Canine Lymphoma: Review and What’s New
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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 develop significant toxicity.

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 lymphoreticular 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-pees over-represented. Weight loss, anorexia, panhypoproteinemia, 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 T-cell (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
Confimation 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 Cocker 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

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-asparaginase 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 (multi-drug-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 the protocol. 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 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-asparaginase/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 non-Hodgkin’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


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.

**Biology of lymphoma**

Lymphoma is a collection of cancers arising from the malignant transformation of lymphocytes and is a diverse group of neoplasms with the common origin of the lymphoreticular 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 form, 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 malignanct. 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 >0.28 cm in ≥2 locations. These cats had ≥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 ≥2x 61%, diarrhea 11%, and V/D 13%. 92% had at least 1 AUS measurement ≥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
These 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/m² every 2 weeks or 15 mg/m² 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.

References
Why is oncology important?
The statistics are overwhelming. One in 3 dogs of any age will get cancer, and 50% of dogs over 10 years old will be affected by some tumor. Cancer is the number one cause of canine death. Many pets are considered important family members, and owners have increasing expectations. They want the same standard of care, highest quality medical care, compassionate care, and respectful communication. But when the pet is sick and has cancer, the human animal bond becomes stressed and fragile, making communication between the veterinarian and the owner more challenging.

Cancer communication challenges
Veterinarian/client communication is critical to optimal patient care. Yet there is a lack of guidelines and training to help veterinarians and clients broach difficult conversations about prognosis, treatment and palliative care options for pets diagnosed with cancer. As veterinarians and oncologists, we need clinical guidance to help initiate these conversations and better integrate both definitive and palliative therapy into our oncology practice.

Cancer communication training varies with regard to content, duration and methods. There is often a skills gap between veterinary school curriculum content and actual skills to be successful in practice. As a result, many veterinarians feel unprepared for difficult conversations about cancer.

Since the cancer diagnosis is typically made by the primary care veterinarian, the primary care veterinarians often have the more difficult job compared to the oncologist. The primary care veterinarians have the relationship with the client. On the other hand, when the client visits the oncologist, the owner usually knows cancer is the diagnosis, and the focus is treatment options and decision making, but there is no pre-existing relationship, familiarity, or trust.

Many barriers currently prevent veterinarians and clients from engaging in cancer conversations and optimal cancer care planning. To address barriers to advanced cancer care planning, we must first identify the challenges.

For the veterinarian, challenges may include general discomfort in talking about cancer and death, lack of training, shortness of time, practice culture, feelings of responsibility for cancer or a late diagnosis, perception of failure, unease with death and dying, uncertainty of outcome, impact on relationship with client, and the worry about patient quality of life (QOL), about client response, about costs, and about the veterinarian’s own response.

For the client, conversations are challenging as clients are often emotional and dealing with their feelings of self-blame, guilt, anxiety, fear, and frustration. There is the unease with death and dying, anticipatory grief, and concerns about the effect on human-animal bond. The client is also concerned for the pet’s QOL, the costs, the time required to treat the cancer.

How do you give your information?
The first method is called Data Dump, and is often nick-named the Shot-put technique. The oncologist does most of the talking like a monologue, and the client is more passive. The intent is on delivery of information, but it is often too much information for the client to absorb and too challenging to receive the message. One way to improve this is to add open ended questions, so we know we are all on same page with cancer information.

A better method is the collaborative approach, is often nick-named the Frisbee technique. This reciprocal interaction focuses on a dialogue. The delivery is light and airy, and information delivery is given in small pieces. Here the emphasis is on eliciting client feedback.

Core cancer communication skills
Gathering information
It is very helpful to identify the client’s full agenda and help the client identify concerns. Use open ended questions that start with: how, what, and tell me. Examples are “What other questions do you have?” or “Anything else you’d like to discuss?”

Elicit the client’s perspective. Does the client have a previous experience with cancer in people or another pet? It is important to identify misconceptions of cancer and barriers to care. Examples are “What are you goals with treating Bo’s cancer?” “What are your hopes?” and “What are your fears?”

Explaining and planning
Assess the client’s knowledge level and what level of information to give. It is also important to determine what degree the client wants information, and be aware this may change with time. Since many clients are overwhelmed in the beginning, it is often helpful to start with the big picture and ask what they know already and to what additional information they are seeking. “Chunks and check”
is very helpful when having cancer conversations. You give information in small chunks, and then follow with checks for understanding. This is less lecturing and aims to increase recall, understanding and commitment. Use questions like: “What questions do you have?” or “What part of the plan is most difficult?”

**Building relationships**
Offer partnership and use inclusive language like let’s, we, our, us, such as “We’ll work together for Teddy.” Asking permission during the conversation will allow you to assess the client’s readiness to take next step with questions like: Would you like to schedule surgery? Are you ready to start treatment?

Express Empathy: Acknowledge clients emotions and put yourself in their shoes and communicate that you know where they are coming from. Example: I can only imagine how hard this is. Nemo has been part of your family for so long.

Demonstrate appropriate nonverbal behavior: This can be helped with an attentive body posture, sit at same level, sit close, and maintain good eye contact. Use a slow pace, lean forward, reach out to touch.

**Provide structure and summarize**
It is useful to take time to reflect what the client heard, to repeat key aspects of diagnostics and treatment, and to provide a summary at end of appointment. For example, “I recommend these tests and this treatment for Bo’s melanoma but there are options. What questions do you have?”

“I don’t have time for this!” Core communication skills actually save time and allows for more efficient veterinarian-client-patient interaction. If you spend time to build a relationship early, it will pay dividends through diagnosis and treatment.

**Delivering bad news**
I was never taught this in school, my internship, or my residency. Most oncologists learn to break bad news by observing more experienced colleagues in clinical situations, typically during their residencies. Many veterinarians report a lack of confidence in their ability to break bad news.

The specific lack of training opportunities appears to play a major role in leading to this problem. In a human study, almost 40% of respondents not only had no didactic training, but also did not have an opportunity to gain experience from observing other clinicians breaking bad news.

Delivering bad news is a complex communication task that you may have to do thousands of times. It is stressful for clinicians to carry the burden of responsibility for communicating bad news. Complicating factors include our experience (or inexperience) giving bad news, the relationship with the client and their pet, and often the limited treatment options.

For the client, the response is affected by their relationship to their pet, severity of the diagnosis, past experiences with other pets or human family members, other stressors in their life, and their support system.

When saying “Your pet has cancer”, be aware of where and when you deliver the bad news. Too many clients hear those fateful words with less than an appropriate manner in less than an appropriate setting. Common mistakes include having the conversation in a space with no privacy, having a conversation that is too short, and having no treatment plan to discuss. Poor communication can lead to general dissatisfaction and a loss of trust.

Instead, when saying, “Your pet has cancer”, think empathy and respect, go to a private location, have sufficient time and attention, and be sensitive.

**Six step strategy: SPIKES**

**SETTING UP the interview**
- Mental rehearsal
- Privacy
- Involve significant others
- Sit down
- Make connection
- Eye contact
- Touch

**Assessing the client’s PERCEPTION**
- Before you tell, ask
- Open ended questions
- “What have you been told about...”

**Obtaining the client’s INVITATION**
- Some want full information for diagnosis, prognosis and details of the illness
- Some do not
• Some may want more information later

**Giving KNOWLEDGE and information to the client**
• Warning that bad news is coming “Unfortunately I have some bad news”
• Use non-technical terms: Spread vs metastasis, Sample of tissue vs biopsy
• Chunk and check

**Addressing the Client’s EMOTIONS with empathetic responses**
• Observe: silence, disbelief, crying, denial, anger
• Let client express feelings
• Make a connecting statement
• Examples of empathic, exploratory, and validating responses (Baile, 2000)

**STRATEGY and SUMMARY**
• Make a clear plan
• Consider a referral,
• Address pain control and symptom relief

**Discussing prognosis**
There are a few approaches to discussing prognosis. The first is realism. Interestingly, in people, 20% of patients do not want full prognosis information. Second is optimism. If overly optimistic, clients may lose opportunities to fulfill last wishes, prepare themselves and family, and spend quality time with their pet. With avoidance, you may appear evasive or dishonest. In addition, the veterinarian risks the trust and relationship with client, and the client could compromise pet’s care.

Do not make assumptions about what the client wants to know. Ask. “How much would you like to know about course of Myles’ lymphoma?” Some like details or the big picture. This is a good time to use chunk and check.

Balance hope and reality. The median survival time can be helpful. Acknowledge the client's emotional reaction and remember to compose yourself, pace yourself, and allow time to reflect.

**First reaction**
Remember the client’s initial reaction may be to not treat at all. It is okay not to treat after we provide information about the diagnosis, treatment options and prognosis. We must provide accurate information about cancer, and a range of treatment options. We can replace misperceptions and fear with knowledge and hope and educate the client that pets with cancer can live longer, and live well – not only after treatment, but during treatment too.
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.

**Importance of oncology**

The pet is a family member, and owners often want the same standard of care for their dogs and cats as they do themselves. Sadly, cancer is the 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 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 cats 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 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 attack rapidly dividing cells. The normal tissues that are most sensitive to 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 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.

When giving a potentially myelosuppressive drug like doxorubicin, carboplatin, and Lomustine, I personally like to check the expected nadir (low neutrophil count) to see if antibiotics and/or a dose reduction are needed. The nadir typically occurs 7 days after chemo 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.

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 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.

**How toxic is chemotherapy?**

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.

If there are side effects, I also typically will add prophylactic medications to prevent side effects like nausea, vomiting or diarrhea as indicated. I recommend Cerenia SQ with the following drugs: vincas, doxorubicin, mitoxantrone, carboplatin, and the MOPP protocol. I always recommend oral Cerenia for 4 days after doxorubicin in dogs to prevent nausea and vomiting. 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.

When a chemotherapy drug is used that is known to have a high potential for bone marrow suppression, a complete blood count (CBC) is often checked after the treatment to see if the WBC are low. Antibiotics may be prescribed as a preventive measure. Subsequent doses of chemotherapy are adjusted based on the results of the CBC. Unlike dogs, I do not routinely use prophylactic antibiotics or GI medications 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.

**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.

**What to do at the nadir visit?**

In addition to running a CBC, it is important to get a good history, TPR (that temperature is so important in chemotherapy patients), and a complete physical examination. I am always interested in knowing how the patient handled chemo – 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 chemo 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.

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.

<table>
<thead>
<tr>
<th>Neutrophil count (per uL)</th>
<th>Fever, systemic signs</th>
<th>Plan</th>
</tr>
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<tbody>
<tr>
<td>1500-2500</td>
<td>No</td>
<td>Monitor +/- treatment delay 2 to 4 days</td>
</tr>
<tr>
<td>&lt;1500</td>
<td>No</td>
<td>Oral antibiotics treatment delay Consider dose change</td>
</tr>
<tr>
<td>&lt;1500</td>
<td>Yes</td>
<td>ATH for IVF &amp; IV antibiotics treatment delay Dose change</td>
</tr>
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**Sepsis**

Sepsis in chemotherapy patients is typically due to patient’s own flora - Gram negative from GI bacteria: *E. coli, Klebsiella, Pseudomonas;* Gram positive from skin bacteria: *Staphylococcus epidermidis 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.

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, + dehydration.

For work up, I recommend CBC, chemistry panel, UA, +/- fecal floatations 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.

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.

Don’t monitor the bump or lump. Do get an aspirate or biopsy. Why wait? Aspirate. ©
Visual monitoring of skin and subcutaneous masses is not enough. Even the most experienced veterinarian or oncologist cannot look at or palpate a mass and know whether it is benign 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.

“See Something Do Something, Why Wait? Aspirate. Dr. Sue Cancer Vet®” (SSDS) provides guidelines for evaluating superficial masses in dogs and cats. These guidelines will increase client awareness and will promote early cancer detection, diagnosis, and 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: When a skin mass is the size of a pea (1 cm) and has been present for at least 1 month,
Do Something: Aspirate or biopsy, and treat appropriately!

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 – this is especially true for 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.

- 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

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References
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.

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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 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 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 doxycycline. 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 endothelial 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+ T-lymphocyte 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 TKI
Most Receptor Tyrosine Kinase Inhibitors (RCKI) 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-in-case: 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 metalloproteinases, 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.

Additional resources
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Dr. Sue Cancer Vet PLLC
Tarrytown, NY

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 an inadequate 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 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 non-diagnostic 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 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-existing 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 non-metastatic. If tumors are detected and removed earlier – when they are small and with clean margins, 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®

References/suggested reading