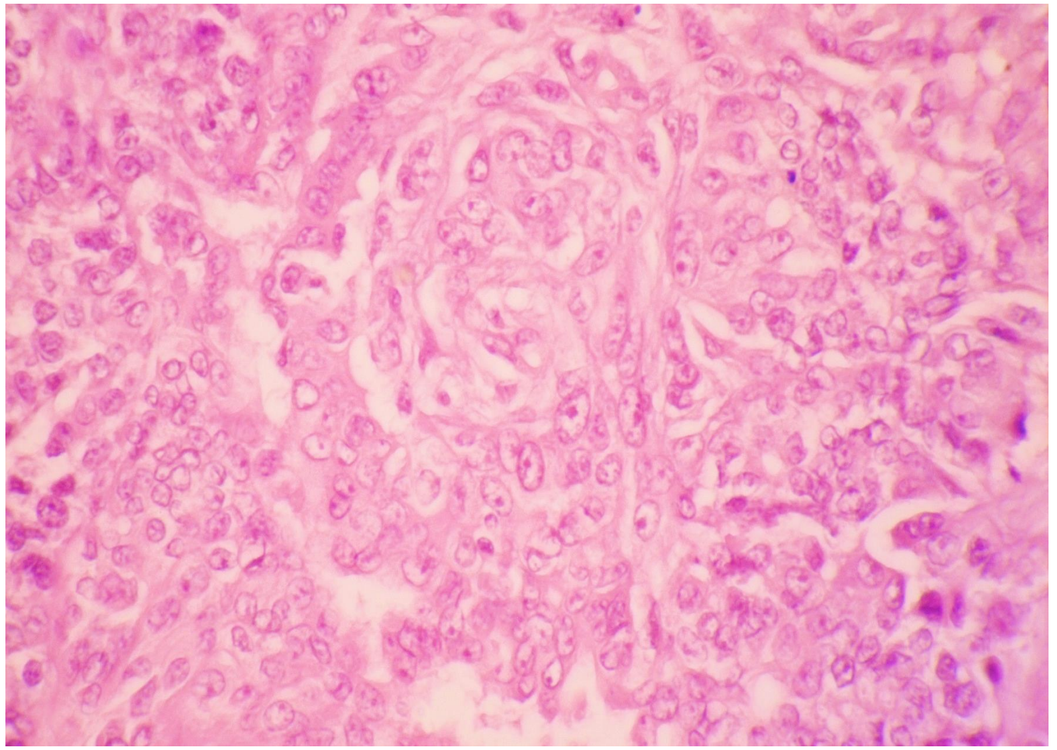


C. SOLID CARCINOMA

- The cells are arranged predominantly in solid sheets
- It is composed of irregularly sized lobules that are supported by a fine fibrovascular stroma
- Polygonal to oval cell with often poorly demarcated cell margins
- Scant, lightly eosinophilic to basophilic cytoplasm
- Oval, hyperchromatic nuclei with a single central nucleolus

- Moderate to severe Pleomorphism
- Variable number of mitoses
- Infiltration of neoplastic cells into lymphatic vessels is commonly





D. ANAPLASTIC CARCINOMA

- This is the most malignant of the mammary carcinomas
- The neoplastic cells are often individualized or in small nests
- Round, oval, or polygonal
- Moderate to abundant eosinophilic cytoplasm
- Round to oval nuclei with multiple nucleoli
- Severe pleomorphism
- Mitoses are common

- Vasculogenic mimicry → generation of microvascular channels by malignant tumor cells without endothelial cell participation

- Neoplastic cells are often present within lymphatic vessels with metastasis to regional lymph nodes and subsequently to the lung

- Immunohistochemistry: Cytokeratin 7

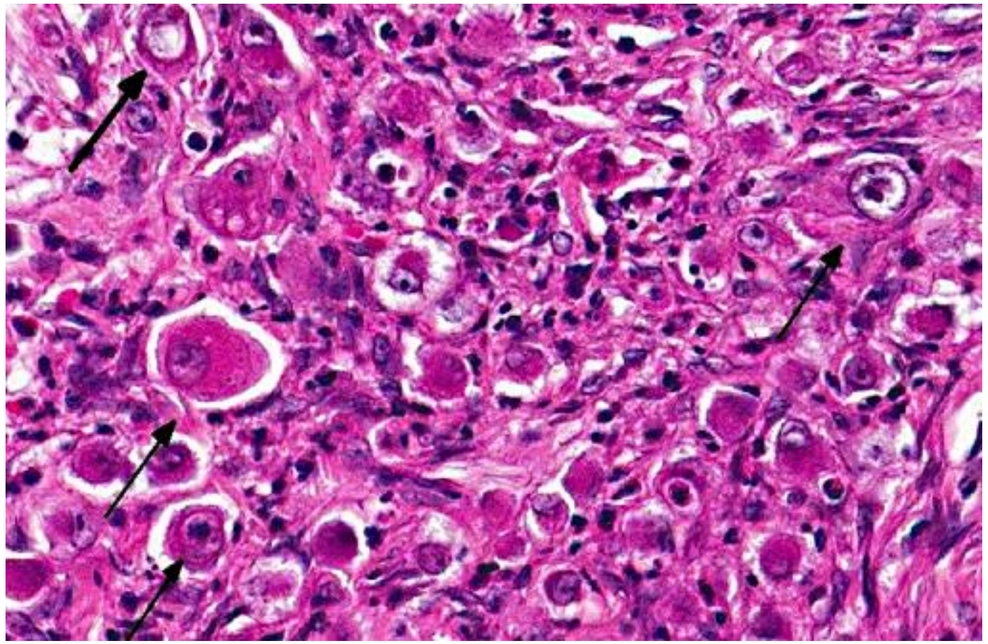


Table 17.5 Histologic grading of canine mammary neoplasms

A.

	Points	
A. Tubule formation[a]	1	Formation of tubules in >75%
	2	Formation of tubules in 10–75% (moderate formation of tubular arrangements admixed with areas of solid growth)
	3	Formation of tubules in (<10%) (minimal or no tubule formation)
B. Nuclear pleomorphism[b]	1	Uniform or regular small nucleus, and occasional nucleoli
	2	Moderate degree of variation in nuclear size and shape, hyperchromatic nucleus, presence of nucleoli (some of which can be prominent)
	3	Marked variation in nuclear size, hyperchromatic nucleus, often with one or more prominent nucleoli
C. Mitoses per 10 HPF[c]	1	0–9 mitoses/10 HPF
	2	10–19 mitoses/10 HPF
	3	≥20 mitoses/10 HPF

B. Histologic malignancy grade

Total score (A + B + C)	Grade of malignancy
3–5	I (low)
6–7	II (intermediate)
8–9	III (high)

Table 17.7 Staging of canine mammary tumors

	Tumor size	Lymph node status	Metastasis
Stage I	T1 < 3 cm	N0	M0
Stage II	T2 3–5 cm	N0	M0
Stage III	T3 > 5 cm	N0	M0
Stage IV	Any T	N1 (positive)	M0
Stage V	Any T	Any N	M1(metastasis)

Table 17.6 Grading of feline mammary carcinomas

A. Elston and Ellis system: Human

	Points	
A. Tubule formation	1	Formation of tubules in >75%
	2	Formation of tubules in 10–75%
	3	Formation of tubules in (<10%)
B. Nuclear pleomorphism	1	Uniform or regular small nuclei
	2	Moderate increase and variability in nuclear size and shape, vesiculation
	3	Marked variation in nuclear shape and size, vesicular chromatin
C. Mitoses per 10 HPF	1	0–8 mitoses/10 HPF
	2	9–16 mitoses/10 HPF
	3	≥17 mitoses/10 HPF
Points total (A+B+C)	Grade	
3–5	I	Well differentiated
6–7	II	Moderately differentiated
8–9	III	Poorly differentiated

B. Novel grading system: Feline[a]

Histologic features		Score
Lymphovascular invasion	Absent	0
	Present	1
Nuclear form[b]	<5% abnormal	0
	≥5% abnormal	1
Mitotic count (10 consecutive HPF)	≤62	0
	>62	1
Total score	Grade	
0	I	Low grade
1	II	Intermediate grade
2–3	III	High grade

[a]The human grading system has been revised and used to grade feline mammary tumors; a novel system has also been proposed.[2]

Table 17.8 Staging of feline mammary tumors

	Tumor size	Lymph node status	Metastasis
Stage 1	T1 < 2 cm	N0	M0
Stage 2	T2 2–3 cm	N0	M0
Stage 3	T1 or T2	N1 (positive)	M0
	T3 > 3 cm	N0 or N1	M0
Stage 4	Any	Any	M1

MAST CELL TUMORS

General considerations

- Mast cell (MCTs) are very common in dogs, less common in cats
- The great majority of MCTs occur as solitary nodules in the skin

Incidence, age, breed, and sex

- Cutaneous MCTs are the most frequently diagnosed malignant
- The risk of developing cutaneous MCTs increases with age
- The mean age 9 years

Clinical characteristics

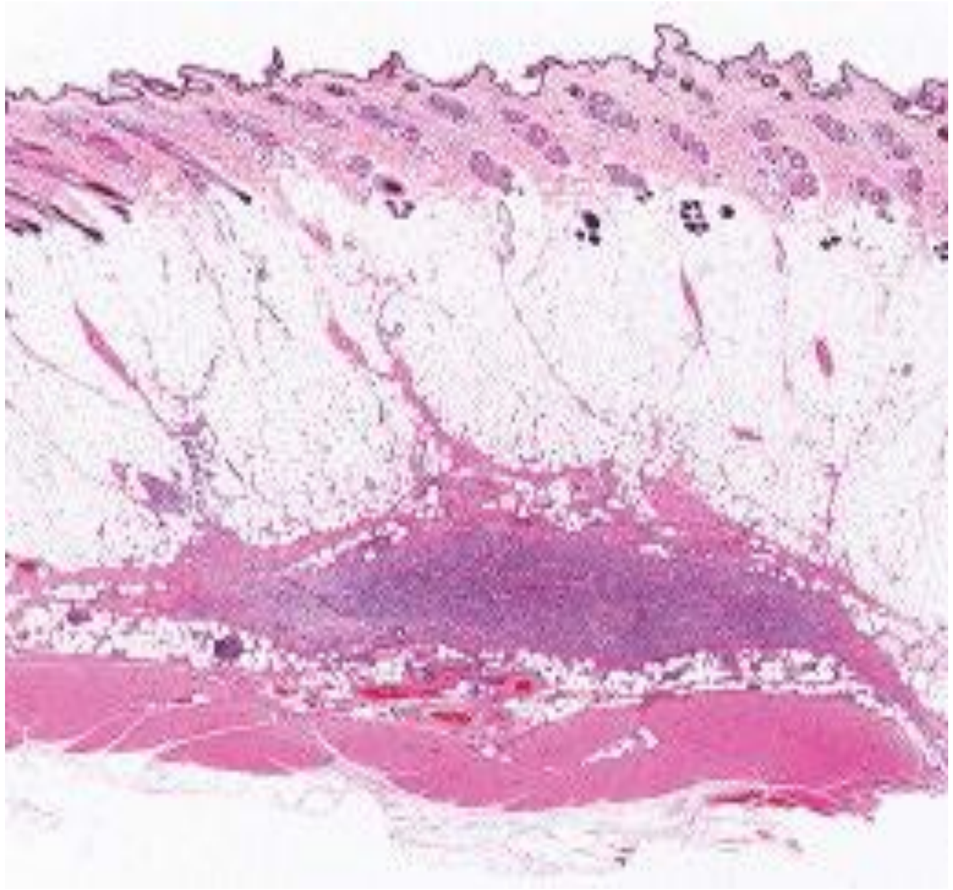
- Local and systemic paraneoplastic signs are frequently seen → release of histamine, heparin, proteases
- Some dogs, manipulated during examination → degranulation of neoplastic mast cells → erythema and wheal
- Local swelling, erythema, and pruritus
- Gastrointestinal ulceration and hemorrhages, vomiting, anorexia, abdominal pain
- Secondary anemia → iron deficiency from gastrointestinal bleeding

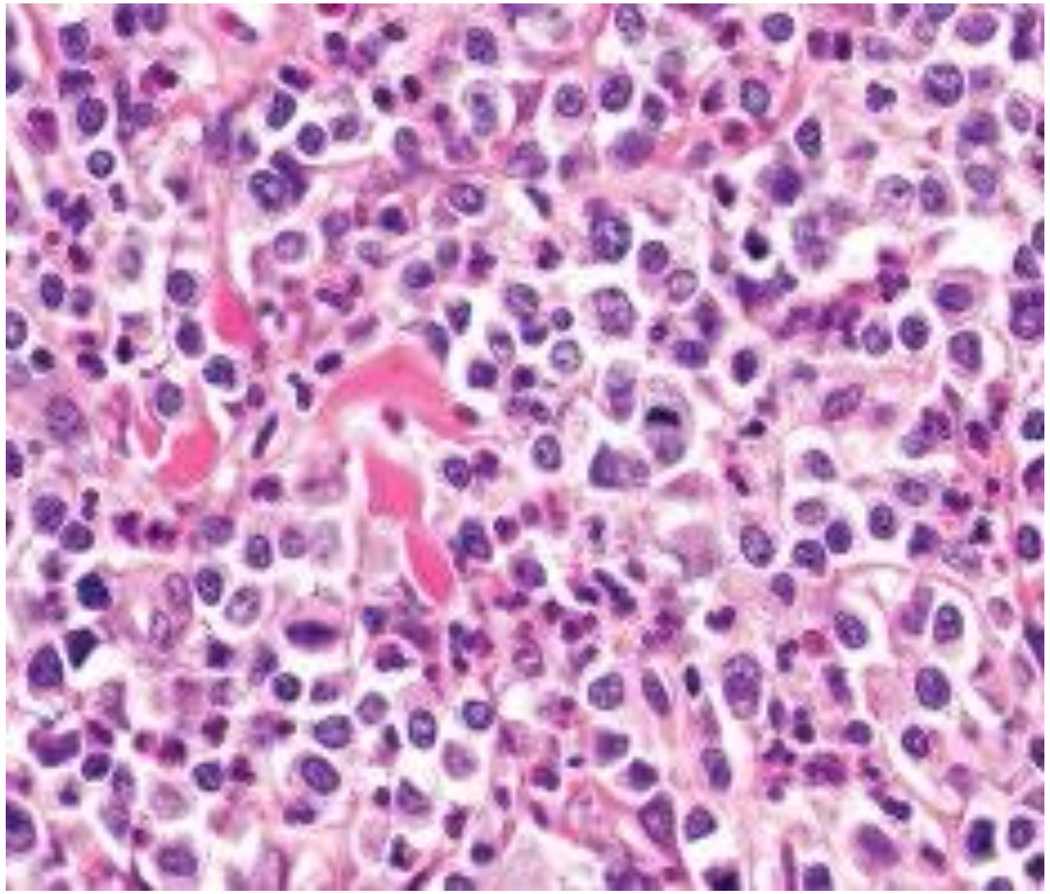
Sites and gross morphology

- Skin is the most common site in dogs
- Highly variable → hairless, raised, erythematous tumors
- Ulcerated and pruritic MCTs → tend to grow rapidly
- Subcutaneous MCTs → any place on the body, but more at legs, back, and thorax → often soft, fleshy masses

Histological features

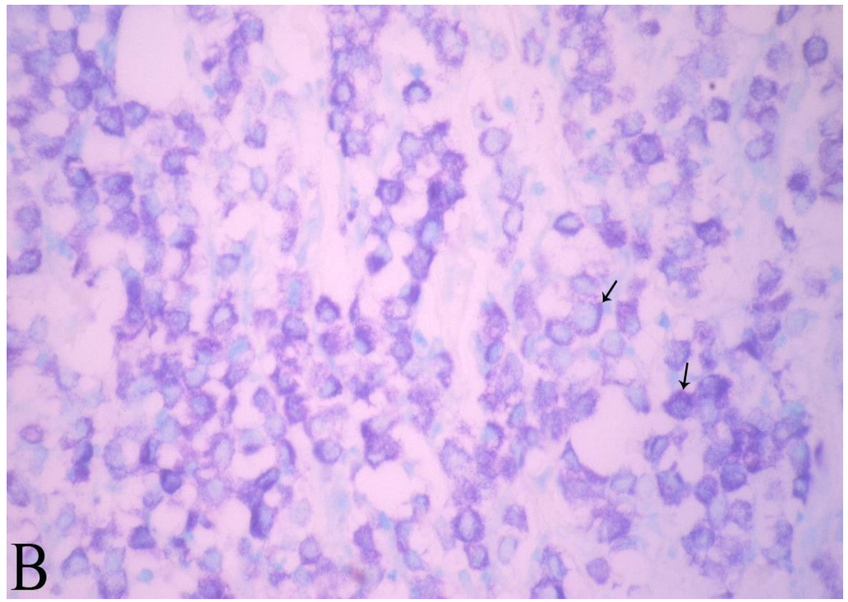
- **Cutaneous** MCTs are located in the epidermis or dermis
- **Subcutaneous** MCTs are located in the subcutis and are surrounded by adipose tissue
- Round to polygonal cells
- Round central to slightly eccentric nuclei
- A moderate amount of pale pink cytoplasm contains granules
- Eosinophils are almost always found in canine MCTs
- Collagenolysis, edema, necrosis, lymphocytic inflammation are often seen in MCTs





- Granules stain with toluidine blue staining
- Granules stain reliably with **Wright's stain**

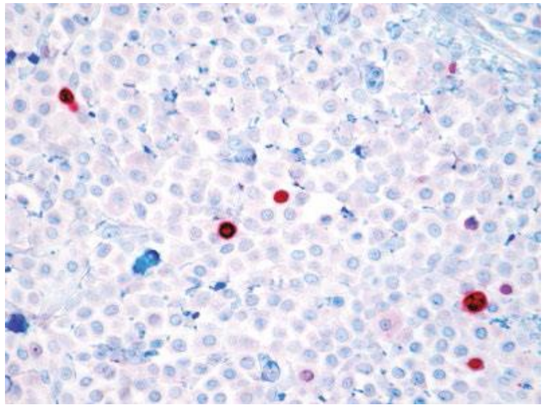
- Granules occasionally do not stain with Diff-Quik, especially in cats
- Round cell tumor stained with Diff-Quik → Before ruling out MCT → Wright stain

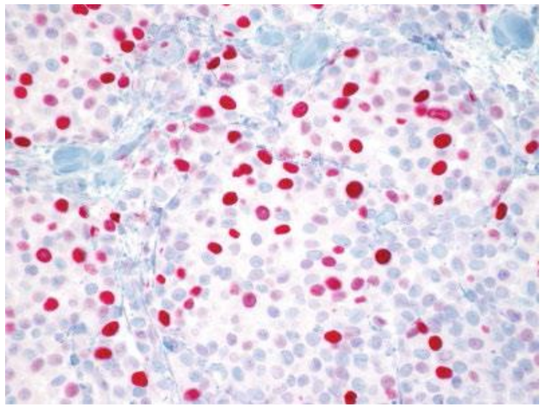


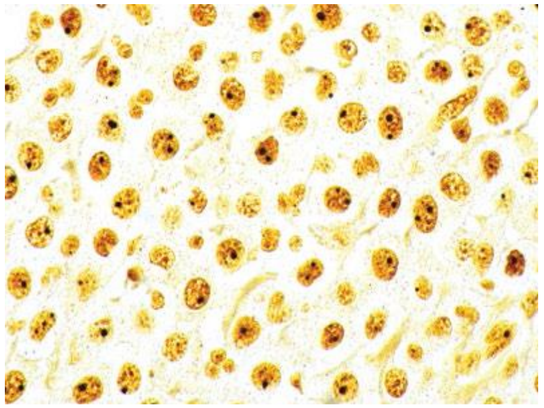
- **Immunohistochemistry**

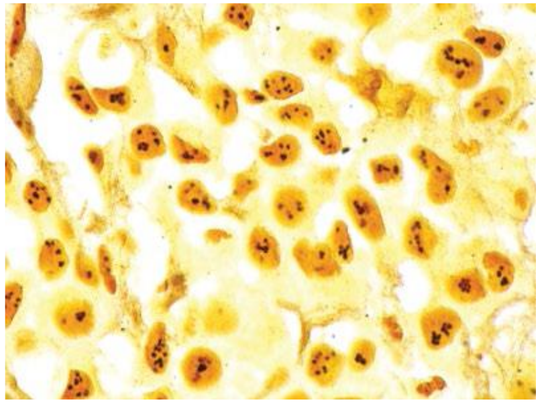
✓ Ki67

✓ Panel- Ki67, c-KIT, AgNOR (prognostic panel)









MARGIN EVALUATION

- Evaluation of tumor margins is an important while challenging part of the prognostic evaluation

- One of the most difficult aspects of this is differentiating neoplastic from non-neoplastic mast cells

- Many cutaneous MCTs have a reactive halo composed of:

✓ Edema, inflammatory cells, mast cells, and stromal cells surrounding newly formed capillaries

➢ Single mast cells as well as clusters of five or more mast cells, so-called satellites, can be found within this halo

✓ Currently, satellites (clusters) → neoplastic cells

✓ Single, well-differentiated mast cells → inflammatory

- CD25 has been used successfully to identify neoplastic mast cells in human

- But this has not proven to be definitive in canine tumors

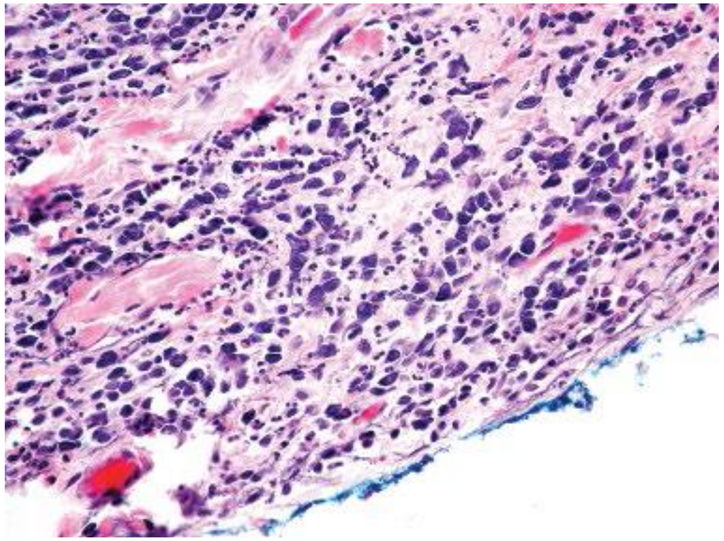
- Numeric margins:

✓ M1 = margin infiltrated

✓ M2 = margin is close, within 1–2 mm

✓ M3 = margin is clean 2–5 mm

✓ M4 = margin is clean >5 mm



STAGING

- The most important prognostic tool → using clinical criteria, histopathology, cytology

STAGE 1:

- Solitary tumors that are confined to the dermis without lymph node involvement **OR** <2 cm

STAGE 2:

- Tumors are confined to the dermis, but the regional lymph nodes are affected **OR** 2-4 cm

STAGE 3:

- Multiple dermal tumors or large infiltrating tumors with or without regional lymph node involvement **OR** ≥4 cm, And/or lymph node metastasis

STAGE 4:

- Distant metastases

- Unfortunately, a number of studies have reported various problems with the current staging system

✓ One study found no difference in outcome between stage 1 and stage 3 dogs, while stage 2 dogs had a worse prognosis than stage 3 dogs

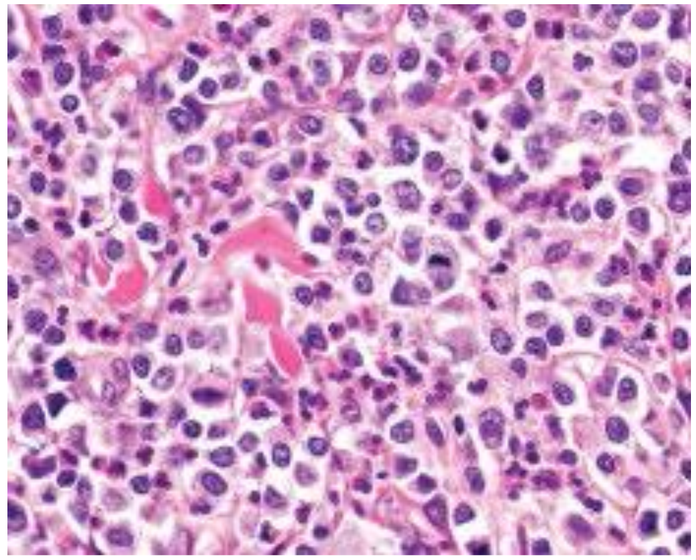
- Buffy coat smears are not useful for the diagnosis or staging of canine MCTs:

✓ Higher numbers of mast cells were seen on the buffy coat smears of dogs with non-MCT diseases compared to dogs with MCT

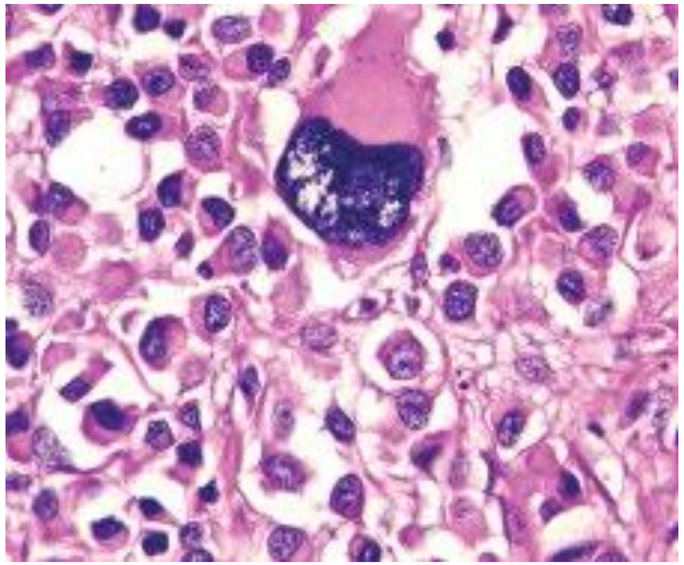
GRADING

- Two-tier scheme that classifies MCTs as **low grade** or **high grade**
- High-grade MCTs is based on the presence of any one of the following criteria:

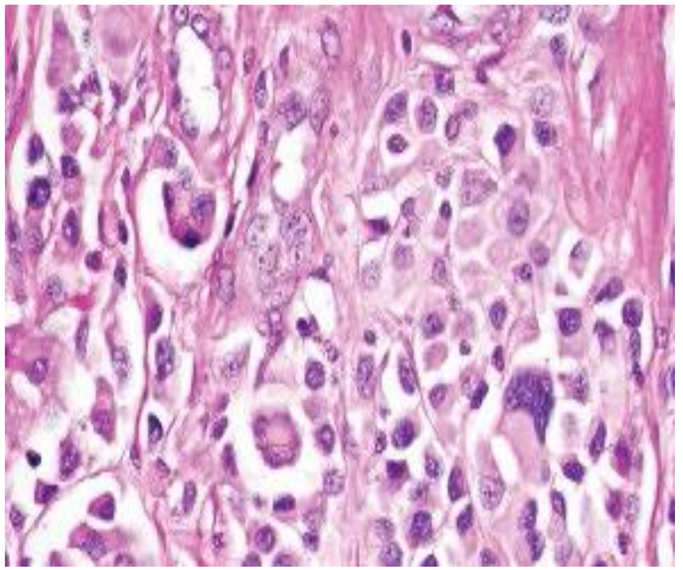
✓ At least 7 mitotic figures in 10 HPF



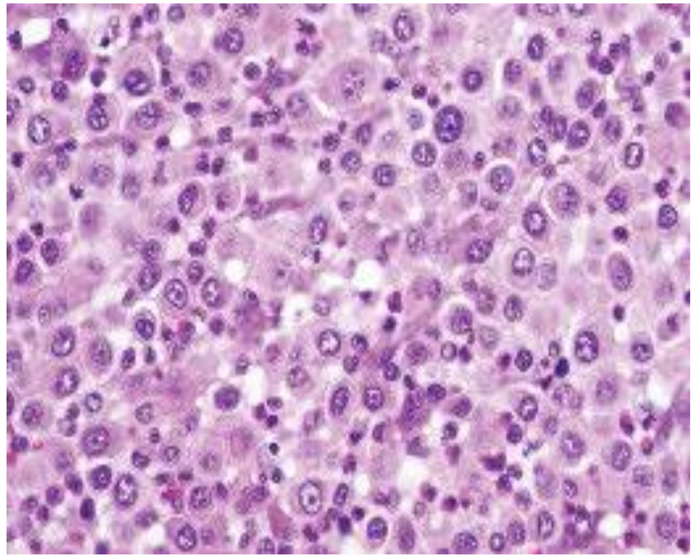
✓ At least 3 bizarre nuclei in 10 HPF



- ✓ At least 3 multinucleated (3 or more nuclei) cells in 10 HPF



- ✓ Karyomegaly (nuclear diameters of at least 10% of neoplastic cells vary by at least two times)



FELINE MAST CELL TUMORS

- MCTs in cats are cutaneous or visceral
- MCTs in the skin of cats are not presently subdivided into cutaneous and subcutaneous

Incidence, age, breed, and sex

- The majority of cutaneous MCTs occur over 4 years → mean age is 10 years
- Visceral MCTs are much more common in cats than in dogs → spleen, liver, intestines

Clinical characteristics

- Diarrhea → MCT in gastrointestinal tract
- Anemia → secondary to inflammatory disease or gastric ulceration
- Maybe secondary to erythrophagocytosis by neoplastic mast cells
  - Other causes of anemia should be excluded before diagnosing a paraneoplastic syndrome as the cause of anemia in cats with MCTs
- Mastocytemia associated with MCT is more common in cats than dogs
- Buffy coat smear can be included in the routine examination of feline MCTS

Histological features

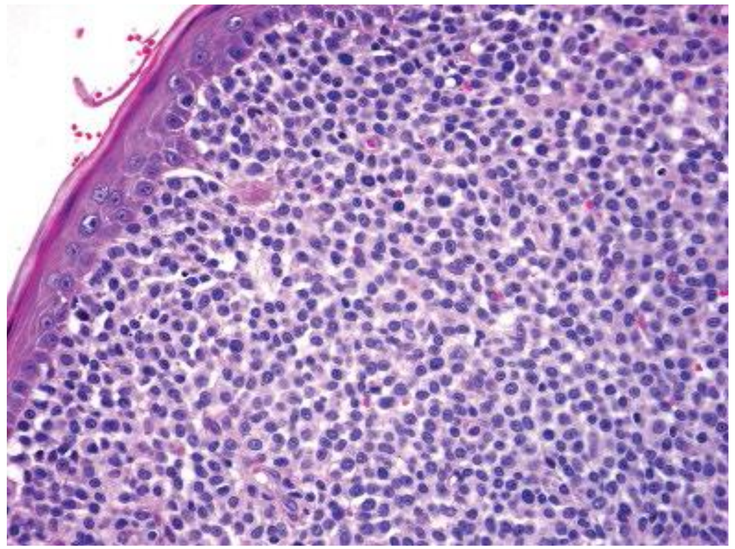
- Cutaneous MCTs are located superficially in the dermis and are sharply demarcated

1. Well-differentiated

- Neoplastic cells resemble normal mast cells with no or very little pleomorphism

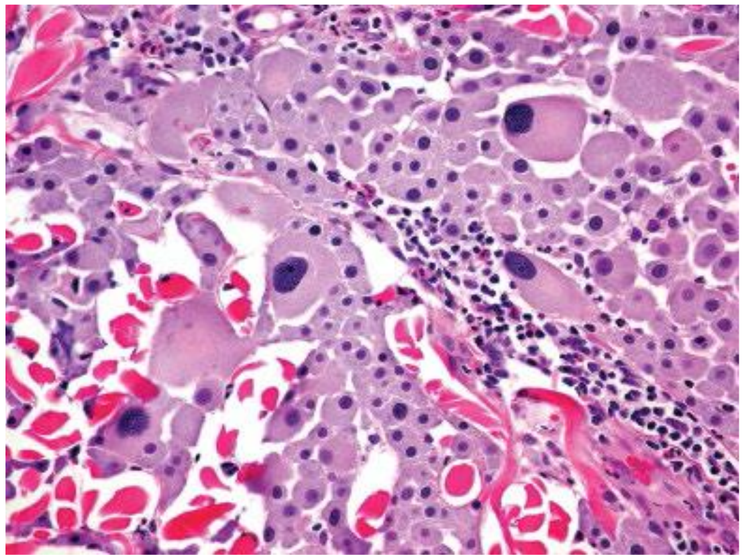
- Rare mitotic figures

- Eosinophil infiltrates are rare to absent



2. Pleomorphic

- Neoplastic mast cells are generally larger, with eccentric nuclei and prominent nucleoli
- Giant cells with bizarre or multinucleated nuclei may also be present
- These pleomorphic cellular and nuclear features do not correlate with malignant behavior
- Often infiltrated by large numbers of eosinophils

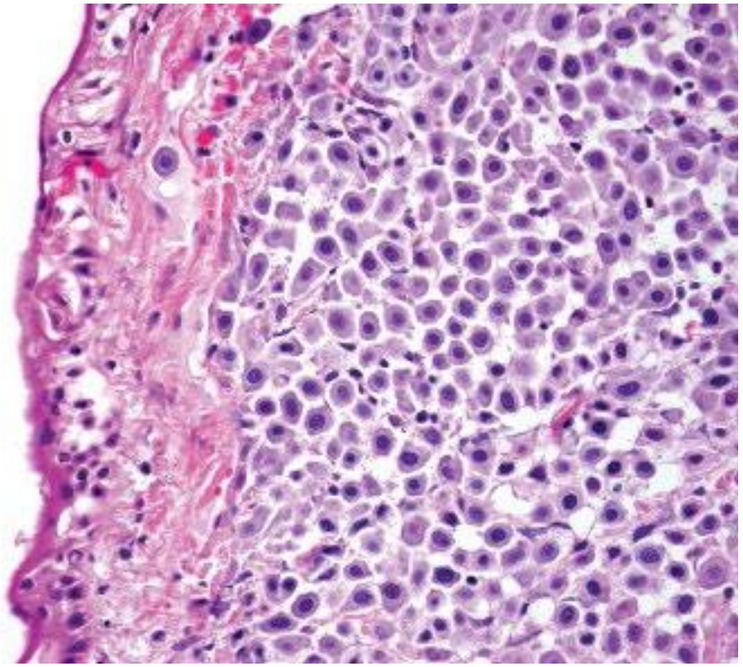


3. Atypical

- They consist of large, polygonal to round neoplastic mast cells with abundant amphophilic cytoplasm

- Large, hypochromatic, slightly indented nuclei

- Eosinophils and lymphocytes tend to be more numerous in atypical MCTs than in other types



- Collagenolysis is not a prominent feature in feline MCTs as in canine tumors

- There is no established histologic grading system for feline MCTs

✓ These are benign and surgical excision is usually curative

✓ A high MC and/or low cytoplasmic granularity suggest an aggressive course

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Immunohistochemical

- Presently there is no immunohistochemical stain that is highly specific and sensitive for mast cell tumors in cats

LYMPHOMA

Incidence, age, breed, sex, and site

- Lymphoma is more commonly seen in dogs and cats → mean age 10 years

Gross morphology

- Variability in the gross appearance of cutaneous lymphoma
- It can show ulceration, crusting, and alopecia

Histological features

- Cutaneous lymphoma has been divided into **epitheliotropic** and **non-epitheliotropic** forms

EPITHELIOTROPIC TUMORS

- The neoplastic cells are T cells
- Epidermis and adnexal epithelium
- Infiltrates are seen in hair follicular and apocrine gland epithelial cells → important feature to distinguish lymphoma from inflammation or other round cell tumors
- Neoplastic lymphocytes can range from small and well differentiated to large

- Diffusely or in small clusters

- Mitotic activity in this form is usually low

- Sézary syndrome → when simultaneous:

✓ Epitheliotropic lymphoma

✓ Involvement of the lymph nodes

✓ Involvement peripheral blood

NON-EPITHELIOTROPIC TUMORS

- Non-epitheliotropic tumors are of B- or T-cell origin
- Predominantly in the dermis

- There can be mild epidermal infiltrates, but adnexa are not affected

- Sheets and clusters

- Lymphoblastic forms are the most common phenotypes of non-epitheliotropic lymphoma in dogs and cats

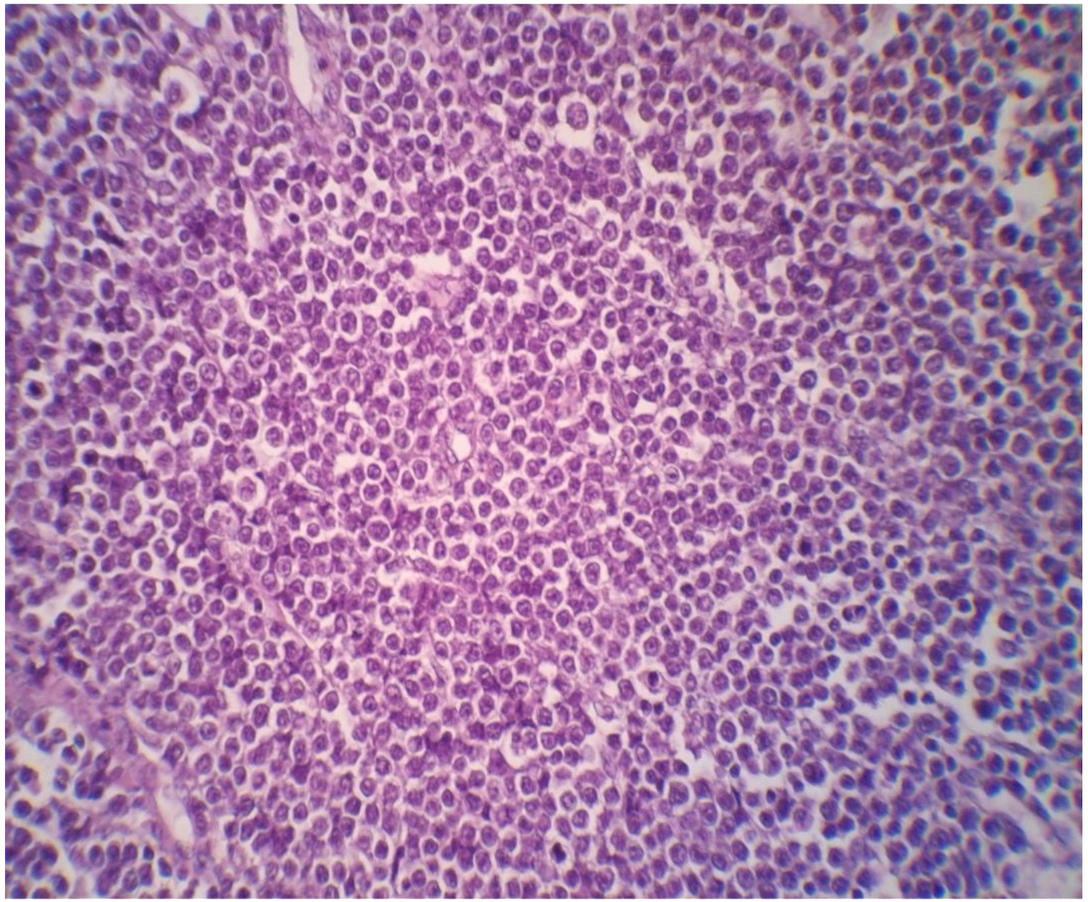
- Mitotic indices vary from moderate to high

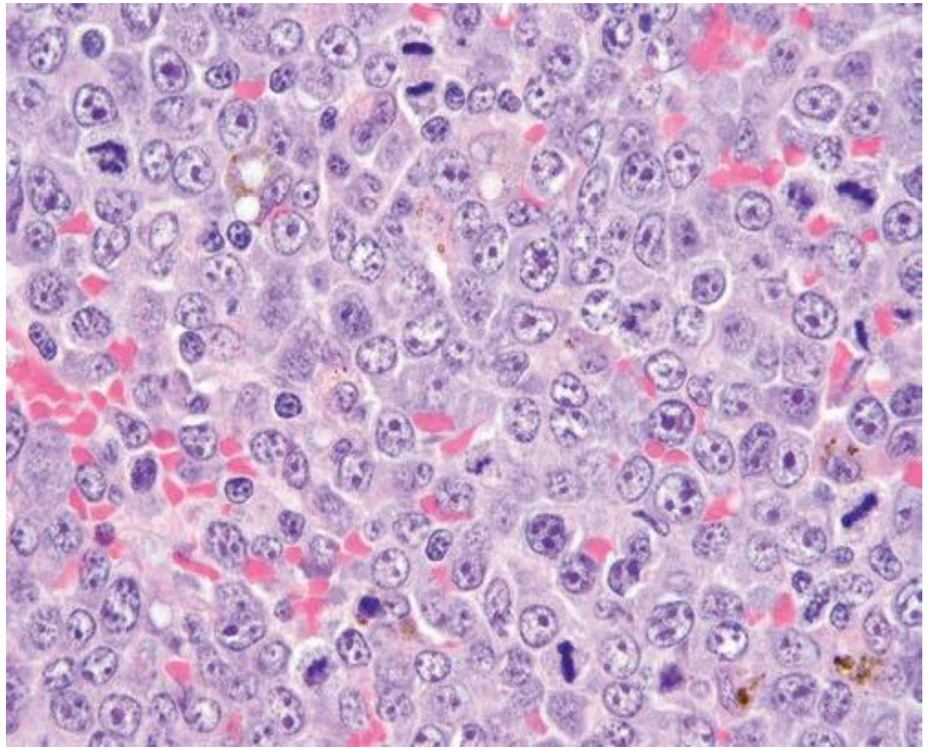
VISCERAL LYMPHOMA

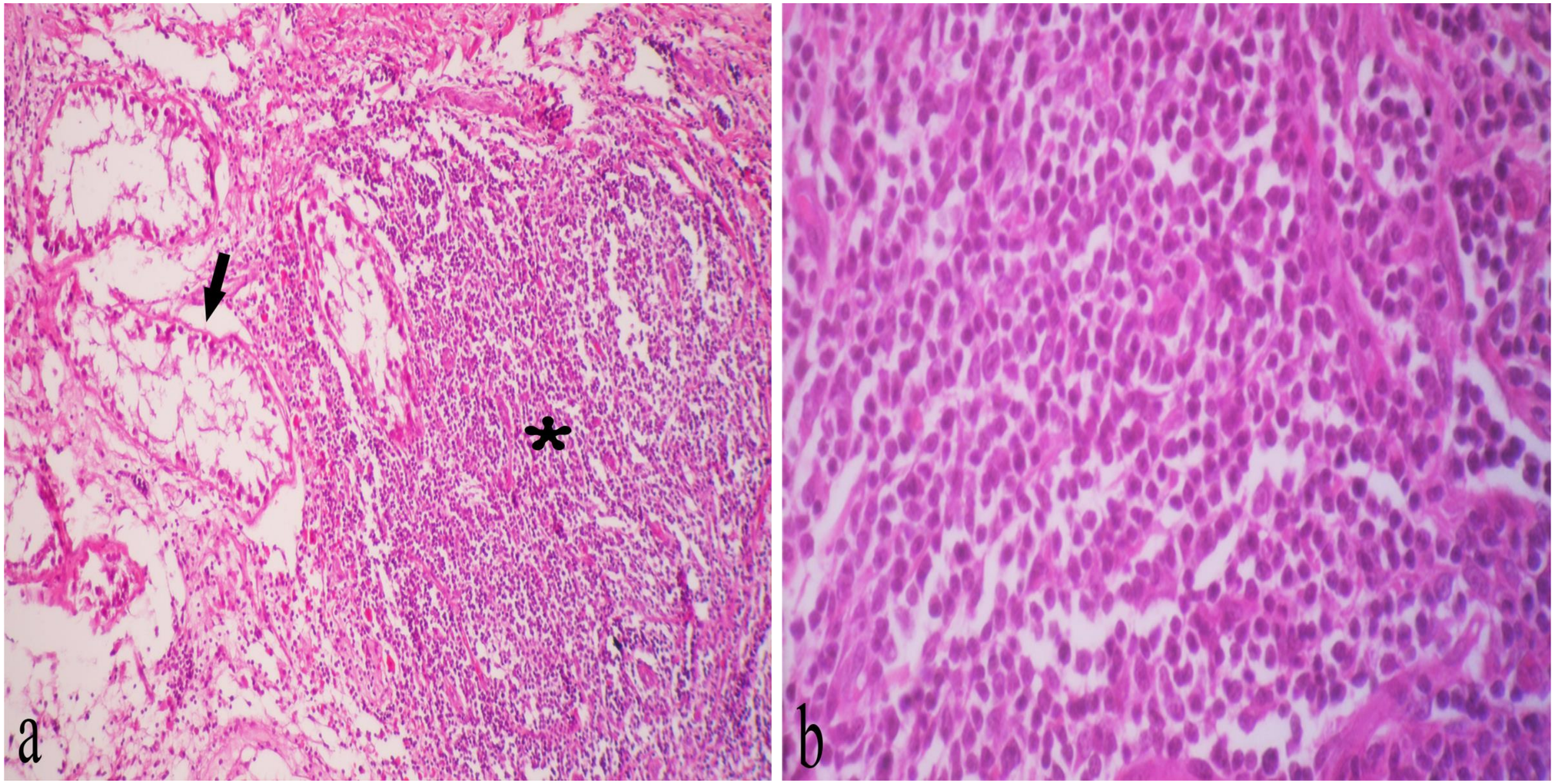
- Disruption of normal tissue architecture
- Sheaths of medium-sized or large lymphocytes
- Low to high mitotic figures

Growth and metastasis

- Cutaneous and Visceral lymphoma tends to be progressive
- Non-epitheliotropic lymphomas → more aggressive and rapidly progressive



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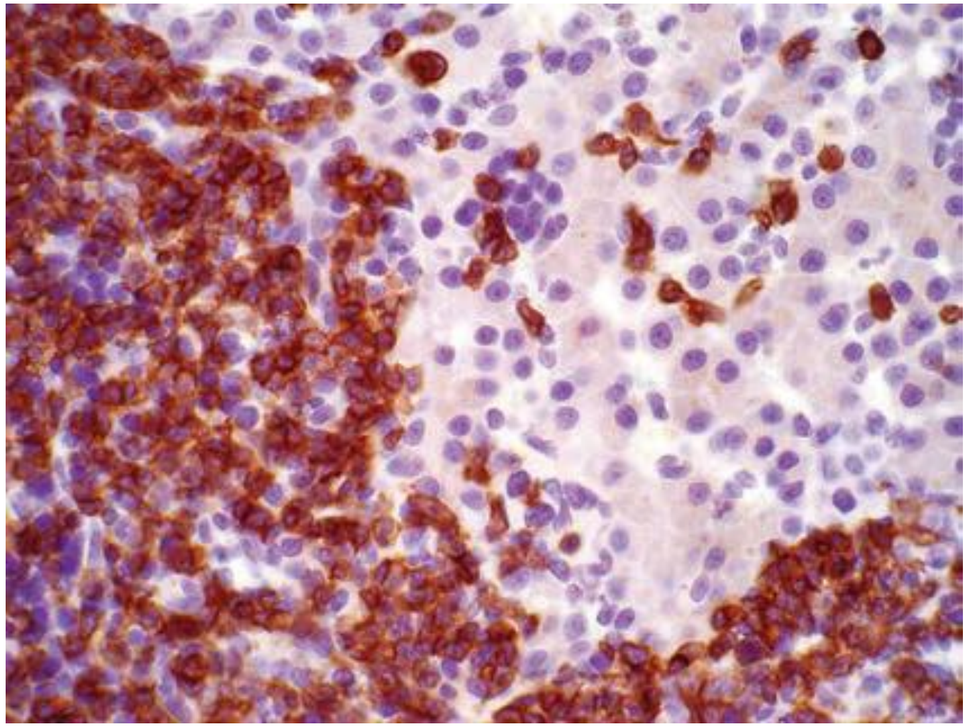
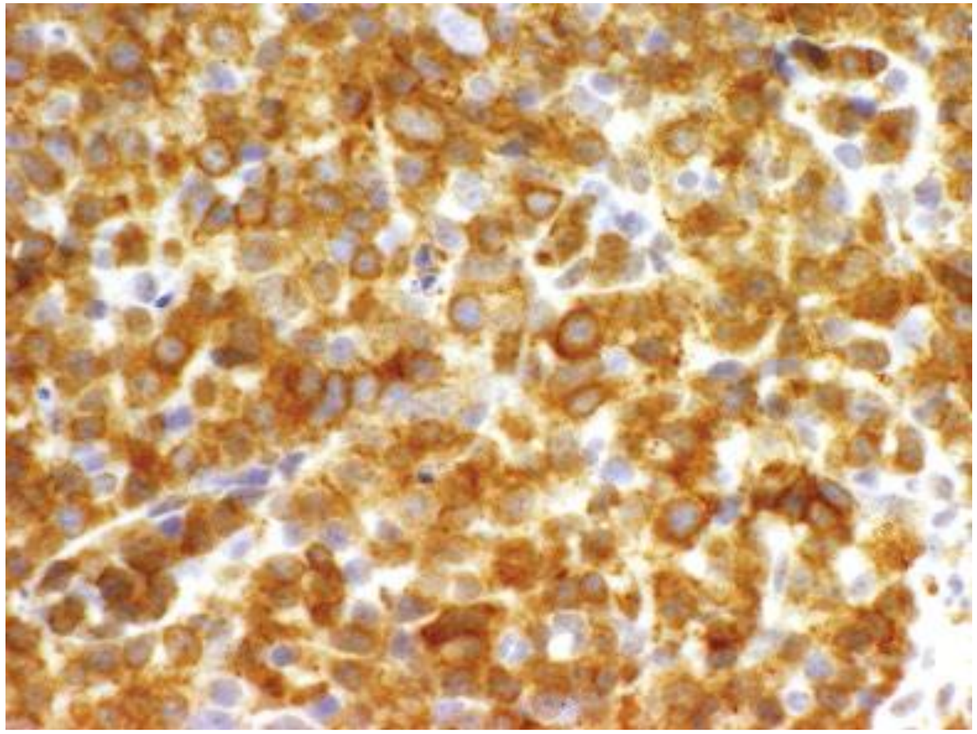
Immunohistochemistry

T cells → CD3



B cells → CD20, CD79a



CANINE TRANSMISSIBLE VENEREAL TUMOR (TVT)

- This tumor is unusual in many regards
- It is of unknown cell origin
- Transmitted by physical transplantation between dogs
- The chromosome counts of neoplastic cells vary from 57 to 64 (averaging 59) rather than the normal 78 found in other cells

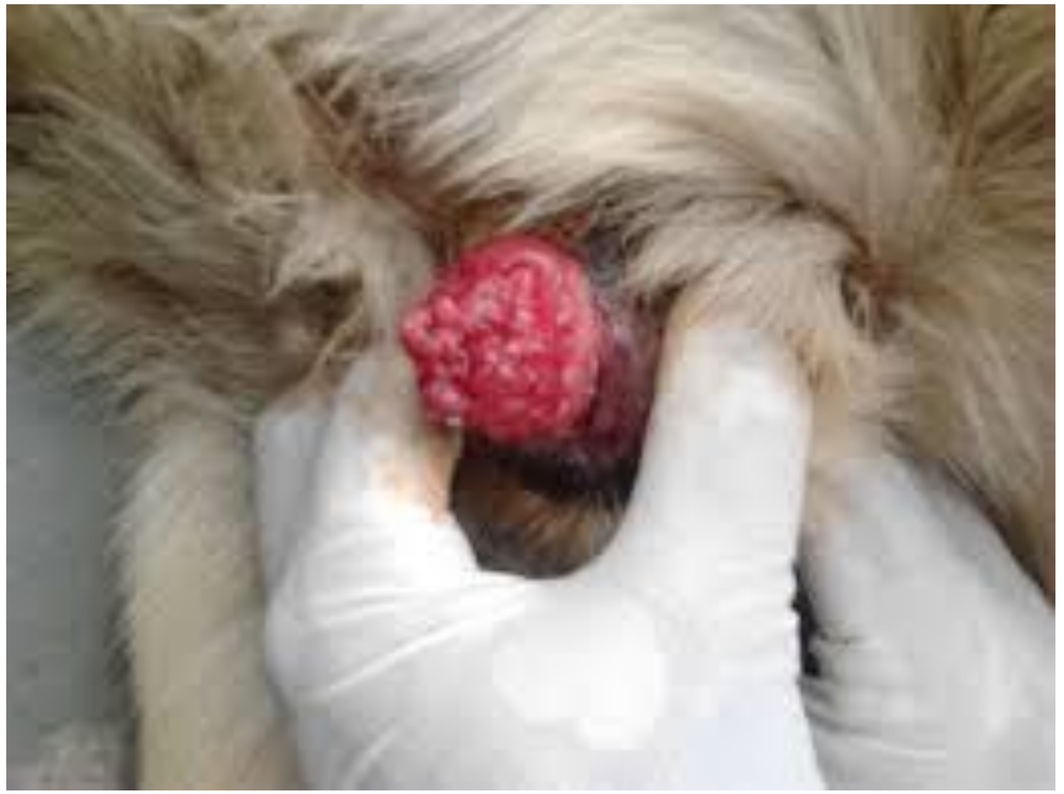
Incidence, age, breed, and sex

- In both sexes and all ages → more commonly in young
- Rare in pet and house dogs but is seen frequently in homeless dogs

Gross morphology

- Vary in gross appearance, but most are proliferative papillary or nodular masses protruding from the surface of the penis or vulva

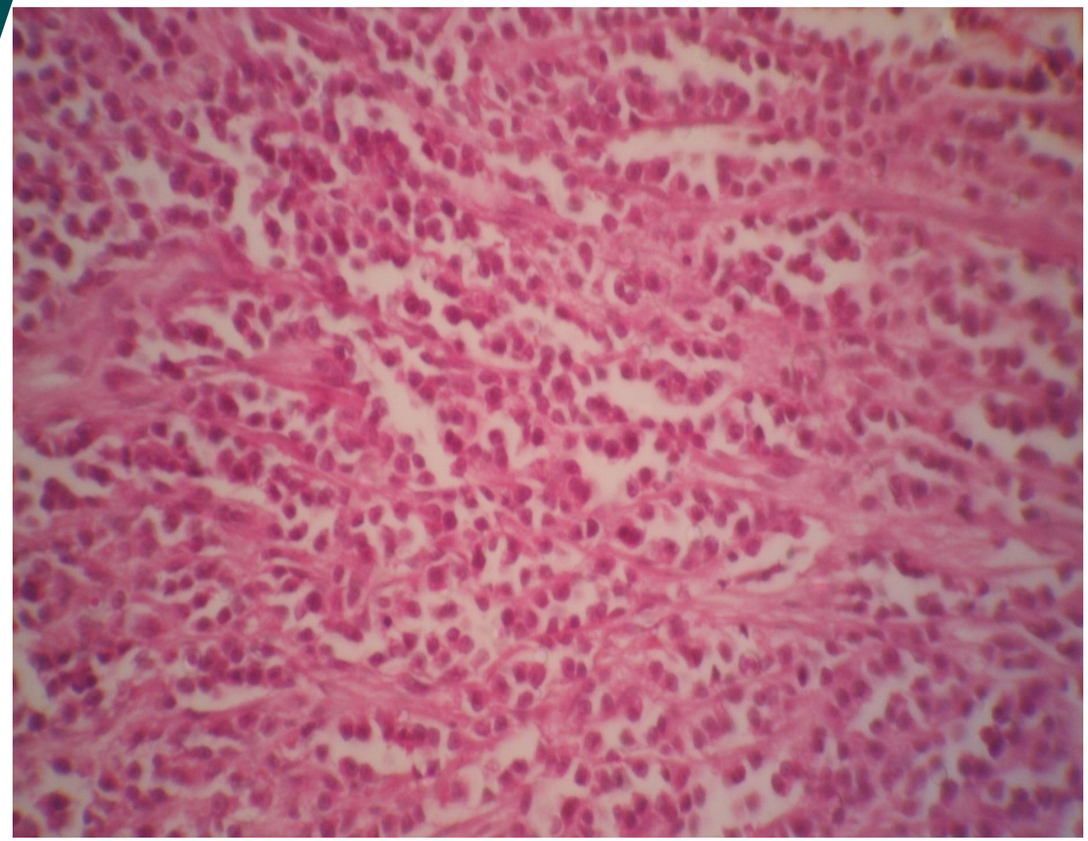
- The surface is usually ulcerated

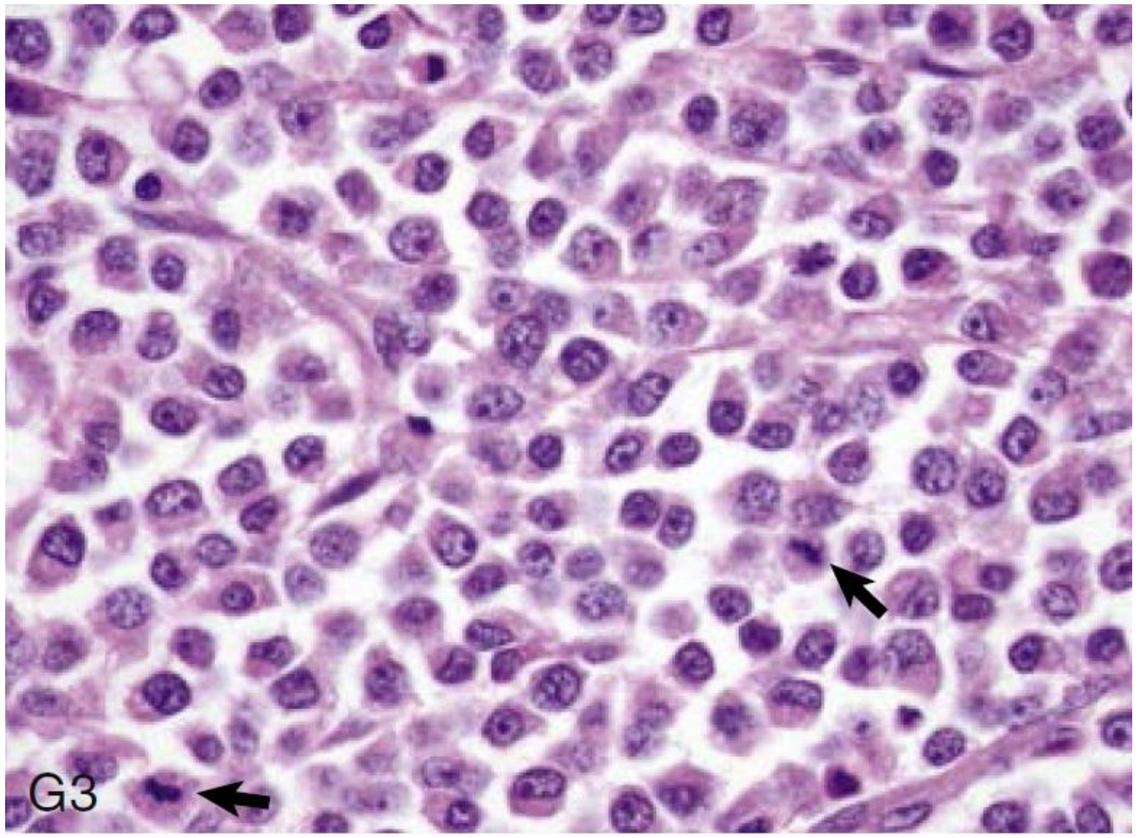


Histological features

- Loose sheets, cords
- Relatively uniform round to ovoid cells with indistinct cell margins
- Nuclei are large, and round, with a single central nucleolus
- Moderate amount of light amphophilic to clear cytoplasm
- High mitotic count
- Variable numbers of lymphocytes, plasma cells, eosinophils, macrophages infiltrate the tumor

- In regressing tumors, increased inflammation and zones of necrosis and fibrosis are often present





Growth and metastasis

- Tumors rapidly grow at first and then remain static for a time
- Spontaneous regression can occur and is the result of cellular and humoral immune responses
- There is infrequent metastasis to regional lymph nodes and to viscera, primarily in animals with compromised immunocompetency

Immunohistochemistry

- Positive → lysozyme, alpha-1-antitrypsin, vimentin
- Negative → keratins, S100 protein, CD3

MALIGNANT MELANOMA

This is a malignant neoplasm of melanocytes

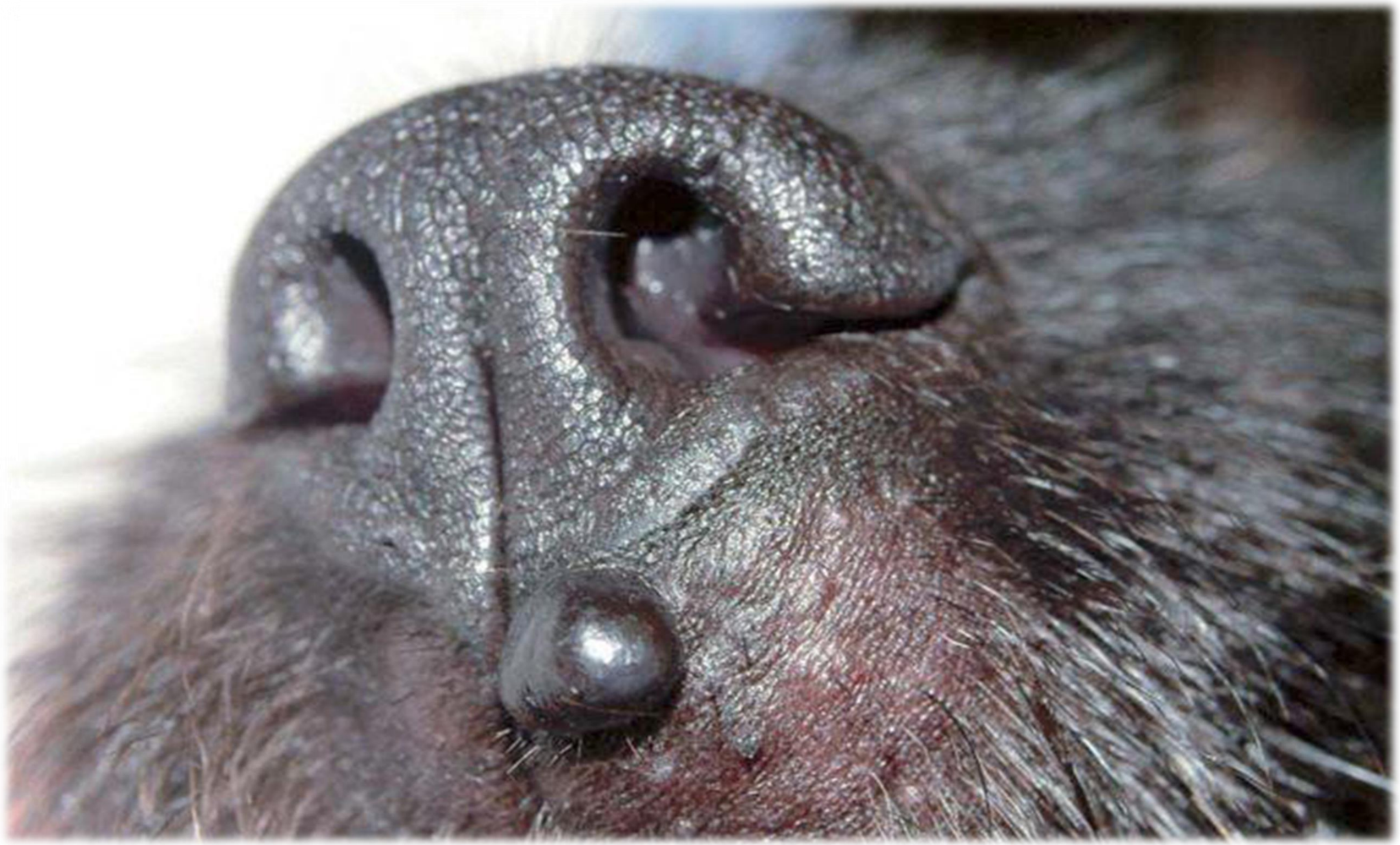
Incidence, age, breed, and sex

- Malignant melanoma is common in dogs and uncommon in other domestic species

- Dogs between 6 and 15 years old are primarily affected

Sites and gross morphology

- The majority of cases in dogs involve the oral cavity and mucocutaneous junction of the lips
- Approximately 10% of malignant melanomas arise from the haired skin → head and scrotum
- In cats, a greater proportion of malignant melanomas arise in the skin → head and back
- The neoplasms may be highly pigmented or lack pigment
- Size and degree of pigmentation are not reliable indicators of malignancy



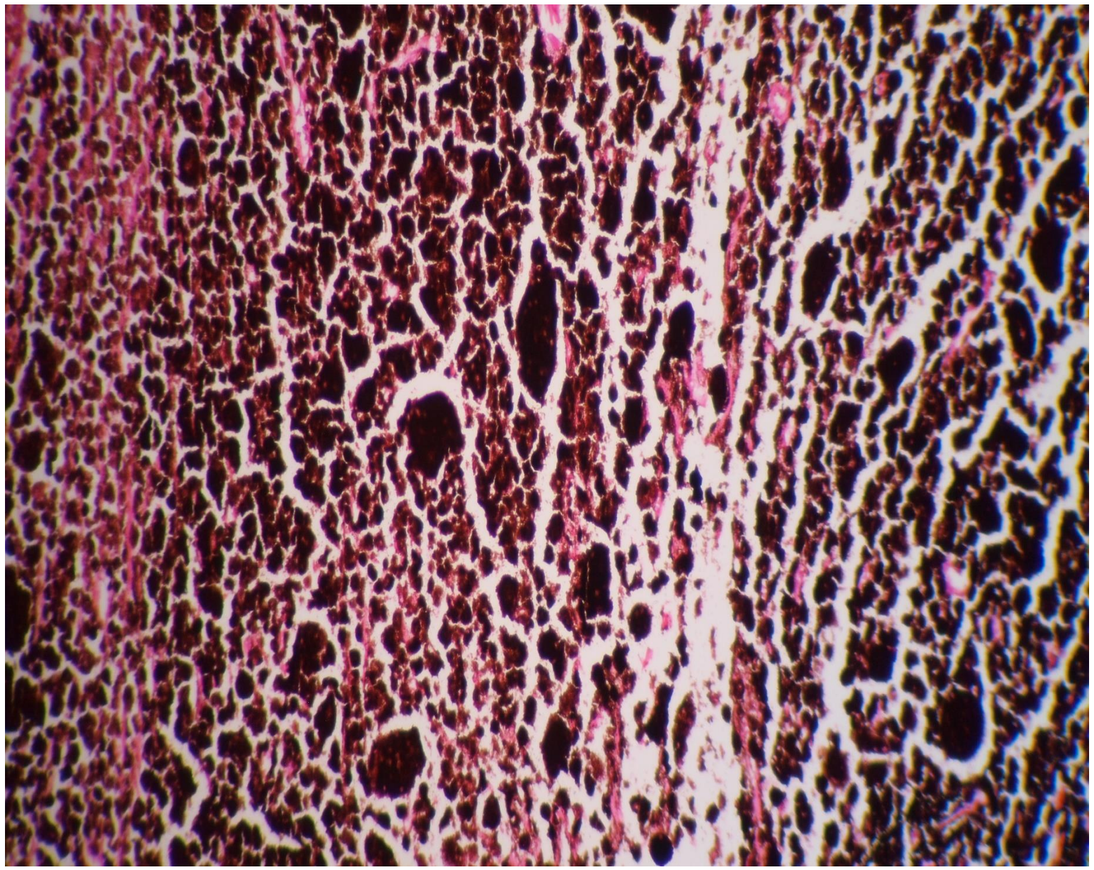
Histological features

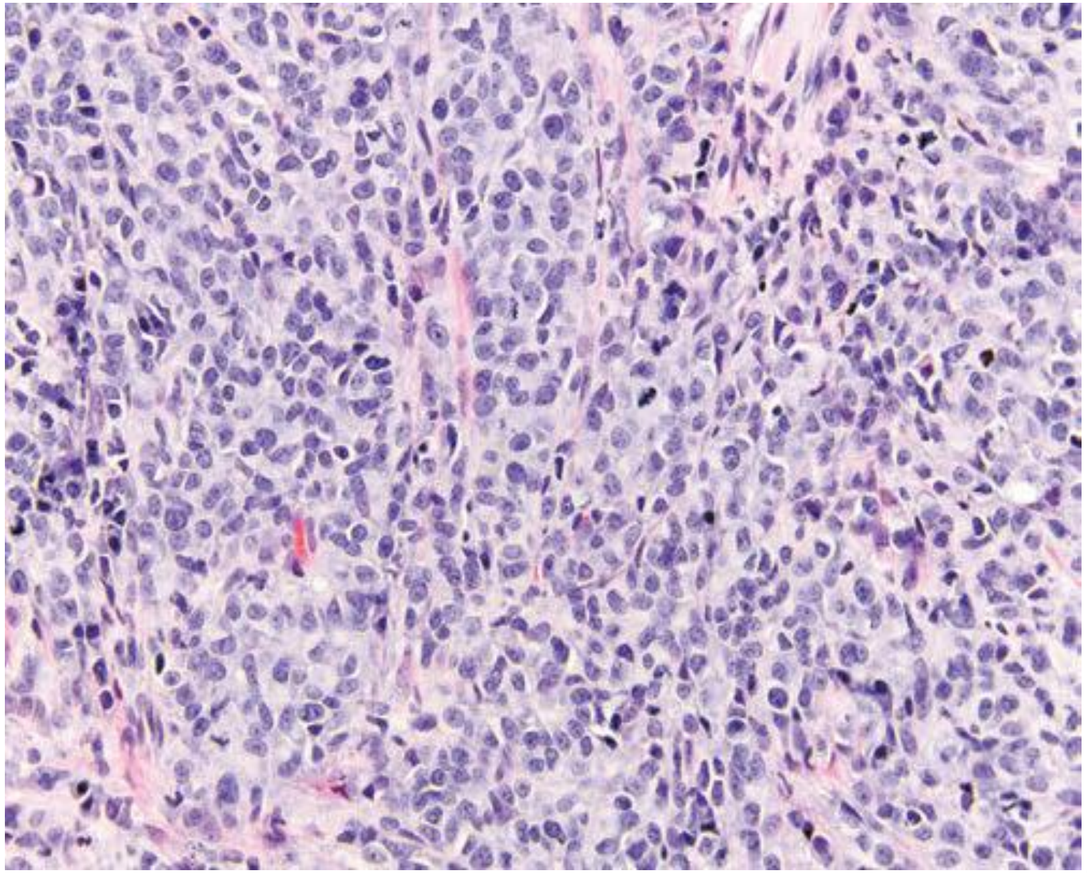
- Single cells or small nests within the basal portion of the epidermis
- Intraepidermal nests are a very useful feature for confirming the diagnosis of melanoma, particularly when melanin cannot be demonstrated in the dermal component
- Mitoses are more frequently observed
- The dermal component often consists of more pleomorphic melanocytes which may be polygonal or fusiform in shape or in some cases a combination of both cell types

✓ Polygonal cells often form nests surrounded by a fine, fibrovascular stroma

✓ Fusiform cells often have an interwoven pattern

- Cells contain a variable amount of intracytoplasmic melanin





Growth and metastasis

- Malignant melanomas are often rapidly growing and can be fatal
- Surgical margins: at least 1 mm of uninvolved tissue is suggested for margins
- Metastasis: regional lymph nodes, Brain, heart, and spleen
- When undertaking evaluation of the regional lymph nodes for metastasis:

✓ Care must be taken to differentiate **melanophages** (in cases of chronic dermatitis where there is destruction of the basal epidermis or hair follicle bulbs) from neoplastic melanocytes:

- Neoplastic melanocytes tend to be arranged in small nests rather than as single cells

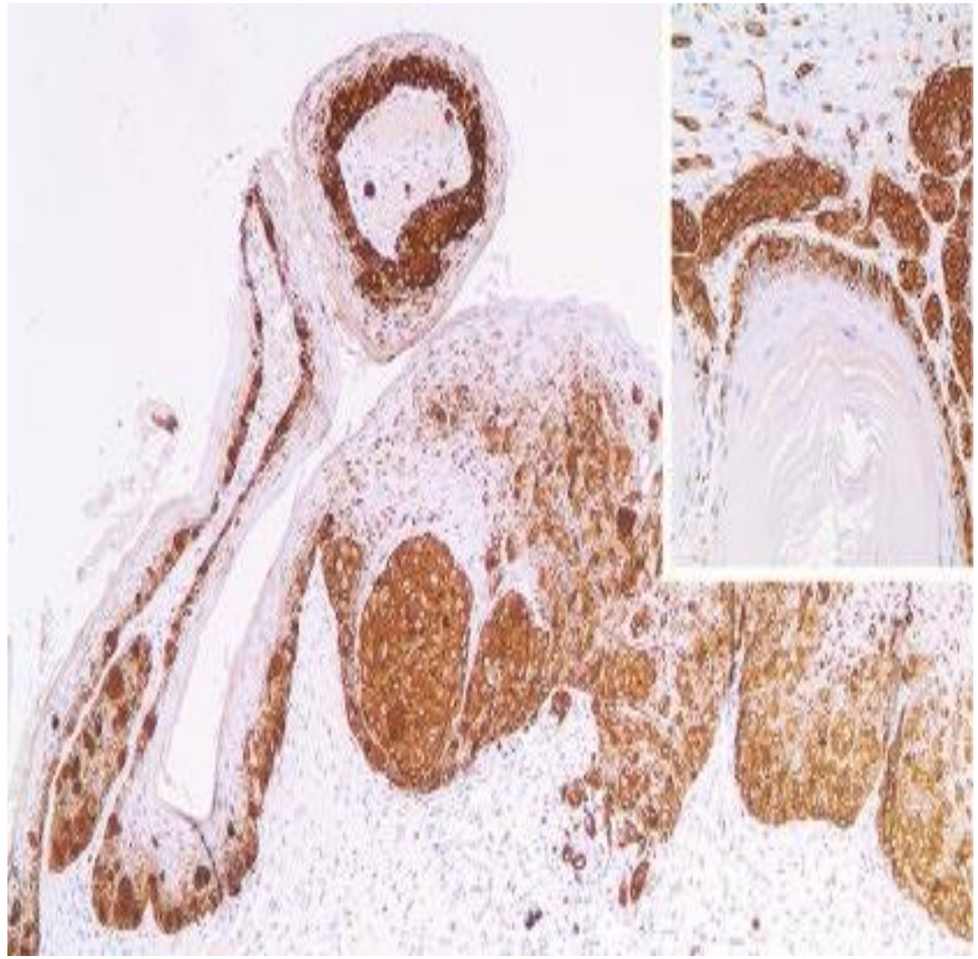
- The pigment within melanophages tends to be coarser than in melanocytes (personal communication, D.J. Meuten)

Immunohistochemistry

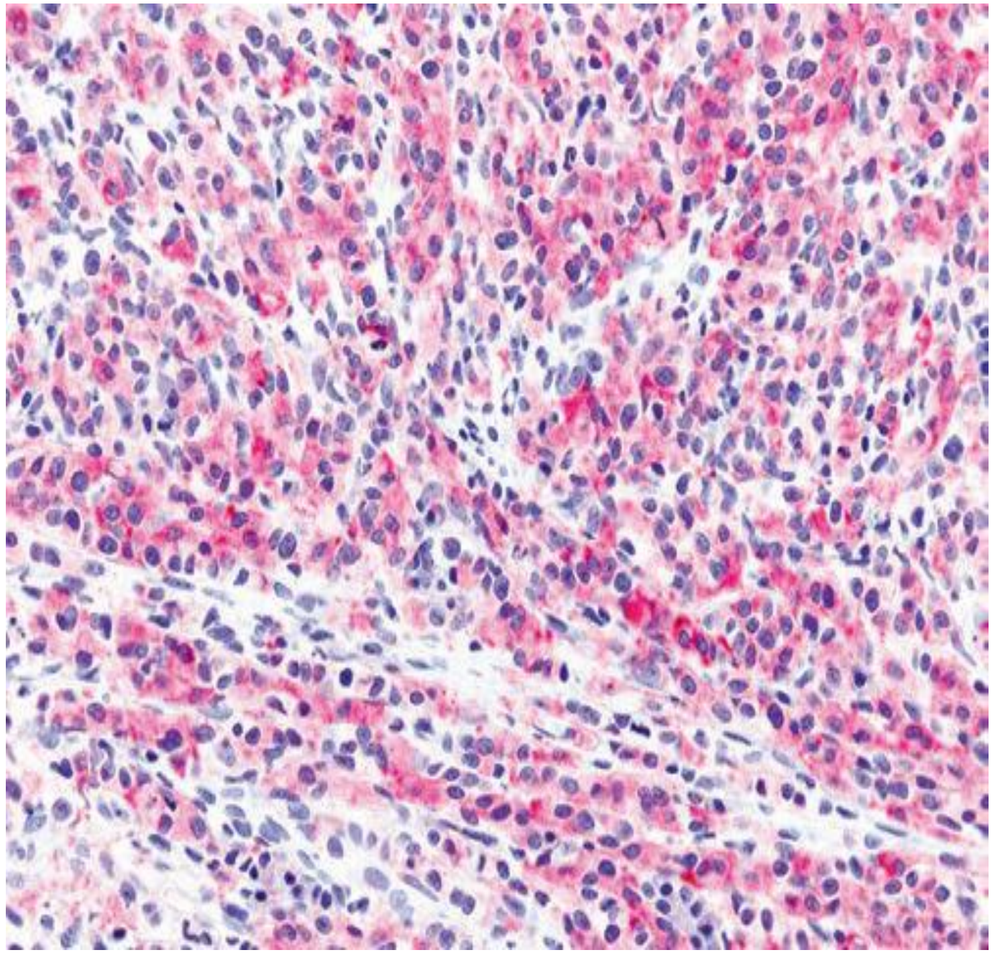
- Amelanotic tumors and spindle cell variants with little pigment can be problematic
- **Melan-A**, PNL2, TRP-1, and TRP-2 are highly sensitive

➢ Histochemical stains (Fontana–Masson)

DAB



AEC (3-amino-9-ethylcarbazole)



SQUAMOUS CELL CARCINOMA

- Squamous cell carcinoma (SCC) is a malignant neoplasm of epidermal cells in which the cells show differentiation to keratinocytes

- It is one of the most common malignant skin tumors

- Several factors are associated with the development of SCC:

✓ Prolonged exposure to ultraviolet light

✓ Lack of pigment within the epidermis

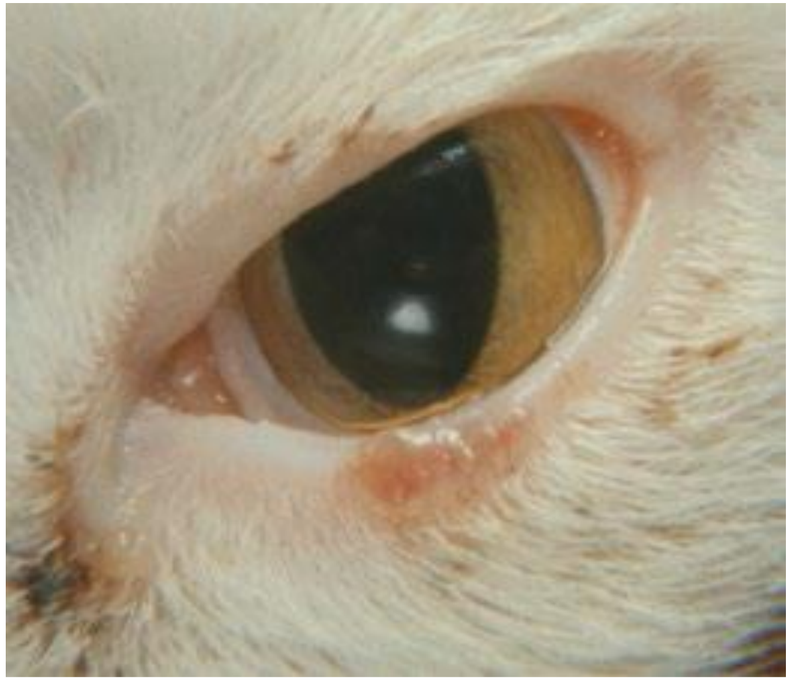
✓ Lack of hair or a very sparse hair coat

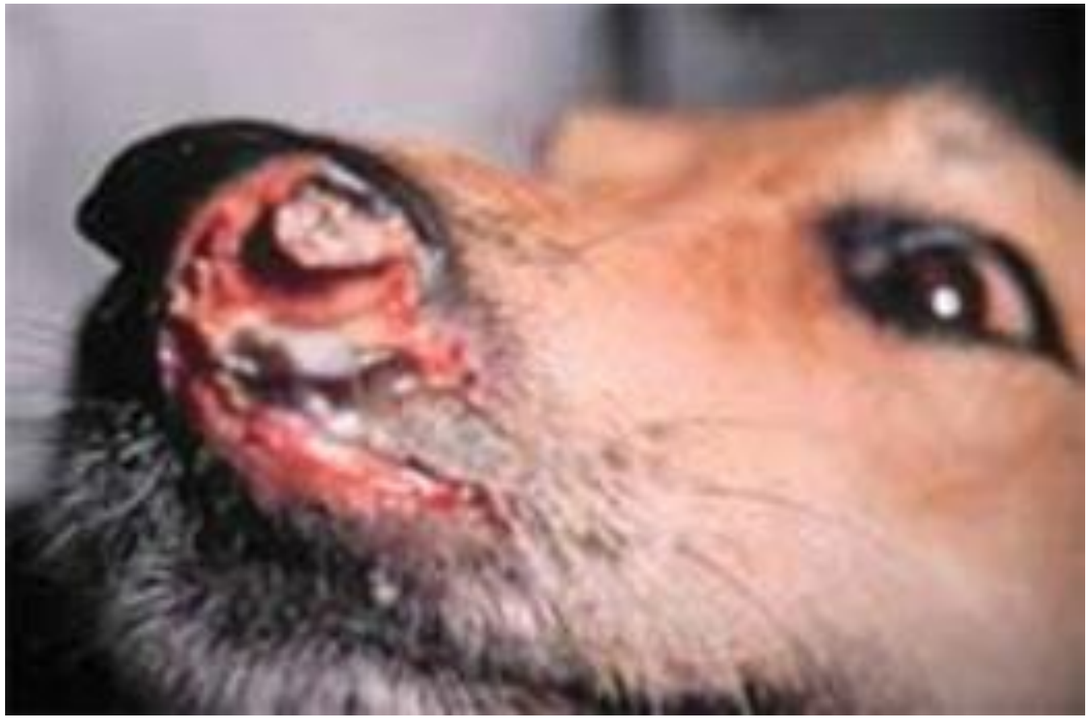
Incidence, age, breed, and sex

- In cats between 9 and 14 years of age
- In dogs between 6 and 13 years of age

Sites and gross morphology

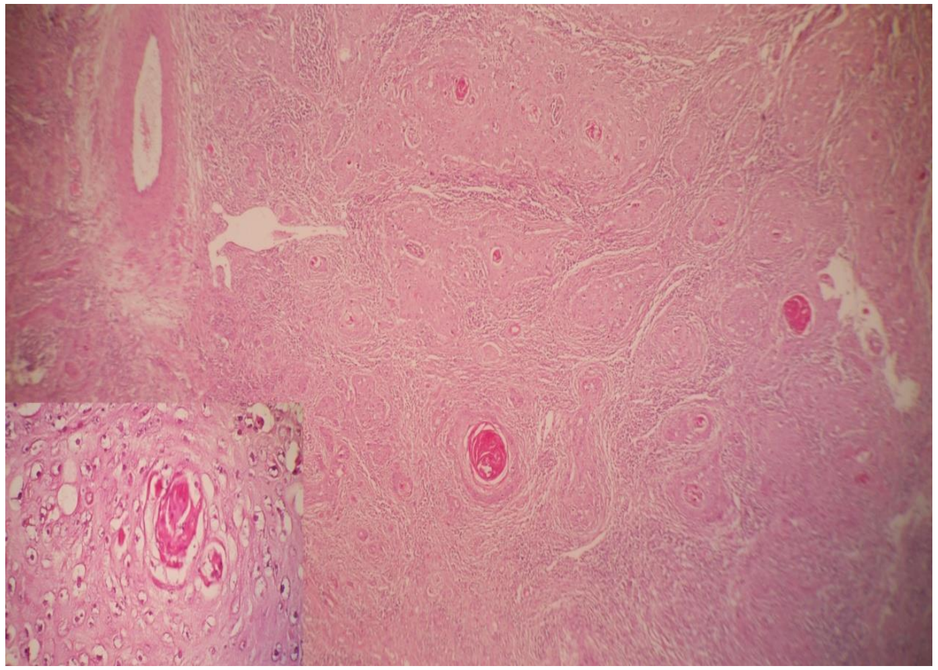
- In cats → pinna, eyelids, and planum nasale
- In dogs → head, abdomen, limbs
- Erythema, edema, scaling → crusting and thickening of the epidermis → ulceration

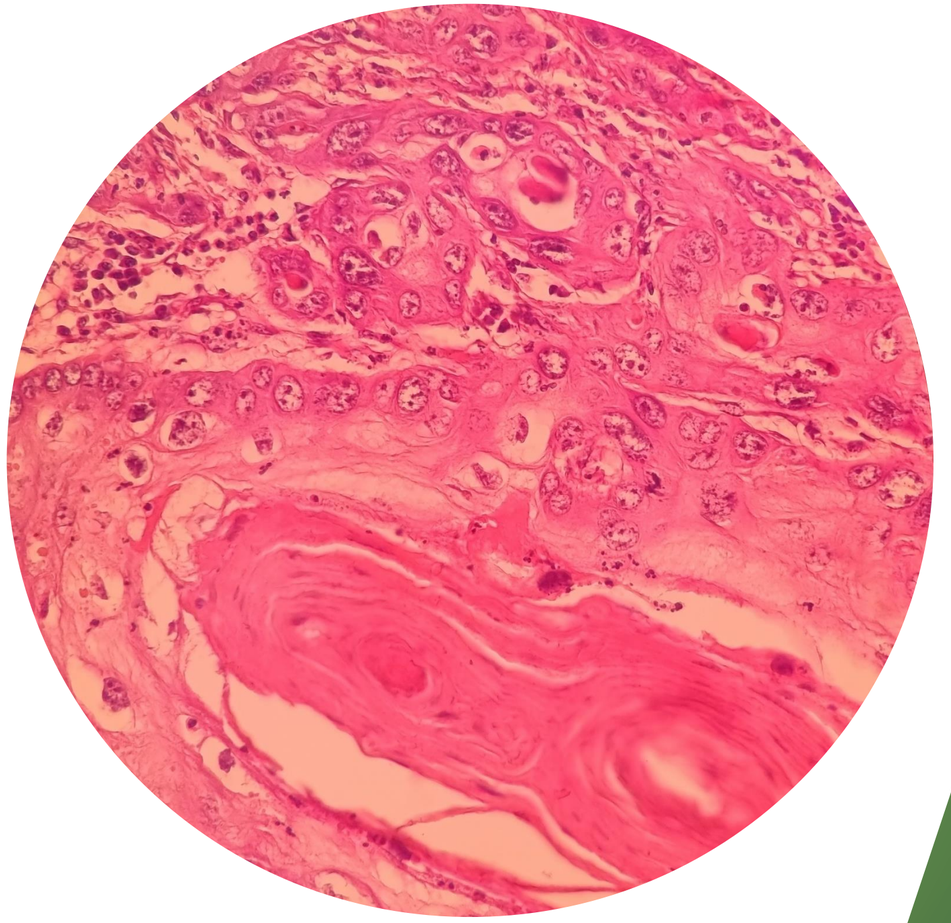


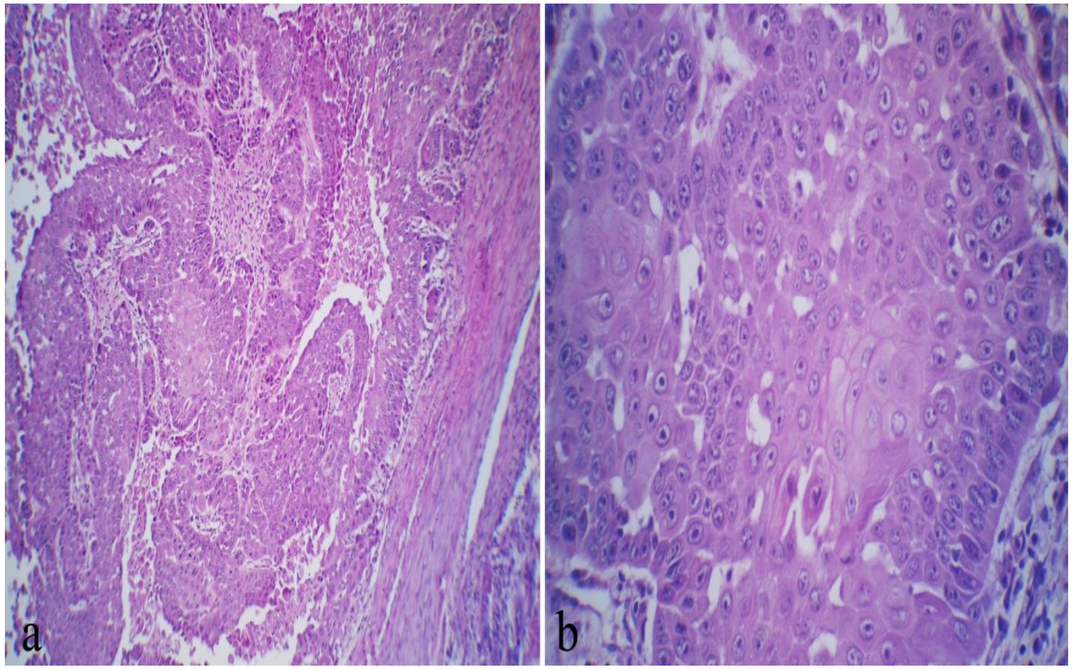


Histological features

- Islands, cords, trabeculae
- Large, ovoid, often vesicular nuclei
- Single, central, prominent nucleolus
- Abundant brightly eosinophilic cytoplasm with distinct cell borders
- Keratin tonofilaments seen as intracytoplasmic, eosinophilic fibrillar material
- Keratin pearls
- Variable number of mitotic figures



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- In poorly differentiated neoplasms → few keratin pearls
- Often an infiltrate of neutrophils into the islands, while plasma cells and lymphocytes are found in the connective tissue stroma

Growth and metastasis

- SCCs are usually slow-growing
- In most neoplasms, although invasive, metastasis is uncommon

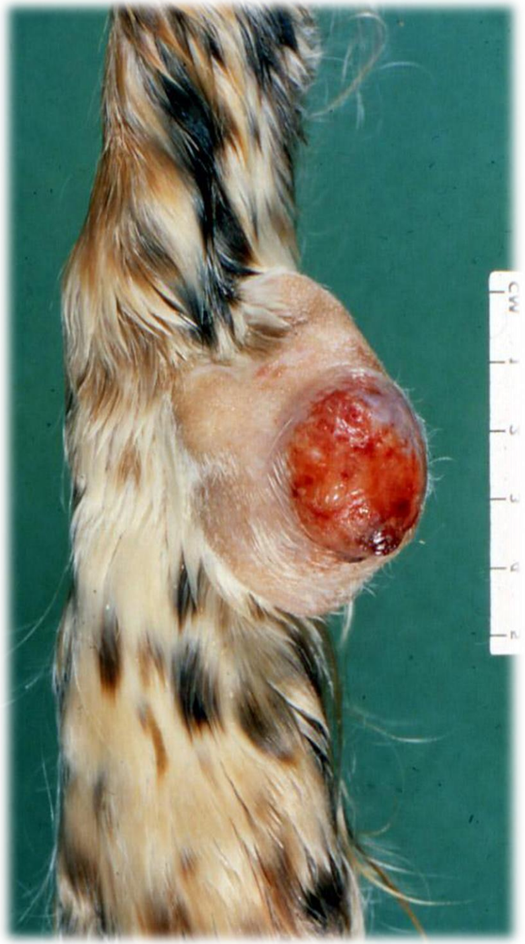
FIBROSARCOMA

Incidence, age, breed, and sex

- They are most commonly seen in adult and aged cats and dogs → mean age of 9 years
- Most tumors are focal and can develop anywhere on the body → mostly head and limbs

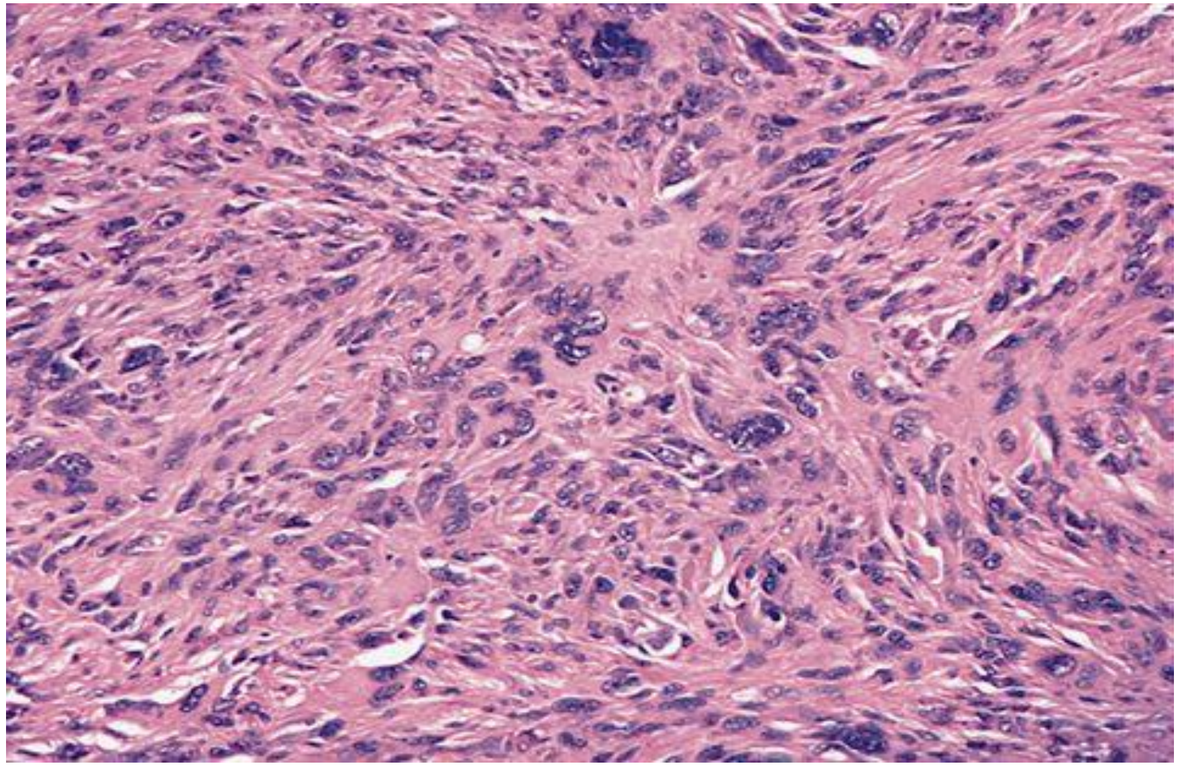
Gross morphology

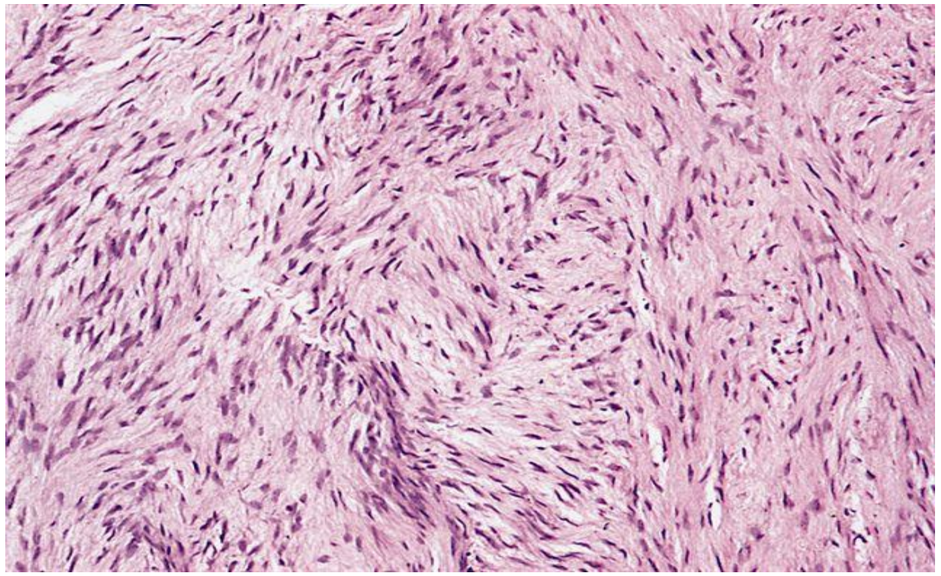
- Fibrosarcomas can be circumscribed or infiltrative
- The cut surface is gray/white

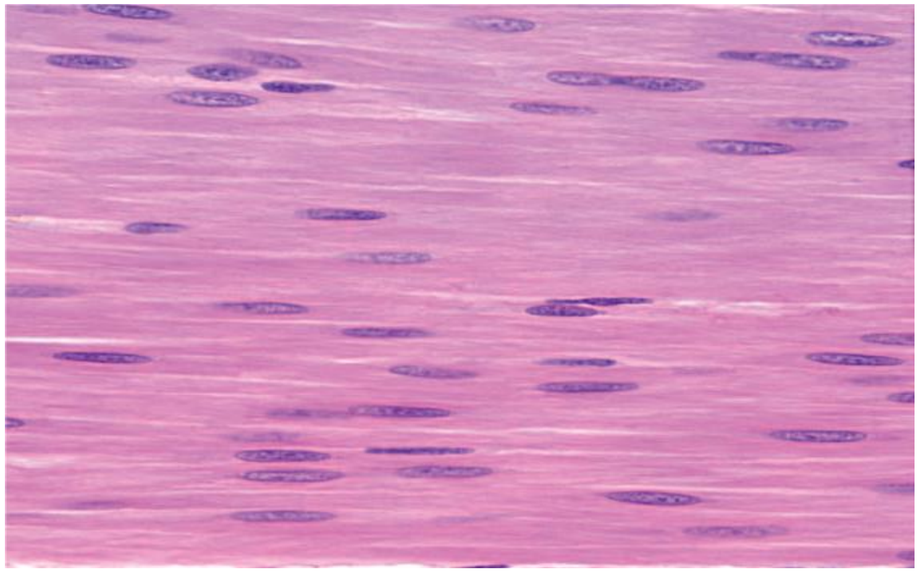


Histological features

- Interwoven pattern
- Pleomorphic spindle-shaped tumor cells
- Scant cytoplasm
- Elongated to oval nuclei
- Infrequent mitotic figures







Additional diagnostic criteria

- In rare instances, differentiation from peripheral nerve sheath tumors (PNSTs) and leiomyosarcomas can be problematic
- PNSTs usually have finer, more delicate cells arranged in shorter interwoven fascicles
- The collagenous stroma can be more pronounced in fibrosarcomas than in PNSTs or leiomyosarcomas
- Masson’s trichrome stain will distinguish between collagen and smooth muscle

Immunohistochemistry

- All these tumors are positive for vimentin

- Leiomyosarcoma are positive for actin

Growth and metastasis

- Tumors are infiltrative and recurrent, but metastasis is uncommon

FELINE VACCINE-ASSOCIATED FIBROSARCOMA

Incidence, age, breed, and sex

- The mean age is younger than that seen in cats with fibrosarcomas that are not vaccine-associated

Site and gross morphology

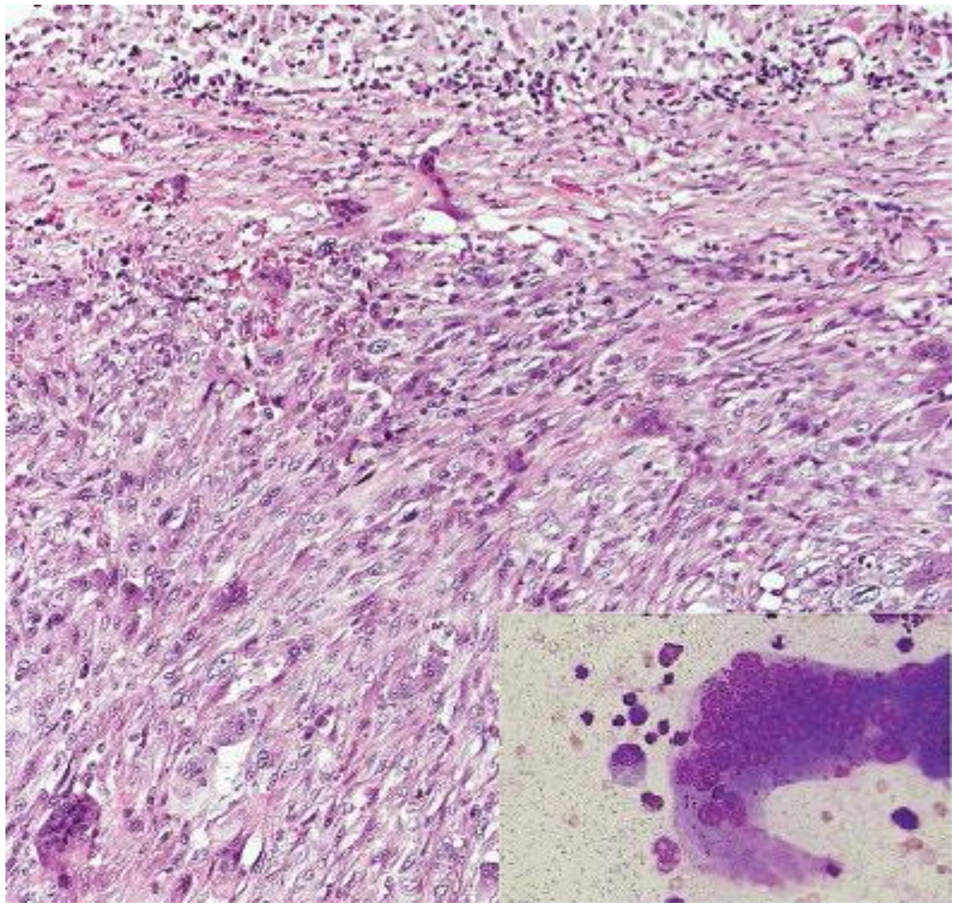
- Vaccine-associated sarcomas arise at vaccination sites
- The most typical presentation is a well-circumscribed, firm white mass
- With a cystic center containing thin watery or mucinous fluid

Vaccine-associated fibrosarcoma in the interscapular region

Histological features

- Spindle cells arranged in interwoven bundles
- Pleomorphic nuclei
- Increased numbers of multinucleated cells
- Peripheral inflammation:

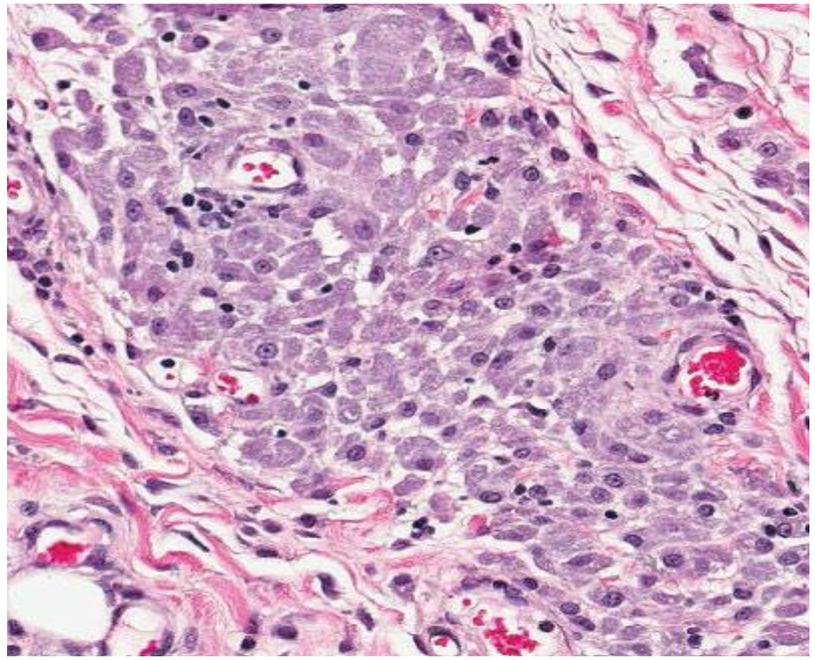
✓ Lymphocytes and macrophages



Additional diagnostic criteria

- The presence of peripheral aggregates of macrophages containing gray/brown intracytoplasmic material (shown to be aluminum, a common vaccine adjuvant) supports the diagnosis of vaccine-associated sarcoma

- However, this material is found in a minority of cases



Growth and metastasis

- These tumors are highly recurrent, requiring surgical excision one, two, or three times within a 1- or 2-year period
- The majority of cats end up being euthanized after repeated surgeries
- The metastatic potential of these neoplasms is low

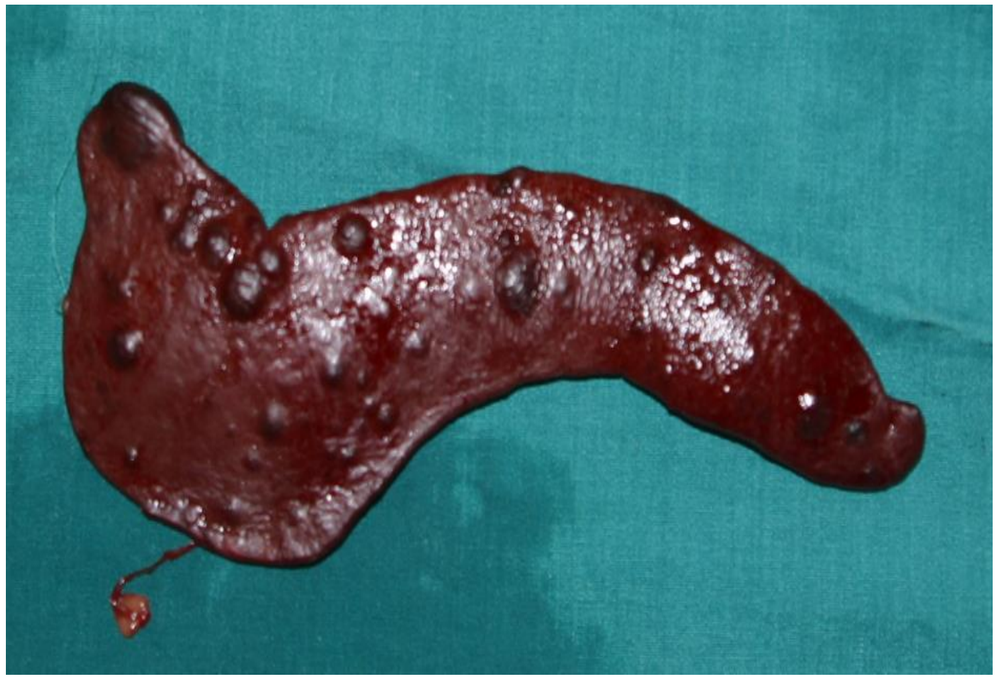
HEMANGIOSARCOMA

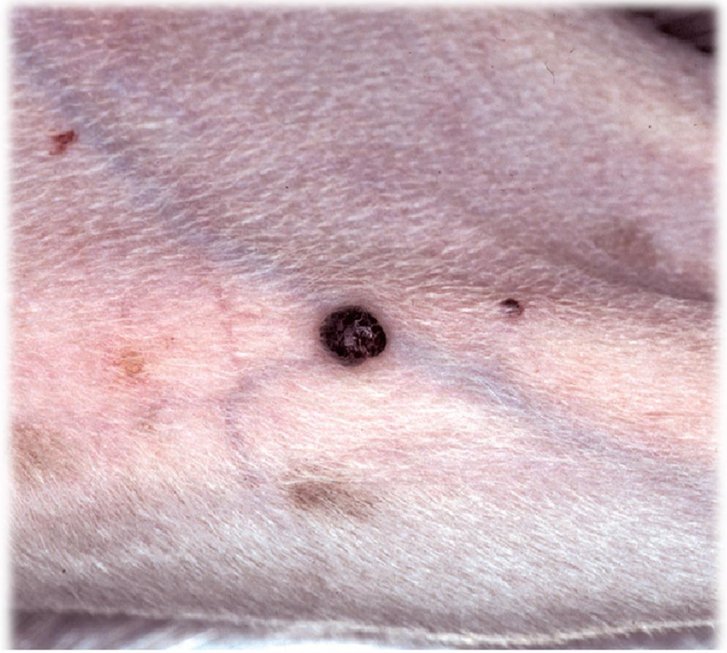
Incidence, age, breed, and sex

- Most commonly presents as a multicentric disease involving the spleen, liver, lungs, right auricle of dogs
- Unusual solitary sites of hemangiosarcoma in the dog → urinary bladder serosa and capsule of the kidney
- Cutaneous → solitary or, rarely, part of the multicentric syndrome
- The tumor is less frequently seen in the cat
- In cats → on the head (eyelids, especially), distal limbs

Gross morphology

- Usually, well-defined mass that is red to black, soft to firm, and exudes blood when cut

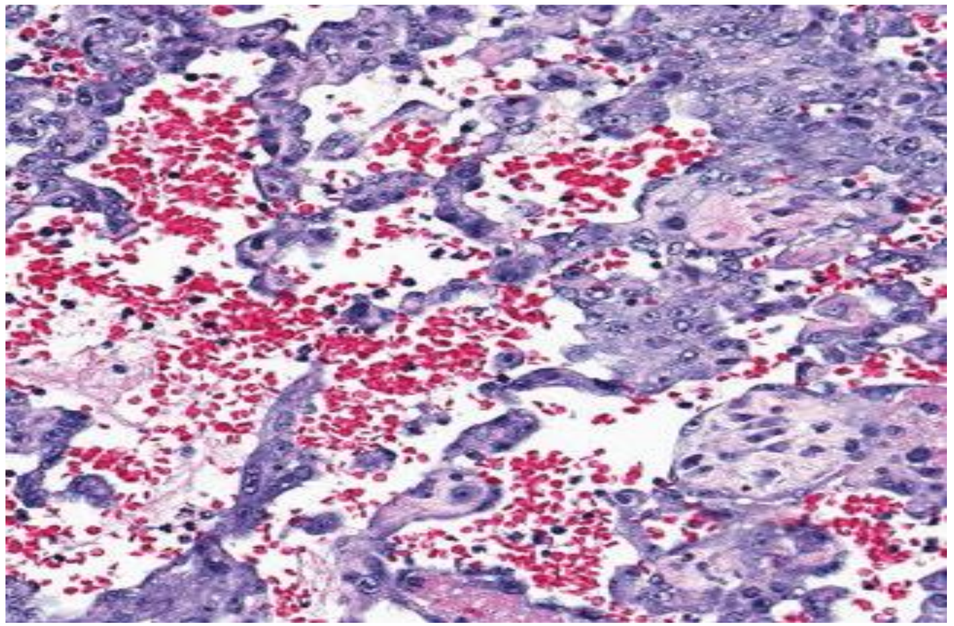


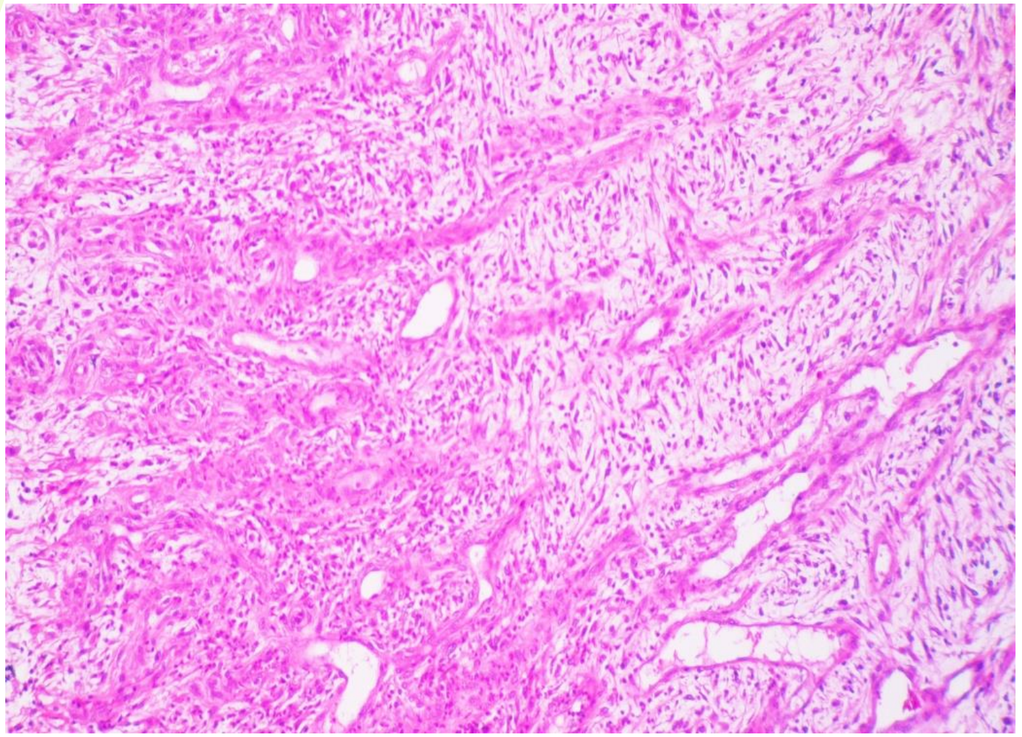


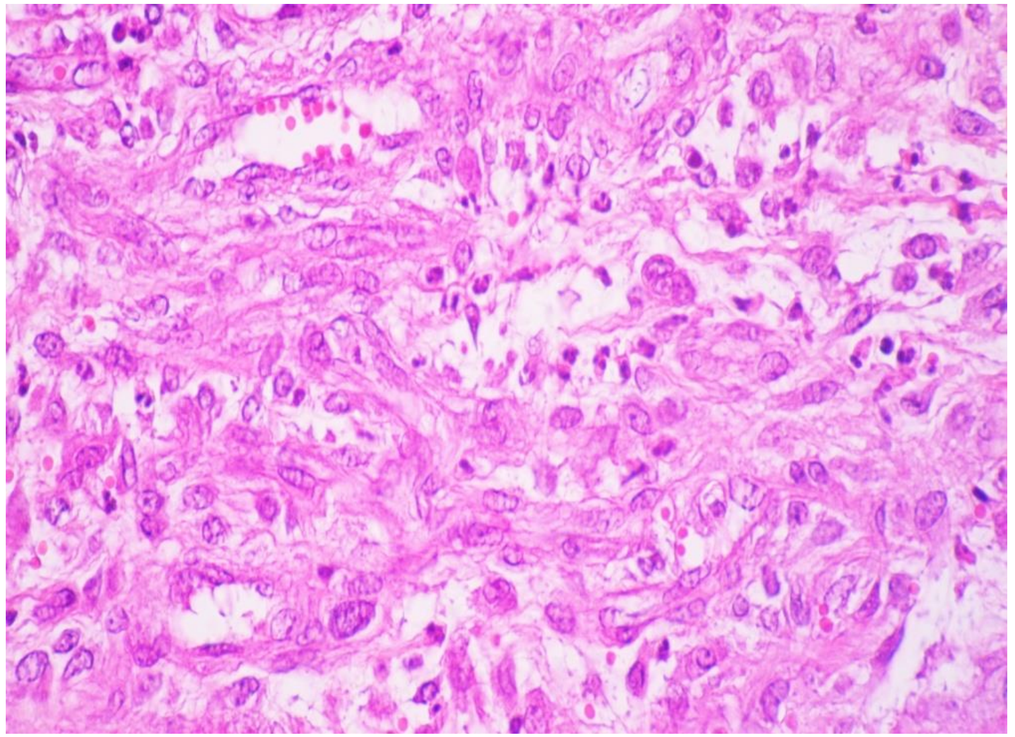
Zachary and McGavin: Pathologic Basis of Veterinary Disease, 5th edition.

Histologic features

- Spindle-shaped to ovoid cells
- Usually form recognizable vascular clefts or channels
- Bulging, pleomorphic and hyperchromatic nuclei
- Frequent mitotic figures







Immunohistochemistry

- Traditionally, factor VIII immunopositivity has been considered diagnostic of hemangiosarcoma
- Unfortunately, experience has shown that some hemangiosarcomas will not stain with this antibody
- **CD31** alone or in concert with factor VIII has been shown to be more specific

Growth and metastasis

- Cutaneous hemangiosarcomas are less aggressive than their visceral counterparts, with lower metastatic potential and longer survival times

OSTEOSARCOMA

- Osteosarcomas is characterized by the production of osteoid or immature bone by malignant osteoblasts
- The tumor generally occurs in middle-aged to older dogs → median age of around 7 years
- There is a small peak in incidence around 18–24 months of age

Clinical characteristics

- In general, osteosarcoma is a rapidly progressive neoplasm resulting in early mortality
- It is one of the most malignant tumors in veterinary medicine

- Appendicular skeleton is most commonly affected → lameness is the earliest sign in most cases

- In young dogs → more aggressive with shorter survival times

- The clinical course of osteosarcoma in cats is slower than in dogs with more survival time

- Serum alkaline phosphatase (ALP) activity is often increased in affected dogs

- Increased activities of both total and bone-specific ALP before surgery have been associated with shorter survival time after surgery in dogs

Site

- The appendicular skeleton is affected 3–4 times as often as the axial skeleton
- Forelimbs approximately twice as often as the hindlimbs
- Although a single traumatic event does not appear to predispose to osteosarcoma, chronic irritation and repair associated with osteomyelitis, or the presence of an internal fixation device is occasionally linked to tumor development
- Predilection sites for osteosarcomas in cats are not as well defined as in dogs because the tumor is less common in cats and there are fewer large-scale studies

Gross morphology

- Osteosarcomas vary markedly in their gross and imaging appearance

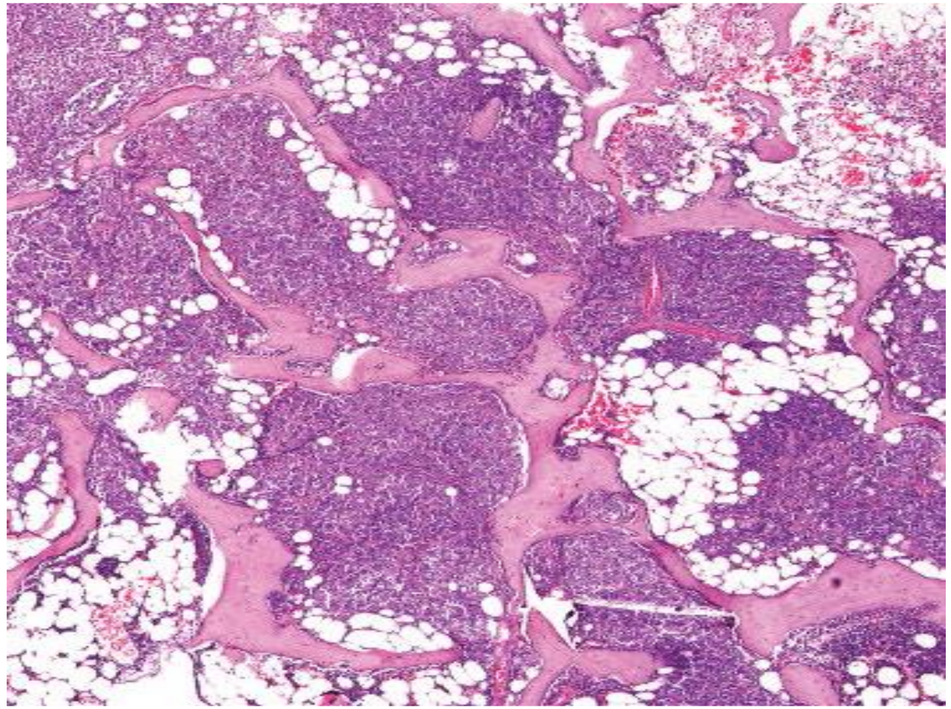
Histological features

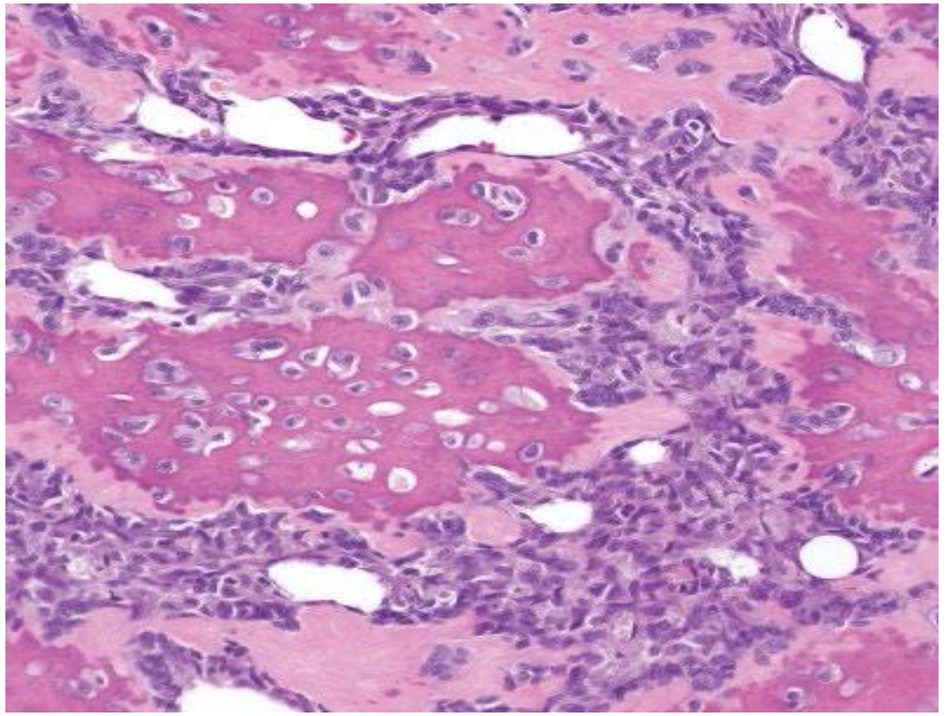
- Osteosarcomas may vary widely in their histological appearance, but in all cases a definitive diagnosis is based on the production of osteoid

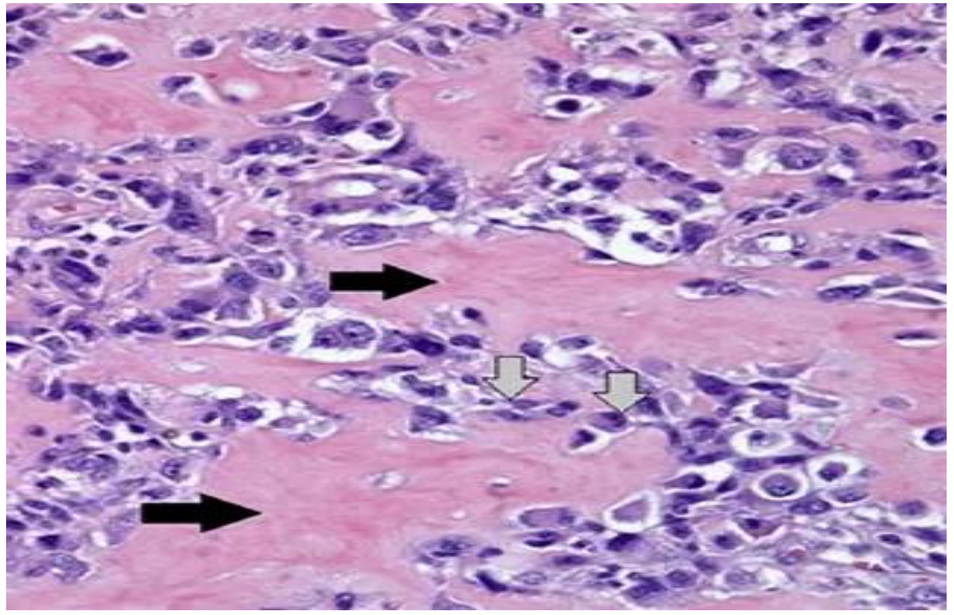
- Examination of several specimens, ideally at least three, from different areas of the tumor may be necessary before evidence of osteoid production is detected

- Tumor cells invading the marrow spaces

- Highly pleomorphic, oval or rounded cells
- Basophilic cytoplasm
- Eccentric, hyperchromatic nuclei
- A hallmark of osteosarcoma is the production of osteoid
- Many mitotic figures







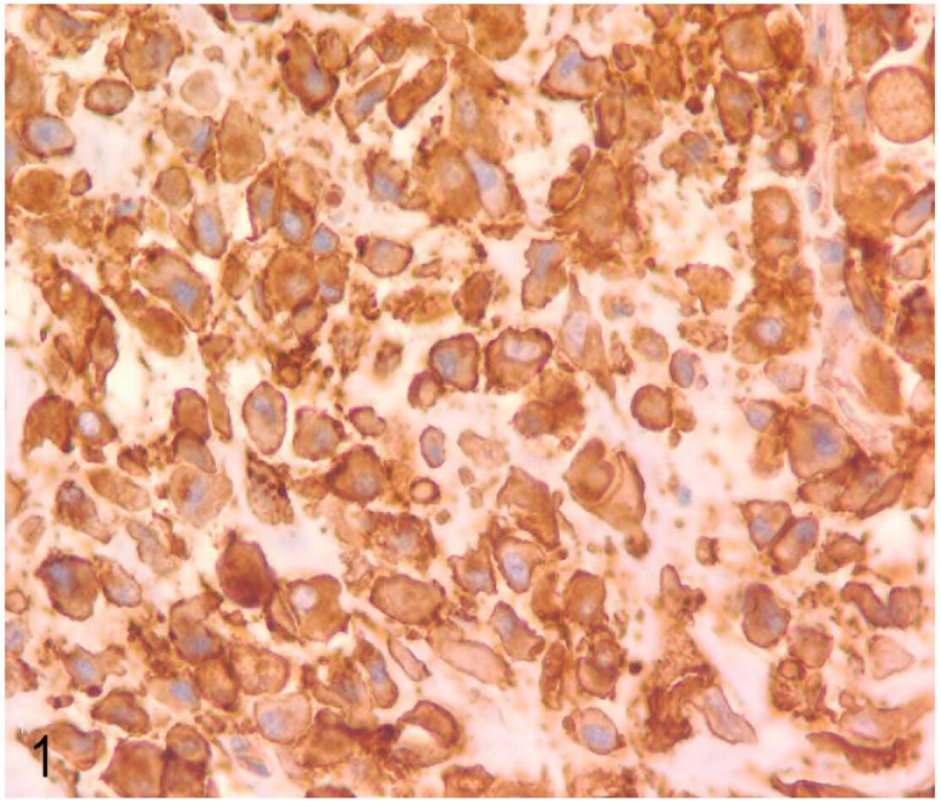
Grading

- No histological grading system has gained widespread application by veterinary pathologists
- This is not surprising since osteosarcomas can vary markedly in histological appearance in different regions of the same tumor and the core biopsy samples usually received for routine diagnosis cannot be assumed to represent the entire lesion.

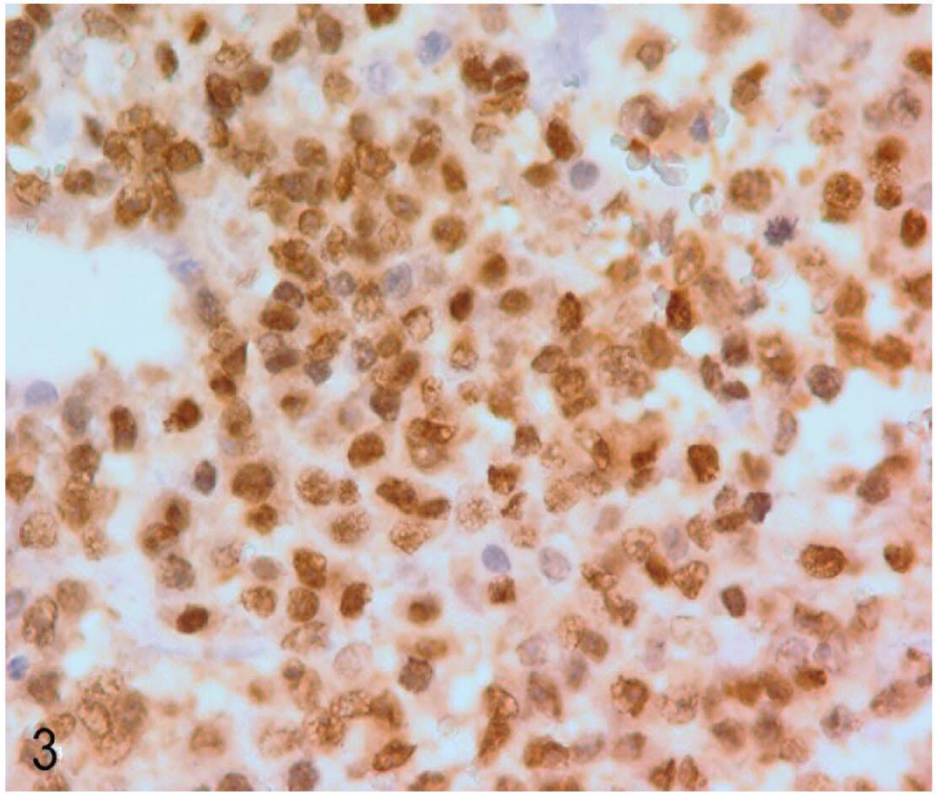
Growth and metastasis

- Highly malignant at least in dogs, and the prognosis is very poor
- Hematogenous metastasis to the lungs commonly occurs early in the disease
- Immunohistochemistry → panel-Alkaline phosphatase and RUNX2

Alkaline phosphatase → membranous



RUNX2 → nuclear



Have a question?

Thank you