How to work up your cancer patient

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Diagnosing Cancer



- History
- Physical examination
- Hematology/Clinical chemistry/ Serology
- Diagnostic Imaging
- Morphology
  - Cytology (FNAB, effusions etc)
  - Flow-cytometry
  - Histology ± IHC
- Biomarkers
  - Metabolites (calcium, cobalamin, glucose)
  - Proteins (APP, TK1)
  - Hormones (PTH-rp, insulin)
  - Nucleosomes
- DNA-based
  - PARR, *BRAF*, *Kit*

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TREATING CANCER WITHOUT A DIAGNOSIS

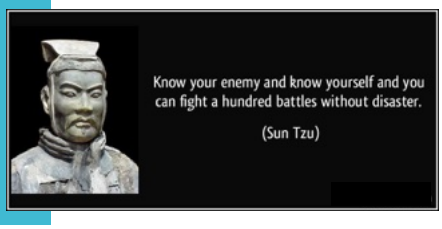
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My roadmap to cancer care

Tumor
Location
Care plan

4

The "war" against cancer



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Step 1. Tumor

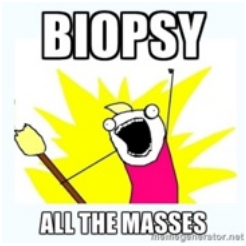
What do we need to know?

1. Tumor type, determines
   - Therapeutic options
   - If and where to look for
     - Metastatic disease
     - Paraneoplastic syndrome(s)
2. Tumor size, determines
   - whether therapy is indicated
   - invasiveness of treatment

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1st rule in oncology

Before you treat, ALWAYS BIOPSY!!



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1st rule in oncology

Before you treat, ALWAYS BIOPSY!!

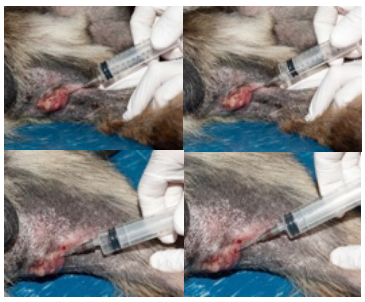
Unless…. biopsy

1. outcome doesn't change (treatment) plan:
   - splenic hemangiosarcoma
   - brain tumor?
   - solitary lung tumor?
   - solitary osteolytic bone lesion??
2. procedure puts the patient at risk e.g.
   - thyroid tumor
   - splenic hemangiosarcoma

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Biopsy - Techniques

1. Fine needle aspiration biopsy

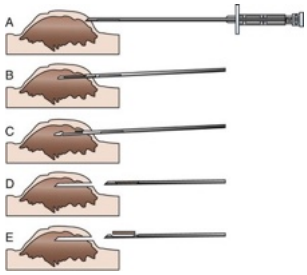


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Biopsy - Techniques



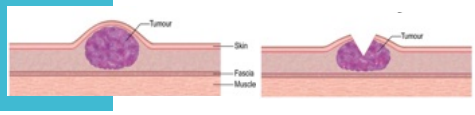
2. **Core needle biopsy (Tru-cut)**



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Biopsy - Techniques

3. **Incisional biopsy (wedge/punch)**
   - Will give most relevant information,
   - but **NOT** always the correct grade (STS/MCT)
   - Biopsy should **NEVER** interfere with the definitive surgical resection!!
     1. Don't breach anatomical barriers!
     2. Biopsy the center and not the edge of the tumor!
        - pathologists don't need "normal" tissue
        - possible strong peripheral reactive changes
     3. Sometimes necrosis in deep center



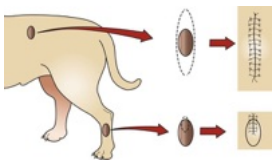
North, 2009

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Biopsy - Techniques

4. **Excisional biopsy**
   - Often leads to poorly performed marginal excision
   - ***Never*** the right choice for malignant neoplasia
   - Possibly suitable for small, benign neoplasms

5. **Lymph node biopsy**
   - More for staging purpose



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Biopsy - Cytology *vs* Histology

CYTOLOGY	HISTOLOGY
Should ALWAYS be tried	Should NEVER be forgotten
Round cell tumors Epithelial & neuroendocrine tumors Evaluating metastatic disease (lymph nodes, internal organs) Mesenchymal tumors Tumor grade Margin evaluation	Necessary for: • Confirming cytological diagnosis • All mesenchymal proliferations • Tumor grade • Evaluation surgical margins

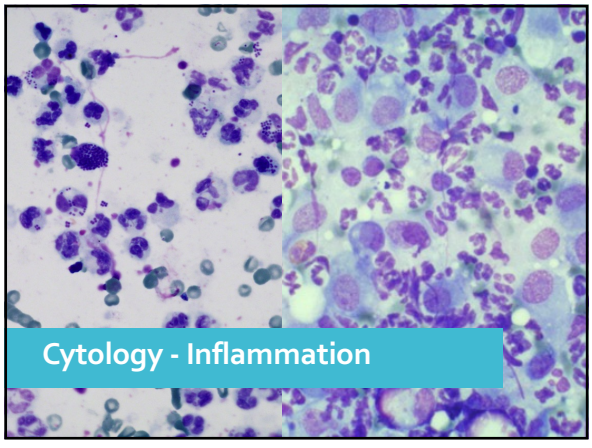
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Cytology (a crash course)

How to read cytology?

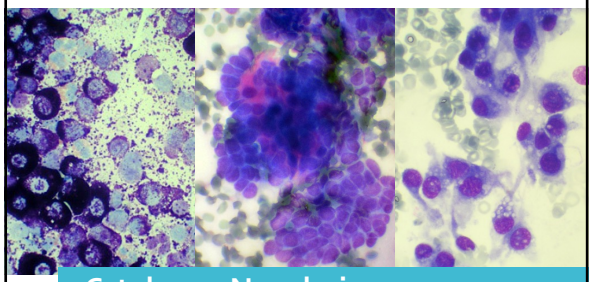
1. Assess diagnostic value of the sample
   - hemodilution, cellularity, quality of cells
2. Monomorphic *vs* Pleomorphic
3. Inflammation vs Neoplasia
   - Cave: neoplasia with secondary inflammation
4. If neoplastic
   Round cell / Epithelial / Mesenchymal / Neuroendocrine
5. Malignant *vs* Benign

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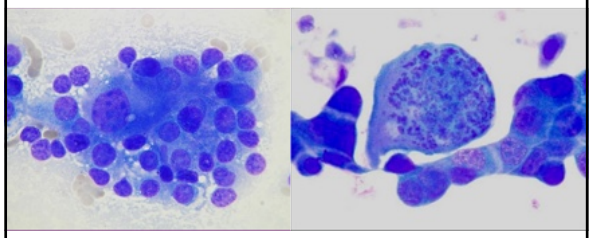
Cytology - Inflammation

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Cytology – Neoplasia

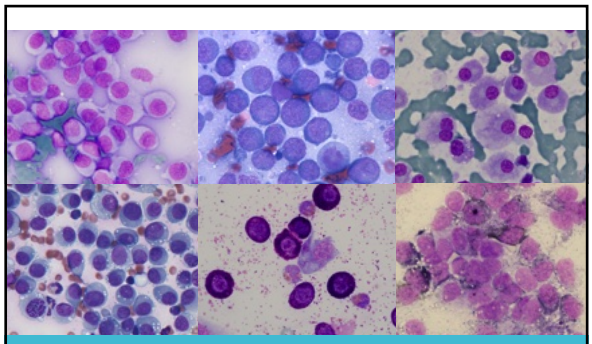
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Cytology – Malignancy criteria

apply (mostly) to epithelial tumors

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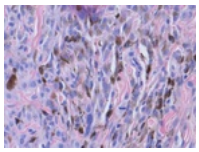
Cytology – round cell tumors

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Histology Goals

1. Diagnosis
   - additional stains/IHC
2. Indication of aggressiveness
   - grade mitotic index
3. Indication of metastatic capacity
   - vascular and/ or lymphatic invasion
4. Degree of excision
   - only following curative-intent surgery





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Histology

Subtype	MST/mST	Survival Rate	
		1 Year	2 Year
Complex carcinoma	nr/36	100% (23/23)	96% (22/23)
Simple tubular carcinoma	nr/29.1	93% (14/15)	73% (11/15)
Simple tubulopapillary carcinoma	nr/24.9	75% (9/12)	67% (8/12)
Intraductal papillary carcinoma	nr/19.8	83% (10/12)	50% (6/12)
Carcinoma and malignant myoepithelioma	nr/26.8	70% (14/20)	55% (11/20)
Adenosquamous carcinoma	18/12.6	60% (6/10)	0% (0/10)
Comedocarcinoma	14/18	71% (12/17)	29% (5/17)
Solid carcinoma	8/15.6	45% (9/20)	25% (5/20)
Anaplastic carcinoma	3/4.2	0% (0/18)	0% (0/18)
Carcinosarcoma	3/4.2	0% (0/8)	0% (0/8)

Abbreviations: HR, hazard ratio; mST, mean survival time; MST, median survival time; nr, not reached; NS, nonsignificant.
*P < .05.

Obtain an accurate histopathological diagnosis!!

Rasotto *et al*, 2017

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Histology

Obtain a grade (when possible)

Patnaik grading system

	Grade		
	I (<40%)	II (40%)	III (≥20%)
Location	Dermis and interfollicular spaces	Infiltrate lower dermal and subcutaneous tissue; some extend tot skeletal muscles or surrounding tissues	Replace subcutaneous and deep tissues
Cell morphology	Round, monomorphic, ample, distinct cytoplasm with medium-sized granules	Round to ovoid, moderately pleomorphic, with scattered spindle and giant cells; most cells distinct cytoplasm with fine granules, but some with indistinct cytoplasm and large/hyperchromatic granules	Round, ovoid, or spindle shaped, pleomorphic, medium sized; cytoplasm indistinct with granules that are fine or not obvious, many giant cells and scattered multinucleated cells
Nuclear morphology	Round, condensed chromatin	Round to indented with scattered chromatin and single nucleoli; some with double nuche	Indented to round vesiculated with 1 or more prominent nucleoli; common binucleated cells
Architecture, cellularity, stromal reaction	Arranged in rows or small groups, separated by mature collagen fibers of the dermis	Moderately to highly cellular, arranged in groups with thin, fibrovascular stroma (sometimes thick and fibrocollagenous with areas of hyalinization)	Cellular, arranged in closely packed sheets, stroma fibrovascular or thick and fibrocollagenous with areas of hyalinization
Mitotic figures	None	Rare (0-2/HPF)	Common (3-6/HPF)
Edema and necrosis	Minimal	Areas of diffuse edema and necrosis	Edema, hemorrhage and necrosis common

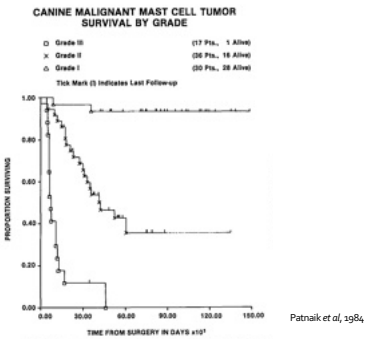
Grading System for Cutaneous and Subcutaneous Soft Tissue Sarcoma in the Dog (Dennis et al.)

Score Criteria	Score = 1	Score = 2	Score = 3
Differentiation	Closely resembling normal adult mesenchymal tissue	Histologic type can be determined, although differentiation is poor	Undifferentiated sarcomas, sarcomas of unknown type
Mitotic score	<10	10–19	≥20
Tumor necrosis	no	<50%	>50%

Mitotic score: # mitoses per 10 HPF (400×)
Histologic grade = differentiation score + mitotic score + tumor necrosis score; Grade I score = ≤4; Grade II score = 5-6; Grade III score ≥7.

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Histology
Grade



Patnaik *et al*, 1984

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Other diagnostics

Tumor Markers

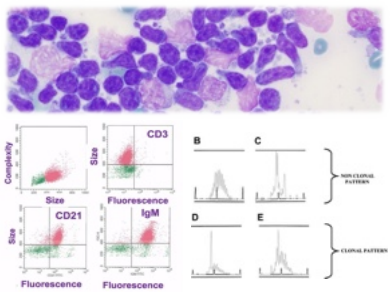
Aspecific
- cCRP ± haptoglobin (lymphoma)
- LDH (lymphoma)
- ALP (osteosarcoma)
- alpha-fetoprotein (hepatocellular carcinoma)

More or less specific
- Calcium (lymphoma)
- Glucose (many)
- PTH-rp (many)
- TK1 (lymphoma)
- cTnI (HSA, cardiac in particular)
- Big Endothelin (HSA, splenic in particular)
- CA 15-3 (cancer antigen; metastatic vs non-metastatic mammary carcinoma)

Specific
- Hormones: T_4, PTH, insulin

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Other diagnostics



Flow cytometry
(hematopoietic neoplasia)

Clonality assay (PARR)
(lymphoid neoplasia)

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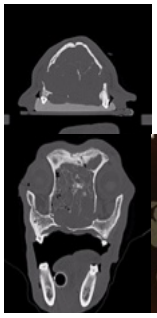
KOKI

- Labrador X, 4Y, M
- Has lived in Macedonia
- Hx: sinonasal aspergillosis, ehrlichiosis, leishmaniasis
- Tx: allopurinol, doxycycline
- Referred for radiotherapy

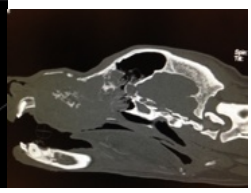


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KOKI - diagnostic imaging

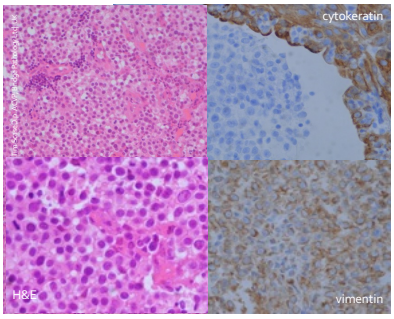


A large expansile nasal mass, with widespread bony destruction and invasion of adjacent structures. Non-neoplastic pathology is considered unlikely.



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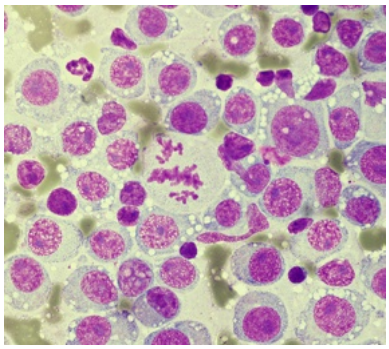
KOKI - histology and IHC



"poorly differentiated tumor of neuroendocrine origin"

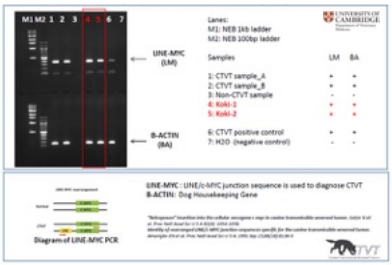
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KOKI - cytology



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KOKI - PCR for LINE/c-MYC



Confirmation of cTVT

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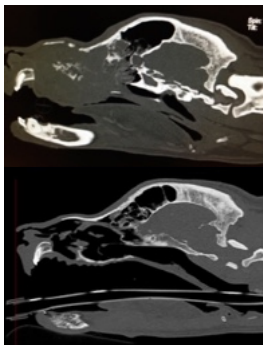
KOKI - intranasal cTVT



Diagnosis	Extensive, destructive nasal neoplasia stage 4	Intranasal cTVT
Therapy	Radiotherapy	Chemotherapy
Costs	± €3.500	± €900
Prognosis	Palliative (short tot medium-term control)	Curative

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KOKI – intranasal cTVT



At presentation

After 6x vincristine *iv*

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Step 2. Location

Lab-work and CAT-scans



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Staging

The process of localizing the tumor(s) and assess possible spread to lymph nodes and/or other organs

The goal of staging is to assess the severity/extent of the cancer and should prove capable of

1. Predicting patient prognosis, and
2. Guide the clinician in choosing the appropriate therapy (neither over- nor undertreat a patient)

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Staging

Physical Exam

- (History)
- General impression (BW/BCS/MCS)
- General physical examination
  - Lymph node size, abdominal palpation (liver/spleen, kidneys (C)), thoracic percussion, digital rectal exam
- Assess organ systems relevant to anesthesia (cardiac/pulmonary)
- Consider
  - Ophthalmic exam (fundoscopy)
  - Orthopedic evaluation other limbs in case of orthopedic malignancies
  - Neurologic examination

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Staging

Clinical Pathology

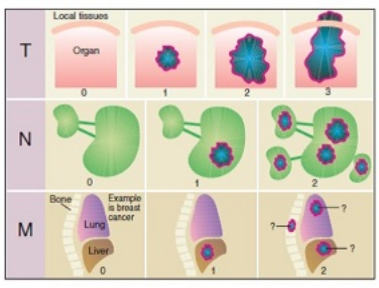
Routine laboratory tests
- Blood, urine, effusions, CSF
- Rarely diagnostics/specific for neoplasia
  - Exception leukemia/stage V lymphoma

Assess
- Bone marrow, liver and kidney function
  - Anesthesia (surgery/radiotherapy)
  - Use of chemotherapy
- Paraneoplastic signs
  - Hematology
  - Calcium
  - Glucose
  - Total protein
- Coagulation profile
  - Histological biopsies
  - Paraneoplastic

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Staging

TNM-system



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Staging

general TNM-system

Primary Tumor (T)

T_X	Primary tumor cannot be evaluated
T_0	No evidence of primary tumor
T_{is}	Carcinoma *in situ*
T_1, T_2, T_3, T_4	Size and/or extent of the primary tumor

Regional Lymph Nodes (N)

N_X	Regional lymph nodes cannot be evaluated
N_0	No regional lymph node involvement
N_1, N_2, N_3	Involvement of regional lymph nodes (number of lymph nodes and/or extent of spread)

Distant Metastasis (M)

M_X	Distant metastasis cannot be evaluated
M_0	No distant metastasis
M_1	Distant metastasis is present

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Staging

scheme solid tumor

WHO-classification for oral tumors

Tumor Stage	Characteristics
I	T_1, N_0, M_0
II	T_2, N_0, M_0
III	T_3, N_0, M_0
IV	Any T, N_1, $M_{0/1}$

Tumor (largest diameter)

T_1	< 2 cm
T_2	2-4 cm
T_3	> 4 cm
a	no bone involvement
b	bone involvement

N = regional lymph node

N_0	No metastasis
N_1	Metastasis

M = distant metastasis

M_0	No metastasis
M_1	Metastasis

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Staging

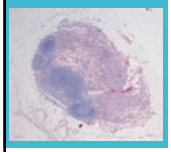
scheme hematopoietic tumor

WHO-classification for canine multicentric lymphoma

Stage	Description
I	Single lymph node
II	Multiple lymph nodes in a region of the body
III	Generalized lymphadenopathy
IV	I – III with involvement liver and/or spleen
V	Extra-nodal, I – IV with involvement blood and/or bone marrow
Substage	**Description**
a	No systemic signs
b	Systemic signs (anorexia, >10% weight loss, fever, pu/pd – hypercalcemia)

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Node

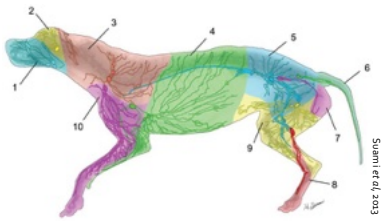


- Be familiar with regional lymph nodes
  - Sentinel node procedures!
- Assess lymph node size
  - Up to ½ of enlarged lymph nodes are reactive
  - Up to ⅓ of Ln metastases do not result in Ln enlargement (melanoma, MCT)
- Cytology *vs* Histology
- Lymphogenic spread: carcinomas, round cell tumors
- Hematogenic spread: sarcomas

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Node

lymphosomes



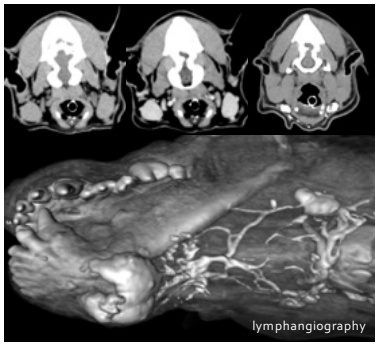
Sumner et al, 2013

1. Submandibular
2. Parotid
3. Dorsal superficial cervical
4. Axillary
5. Medial iliac
6. Lateral sacral
7. Hypogastric
8. Popliteal
9. Superficial inguinal
10. Ventral superficial cervical

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Node

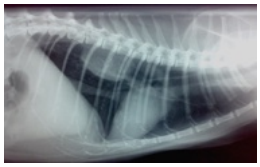
sentinel node procedure



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Metastasis

- Distant sites = beyond regional lymph node
- Where to look?
  - Lungs: carcinomas (mammary, thyroid, anal sac), sarcomas (osteosarcoma), histiocytic sarcoma
  - Liver/spleen: mast cell tumors (D), histiocytic sarcoma
  - Anywhere: hemangiosarcoma, melanoma
  - Odd ones: right auricle in canine hemangiosarcoma; feline lung-digit syndrome

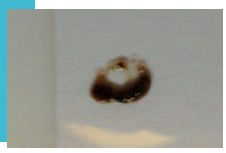
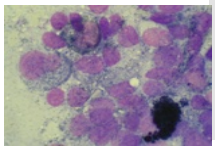
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Staging

Biopsy

Regional lymph node
- Always biopsy, regardless of Ln size!
- Less reliable for assessing Ln involvement:
  - feline intestinal low-grade T-cell lymphoma,
  - canine MCT

Distant sites
- Liver, spleen, abdominal lymph nodes
- Lungs
- Blood, bone marrow

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Paraneoplastic syndromes

Constitutional
- Weight loss/Cachexia
- Fever
- Hyperviscosity
- Hypertrophic osteopathy

Cutaneous
- Nodular dermatofibrosis
- Superficial necrolytic dermatitis
- Pemphigus vulgaris
- Alopecia

Neurologic
- Myasthenia gravis
- Neuropathy

Gastrointestinal
- GI ulceration
- Diarrhea

Secondary auto-imune/immune-mediated disease

Hematologic
- Anemia
- Polycythkimemia
- Leucocytosis (neutrophilia; eosinophilia)
- Thrombocytosis
- Pancytopenia

Coagulation disturbances
- Thrombocytopenia
- Thrombocyopathy
- DIC

Metabolic
- Hypercalcemia
- Hypoglycemia
- Hyperhistaminemia
- Hypokalemia

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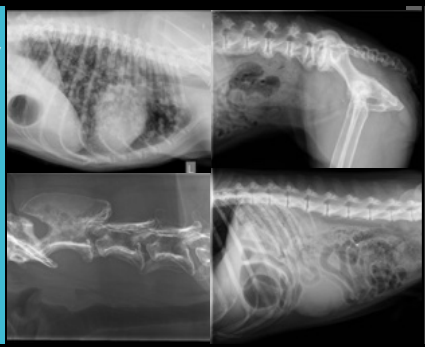
Diagnostic Imaging

Indications:
- Diagnosis
- Staging
- Obtaining biopsies (cytology/histology)
- Treatment planning
  - Surgery
  - Radiotherapy



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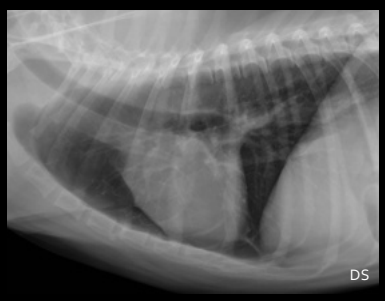
Radiography



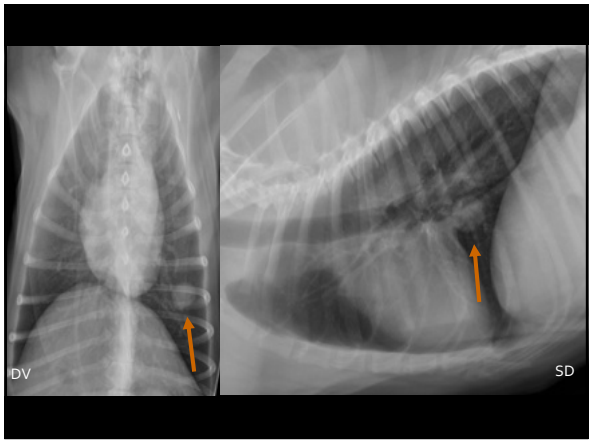
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Radiography

Metastatic screening

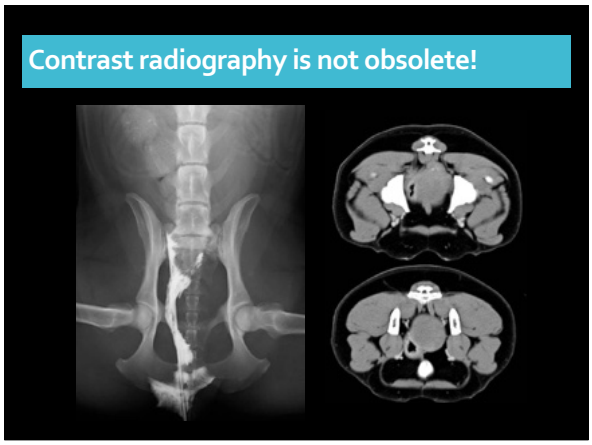


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Contrast radiography is not obsolete!



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Ultrasonography

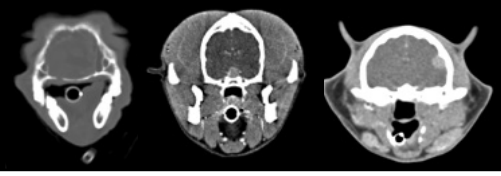
- Diagnosis
  - Neck
  - Thoracic masses: cranial mediastinum, superficial lung lesions
  - Abdominal masses
- Staging
  - Tumor, Lymph nodes, Metastases
- US-guided biopsies: cytology/histology



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CT-scan

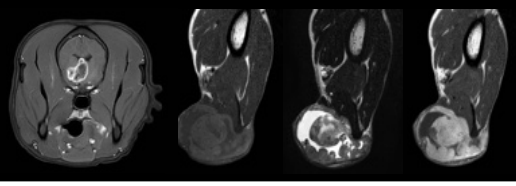
- Diagnosis
  - ✓ Nasal neoplasia
  - ✓ Oral neoplasia
  - ✓ Some CNS neoplasia: meningioma, pituitary, spinal and, nerve root tumors
  - ✓ Bone tumors
  - ✓ Thoracic and abdominal tumors
- Staging: metastatic disease thorax, abdomen
- Treatment planning



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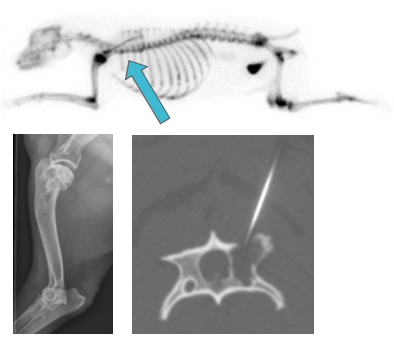
MRI

- Diagnosis
  - ✓ Nervous system neoplasia
  - ✓ Soft tissue tumors (sarcomas)
- Staging: no
- Treatment planning:
  - pre-surgical evaluation, especially soft tissue sarcomas



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Scintigraphy

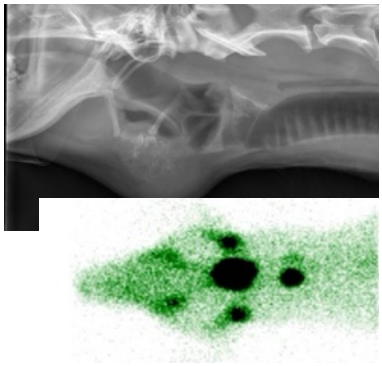


Osteosarcoma (dog)

skeletal metastases

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Scintigraphy



Thyroid carcinoma (dog)

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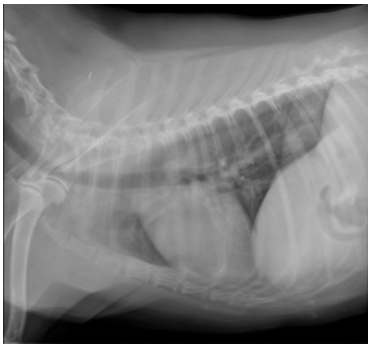
Nanouk

Siberian Husky F 10Y5M

- Recently noted firm mass on the right chest wall
- Hx: ±1 years ago soft tissue sarcoma Gr1 incompletely excised at same location
- PE: large firm SC mass, locally fixed to the underlying tissues, extending into the right axilla
- Cytology: mesenchymal proliferation suspect for sarcoma
- Assessment: large tumor size and recurrence, more likely to be aggressive sarcoma (>Gr1)
- Therapy: aggressive surgery and most likely adjuvant radiotherapy.
- Prognosis: depends on grade of the new tumor and degree of resection, varying from months to years
- Costs: 3.500 - 5000€

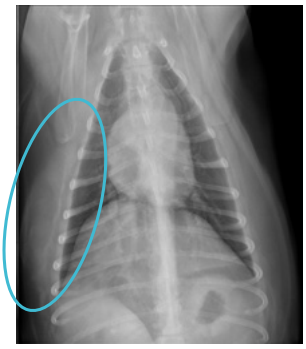
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Nanouk



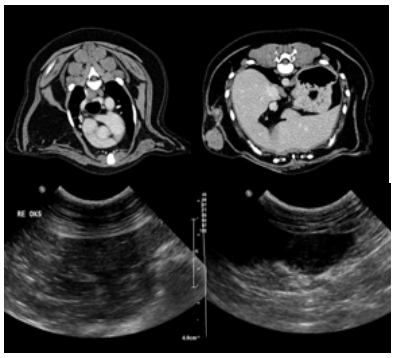
63

Nanouk



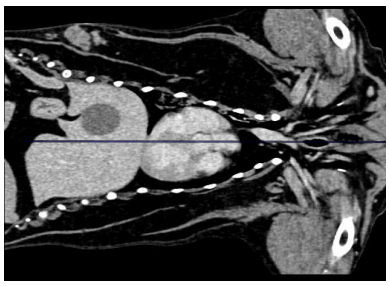
64

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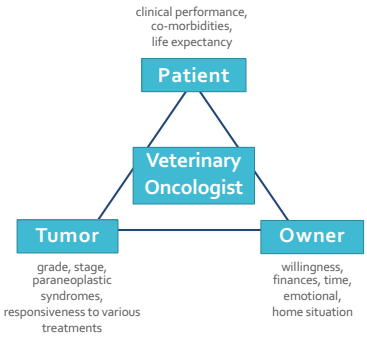
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Nanouk



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STEP 3. Care plan



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Treatment options

What options are there?

- Surgery
- Cryotherapy
- Chemotherapy
- Electrochemotherapy
- Protein-kinase inhibitors
- Hyperthermia
- Photodynamic therapy
- Radiotherapy
  - Strontium-90 plesiotherapy
  - External beam radiotherapy (ortho-/megavoltage)
  - Systemic
- And many more.....

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Bentley

Rottweiler, M 6Y





- L front limb lameness
- Hx; chronic R elbow disease
- PE: thickened elbow

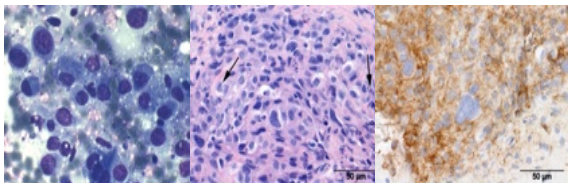
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Periarticular tumors in the dog

	Synovial cell sarcoma	Histiocytic sarcoma
Metastatic rate	±25%	±90%
Metastases	Regional lymph node, lung	Regional lymph node, lung, liver, spleen
Median survival time	30M	5M
IHC	cytokeratin	IBA-1/CD18
Primary treatment	Limb amputation	Limb amputation, radiotherapy
Adjuvant treatment	None	Chemotherapy (CCNU)

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Bentley



CD3	CD79	MUM-1	Toluidine blue	IBA-1	Melan A
T-cells	B-cells	Plasma cells	Mast cells	Histiocytes	Melanocytes
-	-	-	-	+	-

- Initial therapy
  - Radiotherapy (4x 6Gyq1W) + Chemotherapy (6x CCNU 80mg q3W PO → 10x)
- @ 14 months - New mass near L shoulder → Surgery
- @ 23 months - Euthanasia due to metastatic disease

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Questions?



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