SEE SOMETHING, DO SOMETHING. WHY WAIT? ASPIRATE. ®

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WHAT IS "SEE SOMETHING, DO SOMETHING. WHY WAIT? ASPIRATE. DR SUE CANCER VET? ®"

"See Something, Do Something" (SSDS) is a lumps and bumps cancer awareness program that provides guidelines for evaluating superficial masses in dogs and cats. We hope these guidelines to increase client awareness will promote early cancer detection and diagnosis, as well as early surgical intervention. **In veterinary medicine, most skin and subcutaneous tumors can be cured with surgery alone if diagnosed early when tumors are small.**

See Something: If a skin mass is the size of a pea (1 cm) and has been there 1 month, **Do Something**: Aspirate or biopsy, and treat appropriately!

WHY DO WE NEED SSDS?

It is well documented that cytologic and histologic evaluations are important diagnostic tools in veterinary oncology and that obtaining a preliminary diagnosis optimizes treatment planning. It is also recommended to evaluate masses that are growing, changing in appearance, or irritating to the patient. At this time, no specific guidelines exist for determining when to aspirate or biopsy or when to monitor canine and feline skin and subcutaneous masses.

Without standard of care guidelines, superficial masses may be monitored for too long. This can negatively impact our patient's prognosis as well as limit their treatment options. Larger tumors that are diagnosed later may require more advanced treatments. Surgical excision of larger masses may result in less than adequate surgical margins (narrow or incomplete), leading to recurrence and additional costly therapy (second more aggressive local surgery, radiation therapy and/or chemotherapy).

With significant time delays and prolonged monitoring, there may be no reasonable surgical treatment options to remove large advanced tumors. These are often the most frustrating and heartbreaking cases.

WHY DIAGNOSE EARLY?

Obtaining a definitive diagnosis with cytology or biopsy *early and before excision* **will** lead to improved patient outcomes for superficial masses. When smaller, superficial tumors are detected early, surgery is likely curative - especially benign lesions and tumors that are only locally invasive with a low probability of metastasis. If tumors are removed with complete surgical margins, the prognosis is often good with no additional treatments needed.

- Visual monitoring is not enough.
- Pet owners need to be aware of the "pea" size requirement to have masses evaluated
- Veterinarians must measure and document the size of the mass in order to compare growth.
- If > 1 cm (or size of large pea) and present for a month, the mass should be aspirated or biopsied.
- Knowing the tumor type prior to the FIRST surgery will increase success of a curative-intent surgery.

WHAT ARE THE MOST COMMON TUMORS?

Primary skin and subcutaneous tumors are common in dogs and cats. While the overall incidence in dogs and cats is difficult to determine, approximately 25 to 43% of biopsies submitted in dogs and cats are of the skin. Of submitted samples, 20 to 40% are reported to be malignant.

The most common malignant skin tumors in **dogs** are mast cell tumors (MCT) (10-17%), soft tissue sarcomas (including fibrosarcomas [2-6%], malignant nerve sheath tumors [4-7%]), and squamous cell carcinomas (2-6%). The most common benign canine skin and subcutaneous benign tumors include lipomas (8%), histiocytomas (8-12%), perianal gland adenomas (8-12%), sebaceous gland adenomas/hyperplasia (4-6%), trichoepitheliomas (4%), papillomas (3%), and basal cell tumors (4-5%).

In **cats**, the most common superficial tumors include basal cell tumors (BCT) (15-26%), mast cell tumors (13-21%), squamous cell carcinomas (10-15%), fibrosarcomas (15-17%). These four tumor types make up about 70% of all skin tumors in cats. Sebaceous gland adenomas are much less common (2-4%). If BCT are excluded, the percentage of malignant skin tumors in cats is higher than dogs, with studies reporting 70 to 80%.

IS VISUAL MONITORING ACCEPTABLE?

Even the most experienced veterinarian or oncologist cannot look at or palpate a mass and know whether it is malignant or not. Cancer is a cellular diagnosis! It is always recommended to evaluate masses that are growing, changing in appearance, or irritating to the patient. But these guidelines are not enough. All skin and SQ masses that are >1 cm and have been present for 1 month should be aspirated for cytologic evaluation. Biopsy is indicated if cytology does not provide a diagnosis.

METHODS OF DIAGNOSIS

Aspirate and Cytology

Fine needle aspiration (FNA) and cytology provide a diagnosis for many skin and SQ masses, especially those that that exfoliate well. FNA is useful to distinguish neoplasia from inflammation. Cellular morphology may also allow for the determination of benign or malignant phenotype. FNA is useful for identifying benign masses including lipomas and sebaceous adenomas. For malignant tumors, cytology provides information that assists in formulating diagnostic and treatment plans.

The advantages of cytology include: minimally invasive approach, low risk, low cost procedure, and results are available more quickly than biopsy results. The disadvantages of cytology are that it may be nondiagnostic or equivocal. This may be due to a small number of cells in the sample, poor exfoliation of the cells, or poor sample quality. If the sample is non-diagnostic or equivocal, histopathological confirmation may be required for definitive diagnosis.

Unless the sample is comprised exclusively of only fat, clear cystic fluid, or acellular debris, the sample should be submitted to a trained cytopathologist. WHEN IN DOUBT, SEND IT OUT. Including an adequate history helps the pathologist in diagnostic accuracy.

Biopsy

If cytology is non-diagnostic, a pre-treatment biopsy is recommended PRIOR to complete tumor removal. The pre-treatment biopsy will determine the optimal treatment plan.

The role of excisional biopsy is controversial, even among oncologic surgeons. A practical

recommendation for non-diagnostic cytology and the lesion fits in an 8 mm punch biopsy, then PUNCH IT OUT. If the mass is larger than an 8 mm punch biopsy, an incisional biopsy (wedge, tru-cut, punch) is required for diagnostic confirmation.

It is tempting to remove the mass right away. An excisional biopsy establishes a diagnosis and removes the tumor at the same time. However it is not recommended for undiagnosed skin and superficial masses. Malignant tumors often require 2 to 3 cm margins. When an excisional biopsy (or debulking surgery) leads to incomplete margins for malignant tumors, more treatment, more morbidity, and more expense ensue. **Thus removing the mass entirely is not recommended without a cellular diagnosis prior to definitive excision. Surgical approaches vary with different tumor types. Research confirms that the first surgery is the best chance for a cure.**

Staging diagnostics are often indicated prior to curative intent surgery. Consultation with a veterinary oncologist is recommended.

AFTER THE ASPIRATE/BIOPSY

If the mass is benign:

Benign tumors may not need to be removed. A variety of factors, including mass location should be considered. Surgery should be recommended when a benign tumor is causing pain, irritation, bleeding, or infection. Surgery should also be recommended if an increase in growth would prevent a surgery in the future.

Alternatively, if removing the tumor requires a complicated surgery (i.e. near a joint, on the distal limb with minimal surrounding tissue for reconstruction) or the pet has other pre-exiting issues, you and the pet owner may make an educated decision as to whether proceeding to surgical removal is warranted. **PETS WITH MASSES NOT REMOVED SHOULD BE MONITORED (via measurement) BY THE VETERINARIAN EVERY 3 TO 6 MONTHS.**

If surgery is performed, most benign masses require smaller surgeries, as wide margins are typically not needed.

If the mass is malignant:

If the aspirate/biopsy reveals malignancy, consult with veterinary oncologist for appropriate staging recommendations. For malignant tumors, the first surgery should be a wide excisional surgery.

If wide excisional surgery is not possible due to the size or anatomic location of the mass, consultation with a veterinary oncologist or board-certified surgeon is indicated. Surgeons may be able to perform specialized surgeries such as axial pattern flaps to remove the tumor completely.

Debulking (cytoreductive) surgery may not be recommended, as this will not obtain margins, and additional post-operative treatments such as radiation will be required to prevent recurrence. In some cases, cytoreductive surgery may be performed for palliation, or with an understanding that adjunctive therapy such as radiation therapy will follow the procedure.

After surgery:

- Review the histopathology report – tumor type, grade, vascular and lymphatic invasion.
- Consult with a veterinary oncologist for additional therapeutic considerations for malignant tumors.
- Assess the QUANTITY of surgical margins in consideration of tumor type and biologic behavior.

(One mm margins for a malignant tumor may be called "clean" on a biopsy report, but size of margins must be considered in light of tumor histology.)
- If margins are inadequate, recommend adjunctive treatment before tumor recurrence for optimum patient outcome. Post-operative options include scar revision (second surgery), radiation to prevent regrowth, or chemotherapy which may slow recurrence in some cases.
- It is important to consult a board certified surgeon before attempting scar revision.
- Monitor for local tumor recurrence and metastasis as indicated by the histologic diagnosis and margin assessment.

RECURRENCE AND MONITORING

Patients with reported complete surgical margins can potentially suffer tumor recurrence due to microscopic cancer extension that is not seen in the evaluated sections. Therefore, it is essential to monitor for local regrowth, and to recruit the pet owner to monitor the surgical scar as well, to identify early relapse.

For malignant tumors with wide, clean margins and low metastatic potential, follow-up rechecks are recommended every two to three months after the surgery for as much as one year of follow up. Early detection is key to addressing recurrence and metastasis to ensure the highest possible chance of success.

Owners are encouraged to check their pets regularly at home for new masses.

- Owners should check their pet monthly for superficial masses by noting their location and size.
- Create a "body map" with size and location of superficial masses recorded, along with fine needle aspiration cytology results. This body map can serve as an objective medical record document and owner guide to follow masses longitudinally, and to allow for identification of new masses over time.
- All masses should be aspirated and submitted for cytology. Masses that do not need cytologic assessment include lipomas, cysts, and those containing acellular debris.
- If cytology is non-diagnostic, discuss repeating the aspirate, or proceeding to biopsy.
- **Know the tumor type prior to surgery. The first surgery is your patient's best chance for cure.**

SURGERY MAY BE ALL THAT IS NEEDED

We all must be proactive to advocate for early cancer detection. Visual monitoring of superficial masses is not enough. Obtaining a definitive diagnosis via either cytology or biopsy *early and before excision* **will** lead to improved patient outcomes for superficial masses. Surgery is likely curative for the majority of these cases, especially for benign masses and those locally invasive malignancies that are nonmetastatic. **If tumors are detected and removed earlier – when they are small and with clean margin**s, the prognosis is often good and the patient may not require additional therapy.
> **See Something: When a skin mass is the size of a pea (1 cm) and has been present for 1 month,**
> **Do Something: Aspirate or biopsy, and treat appropriately! Early**
> **detection saves lives. Why wait? Aspirate.®**

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PRACTICAL TIPS FOR CHEMOTHERAPY PATIENTS IN YOUR PRACTICE

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Cancer is not a death sentence in pets. Chemotherapy is well tolerated in the majority of dogs and cats undergoing treatment. With treatment, many cancer patients are not only living longer, but living well.

The pet is a family member, and owners often want same standard of care for their dogs and cats as they do themselves. Sadly, cancer is leading cause of death in pets. "Cancer" is a scary word that is often equated with death. There is often a visceral fear of cancer, and people think cancer equals pain and suffering. Owners think cancer treatment will just make the patient sicker. With cancer, there is no hope. I disagree. Cancer is not a death sentence. While we all want a cure for cancer, I encourage thinking about many cancers as chronic conditions that may require chronic therapy, such as kidney or heart disease. As an oncologist, I recommend treatment when the pet is likely to live longer with it than without. Thankfully, most pets feel good, if not great, during treatment. I believe it is important to approach the topic of cancer with knowledge, compassion, and a positive attitude.

CHEMOTHERAPY

Conventional Chemotherapy Conventional chemotherapy is typically given at high dosages, known as maximum tolerated dose, or MTD. The goal is to kill the rapidly dividing cancer cells. But some normal cells that also have high turnover often can be temporarily damaged by MTD chemotherapy. The normal tissues that typically are most sensitive to chemotherapy are the bone marrow, hair follicles (alopecia), and the gastrointestinal lining. This is often referred to as "BAG". As a result there is a break period to allow these cell populations to recover. MTD is typically given weekly to every 3 weeks.

The overall toxicity rate is very low in veterinary chemotherapy patients. In my experience, only 15-20% experience side effects, and this is even less common in cats than dogs. The primary goal is to provide the best quality of life possible for as long as possible. As I say**, live longer, live well.** Most side effects are mild and medically manageable.

Metronomic chemotherapy In contrast to MTD chemotherapy, metronomic chemotherapy is pulse or low-dose continuous chemotherapy. This is typically administered daily or every other day. The target is endothelial cells in that line tumor blood vessel. The goal may be tumor is stabilized, but this prevents further growth and spread. Common chemotherapy drugs include Palladia, cyclophosphamide, and chlorambucil and also with NSAIDS. There is still much to be learned including best drugs, dose, schedule, tumor types, and toxicity. This can be considered for some dogs and cats with advanced metastatic disease.

SIDE EFFECTS

Alopecia Alopecia (hair loss) is due to damaging the rapidly dividing hair follicle. In dogs, potentially affected breeds have continuously growing coats and include Poodles, Scottish Terriers, and Westies. In cats, alopecia is rare, but shaved areas tend to grow back more slowly (limb catheters, abdominal ultrasounds). Cats more commonly lose their whiskers. The good news is that hair and whiskers will re-grow once the treatments have completed.

Occasionally, hair will grow back a different texture or color. In cats it is typically softer, aka the "chemo coat". It is important to remember pets do not care about this cosmetic side effect, and it does not impact the quality of life. However, pet owners like to be advised about the whiskers and coat so they are not surprised.

Gastrointestinal (GI) toxicity Gastrointestinal (GI) toxicity includes vomiting, diarrhea, decreased appetite, nausea. It typically 1 to 5 days after chemotherapy and is self-limiting – lasting on average 2-3 days. These side effects are less common in feline chemotherapy patients than dogs. I recommend being very proactive with nausea/anti-emetic drugs. I often will use Cerenia or mirtazapine preventatively and as needed.

I recommend giving Cerenia at administration with the following drugs: doxorubicin, vincristine, vinblastine, carboplatin, mitoxantrone, dacarbazine, and the MOPP protocol. If the pet has nausea/vomiting event within 24 hours of administration, I will add Cerenia SQ or IV at the time of administration at the subsequent treatment. For oral chemotherapy being given at home, I advise the owner give oral Cerenia 1 hour before chemotherapy pill dosing.

I always recommend oral Cerenia for 4 days after doxorubicin in dogs to prevent nausea and vomiting. If there are side effects with other chemotherapeutics, I also typically will add prophylactic medications to prevent side effects like nausea, vomiting or diarrhea as indicated. If the GI side effects are more severe in a patient, the drug type or dosage may be adjusted at subsequent treatments to minimize the chance of side effects recurring.

Unlike dogs, I do not routinely use GI medications unless the cat had issues with a prior treatment or had GI clinical signs prior to treatment (i.e. GI lymphoma)

For diarrhea, I typically send my patients home with metronidazole and a probiotic. Metronidazole is a synthetic nitroimidazole with antibacterial, anti-protozoal and antiinflammatory properties and is commonly prescribed for acute and chronic diarrhea. It is metabolized and excreted by the liver, so take care with patients with impaired liver function. Neurotoxicity is associated with higher doses and chronic use, so I do not recommend chronic use. Dose: 15 mg/kg PO BID for 5 days. Rx Clay is a good option for chronic diarrhea and patients needing multiple courses of metronidazole. Rx Clay is a calcium aluminosilicate (CAS), which is geological nanomaterial that adsorbs bacterial enterotoxins and increases reabsorption of intraluminal water in GIT/

VOMITING AND DIARRHEA

Acute vomiting is typically associated with cisplatin, doxorubicin (Adriamycin), dacarbazine (DTIC), cyclophosphamide, actinomycin, 5-FU streptozoticin. This can typically be prevented with pre-treatment.

Delayed vomiting is more common in our patients. This is due to direct damage to rapidly dividing GIT cells (crypt cells) or via the centrally mediated CRTZ stimulated via gut vagal efferents. Delayed vomiting is most commonly 2 to 5 days post-chemo and seen with doxorubicin and the vinca alkaloids. Clinical signs include vomiting, diarrhea, anorexia, lethargy, weakness, $\pm$ dehydration.

For work up, I recommend CBC, chemistry panel, UA, +/- fecal floatation and cultures. If abdominal pain is present, consider AXR or AUS to rule out foreign body, obstruction, and

intussusception. For patients with GI neoplasia, it can be challenging to differentiate chemotherapy side effects vs. disease, and a good history can be key.

For outpatient treatment, I recommend NPO, food & water trial, bland diet, anti-emetics, antibiotics with severe diarrhea and a probiotic. Do not forget to discontinue oral chemotherapy or delay chemotherapy treatment. In addition, I recommend prophylactic therapy with the next chemotherapy.

For inpatient, I add injectable antiemetics, IV fluid therapy, and IV antibiotics. An important note,
I strongly encourage owners to NOT EUTHANIZE at this time. It is amazing with 1 to 2 days of
good supportive care how quickly these patients improve. And with prophylactic therapy and a dose reduction, these patients can tolerate the same chemotherapy drug.

MYELOSUPPRESSION AND NEUTROPENIA

Bone marrow suppression most commonly results in a neutropenia but cats seem to be more tolerant than dogs. Neutrophils and platelets are at greatest risk due to the shorter circulating lifespan and shorter bone marrow transit times. Neutropenia is the dose-limiting toxicity in veterinary oncology.

In addition to the chemotherapy targeting rapidly dividing bone marrow stem cells, other mechanisms for neutropenia includes bone marrow infiltration with neoplastic cells (leukemia, advanced stage lymphoma, multiple myeloma) and increased consumption due to infection. When a chemotherapy drug is used that is known to have a high potential for bone marrow suppression (like doxorubicin, carboplatin and Lomustine), a complete blood count (CBC) is often checked after the treatment to check the expected nadir (low neutrophil count) and see if antibiotics and/or a dose reduction are needed. I recommend a nadir be checked with all chemotherapy drugs except L-aspariginase.

The nadir typically occurs 7 days after chemotherapy administration. Pay attention to the *neutrophil* count, not the total white blood cell count. For some chemotherapy drugs the nadir is more variable such as carboplatin and Lomustine. For cats, the nadir is can occur 7 to 28 days after treatment. In dogs the nadir for carboplatin in day 10-14. Chlorambucil tends to cause delayed neutropenias and thrombocytopenias after chronic use. Subsequent doses of chemotherapy are adjusted based on the results of the CBC.

Antibiotics may be prescribed as a preventive measure but its use is controversial. Common antibiotics are TMS and Clavamox. I recommend prophylactic use with the more myelosuprressive drugs (doxorubicin, carboplatin and Lomustine) or if the previous nadir was <1500 neutrophils. Unlike dogs, I do not routinely use prophylactic antibiotics unless the cat had issues with a prior treatment.

In my experience, there is less than a 5% chance that a patient will need hospitalization. If this does occur, these patients are usually hospitalized for typically 24-48 hours with supportive care including IV fluids and antibiotics. In my experience most chemotherapy patients can successfully receive that drug again with a dose reduction.

WHAT TO DO AT THE NADIR VISIT?

In addition to running a CBC, it is important to get a good history, TPR (fever is so important in neutropenic patients), and a complete physical examination. I am always interested in knowing how the patient handled chemotherapy –did she eat well, any vomiting/diarrhea, did the owner use any nausea or diarrheal medications? For the exam, did he lose weight, was she febrile? The nadir CBC should not be a technician appointment to just pull the blood sample. The history and exam are very important.

Pay attention to the *neutrophil* count, not the total white blood cell count. The nadir typically occurs 7 days after chemotherapy administration, but can vary (see above). I recommend antibiotics if the neutrophil count is <1500. If the patient has <1500 neutrophils and is afebrile and feeling well, I recommend managing as an outpatient. However, if the patient has <1500 neutrophils and is febrile and sick, I recommend admitting for supportive care. Remember a febrile neutropenic is an oncologic emergency.

Also, I prefer that we get blood samples from the jugular veins for patients getting IV chemotherapy (unless thrombocytopenic). Save those peripheral veins for treatment please. Finally many times the oncologist has run a recent chemistry panel, so check with the oncologist, and try not to repeat unneeded blood work to keep costs down.

Neutrophil count (per uL)	Fever, systemic signs	Plan
1500-2500	No	Monitor +/- treatment delay 2 to 4 days
<1500	No	Oral antibiotics treatment delay Consider dose change
<1500	Yes	ATH for IVF & IV antibiotics treatment delay Dose reduction

SEPSIS

Sepsis in chemotherapy patients is typically due to patient's own flora - Gram negative from GI bacteria: *E. coli, Klebsiella, Pseudomona;* Gram positive from skin bacteria: *Staphylococcus epidermitidis and aureus*, Anaerobes from oral bacteria. Predisposing factors include neutropenia (infection risk well correlated with degree and duration), cellular immune dysfunction, humoral immune dysfunction, prolonged hospitalizations, indwelling catheters, and poor nutrition.

History and clinical signs are typically straightforward - cytotoxic chemotherapy was administered typically 5 to 7 days ago. Remember, the **febrile neutropenic patient is an oncologic emergency!!!** In addition the patient may have an inability to mount an inflammatory response, so the lack of fever, pyuria, or radiographic changes of pneumonia does not rule out sepsis. Signs of illness are unrelated to absolute neutrophil count, but are related to an increased susceptibility to local and systemic infections when neutropenic. Gastrointestinal, urogenital, and respiratory infections are most common. Shock is also possible

The sepsis work up includes: CBC, Chemistry panel, UA & UCS (if >50,000 platelets). If respiratory signs are present, chest radiographs are recommended, and TTW should be considered. Blood cultures may be needed, but uncommon in my experience. Culture any catheters suspected as the infection source.

Treatment for sepsis includes: IVF and broad-spectrum IV antibiotics. Neupogen is human recombinant G-CSF. The MOA is stimulation of proliferation & maturation of neutrophil precursors, and monocyte precursors to a lesser extent. It also primes neutrophil for cell killing & neutrophil migration. The benefit for the febrile & febrile neutropenic patient is contradictory, and in my experience, Neupogen is rarely needed. The recommended dose is 5 ug/kg SQ SID until neutrophil >1000.

WHEN SHOULD I LOWER CHEMOTHERAPY DOSE?

Dose Intensity is chemotherapy given at MTD & shortest possible interval. It is important to remember than small dose changes can have significant impact on cancer control. Dose reductions as small as 20% can decrease drug efficacy up to 50%. ***Dose reductions should not be considered lightly.***

DON'T TREAT CATS LIKE SMALL DOGS WHEN IT COMES TO CHEMOTHERAPY

Some chemotherapy drugs are dosed differently in cats. In dogs, weight and body surface area are used to determine the carboplatin dose. In cats there is now a more accurate method to dose carboplatin in cats based on glomerular filtration rate, which is determined with an Iohexol clearance test.

Side effects in cats are also different. Cardiotoxicity is a well-described adverse effect in dogs treated with doxorubicin, but it has not been reported in cats. Sterile hemorrhagic cystitis (SHC) is a relatively uncommon complication of cyclophosphamide in dogs and ifosfamide therapy in dogs and cats. SHC is typically associated with long-term use, but possible after single dose, and can progress to bladder fibrosis. The incidence with cyclophosphamide has been reported to be 9% in dogs (7-24%), 3% in cats, and 24% in humans. Unlike dogs, concurrent administration of furosemide with cyclophosphamide is not recommended in cats. Mesna, which binds the SHC-inducing acrolein, is recommended for cats and dogs when administering ifosfamide.

CHEMOTHERAPY SAFETY

Chemotherapy requires careful prescription preparation, drug dispensing, drug administration, client education, and safe handling of patients by ALL staff. Chemotherapy exposure has been documented in nurses and pharmacy workers. It is important to protect your team, our clients, & follow protocols.

To protect your staff, the following are recommended a hood, closed system transfer device, dedicated counting equipment, dedicated chemo fridge, and Personal protective equipment (PPE) including gloves, gowns, chemo mat, and eye protection. Closed system transfer device such as PhaSeal® are leak-proof and airtight closed system transfer devices. Studies show closed systems reduce contamination and should be combined with other safe handling practices.

Active drug & metabolites are excreted in urine & feces, and there is some in saliva but research six limited. In the hospital identify patients after chemotherapy and dispose of wastes separately. Spill kits should be on hand and stocked.

Protect your entire staff and make sure staff is aware patient is getting chemotherapy. Special precautions are recommended for staff and clients that are pregnant, trying to become pregnant, breast-feeding, immunosuppressed, ir taking immunosuppressive medication. Recommend they talk to their physician.

Protect your client and discuss safety tips including common sense precautions, good basic hygiene, and provide an information sheet. Recommend they wear gloves when handling urine, feces, or vomit for at least 72 hours after treatment and when cleaning litter box. Wash soiled bedding separately & 2 wash cycles before use again, use detergent to clean floors, carpets, or countertops, and wear gloves when cleaning

It is safe to be around pets undergoing chemotherapy. Metabolites are far less active than original drug.
Being around family members – human and other pets in the home - is an important part of a pet's life. Normal activities are safe, but owners need to be careful with excretions.

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OSTEOSARCOMA SURVIVAL GUIDE
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KEY POINTS

- **Osteosarcoma (OSA)** is the most common primary canine bone cancer in dogs, and it is locally aggressive and highly metastatic.
- The majority of dogs with appendicular osteosarcoma have no evidence of metastasis at diagnosis, but most will likely succumb to metastasis.
- Early diagnostics are key. If you are presented with a large- or giant-breed dog that is lame and has swelling at metaphyseal site, it is osteosarcoma until proven otherwise, and do radiographs promptly.
- To determine the best treatment plan for a patient and owners, it is important to understand efficacy of the various protocols, the potential toxicities, and prognostic factors.
- Dogs treated with local therapy and chemotherapy live significantly longer than dogs without treatment and with local therapy only, and chemotherapy is generally welltolerated in most dogs. Only a minority develop significant toxicity.

WHO, WHAT, WHERE, WHY

What: Osteosarcoma is the most common primary bone cancer, accounting for 85% of all skeletal cancers and 5% of all neoplasia. OSA is a malignant mesenchymal tumor of primitive bone cells that produce ECM of osteoid. The biologic behavior is aggressive locally and highly metastatic. At the primary site, there may be bone lysis or bone production or both, soft tissue swelling, and pathologic fracture (not negative prognostic). While OSA is highly metastatic, <10-15% have detectable metastasis at diagnosis, but 90% die within 1 year with amputation alone due to metastasis

Who: OSA is estimated to occur in > 10,000 dogs per year, but this is likely an underestimate. It typically occurs in middle aged and older dogs, but there is a small peak at 1.5 to 2 years old. Rib OSA occurs in younger adults (5 y.o.). OSA is common in large and giant breeds with increasing weight and height. In the U.S., breeds most at risk are St Bernard, Great Dane, Irish Setter, GSD, Rottweilers, Dobies, and Golden Retrievers. The dog SIZE IS MORE IMPORTANT than breed. The risk of OSA is 60 times higher in dogs weighing > 30 kg, and 8 times higher in dogs weighing 20-30 kg. Appendicular OSA accounts for 95% of all cases in dogs >40 kg but only 40-80% of all cases <15 kg. Axial OSA can occur in any breed and at any location.

Why: Large and giant-breed dogs are predisposed. Body size (increasing weight and more specifically height) appears to be most predictive factors for OSA, and it is more important than breed. Hereditary basis is suspected based on the large breed prevalence. The most thoroughly described mutation that contributes to formation and/or progression is p53. Additional genetic factors studied are RB and PTEN tumor suppressor genes. OSA is more prevalent in males than females, but in the St Bernard, Great Dane, and Rottweilers, females outnumber the males, and females more affected by axial (except rib and spine). Sex hormones also appear to have a protective role. In Rottweilers neutered before 1 yo, 1 in 4 developed OSA and more likely than intact dogs. OSA has also been associated with fractures, metallic implants, chronic osteomyelitis and ionizing radiation.

Where: 75% of OSA is appendicular, and 25% is in axial bones. It typically occurs in the metaphyseal region of long bones, towards the knee and away from the elbow, front limbs are two times more affected than hind limbs. The most common sites are the distal radius bad proximal humerus, while in the hind limbs, OSA lesions are evenly distributed among the distal femur, distal tibia, and proximal tibia. The proximal femur less common and OSA distal to carpus and hock is rare.

In the axial location: 27% mandible, 22% maxilla, 15% spine, 14% cranium, 10% ribs, 9% sinonasal, and 6% pelvis. Multicentric is uncommon reported in <10% cases. Extraskeletal OSA is rare and some reported sites include mammary, SQ, spleen, GIT, eye, and kidney.

What do we see? Most dogs appear in pain, and many are presented with progressive lameness. Palpable swelling may or may not be present. Acute severe swelling is typical with pathologic fracture, but only 3% pathologic fractures due to OSA. If you are presented with a large- or giant-breed dog that is lame and has swelling at metaphyseal site, it is OSA until proven otherwise and do radiographs promptly.

DIAGNOSTIC WORK UP When taking radiographs, take good quality lateral and craniocaudal views. The abnormalities vary from mostly lysis to mostly osteoblastic. Common features include cortical lysis, soft tissue extension and swelling, new bone extension in sunburst pattern, Codman's triangle deposition of new bone on cortex at periphery. While OSA does not cross joint, it can invade adjacent bones. Radiographic changed can be similar to fungal osteomyelitis.

A presumptive diagnosis is based on signalment, history, PE, and radiographs. Differentials include other primary bone (CSA, FSA, HAS, HS), metastatic bone cancer (usually diaphyseal), multiple myeloma or LSA of bone, systemic mycosis, bacterial osteomyelitis, bone cysts, and healing bone injury.

Preliminary Diagnosis: Cytology While cytology is not definitive, it is supportive and can distinguish malignant vs non-malignant with an accuracy of 70-85%. In diagnostic samples, ALP staining can differentiate OSA from other sarcomas. Ultrasound-guidance can be helpful to aid sample collection.

Pre-op biopsy is not required in cases with classic signalment, history, PE/location, and radiographic appearance, there is little possibility of fungal or bacterial osteomyelitis, and the owners are willing to treat aggressively. On the other hand, biopsy is recommended if there is non-diagnostic cytology, the owner wants confirmation, or it is not a classic case. Always submit larger specimen at surgery to confirm.

When doing pre-op biopsy, plan carefully if limb spare is option so contaminated tissue is removed. There is also 10-20% false negatives rate. The open incisional approach collects a large sample but post-surgical complications include hematoma, seeding, infection, fracture, and wound breakdown. The trephine technique is 94% diagnostic but increases the fracture risk. Closed needle biopsy can be done with a Jamshidi and is 92% accurate for tumor diagnosis and 83% accurate for tumor subtype, but accuracy is dependent on experience and comfort level. In some case, repeated attempts may yield "reactive bone". Biopsy at CENTER of lesion, and incision and biopsy tract should be planned that will be removed a definitive surgery. Fluoroscopy or CT-guided biopsy can be useful. Samples collected from the peripheral bone lesion are more likely to be non-diagnostic and contain reactive bone.

Staging included local LN FNA, Orthopedic exam for bone mets, 3-view chest radiographs or chest CT. Treatment recommendations and prognosis are based on plain radiographs, not advanced imaging. Less than 5% of dogs have LN metastasis. Bone survey radiographs are not typically recommended unless there are suspicious or painful lesions. I involves taking a lateral of all bone and VD of the pelvis and can be considered to rule out bone metastasis and 6% of dogs have bone metastasis detected (vs 4% chest). Bone scans have conflicting reports of usefulness. AUS is not recommended for OSA staging, but can be considered if determining is the bone lesion is a metastatic lesion or there are abnormalities on the chemistry panel. CT is recommended for axial tumors.

PROGNOSTIC FACTORS: For appendicular OSA, the MST with surgery alone is 4 to 5 months. Well-established negative predictors include young age (<5 years old), large tumor size, humerus location, and

high histologic grade. Other factors include small body size, larger tumors, extraskeletal tumors, percent bone necrosis, mitotic index, and over metastasis (lungs, LN)

For non-appendicular, the head locations (mandible, maxilla, skull) are locally aggressive but have a lower metastatic rate (37%). With skull surgery alone, the MST is longer than limb at 7 months. The 1-year survival with mandibulectomy is 71%, but the MST is 5 months for maxillectomy. Following rib resection, the MST is 3 month, and 8 months for surgery and chemo.

Stage III dogs with measurable metastasis have a worse prognosis with a MST of 2 months. Dogs with bone metastasis do better than lung (4 m vs 2 m), and LN metastasis is a
negative prognostic factor (2 m vs 8 months) Dog with elevated ALP have shorter DFI and ST. Remember, prognostic factors cannot predict an individual's response.

TREATMENT MODALITIES

Treatment pearls Treatment for OSA is ideally both local and systemic. Since chemotherapy significantly improves the MST, it is considered part of the standard of care. The majority of dogs tolerates chemotherapy quite well and will maintain a good to excellent quality of life even during chemotherapy.

Treatment: Surgery

Surgical options include amputation or limb spare techniques to address the primary tumor. Amputation is the standard treatment for appendicular OSA. It is palliative and a very effective way to remove the source of pain, but amputation alone does not increase survival (other than preventing pain-related death) and most dogs succumb to metastasis. While we as veterinarians know that amputation is well-tolerated, many owners are shocked by the procedure and often reluctant to consider the radical procedure. It is important to screen the patient well and rule out concurrent musculoskeletal and neurologic abnormalities. Even middleaged and older large-breed dogs with moderate arthritis are typically candidates. Owner satisfaction is typically excellent post-op, and most dogs compensate well,
Surgical limb-spare procedures allow the preservation of limb function, and are an alternative when amputation is not physically an option or is declined by the owner. Limb-spare procedures do not increased survival times and systemic therapy is still recommended after the delay metastasis. There are various limb-spare procedures described but the techniques involve surgical resection of the effected bone and replacement with a bone implant, bone plating and arthrodesis to stabilize the joint. Since residual disease likely remains, the region is treated with radiation, IA cisplatin or chemotherapy impregnated beads. Distal radius and ulnar lesions are most amenable. These techniques have similar survival times but have much higher complication rates.

Treatment: Radiation

Like surgery, radiation is a local treatment option. Palliative radiation can be very effective for bone tumors, and is a good option if amputation is declined. Most dogs (75 to 90%) respond favorably and analgesia is improved. There is variation with duration of analgesia and most typically lasts 4 to 6 month but it can be durable for greater than 1 year, and palliative radiation can be combined with adjuvant IV chemotherapy.
Stereotactic radiosurgery (SRS, aka stereotactic radiation therapy (SRT) is an alternative limb-spare technique for local control. SRS delivers extremely precise high dose radiation with multiple beams within submillimeter accuracy. Less normal tissue that surrounds the tumor is irradiated, so there are fewer radiation side effects, higher dose to tumor, and fewer treatments (typically 3).
For OSA, preliminary results are encouraging with MST of approximately 1 year, when combined with chemotherapy for systemic disease. One type of SRS is called CyberKnife Radiosurgery, which I did with our radiation oncologist for 7 years at my previous practice. OSA was the 3rd most common tumor we

treated (after brain and nasal tumors). Not every dog with appendicular OSA is a candidate for SRS, especially if there is more bone destruction and increased risk of pathologic fracture. CT-based prognostic factors can help predict the likelihood of fracture.

Treatment: Chemotherapy

The goal of chemotherapy is to achieve is to delay the metastatic disease that develops quickly after amputation or limb-spare procedure. Since chemotherapy significantly improves the MST, it is considered part of the standard of care.

For appendicular OSA, the MST with surgery alone is 4 to 5 months, with 90 to 100% mortality rate in one year. With chemotherapy the 1-year survival rate is 40-50% and 20-25% of dogs are alive at 2 years. Most studies have evaluated doxorubicin, cisplatin, or carboplatin in varying combinations. Choice of protocol (single vs combination) does not result in significant differences in DFI or ST, the carboplatin protocol resulted in a lower proportion of dogs experiencing side effects, and helpful in maintaining high quality of life during treatment.
Unfortunately, 95% of dogs will eventually succeed to metastasis.

Other treatment options Other treatment options include bisphosphonates, immunotherapy, and COX-2 inhibitors. Pain control for the patients is a priority,
Bisphosphonates are osteoclast inhibitors than inhibit bone resorption and are used in human patients with diffuse skeletal metastasis. Approximately 30% dogs have decreased pain. Direct cytotoxicity to has also been reported suggesting interaction with radiation therapy and/or chemotherapy.

A canine OSA vaccine is currently being developed by Aratana. This is a recombinant HER2/neu expressing Listeria therapeutic vaccine being studied at UPenn. In a recent study by Dr Mason, 18 dogs were treated with amputation, 4 doses of carboplatin, and the vaccine. The MST has not been reached but 11 of 18 dogs surpassed the MST of the control group (318 days). Adverse effects were mild to moderate and included fever, lethargy, nausea and vomiting.

SUMMARY: OSA is the most common primary bone tumor is dogs. The biologic behavior is aggressive locally and highly metastatic, so its therapy requires both local and systemic treatments. For appendicular OSA, amputation addresses the local disease and is palliative. The MST with surgery alone is 4 to 5 months, with 90 to 100% mortality rate in one year. The ability to control the progression of OSA metastasis remains the challenge for our patients, and systemic chemotherapy is the backbone for therapy. With chemotherapy, the 1-year survival rate is 40-50% and 20-25% of dogs are alive at 2 years. Well established prognostic factors include adjuvant chemotherapy, low grade (rare for OSA), and normal total and bone ALP. Dogs treated with chemotherapy live significantly longer than dogs only treated with local therapy, and chemotherapy is generally well-tolerated in most dogs.

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METRONOMIC CHEMOTHERAPY FAQ: WHY, WHEN & HOW
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Cancer, even advanced metastatic disease, is not a death sentence in pets. Chemotherapy is well tolerated in the majority of dogs and cats undergoing treatment. With treatment, many cancer patients with metastasis can live longer and living well.

CONVENTIONAL CHEMOTHERAPY

Conventional chemotherapy is typically given at high dosages, known as maximum tolerated dose, or MTD. The goal is to kill the rapidly dividing cancer cells. But some normal cells that also have high turnover often can be temporarily damaged by MTD chemo. Most commonly, it is the GI tract cells and the neutrophils that are temporarily damaged. As a result there is a break period to allow these cell populations to recover. MTD is typically given weekly to every 3 weeks.

Chemotherapy drugs given at MTD attack rapidly dividing cells. The normal tissues that typically are most sensitive to MTD chemotherapy are the bone marrow, hair follicles (alopecia), and the gastrointestinal lining. This is often referred to as "BAG".

Bone marrow suppression most commonly results in a neutropenia. Neutrophils and platelets are at greatest risk due to the shorter circulating lifespan, and shorter bone marrow transit times. Neutropenia is the dose-limiting toxicity in veterinary oncology. Cats seem to be more tolerant than dogs.

Alopecia (hair loss) is due to damaging the rapidly dividing hair follicle. In dogs, potentially affected breeds have continuously growing coats and include Poodles, Scottish Terriers, and Westies. In cats, alopecia is rare, but shaved areas tend to grow back more slowly (limb catheters, abdominal ultrasounds). Cats more commonly lose their whiskers. The good news is that hair and whiskers will re-grow once the treatments have completed. Occasionally, hair will grow back a different texture or color. In cats it is typically softer, aka the "chemo coat". It is important to remember pets do not care about this cosmetic side effect, and it does not impact the quality of life. However, pet owners like to be advised about the whiskers and hair coat so they are not surprised.

Gastrointestinal (GI) toxicity includes vomiting, diarrhea, decreased appetite, nausea. It typically 1 to 5 days after chemotherapy and is self-limiting – lasting on average 2-3 days. These side effects are less common in feline chemotherapy patients than dogs. I often will use Cerenia or mirtazapine as needed.

The overall toxicity rate is very low in veterinary chemotherapy patients treated at MTD. In my experience, only 15-20% experience side effects, and this is even less common in cats than dogs. The primary goal is to provide the best quality of life possible for as long as possible. As I say, **live longer, live well.** Most side effects are mild and medically manageable. If there are side effects, I also typically will add prophylactic medications to prevent side effects like nausea, vomiting or diarrhea as indicated. It is important to be proactive and educate clients.

In my experience, there is less than a 5% chance that a patient will need hospitalization. If this does occur, these patients are usually hospitalized for typically 2448 hours with supportive care including IV fluids and antibiotics. In my experience most chemotherapy patients can successfully receive that drug again with a dose reduction and prophylactic medications.

METRONOMIC CHEMOTHERAPY

In contrast to MTD (high dose) chemotherapy, metronomic chemotherapy is pulse or low-dose chemotherapy. Metronomic chemotherapy is the uninterrupted administration or low doses of cytotoxic drugs at regular, continuous and frequent intervals without breaks. This is typically administered orally daily or every other day Elimination of breaks between dosages reduces or eliminates the ability of the tumor cells to repair damage or alter their microenvironment.

With MTD chemotherapy, the goal is to target and kill tumor cells directly. The target of metronomic chemotherapy is the tumor-associated vasculature. These are the endothelial cells in that line tumor blood vessel. In contrast to the quiescent endothelial cells throughout the body, tumor endothelial cells are much more proliferative. In metronomic chemotherapy, the result may be that the tumor is stabilized, but this prevents further growth and spread.

The key to metronomic chemotherapy is the reduction or elimination of breaks between dosages – to prevent repair and repopulation of the endothelial cells. This is also different than MTD chemotherapy in which the break between dosages allows for recovery of the normal cell populations, like neutrophils and GI tract cells. Another important distinction of metronomic chemotherapy is that chemotherapy is given at low dosages to allow for the continuous often daily dosages.

Overall, metronomic chemotherapy protocols are well-tolerated with low toxicity profiles. Depending on the drugs used, some protocols are also lower in cost. Common chemotherapy drugs include low dose cyclophosphamide, chlorambucil, and Lomustine. Toceranib (Palladia) is also used in metronomic protocols. Other drugs included in some protocol are NSAIDS and doxycyline. There is still much to be learned including best drugs, dose, schedule, tumor types, and toxicity.

How does metronomic chemotherapy work?

In the cancer patient, tumor angiogenesis occurs locally in the tumor microenvironment   where circulating endothelial cells (CECs) are stimulated and due to systemic effects of circulating endothelia progenitor cells (CEPs) that are derived in the bone marrow. Continuous low dosages of many chemotherapy drugs are cytotoxic to both CECs and CEPs. There seems to be little toxic effects on non-endothelial cells like white blood cells and epithelial cells. Tumor cells are also not effected by metronomic chemotherapy.

Another interesting target is the regulatory T-cell (Treg), a subset of the CD4+ Tlymphocyte population that helps tumor cell survival by contributing the immune suppression. Low dose cyclophosphamide (CYC) has been demonstrated to be selectively toxic to the Treg cells. It is also believed that NSAIDs can also decrease Treg cells with COX inhibition. Many metronomic protocols combine a chemotherapy drug like low dose CYC and a NSAID.

There is concern for the risk of sterile hemorrhagic cystitis (SHC) with cyclophosphamide, and this risk may increase with cumulative CYC administration. Owners should be advised of the risk of SHC and appropriate and regular patient monitoring is highly recommended. Cyclophosphamide should be discontinued.

In some cases when MTD high dose chemo is no longer effective, metronomic chemotherapy may still inhibit tumor growth. This can be considered for some dogs and cats with advanced metastatic disease.

ANTIANGIOGENIC CHEMOTHERAPY WITH RTKI

Most Receptor Tyrosine Kinase Inhibitors (RTKI) target numerous receptors. Toceranib (Palladia) is a RTKI approved for MCT in dogs that targets the mutated c-kit to directly kill tumor cells. In addition, Palladia also inhibits angiogenesis by targeting other receptors like VEGFR and PDGFR. Palladia may be useful in metronomic chemotherapy protocols.

There is evidence that good biologic activity occurs when Palladia dosages are lower than the label dose of 3.25 mg/kg EOD. This was noted in the Phase I study of dogs with a variety of solid tumors where response was noted at 2.5 mg/kg EOD. Additional studies with solid tumors found lower dosages were associated with good clinical activity and reduced side effects. Biologic activity has been observed in anal gland anal sac ACA, thyroid carcinomas, metastatic OSA, nasal carcinoma, and head and neck carcinoma

I typically recommend 3 times per week dosing with a target dose of 2.5 to 2.8 mg/kg (ie MWF) and will use low dose compounded CYC on TuThSat. I typically use a NSAID on non-Palladia days if included.

TOXICITY AND SUPPORTIVE MEDICATIONS

In general, metronomic chemotherapy is well tolerated with minimal toxicity. In my experience, side effects are most likely to occur with Palladia and are usually GI-related. so I typically start Palladia first and make sure the patient is tolerating it before adding additional medications such as low dose CYC. I start omeprazole with Palladia. I avoid metronomic chemotherapy in patients presenting with inappetance and/or vomiting and diarrhea

Gastrointestinal (GI) adverse effects include vomiting, diarrhea, decreased appetite, nausea. I monitor my patients at 2 week intervals for the 1st 4 to 8 weeks. Good patient history and careful monitoring of body weight is critical. All my Palladia patients go home with a "just-incase: bag including Cerenia, metronidazole and a probiotic, +/- mirtazapine. In some cases experiencing GI issues, I will recommend Cerenia be given 1 hour prior to Palladia, or Palladia dose will be adjusted.

CBC and chemistry panel should be monitored at each visit. Palladia and chlorambucil tend to cause delayed neutropenias and thrombocytopenias after chronic use. I also recommend periodic urinalysis and UPC.

The goal of metronomic chemotherapy is stable disease which requires chronic administration. It is very important our patients are experiencing minimal side effects and a great quality of life on the protocol, so they can stay on the protocol long term

DOXYCYCLINE

Doxycycline has been documented to have some antiangiogenic effects by inhibiting matrix metalloprotineases, so it is thought that the addition of doxycycline metronomic chemotherapy protocols may enhance the antiangiogenic effects. Further studies are needed to confirm its efficacy and best dosing.

SUMMARY

Conventional chemotherapy is typically ineffective for patients with gross metastatic disease. Metronomic chemotherapy is well tolerated and appealing with the low toxicity and use of oral forms. But metronomic chemotherapy is still in its early use in terms of efficacy and potential for toxicity. Stable disease is typically the goal, so therapy is often chronic and stable disease should be expected to maintain a good QOL for the patient. There is still much to be learned including best drugs, dose, schedule, tumor types, and toxicity.

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CANCER TOOLS YOU CAN USE TOMORROW: CANINE LYMPHOMA

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Key Points

• Lymphoma is a common canine cancer and is a systemic disease that requires chemotherapy in almost all cases.
• The majority of dogs achieve a complete remission with chemotherapy (approximately 80%). Higher remission rates are typical with CHOP multi-agent chemotherapy protocols.
• Early accurate diagnostics and careful staging are keys to proper clinical decision-making.
• To determine the best protocol for a patient and owners, it is important to understand efficacy of the various protocols, the potential toxicities, and prognostic factors.
• Dogs treated with chemotherapy live significantly longer than untreated dogs, and chemotherapy is generally well-tolerated in most dogs. Only a minority develops significant toxicity.
• **The diagnostic and treatment choices can be confusing and overwhelming. In this talk, we will take "My 3 P's" approach – prognostic, practical and pertinent.**

Biology of lymphoma

Lymphoma is a collection of cancers arising from the malignant transformation of lymphocytes. Even though lymphoma is clinically a diverse group of neoplasms, the common origin is the lymphorecticular cells. Lymphoma is one of the most common canine cancers, accounting for 7-24% of all canine tumors and 85% of hematopoietic tumors. Dogs of any age, gender, and breed can be affected with lymphoma. Affected dogs are typically middle aged to older dog.

Anatomic Classification

Multicentric (PLN) is the most common form**,** accounting for 80% of lymphomas. Most dogs are typically asymptomatic, and 20-40% are clinical (substage b) with anorexia, lethargy, fever, V/D, weight loss, melena

Gastrointestinal (GI) involvement is less common accounting for only 5-7% of LSA cases. It is more common in males, and Boxers and Shar-peis over-represented. Weight loss, anorexia, panhypoproteinenemia, malabsorption are common. It typically involve multifocal & diffuse of submucosa & lamina propria layers of small intestine. Phenotypically, GI LSA is typically T-cell. Histologically, can be challenging to distinguish from lymphoplasmacytic enteritis (LPE). In GI LSA, lymphocytic and plasmacytic inflammation can be adjacent or distant to the neoplastic population of cells. There is also the question of whether LPE a pre-lymphoma change?

Mediastinal forms are also less common, accounting for only 5% of LSA cases. It typically involves the cranial mediastinal LN and/or thymus, but 20% multicentric LSA have cranial mediastinal LN involvement. Hypercalcemia is most common with this form. In one study of 37 hypercalcemic dogs, 16 dogs (43%) had mediastinal lymphoma. Phenotypically, mediastinal LSA is typically T-cell

Cutaneous LSA can be a solitary lesion or generalized lesions, and may have oral mucosa lesions, +/- extracutaneous involvement of LN, liver, spleen, BM. This form is referred to epitheliotrophic form or as mycosis fungoides. It is more common in dogs than cats. The immunophenotype is typically Tcell (CD8+). In contrast, B-cell cutaneous LSA spares the epidermis and papillary dermis and affects the deeper dermal layers.

Clinical Appearance

Historic findings: The most common complaint is generalized lymphadenomegaly. Owners commonly report that lymph node size is rapidly increasing – over days to 1 to 3 weeks. In the early stages, dogs appear healthy and are not showing clinical signs. When present, clinical signs tend to be nonspecific and include vomiting, diarrhea, melena, anorexia, fever, and weight loss (substage b).

Common examination findings: Lymphoma can be indolent or aggressive, solitary or multicentric, or node-based or associated with any organ. Non-painful generalized lymphadenomegaly is most common physical exam finding. Multicentric lymphoma involving the peripheral lymph nodes is most common, accounting for 80% of patients.

Most dogs are "healthy" substage a. T-cell dogs tend to be sick (b). In dogs, multicentric LSA is generally the NHL (non-Hodgkin's LSA) form. Hepatosplenomegaly is common. Diffuse pulmonary infiltration has been reported in 27-34% based on CXR but on BAL, lung involvement may be higher. The lack of generalized lymphadenomegaly does not eliminate the possibility of lymphoma, as some dogs will have internal involvement only (i.e. hepatosplenic form, GI). Another scenario that can lead to confusion is hypercalcemia, often without peripheral lymphadenomegaly so lymphoma is not suspected.

Preliminary Diagnosis: Cytology Confirmation of lymphoma starts with fine needle aspirate of an affected lymph node. Cytology is minimally invasive, less expensive than biopsy, and typically provides rapid results, in 1 to 2 days. Cytology reveals monomorphic abnormal lymphocyte populations. Cytology does not provide complete classification, grading, or phenotype. Avoid reactive LN, such as the mandibular LN.

 Diagnostic Work Up The minimum tests required for treatment are cytological confirmation (lymph node or affected organ), CBC, chemistry panel and urinalysis. The next diagnostic I encourage owners to submit is phenotyping to determine B vs T-cell subtype. Phenotyping is typically determined with immunocytochemistry from aspirates, immunohistochemistry from biopsy, or flow cytometry or PARR from aspirates. If there is a peripheral lymphocytosis on CBC (stage V), flow cytometry can be submitted on a whole blood sample to determine phenotype. Phenotype is the best independent prognostic factor; prognosis is worse with T-cell than B-cell.

Lymph node biopsy is ideally performed for histologic grading but is often only collected when cytology was inconclusive. Baseline chest radiographs and abdominal ultrasound are recommended for staging purposes to determine extent of disease. While stage is prognostic, I also find it valuable to have these baseline imaging tests to be able to compare treatment response or progression. Bone marrow cytology is also considered part of the basic staging but it is often not done is the majority of cases, factoring in the additional cost and sedation for most cases.

Bone marrow cytology is of less clinical utility in most cases. However, if there are cytopenias and/or a lymphocytosis, a bone marrow should be considered to identify bone marrow involvement.

To stage or not to stage?

Complete lymphoma staging includes lymph node cytological confirmation, CBC, chemistry panel, urinalysis, lymph node histology, urinalysis, thoracic radiographs, abdominal ultrasound, bone marrow cytology and phenotyping. These tests are useful and informative, as they provide prognostic factors and a baseline for a patient's response. These tests can also help determine if there large tumor burden and risk for acute tumor lysis syndrome with induction chemotherapy. Still, we must consider the owner's financial issues. While it is ideal to perform all the tests, we can also consider each test on a case by case basis and help the owner make an educated decision. We can treat without but review pros and cons with the owner and let owner make educated decision and maybe choose more important tests for that dog.

Histology

NIH WF & Kiel System most useful, and both describe architecture and cell morphology, including mitotic index, cell size, and cell shape. Why do I care about histology? It's prognostic. **Positive**: Low grade LSA, Including mantle-zone, follicular, T-cell. But low grade LSA may only partially respond to chemotherapy and is often incurable. **Negative**: intermediate and high grade LSA BUT have a high mitotic rate & are more likely to completely respond to chemotherapy.

Phenotype: 60-80% of LSA are B-cell, and this is an important positive predictor, associated with higher rate of CR, longer remission, increased ST, and most high grade are B-cell. Breed prevalence with B-cell includes Cockers and Dobies. Goldens have equal B and T-cell. 10-38% of LSA are T-cell, and this is an important negative predictor, associated with lower rate of CR, shorter remission, shorter ST, and tends to be associated with hypercalcemia. Boxers are over-represented.

Flow Cytometry (FCM) involves staining live cells with labeled antibodies that bind to cell surface proteins. These live cells are suspended in liquid (saline, tissue culture media). Different types of lymphocytes express different proteins. Flow cytometer tells us how many cells of each type are present and can determine the lineage of the cells present. Flow could not identify LSA in 30% of newly diagnosed cases

PARR: PCR Antigen Receptor Rearrangement is a polymerase chain reaction (PCR) assay that amplifies DNA with PCR primers in the dog or cat. It tells us if the majority of cells in the sample are clonal: same original clone - most consistent with neoplasia, or from multiple clones/polyclonal - lymphoid proliferation - most consistent with a reactive process, It is useful to determine: whether lymphoid neoplasia, phenotype (B vs. T), and to monitor for MRD in treated patients, It must be interpreted with history, clinical signs, cytology, flow cytometry, IHC.

For sensitivity & specificity, both are ~90% in dogs, and it is more sensitive for circulating cells > blood, bone marrow. In cats, it is better for T cell (89%, 80%) vs B-cells (60%, 70%). FCM and PARR are NOT useful for neutrophilia to r/o chronic myelogenous leukemia, when hypercalcemia is only sign, not helpful on LN, fluid, etc., or as a screening test for healthy dogs and cats without clinical signs.

Prognostic factors: There are many prognostic factors, but the more significant predictors include:

• Phenotype: B-cell is better than T-cell. 60-80% are B-cell and this is associated with higher rated of CR, longer remission rates, and increased ST. Most high grade LSA are B-cell.
• Histologic grade: high grade has better CR rate than low grade, but low grade often has comparable survival times with less intensive chemotherapy protocols.
• Administration of prednisone prior to chemotherapy is a negative predictor
• Substage: clinically healthy dogs tend to do better than sick dogs
• Higher stage (stage IV and V) tend to do worse than lower stage (I to III)
• Hypercalcemia: negative predictor due to association with T-cell phenotype
• Mediastinal mass: negative predictor due to association with T-cell phenotype
•

Remember, prognostic factors cannot predict an individual's response, and lymphoma is typically treatable and rewarding to treat for the patient, owner and the veterinarian.

Treatment Modalities

Treatment pearls Chemotherapy is the mainstay of therapy to promote a rapid, durable and complete remission (CR), while maintaining a good to excellent quality of life even during chemotherapy. Complete remission is complete disappearance of all detectable lymphoma and resolution of clinical signs. Lymphoma is typically rewarding to treat with high response rates, and most dogs tolerate chemotherapy quite well.

Treatment: Chemotherapy The goal of therapy is to achieve a complete remission and a good to excellent quality of life. Dogs that respond and achieve CR are usually free of clinical signs of lymphoma and live longer and live well. Only a minority develops significant toxicity or do not respond to therapy. Most patients are treated on an outpatient basis. Newly diagnosed lymphoma patients that are sick (substage b), dehydrated, and have a large tumor burden (advanced stages) are at increased risk for acute tumor lysis syndrome with induction chemotherapy. In such cases, the dogs should be admitted for IV fluid therapy, supportive care, and intensive monitoring prior to chemo and for 24 to 72 hours after.

Combination chemotherapy provides improved remission rates and duration in comparison to single agent protocols. Multi-agent CHOP protocols are the most successful, with complete remission rates of > 80% and remission durations of typically 6-11 months. Median survival times (MST) are 1 year when followed by rescue protocol, and 25% of dogs are long term survivors > 2 years. There are numerous CHOP protocols that vary in drug dosages, scheduling, and dose intensity. The UW-Madison protocol is often recommended for owners choosing a combination protocol for its high complete remission rates, higher remission duration, and lower morbidity and mortality rates. Commonly used UW protocols are the 25 and 19 week protocols

Multi-agent CHOP protocols typically combine vincristine, cyclophosphamide, doxorubicin and prednisone. Recent studies suggest the inclusion of l-aspariginase at induction does not significantly impact remission duration or survival times and can be omitted and saved for the rescue protocol.

Additionally recent studies suggest there is no survival benefit of maintenance phase. Most current protocols are discontinuous without a chronic maintenance phase and provide comparable remission durations. It is thought the period without chemotherapy may lead to greater responsiveness at relapse by lack of selection of resistant cells.

For some clients, alternative protocols are elected over the multi-agent CHOP protocol due to budget, toxicity profile on par with clients' willingness to assume risks of chemo, and schedule and time commitment. In some cases, it is to avoid drugs that target a patient's weakness or concurrent illness. For example Lomustine is avoided with liver dysfunction and doxorubicin can cause cardiotoxicity so should be used cautiously in dogs with some pre-existing cardiac disease.

Alternative chemotherapy protocols include COP (vincristine, cyclophosphamide, and prednisone), single agent doxorubicin for B-cell lymphoma, and single agent Lomustine for T-cell lymphoma. These protocols generally have lower response rates ranging from 50-80% and shorter remission durations of 6 to 7 months.

New therapies for lymphoma include monoclonal antibodies and a lymphoma vaccine. It is hopeful these new therapies will increase survival times.

If chemotherapy is declined If chemotherapy is declined, another option is single agent steroids. Typical response rates are 50% with duration of 2 to 3 months. Prednisone should not be started prior to chemotherapy since it may decrease response rate to chemotherapy started after the steroids. Pre- chemotherapy steroids use is associated with shorter remission and survival times due to induction of multi-drug resistance. If staging tests are done after prednisone is started, higher stage patients may appear to be lower stage (down-stage). Without chemotherapy the prognosis for lymphoma is poor, with MST of 1 month.

Relapse The majority of lymphoma patients relapse as there is the emergence of tumor clones that are more resistant to chemotherapy, or survival-of-the-fittest lymphoma cells. These MDR (multidrug-resistance) clones are more likely to express MDR-1 gene that encodes for protein transmembrane pump associated with multidrug

resistance. Other reasons for relapse include inadequate chemotherapy dosing, inadequate chemotherapy frequency, or failure to achieve high chemotherapy concentrations at certain sites, such as the CNS.

When a patient relapses, I recommend reintroducing the initial protocol if it was successful, meaning the expected remission duration was achieved. For example, if a dog relapses one month after completing a CHOP protocol I will not recommend restarting front-line chemotherapy. However if the dog was off chemotherapy for 4-5 months with a 1st remission of 9-10 months, I will recommend restarting the induction protocol as re-induction rates of 90% can be expected. Remember there is a cumulative dose of doxorubicin, so doxorubicin is typically replaced after a total of 6 doses.When a dog no longer responds front-line chemotherapy, rescue protocols are recommended. There is decreased likelihood of response (30-50%) and shorter remission durations, typically half the length of the initial remission. Still some patients experience long-term re-inductions. Some commonly used protocols include MOPP, doxorubicin or mitoxantrone with DTIC, Lomustine/l-aspariginase/prednisone, and single agent Lomustine.

Other treatment options Other treatment options include localized radiation for local disease, such as nasal or CNS lymphoma. Palliative radiation can be used for bulky localized disease such as rectal, bone or mandibular lymph nodes. The addition of half body radiation to multi-agent chemotherapy improved ST and remission duration in some studies, but there is increased costs and toxicity to balance.
Whole body radiation is used in combination with bone marrow transplants.

More recently, monoclonal antibodies have been introduced as targeted therapy for both T- and B-cell canine lymphoma, but efficacy and administration schedule are still being worked out. Canine remission times on CHOP have plateaued at about 9 months.

In human monoclonal antibodies are standard of care. Before rituximab, results of CHOP-based chemotherapy plateaued in human medicine. Since its launch in 1997 it is the standard of care for nonHodgkin's lymphoma in humans and the addition of rituximab to standard CHOP has increased overall survival by 55%.

Recheck frequency After completion of chemotherapy, I recommend monthly rechecks to evaluate for relapse, especially at time of expected relapse depending on the protocol elected. In addition to physical exam, monitoring with lymph node palpation, cytology, chest radiographs, ultrasound, and advanced diagnostics can be helpful. Recently blood tests have been evaluated to look for molecular markers to detect early relapse before clinically detectable. The Canine Lymphoma Blood Test (cLBT, Avacta) has recently been shown to detect relapse earlier, and the lowest score *during* treatment was prognostic for ST and TTP. (Alexandrakis, 2014).

Overall: Lymphoma is one of the most successfully treated cancers in dogs, and many patients with lymphoma outlive animals with other noncancerous diseases such as kidney, heart, and liver disease. Dogs treated with chemotherapy live significantly longer than untreated dogs, and chemotherapy is generally well-tolerated in most dogs.

Additional Resources

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CANCER TOOLS YOU CAN USE TOMORROW: FELINE GI LYMPHOMA
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Key Points

Lymphoma (LSA) is one of the most commonly occurring cancers in cats. Lymphoma is a systemic disease that requires chemotherapy in almost all cases. Outcomes for treated cats are less predictable than dogs, but cats tend to tolerate chemotherapy better than dogs. Treated cats live longer, and chemotherapy is generally well-tolerated. **The diagnostic and treatment choices can be confusing and overwhelming. In this talk, we will take "My 3 P's" approach – prognostic, practical and pertinent.**

Biology of lymphoma

Lymphoma is collection of cancers arising from the malignant transformation of lymphocytes and is a diverse group of neoplasms with the common origin of the lymphorecticular cells. In contrast to dogs, feline lymphoma most commonly affects the gastrointestinal (GI) tract.

Lymphoma is one of the most common feline cancers, reported at 30% of all cancers. In the FeLV era from the 1960-1980s, lymphoma accounted for 50-90% of hematopoietic tumors. However, there was a shift after the 1990s, also called the post FeLV-era. With the aid of FeLV diagnostic assays and elimination regimens in 1970s and 1980s, there was a dramatic decline in FeLV-associated LSA. Still lymphoma prevalence is increasing, especially the alimentary form.

Etiology

Viral: In the FeLV era of the 1960-1980s, two-thirds of lymphoma was associated with FeLV antigen. FeLV-positive cats had a 62 fold increased risk. This form was predominantly seen in younger cats, was the mediastinal form, T-cell, and the virus had a direct role in tumorigenesis. Being FIV-positive increased lymphoma incidence by 5-6x. In contrast to FeLV, FIV has an indirect role secondary to
immunosuppressive effects and is associated with B-cell and the extranodal form. Cats that are both
FeLV and FIV positive have an increased risk of 77 fold
Immunosuppression: FIV has an indirect role with lymphoma secondary to immunosuppressive effects. Ten percent of feline renal transplants develop lymphoma following transplant and associated immunosuppressive therapy.
Environmental: Environmental tobacco smoke (ETS) has been reported to increase the risk of LSA by 2.5 to 3.2 fold.
Genetic and molecular factors: The predisposition of oriental breeds suggests a heritable risk, but this is still being investigated
Chronic inflammation: While definitive proof is lacking, there is growing evidence of the link with chronic inflammation and lymphoma, in particular with and intestinal LSA. This has been as area of interest with IBD and GI LSA.
Diet and GI LSA: While definitive proof is lacking, the diet changes over last 20 years in response to diseases such as urinary tract and the increase in GI LSA has led to the suggestion of a link, but more studies are needed.

Signalment

Lymphoma can occur in cats of any age, any sex, any breed. The median age is 11 years, and a male predisposition is reported and intact females are at decreased risk, suggesting a protective benefit of sex hormones. Overrepresented breeds include Siamese cats, Manx, and Burmese. Signalment varies with anatomic site and FeLV status.

Pathology and Behavior

For the alimentary/GI from, the LSA typically involved the intestines alone or intestines, lymph nodes (LN), and liver. In the GI tract, it can be solitary vs diffuse. 55% of GI tumors are LSA. Siamese are at increased risk. The GI form typically occurs in aged cats of 12 to 13 years old. The small intestines are four times more affected than the large intestines.

Enteropathy-associated T-cell LSA (EATL) has 2 forms. EATL Type I is intermediate to large B-cells, high grade, lymphoblastic lymphoma. This form often has a palpable mass. EATL Type II is called small cell, low grade, lymphocytic lymphoma. This form is more diffuse throughout the GIT and T-cell is more common.

Clinical Appearance:

Alimentary/GI

For low grade small cell LSA, clinical signs include weight loss (83-100%), V/D (73-88%), anorexia (66%), and icterus (7%). 70% have abnormal palpation on exam, either thickened GI or a palpable mass 33%. The history is usually chronic over several months, with a median 6 months.

For high grade LSA, the clinical signs are similar but icterus is more common and the onset is more rapid – days to weeks. A palpable mass is common. Rarely the cat will present with acute abdomen due to obstruction or perforation.

Diagnosis and Staging

Basic diagnostics include CBC, chemistry panel, and UA. For the GI forms, 23% have panhypoproteinemia and 76% are anemic. Test for FeLV/FIV status. Diagnosis typically made with cytology or histology of a LN or organ. Cytology may be inconclusive and be reported as benign hyperplastic and reactive, and histology will be needed. Other diagnostics may include abdominal ultrasound (AUS) and chest radiographs. Bone marrow cytology may be recommended especially for cases with anemia, leukopenia, or cellular atypia. Phenotype can be determined with PARR 80% sensitive or flow cytometry.

For high grade large cell (EATL type I), the diagnosis is typically more straightforward with GI masses, enlarged mesenteric LN, or liver involvement. The diagnosis is typically made with abdominal ultrasound and cytology/histology. Surgery is less commonly needed.

For low grade small cell (EATL type II), intestinal thickening is often modest or absent and similar to IBD. Cytology alone is often insufficient and will come back as benign hyperplasia. To confirm the diagnosis, AUS and histopathology are typically needed, and may require phenotype and clonality.

It can be challenging to distinguish low grade vs IBD with abdominal ultrasound. With low grade GI LSA, 60-90% have an abnormal AUS with 50-70% diffuse SI thickening, predominantly muscularis propria and submucosa layers. Mesenteric lymph nodes are abnormal in 45-80%. Focal GI masses are uncommon. For IBD, 10-50% have diffuse SI thickening and mucosal thickening more common. The incidence of mesenteric LN lymph nodes is lower at 15-20%, and other abnormal organs are typically normal.

Cytology is rarely useful for distinguishing low grade GI LSA vs IBD. The debate rages on regarding endoscopy vs full thickness biopsy (laparotomy vs laparoscopy). On histopathology, lymphoma typically has lymphoid infiltration beyond mucosal layer, epitheliotrophism, heterogeneity, and lymphocyte nuclear size consistent with malignant. If diagnosis is still equivocal, phenotype or PARR is recommended.

Feline Chronic Small Bowel Disease (CSBD)

This study highlights that CSBD often is often considered normal by cat owners. Excuses include: "He just eats fast", "She is a nervous cat", "He has a sensitive stomach", "She gets hairballs", "He's always done this." CSBD includes IBD and enteropathy-associated T-cell LSA (EATL) type 2. EATL type 2 most common infiltrative GI LSA in cats, and treatment is different than IBD.
In this study, the authors looked at the association of clinical signs and disease in 100 cats that had an AUS of small bowel $\geq$0.28 cm in $\geq$ 2 locations. These cats had $\geq$1: vomiting >2x /month for at least 3 months, several weeks of small bowel diarrhea, and weight loss > 0.5 kg in last 6 months. Interestingly, 26 cats were getting wellness exam. 65 cats did not have surgery and were excluded. Clinical signs included weight loss 70%, vomiting $\geq$2x 61%, diarrhea 11%, and V/D 13%. 92% had at least 1 AUS measurement $\geq$0.3 cm, 8 cats 0.29-0.29 cm, and 76 cats 1 measurement <0.28 cm. 99 of 100 had cats had IBD or LSA. Only 1 cat had normal histology. 49% had IBD/chronic

enteritis. 46% had LSA (n=44 EATL type2).Cats <8 years old had enteritis, and cats > 8 years old enteritis or cancer. The 1 normal cat was 5 years old.

Cats with GI clinical signs are common and should undergo diagnostics. Do not let clients make excuses, and get a good history. Chronic vomiting is often considered normal, but vomiting is not normal! Clinical signs should trigger abdominal ultrasound. One of the common excuses is vomiting hairballs is normal. Is vomiting hairballs is normal? Does chronic small bowel disease slow bowel movement and predispose to formation?

Treatment Treatment: Dogs vs cats

There are less feline data than for canine LSA. Papers often lump together small number of cases of multiple subtypes of various anatomic, phenotype and histologic grades. Outcomes are less predictable in cate and there is greater variation in histologic type and anatomic location in cats. But cats tolerate chemotherapy well and better than dogs. Febrile neutropenia is rare. Most owners happy they chose to treat and the QOL improves.

Which protocol?

For intermediate and high grade/EATL I, there is an overall response of 50-80%, a median remission of 4 months, and a median survival 6 months. Cats that achieve a complete remission have a MST of 1 year. I typically recommend a CHOP multi-agent protocol such as the UW 25 week protocol. When using doxorubicin in cats, I use a lower dose (1 mg/kg). Cardiac toxicity is not clinical problem in cats in contrast to dogs, and renal function (BUN, Cr, USG) should be monitored in cats when giving doxorubicin. In dogs, data supports shorter maintenance-free protocol, but there is no data in cats, and some cats may need chronic chemotherapy.

An alternative protocol is the COP protocol with reported complete remissions of 50-70%. This is commonly used in used in Europe with similar results to CHOP in 1 study. While the protocol requires less frequent visits, it is a longer 1 year protocol. Other studies support the addition of doxorubicin to COP for durable responses.

For single agent options, Lomustine can be given at 50-60 mg/m2 every 4-6 weeks, which is given at a lower dose and less frequently than dogs. Single agent doxorubicin is cats is less successful with complete remission rates of <50%.

For low Grade/ EATL type II, less aggressive chemotherapy protocols are typically used. Oral chlorambucil (Leukeran®) can be dose with pulse dosing (20mg/m^2 every 2 weeks or 15 mg/m^2 for 4 days every 3 weeks) or with chronic dose (>4 kg start @ 2 mg PO q 2 day, maintenance q 3 days; <4 kg start @2 mg PO q 3 day, maintenance q 4 days). For cats I prefer prednisolone, typically at 1 - 2 mg/kg orally daily and reduce to 0.5 to 1 mg/kg daily. In some cases, prednisolone may be discontinued.

For relapsed cases, cyclophosphamide, Lomustine, and vinblastine are recommended. For severe or refractory cases, I will used CHOP or COP protocols

Nutrition for EATL type II

With evidence of role of inflammation and many have concurrent IBD, there is thought to consider transition to a novel protein diet and add probiotics. I also recommend running B12 levels, and supplementing as indicated

Prognostic factors

The prognosis and response in cats is more variable than in canine lymphoma. Prognostic factors include anatomic location, achieving a CR, FeLV status, substage, and a multi-agent protocol (CHOP vs COP?). Factors that are NOT prognostic in cats include stage and immunophenotype, age, weight, gender, and FIV

For GI forms, the prognosis is overall extremely variable. For EATL type I, response rates are 50-75%, median remission duration is 4-6 months, and expected survival is 6-8 months. 15-25% can live 1-2 years. For EATL type II, remission is generally defined as improvement or resolution of clinical signs, And 70%-85% will respond for a median survival time of >2 years.

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ESSENTIAL TIPS FOR SPLENIC MASSES
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KEY POINTS

- Dogs with splenomegaly and splenic masses generally follow the "double two-thirds rule": 2/3 have splenic neoplasia, and 2/3 of those have hemangiosarcoma. So 1/3 do not have cancer! Hemangiosarcoma is not the only differential for a dog with a splenic mass.
- Hemangiosarcoma (HSA) is the most common primary canine splenic cancer in dogs, and it is locally aggressive and highly metastatic.
- The likelihood of splenic tumor increases with anemia, nucleated RBC, abnormal RBC morphology, or splenic rupture.
- Prognosis for splenic masses cannot be determined without histology which usually requires surgery. A common clinical error is to assume HSA based on the presence of a splenic mass. Large masses are not necessarily malignant. Several splenic lesions have similar ultrasound and gross appearances.
- Except for lymphoma, splenectomy is the treatment of choice for splenic tumors when there is no evidence of metastasis based on staging tests. Even at surgery, it is often impossible to distinguish various diseases based on gross appearance of the spleen or liver.
- Dogs with HSA treated with local therapy and chemotherapy live longer than dogs without treatment and with local therapy only but 1-year survival rates are still low (10%). Chemotherapy is generally well-tolerated in most dogs, and only a minority develops significant toxicity.

WHO, WHAT, WHERE, WHY

Splenic neoplasia can arise from any of the normal splenic tissues including blood vessels, lymphoid tissue, smooth muscle and connective tissues. Common splenic tumors include HSA, mast cell tumor, lymphoma and various sarcomas. Hematomas are the most common benign splenic masses. Splenic tumors usually occur in large breed dogs. Breeds most at risk are German shepherd dog, golden Retrievers, and Labradors. German shepherds also have a high prevalence of hyperplastic nodules and hematoma.

Clinical signs are typically vague, non-specific and include enlarged abdomen, anorexia, lethargy, depression, vomiting, and diarrhea. Clinical signs also vary with how advanced disease is, so dogs may have acute and often dramatic acute signs including collapse and hypovolemic shock. In one study 80% of dogs with acute abdomen and no history of trauma had malignant cancer and 88% were HSA. Splenomegaly is readily detectable through abdominal palpation, radiography and ultrasonography.

DIFFERENTIALS DIAGNOSES: Hemangiosarcaoma is not the only differential for a dog with a splenic mass. A common clinical error is to assume HSA based on the presence of a splenic mass. Large masses are not necessarily malignant. Several splenic lesions including HSA, hemangioma and hematoma have similar ultrasound and gross appearances.

Lymphoma (LSA): LSA that involves the spleen is most commonly part of multicentric LSA and typically is a diffusely infiltrative disorder. Some lymphomas may occur as solitary splenic nodules, especially marginal zone lymphoma and mantle subtypes of the indolent form.
Similarly acute and chronic leukemias can also diffusely infiltrate the spleen.

Malignant Histiocytosis (MH): MH is an uncommon cancer of atypical histiocytes and has progressive, multicentric involvement of multiple organs, including the spleen, liver, lymph nodes, and bone marrow. The Bernese mountain dog has a familial predilection.

Mast Cell tumors (MCT): Tumors of primary visceral organs including the spleen are rare in dogs. Visceral mastocytosis is typically preceded by a poorly differentiated cutaneous MCT.

Splenic sarcoma: Splenic sarcomas are non-angiomatous, non-lymphoid tumors of connective tissues and include fibrosarcoma, leiomyosarcoma, extraskeletal osteosarcoma, and undifferentiated sarcomas. A high mitotic index (MI) of >9 is a negative prognostic factor for survival. Splenic sarcomas tend to be fatal within 1 year. Splenic leiomyosarcoma have a high metastatic rate but dogs that survive the initial post-surgical period have a MST of 8 months.

Hemangioma Hemangiomas are benign tumors of blood vessels. Surgery is curative,

Non-neoplastic: hematoma, abscess, nodular hyperplasia, granuloma

HEMANGIOSARCAOMA (HSA)

HSA is an aggressive malignant cancer of transformed vascular endothelial cells. It causes local infiltration and rapid systemic metastasis. German shepherds and golden Retrievers are at greatest risk. Gross metastasis is present at diagnosis in more than 50% of cases. Excluding cutaneous cancers, it accounts for about 5% of primary cancers in the dog.

Spleen is the most common primary site, but other common sites include right atrium, liver, skin and subcutis. HSA may be solitary, multifocal in an organ, or widely disseminated. Metastasis is typically hematogenously or via transabdominal transplantation. Metastasis is most commonly to the liver and lungs. Less common sites of metastasis include the omentum, mesentery, brain, muscle and bone. HSA is considered the most common metastatic tumor to the brain.

Diagnostic Work Up

CBC and chemistry panel: The likelihood of splenic tumor increases with anemia, nucleated RBC, abnormal RBC morphology, or splenic rupture. The anemia may be regenerative with splenic rupture depending on the duration. Neutrophilic leukocytosis may also be present. Other abnormalities include Howell-Jolly bodies, poikilocytosis, acanthocytosis, schistocytosis and/or thrombocytopenia. Thrombocytopenia is common in 75-97% cases and rages from mild to severe. A coagulation panel should be run if HSA is suspected.

Imaging Three-view chest radiographs are mandatory to rule out pulmonary metastasis and pleural fluid. Three-views significantly decreases the false-negative rate. Abdominal ultrasound confirms the mass and allows detection of abdominal effusion, defines splenic architecture, and provides detailed evaluation of the abdominal organs and is less affected by abdominal effusion than radiographs.

FNA and cytology: Ultrasound-guided FNA is relatively simple, cost-effective and typically a safe procedure. It is most helpful for cases where the diagnosis eliminates the need for surgery, such as lymphoma. For diffuse splenomegaly, the spleen is accessible for cytology. But even with ultrasound-guidance, if non-representative tissues are sampled, you may get a false negative of benign or reactive. In one study, only 61% of cases did cytology match histologic diagnoses. FNA is not recommended for mixed echogenicity masses suspicious of HSA as the masses are often extremely friable so there is an increased risk of hemorrhage in addition to the low diagnostic yield due to hemodilution.

HSA effusions are serosanguinous or frank blood and usually do not clot. Unfortunately cytology is typically non-diagnostic.

Cardiac evaluation: Since 25 to 45% of dogs with splenic HSA have concurrent right atrial HSA, an echocardiogram is recommended. In my experience this is lower at presentation. Arrhythmias can occur with benign and malignant lesions.

Treatment Modalities for HSA

Treatment pearls Treatment for HSA is ideally both local and systemic. Chemotherapy improves the MST, but HSA is still a frustrating cancer for owners and veterinarians with shorter survival times than many malignant cancers in dogs. The majority of dogs tolerates chemotherapy quite well and will maintain a good to excellent quality of life even during chemotherapy.

Treatment: Surgery

Except for lymphoma, splenectomy is the treatment of choice for splenic tumors when there is no evidence of metastasis based on staging tests. Even at surgery, it is often impossible to distinguish various diseases based on gross appearance of the spleen or liver – including hematoma, nodular hyperplasia, hemangioma and HSA. Ideally the entire spleen should be submitted fresh on cold packs or in formalin. Biopsy of normal liver is controversial and may not be useful. The abdomen should be thoroughly explored and any suspicious lesions removed or biopsied. About 25% of dogs develop arrhythmias post-op. An ECG should be monitored during and after surgery, and they usually resolve within 24-48 hours.

Treatment: Chemotherapy

The goal of chemotherapy is to achieve is to delay the metastatic disease that develops quickly after splenectomy. Since chemotherapy improves the MST, it is considered part of the standard of care. Single agent doxorubicin and combination protocols are most common.

Recently low dose oral chemotherapy (metronomic) was comparable to conventional doxorubicin. This protocol included low dose cyclophosphamide, piroxicam and etoposide. Current studies are evaluating whether conventional chemotherapy followed by maintenance metronomic chemotherapy for VEGF-receptor kinase inhibitors such as tocerinib will improve outcome.

Prognosis: Overall the prognosis with surgery alone is poor and reported MST in dogs treated with surgery alone ranges from 1 to 3 months, and less than 10% survives 1 year. Adjunctive chemotherapy improves the MST to 4 to 6 months, and doxorubicin-based protocols are the mainstay. Stage I, non-ruptured tumors may have an improved prognosis when chemotherapy is administered after surgery. Low grade tumors may also have a better prognosis.

ADDITIONAL RESOURCES

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