Osteosarcoma (OS) is the most common primary bone tumor of dogs, accounting for approximately 85% of malignancies arising in the skeleton. It is a high grade, biologically aggressive neoplasm of mesenchymal origin that closely parallels human OS. It is estimated that 10,000 dogs per year develop OS in the United States. The peak incidence of canine OS occurs primarily in middle-aged to older animals, with a median age of 7 years; although, a bimodal age distribution is reported with a second small peak at 18 to 24 months. Approximately 75% of OS occurs in the appendicular skeleton. Analogous to humans, the metaphysis of long bones is the most common primary location, with the forelimbs affected twice as commonly as the rear limbs. The most frequent anatomical sites are the distal radius (35%) and proximal humerus (18%) followed by the distal femur, proximal tibia, and distal tibia. Osteosarcoma is typically a cancer of large and giant breed dogs with only 5% of tumors occurring in dogs weighing less than 15 kilograms, the majority of which originate in the axial skeleton. The precise etiology of canine OS is unknown; however, likely include genetic predispositions, exposure to ionizing radiation and sustained microtrauma (e.g., repetitive weight bearing stresses, metallic implants) as possible risk factors in dogs for OS development.

Current local therapies
The local effects of OS which result in excessive and pathologic bone resorption have a significant impact on patient mobility and quality of life, and thus, addressing the primary tumor is one of the major goals of OS therapy. Effective local therapy for canine OS necessitates the removal or killing of malignant osteoblasts and various treatment modalities have been employed to this end. The following discussion will focus on the benefits and limitations of current local therapies for canine OS.

Surgery
Surgical resection of the primary tumor followed by either a platinum- or doxorubicin-based chemotherapy protocol generally results in the longest median survival times, with a median survival time approximately 275-300 days. For appendicular OS, surgical options include amputation or limb-sparing procedures. High amputation of the affected limb is the standard local treatment, and most dogs function well after this procedure, retaining good mobility and quality of life. An advantage of amputation is that it usually ensures complete local tumor removal. However, in cases where severe preexisting conditions exist, such as obesity, orthopedic or neurological disease, limb amputation may not be a viable option.

In select cases, a limb-sparing surgery may be an alternative to amputation, in which the affected bone is resected and replaced by a normal bone allograft, metal endoprosthesis, or other less common methods. Overall, outcome has been acceptable following limb salvage, with approximately 80% of dogs experiencing good to excellent limb function; however, even in the hands of the most experienced surgeons, there remains a risk for relatively high rates of local complications including recurrent disease, construct failure, and post-operative infection.

Local palliative strategies
Standard-of-care therapy, defined as the treatment option that results in the longest median survival times, is surgical resection of the primary tumor followed by 3 to 6 cycles of either a platinum- or doxorubicin-based chemotherapy protocol. Unfortunately, not all dogs with OS are considered good candidates for amputation, and alternative palliative treatment options for controlling bone pain should be considered. Reported survival times for canine patients treated with palliative intent therapy ranges from 3 to 10 months. With the commercial boom of pharmacologic pain medications approved for use in dogs and cats, the general practitioner is now offered a plethora of novel analgesics that may provide some moderate relief for chronic osteolytic pain associated with appendicular OS. In addition to the administration of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) or the application of transdermal opioids, newer analgesics such as tramadol and gabapentin may also alleviate cancer-related pain.

Palliative radiation therapy (RT)
Palliative RT is effective for the management of malignant bone pain, and typically involves administering coarse fractions of 8 to 10 Gy of megavoltage irradiation, in 3 treatments at 0, 7 and 21 days. Palliative RT reportedly improves limb function and quality of life in about 75% of patients, and for a median of 2-3 months duration. The concurrent administration of systemic chemotherapy along with palliative RT appears to enhance analgesic response rates and durations, and should be highly recommended.

Radiopharmaceuticals
The use of a therapeutic radionuclide called $^{153}$Samarium-EDTMP has been described for both appendicular and axial OS in dogs, and provided pain relief in many treated patients. By means of delivery concentrated radiation doses to the site of active bone remodeling,
Samarium-EDTMP administration is capable of providing significant and meaningful palliation of bone pain in dogs suffering from appendicular OS. Samarium-EDTMP therapy is well tolerated and alleviates osteolytic bone pain in the majority of dogs treated. Side effects associated with treatment include transient decreases in platelet and white blood cell counts.

**Stereotactic radiosurgery (SRS)**
Radiosurgery involves the precise delivery of a single large dose of radiation to a designated tumor target, and has been used for the treatment of brain tumors, as well as, appendicular OS. The use of SRS in dogs with OS can provide pain alleviation, long-term local tumor control and improvement in limb function. Similar to palliative radiation therapy, combining systemic chemotherapy with SRS appears to enhance response rates and durations.

**Aminobisphosphonates**
The pharmaceutical use of aminobisphosphonates is accepted for the treatment of neoplastic bone disorders in human cancer patients. At low concentrations aminobisphosphonates inhibit bone resorption without inhibiting the process of bone mineralization. This results in stabilization and even enhancement of bone mineral density. Bisphosphonates directly inhibit bone resorption by binding to hydroxyapatite crystals, as well as inducing osteoclast apoptosis. In part, pain associated with bone cancers is a direct consequence of malignant bone resorption. Therefore, inhibiting pathologic bone resorption with aminobisphosphonates would theoretically decrease the likelihood of pathologic fracture, as well as alleviate intense bone pain.

Aminobisphosphonates are synthetic analogs of inorganic pyrophosphate (PPi) that were initially utilized in the detergent industry as demineralizing agents, and then for diagnostic purposes in bone scanning, based on their ability to adsorb to bone mineral. The pharmaceutical use of aminobisphosphonates has now gained wide acceptance in human non-neoplastic bone disorders such as osteoporosis and Paget’s disease. In the last decade, aminobisphosphonates have been intensely investigated as novel antineoplastic agents. Currently, several aminobisphosphonates have demonstrated efficacy for treatment of tumor-induced hypercalcemia, multiple myeloma, and metastatic bone diseases.

The effective treatment of bone disorders by aminobisphosphonates is attributed to their differential effect on bone resorption and bone mineralization. At low concentrations aminobisphosphonates inhibit bone resorption without inhibiting the process of bone mineralization. This results in stabilization and even enhancement of bone mineral density. Aminobisphosphonates directly inhibit bone resorption by binding to hydroxyapatite crystals. Once incorporated into the hydroxyapatite matrix of bone, aminobisphosphonates inhibit further calcium and phosphorous mineral dissolution. Perhaps more importantly, aminobisphosphonates impede osteoclast activity and induce osteoclast apoptosis; both mechanisms result in inhibition of bone resorption.

**Systemic therapies**
Chemotherapy agents that have demonstrated efficacy in the treatment of OS include the platinum agents and doxorubicin. While chemotherapy is primarily used in the management of canine OS for the purpose of delaying onset of metastasis, it may also be employed in local therapy as a pretreatment to amputation or limb salvage. In veterinary medicine, studies that evaluated dogs receiving intra-arterial (IA) cisplatin prior to limb spare surgery found that cisplatin IA with or without radiation therapy induced a significantly greater percent tumor necrosis when compared with dogs receiving no pretreatment, and that percent tumor necrosis was strongly predictive of local tumor control.
Canine Lymphoma: 
What’s on the Horizon? 
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Lymphoma is one of the most commonly diagnosed cancers in dogs, cats and people. Canine lymphoma bears similarity to the non-Hodgkin’s lymphomas (NHL) in humans and both exhibit similar responses to treatment with chemotherapy. Lymphoma is very difficult to cure and a leading cause of cancer death in dogs and people. Despite many efforts over the last 20-30 years, outcomes in canine patients have not significantly improved over those achieved with CHOP-based chemotherapy protocols (cyclophosphamide, doxorubicin, vincristine, and prednisone). These chemotherapy protocols have extended both the longevity and quality of life in dogs with lymphoma but novel strategies are needed to increase survival times. This presentation will cover a general review of lymphoma and recent advances that hold promise for the future.

Diagnostic advances

Lymphomas are a diverse group of cancers arising from lymphoid cells. There are greater than 30 types of canine lymphoma described that differ in anatomic, histologic and immunophenotypic (T vs. B cell) classification. These different types of lymphoma can vary in their biologic behavior and prognosis; however, further studies are currently needed to correlate the various categories of disease with clinical outcome. The majority of canine lymphomas are intermediate or high grade and are generally characterized as being biologically aggressive and rapidly progressing. Indolent lymphomas may progress more slowly and dogs may experience long-term survival with limited or no therapy; however, indolent lymphomas represent a small percentage of lymphoma in dogs. Diagnosis of lymphoma is achieved via cytology or biopsy. While not performed in every case, the following diagnostics may be helpful to establish a diagnosis of lymphoma or to further characterize the tumor.

Immunophenotyping (cytology, histopathology, or flow cytometry): Using antibodies against specific cell surface markers (ex. B cell CD 79a/CD20, T cell CD3/CD4/CD8), this test is primarily used to determine if the lymphoma is B or T cell in origin. However, it can also be helpful to support a diagnosis of lymphoma by documenting a homogenous population of the same immunophenotype within a tissue.

Flow cytometry

This test allows immunophenotyping of cells in suspension (blood, effusions, and aspirates of LNs or organs). Flow cytometry can also provide information regarding cell size and expression of other CD molecules that may correlate with prognostic information.

PARR (PCR for antigen receptor rearrangement)

Theoretically, a malignant cell population should be derived from expansion of a single clone. PARR amplifies the variable regions of the T cell receptor or Immunoglobulin (Ig) receptor gene to detect the presence of clonal lymphocyte populations. When it is not possible to differentiate between malignant and benign lymphocytes based on cytology or histopathology alone, PARR may be helpful to confirm a diagnosis (especially useful when the lymphocyte population is heterogeneous). PARR can be used to detect minimal residual disease but investigations are ongoing to determine if this is a useful clinical marker of early recurrence.

Proteomics (ex. PetScreen)

Proteomics analyzes the protein components of a cell, which may be used to identify cancer specific markers. Preliminary studies have been performed in canine lymphoma but clinical application is limited at this time.

Clinical staging advances

Lymphoma is considered a systemic disease and most dogs are presented in advanced stages (III to IV). Ideally, the extent of disease is determined after diagnosis as a baseline for treatment monitoring. However, the degree of staging necessary is controversial. The completeness of staging in any given case is often dictated by 1) how a diagnostic test affects treatment plan, 2) how it affects client’s decision making and 3) how it affects patient prognosis. A thorough physical exam, CBC, serum chemistry profile, and urinalysis are indicated for every patient to obtain vital information regarding organ and bone marrow function before starting treatment with chemotherapy. Additionally, information regarding prognostic factors (hypercalcemia, anemia) may be obtained. Further diagnostics to consider include thoracic radiographs and abdominal radiographs/ ultrasound. These imaging studies are non-invasive and may provide information regarding areas of significant disease burden (such as mediastinal or sublumbar lymph nodes). This can be important information when monitoring for lymphoma relapse. In the author’s practice, abdominal ultrasound is also highly recommended for any dog with clinical signs attributable to the GI tract in order to rule out involvement, and thoracic radiographs/
Echocardiogram are recommended for any dog predisposed to heart disease. The value of a bone marrow aspirate in the face of a normal CBC is questionable and rarely pursued in the author’s practice.

**PET/CT (positron emission tomography/computed tomography)**

PET/CT combines functional and anatomical imaging to allow detection of metabolic or proliferative activity throughout the body. PET/CT is currently the standard of care for monitoring and predicting response to therapy in people with lymphoma. PET/CT has also shown promise for evaluating response to chemotherapy and predicting relapse in dogs with lymphoma.

**Standard treatment options**

Multi-agent chemotherapy is the mainstay of treatment for lymphoma. For intermediate to high grade lymphomas, CHOP-based protocols are typically advised as first line therapy and provide the best response rates (80-95%) and treatment outcomes. At this time, long term maintenance chemotherapy does not appear to improve remission times. Additionally, dogs that do not receive maintenance therapy appear to be more likely to achieve a second remission following relapse. Several studies suggest that inclusion of L-asparaginase in the protocol does not significantly improve outcome (remission rates or duration of remission). In the author’s practice, the decision to use L-asparaginase is made on a case-by-case basis and typically reserved for particular situations (e.g. sick patient, cytopenic, rescue, etc.). Individual response and remission durations vary depending on prognostic factors. Overall median survival times are 12-14 months with approximately 20-25% of dogs alive at 2 years. Alternative protocols are offered if clients need less costly or more convenient options.

Rescue chemotherapy is associated with lower response rates and shorter remission times. Chemotherapy agents that are commonly used in the rescue setting include lomustine (CCNU), doxorubicin, mitoxantrone, MOPP (mustargen, vincristine, procarbazine and prednisone), actinomycin-D, and dacarbazine (DTIC).

**Novel treatment options**

**Monoclonal antibodies (Mab)**

Outcome improvements in people with non-Hodgkin’s lymphoma have been due in large part to Mab therapies such as rituximab (anti-CD20 antibody used to treat B-cell lymphomas). However, rituximab is not effective in dogs. Currently, clinical studies are ongoing to evaluate two conditionally approved monoclonal antibodies (Aratana Therapeutics) for use in the treatment of canine lymphoma. These promising canine-specific antibodies are directed against CD20 (AT-004) for B-cell lymphoma and CD52 (AT-005) for T-cell lymphoma.

**Bone marrow/stem cell transplantation**

Ablative total body irradiation and/or chemotherapy combined with bone marrow or stem cell transplantation is available for dogs with lymphoma. However, these treatments are not widely accessible, are costly, and are associated with increased morbidity in dogs undergoing treatment. While these treatments present a potential for increased cure rates, results of a large number of treated cases have yet to be reported.

**Adoptive T cell therapy**

Expanded autologous T cells infused after CHOP chemotherapy has been shown to significantly improve overall and disease free survival in a small number of dogs with B cell lymphoma. While quite promising, this therapy is currently available to client-owned dogs only through clinical trials.

**Prognostic marker advances**

Widely accepted negative prognostic factors include T cell immunophenotype (for multicentric lymphoma), substage b (sick), prior treatment with prednisone, and certain anatomic sites (cranial mediastinal involvement, primary diffuse cutaneous, GI, hepatosplenic, and primary CNS). Recently, it has been shown that B-cell lymphomas expressing low levels of class II MHC or lower than normal levels of B5 antigen also had a poorer prognosis. Presence of anemia is also associated with a worse prognosis. Alternatively, it appears that dogs with indolent lymphoma experience prolonged survival times.
Hemangiosarcoma (HSA) is a malignant neoplasm which originates from vascular endothelium and accounts for 0.3-2% of all canine cancers. Large breed dogs such as German Shepherd Dogs, Golden Retrievers, and Labrador Retrievers are over represented with a median age at diagnosis of 9-10 years. Most frequently affected primary sites of HSA in these patients include the spleen, skin, and heart. Other less common sites include the liver, lungs, kidney, muscle, oral cavity, bone, and the urinary bladder. Clinical signs can be nonspecific or consist of acute weakness or collapse with corresponding abdominal distension, tachycardia, tachypnea, pale mucous membranes, and weak pulses. These clinical signs are often secondary to acute blood loss into the peritoneal or pericardial cavity.

Standard of care treatment for HSA depends primarily on tumor location but in large part consists of surgery followed by chemotherapy. The chemotherapeutic agent of choice for HSA is Doxorubicin. For strictly dermal HSA, chemotherapy is not necessary following complete surgical removal with adequate margins. However, for the remaining HSA locations surgery alone affords the patient with a median survival time of less than 2 months. Even with the addition of chemotherapy, the majority of patients will succumb to their disease within 4-8 months. Death is usually secondary to metastatic disease via hematogenous spread to the pulmonary parenchyma and intraabdominal dissemination primarily, but also to the skin, bones, and brain.

Pathology and natural behavior
Malignant endothelium serves as the underlying pathology of HSA, and hence HSA can involve any organ requiring nutrition and oxygen via blood circulation. Often dogs presenting for visceral organ HSA will present with signs associated with acute tumor rupture and resultant hemorrhage and hypovolemic shock. Symptomology reflects the hemodynamic instability of these acutely bleeding patients and include lethargy, weakness, collapse, anorexia, mucous membrane pallor, delayed capillary refill time, tachycardia, tachypnea, cardiac arrhythmias, and poor pulse quality. In circumstances where the patient does not experience a life-threatening hemorrhage event, clinical symptoms might recur and take on an episodic pattern. With primary splenic or hepatic HSA, tumor rupture results in abdominal distention and a noticeable fluid wave secondary to hemorrhagic effusion. With primary cardiac HSA, muffled heart sounds, venous congestion, and signs compatible with cardiac tamponade may be noted. Primary subcutaneous and intramuscular HSA, typically occur as large, firm or fluctuant masses. Overlying skin may be ecchymotic and ulcerated.

Diagnosis and staging
Presumptive diagnosis of HSA can be made based upon multiple clinical and physical findings, as well as patient signalment. However, baseline diagnostics which should be considered in any patient with presumed HSA might include the following:

- Complete blood count
  - Anemia: secondary to hemorrhage
  - Schistocytes: red blood cell morphology
  - Thrombocytopenia: immune mediated destruction, splenic sequestration, severe hemorrhage, and/or disseminated intravascular coagulopathy (DIC)
  - Neutrophilic leukocytosis
- Serum chemistry panel
  - Hypoproteinemia: secondary to blood loss
  - Liver enzyme elevations: involvement of hepatic parenchyma
  - Hypoglycemia: rare paraneoplastic syndrome
- Coagulation panel
  - Elevations in clotting times: disseminated intravascular coagulation
  - Defects in both primary and secondary coagulation cascades
- Thoracic radiography
  - Evaluation of overt lung metastases
  - Cardiac involvement with globoid cardiac silhouette
    - Pericardial effusion
• **Echocardiography**
  - Evaluation of right auricle or atrial mass effects
  - ECG might demonstrate ventricular arrhythmias and electrical alternans

• **Abdominal ultrasound**
  - Evaluate primary abdominal tumor involvement, as well as regional metastases within the visceral organs residing within the peritoneal cavity

• **Cytology**
  - Considered insensitive for diagnosis given poorly exfoliative nature of sarcomas

• **Biopsy**
  - Required for definitive diagnosis
  - Diagnostic and therapeutic

### Canine hemangiosarcoma treatment options

Due to the devastating prognosis for HSA, multiple new therapies outside the realm of surgery and standard doxorubicin administration have been devised and evaluated. These include various alternative chemotherapeutic protocols, intracavitary chemotherapy administration, immune modulation, matrix metalloproteinase inhibitors, antiangiogenic therapy, and tumor vaccines.

Combination chemotherapy protocols with doxorubicin, cyclophosphamide and vincristine (VAC) or doxorubicin and cyclophosphamide (AC) have been evaluated. Unfortunately, the addition of these chemotherapeutic agents to standard treatment with doxorubicin afforded no significant increase in survival times with median survival times of 172 and 179 days respectively. A dose intensified doxorubicin protocol has also been evaluated with doxorubicin being administered every 2 weeks instead of every 3 weeks, however median survival time was not statistically different from that of standard treatment methods. Intraperitoneal administration of liposome encapsulated doxorubicin has been evaluated as the abdomen is a main site of progression of disease and thus it is logical to treat them with a drug that due to its liposome encapsulation and pegylated nature should have a longer half-life in the plasma. Unfortunately, again survival times did not vary significantly from those previously reported.

Tumors require angiogenesis for growth and thus anti-angiogenic drugs have been and are currently being heavily investigated for the use in a multitude of tumors. Minocycline, an antiangiogenic metalloproteinase agent with anticollagenase activity, was evaluated in combination with doxorubicin and cyclophosphamide for treatment of dogs with hemangiosarcoma. Regrettably, the addition of this drug revealed no significant survival advantage with an all too familiar median survival time of 170 days. Additionally continuous low dose chemotherapy with the combination of etoposide, cyclophosphamide, and piroxicam was evaluated in 9 dogs diagnosed with stage II splenic HSA. The goal of this study was to see if this combination of drugs, which targets the tumor neovascularity itself, would improve survival times in contrast to traditional therapy. Survival times of the dogs in this study were comparable to other previously established studies and known survival times.

Immune modulation via administration of a liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE), a synthetic derivative of a component of bacterial cell walls, in combination with chemotherapy afforded the longest survival times of all above novel treatment options. L-MTP-PE activates macrophages and monocytes leading to increased tumoricidal activity. While the survival time of dogs treated with this therapy (277 days) is the longest seen in the literature, there were an equivalent number of dogs with stage I as compared with stage II and this likely biased the results. Further study with a larger sample size of stage II HSA would be interesting but, studies have not been pursued further due to the lack of availability of this product to the veterinary community at this time, due to high cost and limited supply.

As immune modulation seems to be one of limited treatment options which may improve overall survival times in dogs with hemangiosarcoma, a vaccine prepared from lysates of allogenic canine HSA cell lines was evaluated in 28 dogs. Vaccines were given intraperitoneally once per week for 5 weeks then once monthly for three additional treatments. The vaccine was often given in combination with standard doxorubicin doses. Of the 6 dogs evaluated for antibody production, all 6 mounted a strong response to the vaccine and side effects were minimal. No statistically significant improvment in survival time was seen.
Mast Cell Tumors: The Good, the Bad, and the Ugly
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Mast cell tumors are one of the most common cutaneous tumors in the dog. Biologic behavior is variable and clinical outcome is best predicted by histologic grade. Grade I tumors are usually well differentiated, rarely metastasize and are associated with an excellent outcome. Grade II tumors are locally invasive, may spread to local lymph nodes, and uncommonly spread throughout the body. A population of intermediate grade (Patnaik grade II) MCTs appear to follow a more malignant course, spreading locally and to distant sites. Additional factors are often considered in attempt to predict the behavior of grade II tumors. Grade III tumors are usually anaplastic and locally aggressive, with a high rate of metastasis. These tumors are not cured typically, but many dogs can have extended remissions if tumors are caught early and treated aggressively. In practice, deciphering which MCTs will behave aggressively can be difficult, making prognosis and optimal treatment challenging to predict. Consideration of a number of clinical (tumor size, clinical signs, etc.) and histologic factors (mitotic index, c-kit, etc.) can be used to help the clinician best present to and guide clients through a wide range of diagnostic and treatment options.

Diagnosis and staging
In most cases, MCTs can be easily diagnosed via fine needle aspirate and cytology with the rapid hematologic-type stains used in most practices. A small percentage of MCTs may have poorly staining granules, in which case a Wright-Giemsa or toluidine blue stain may be necessary. If histopathology is required for diagnosis, careful consideration of tumor location, size, and clinical factors is needed to plan for biopsy. When possible, wide excisional biopsy is preferred and incisional biopsy is uncommonly pursued in the author’s practice.

Staging is important in the clinical evaluation of canine MCT patients; however, what constitutes adequate staging is controversial. In select cases, an extensive work-up may not be necessary. Generally speaking, a minimum database (complete blood count serum biochemistry profile) and regional lymph node cytology are recommended for all dogs with MCT. These diagnostics are typically inexpensive and quick to perform and are likely sufficient for cases where the tumor is amenable to wide surgical excision and no negative prognostic factors are present. Histologic assessment of a regional lymph node may be required for definitive diagnosis of regional metastasis if cytology is suspicious but not definitive for metastatic disease. If the tumor is in an undesirable surgical location or if negative prognostic factors exist, further staging with abdominal ultrasound is advised. Abdominal ultrasound is non-invasive and allows evaluation of spleen, liver, and intra-abdominal lymph nodes for metastatic disease. Fine needle aspirate of the spleen and liver are always advised if the organs look abnormal. Several studies have suggested that FNA of the spleen and liver is warranted in the case of clinically or histopathologically aggressive disease even if they appear normal on ultrasound. In the author’s practice, splenic aspirate is strongly advised for any high grade II or III tumor or in the case of concerning clinical behavior (see prognostic factors). Thoracic radiographs rarely reveal metastasis. However, it is reasonable to pursue this as a pre-anesthetic screening and to rule out other unrelated disease processes prior to a surgical procedure. Bone marrow aspirate is rarely indicated.

Prognostic factors
Grade
Histologic grade is considered the most consistent prognostic factor available for canine MCT but should be interpreted in light of other prognostic factors when making treatment decisions. Histopathologic grading is complicated by inter-observer variation among pathologists. Currently, two forms of grading are reported in clinical practice. The most commonly utilized grading system is the Patnaik grading system (low- grade I, intermediate- grade II, high- grade III). More recently, a 2-tier histologic grading system (low, high) has been introduced for canine MCTs. The second system was developed in an attempt to compensate for some of the weaknesses of the Patnaik system. However, further validation is needed to determine if this is truly better at predicting behavior and clinical outcome.

Proliferation indices
Mitotic index (MI) is a strong predictor of overall survival in dogs. Using a cutoff of 5/10 high powered fields, dogs with a low MI (<5) had a median survival time of 80 months compared to 3 months for dogs with a high MI (>5). It is advisable that any tumor with a high MI is staged and treated as an aggressive MCT in practice.
Other markers of proliferation that have been evaluated include Ki67 (a protein in the nucleus that correlates with cell proliferation), AGNORs (argyrophilic nucleolar organizer regions), and PCNA. These require the use of special stains and are often included in the MCT prognostic panel. Interpretation of this panel can often be confusing for clinicians. At this point, it appears that Ki67 is most useful clinically as a prognostic factor for intermediate grade tumors to help predict expected survival times when the clinical picture remains confusing based on other factors.

**C-Kit**

KIT (a receptor tyrosine kinase) dysregulation has been implicated in the pathogenesis of MCT development and evaluated as a prognostic factor. While KIT staining patterns (cytoplasmic localization) may be associated with dysregulation and prognosis, clinical application of this as a prognostic factor remains challenging. Alternatively, the presence of c-kit activating mutations is strongly associated with a higher rate of local recurrence, metastasis, and death from disease and should be considered a poor prognostic indicator.

**Tumor location**

Some tumor locations may differ in behavior and prognosis. Subcutaneous tumors may have a better prognosis. Mucous membrane sites, subungual, and visceral tumors are associated with a worse prognosis. Conjunctival tumors and those of the eyelid margin may be an exception with studies showing prolonged survival after surgery alone. Perioral and muzzle MCTs have an increased risk of locoregional metastasis yet prolonged median survival times despite the higher rate of lymph node metastasis. Scrotal and preputial tumors may be associated with a worse prognosis but this remains controversial.

**Clinical stage**

Higher stage disease is associated with a worse prognosis. The effect of lymph node metastasis on outcome may be dependent on grade of the primary tumor and how the lymph node is treated. Thus, clinical judgment is important. Multiple tumors may not negatively affect prognosis.

**Other factors**

Local recurrence, systemic and local clinical signs, growth rate, and tumor size have all been correlated with prognosis and should be considered in the overall evaluation of a patient’s tumor.

**Treatment options**

**Primary therapy**

Wide surgical excision is the primary treatment of choice for tumors localized to the skin and subcutaneous tissues. Adequate tissue margins may be related to grade; however, grade is often unknown prior to therapy. At least 2-3 cm lateral margins and one tissue plane deep is generally recommended; 2 cm margins are likely adequate for grade I and II tumors. One study found no local recurrence at 2 years for primarily low to intermediate grade tumors removed with a lateral histologic margin of >10 mm and a deep histologic margin of >4 mm. However, histologic margin size may not accurately reflect margin size at surgery. Histopathology is advised for every tumor to determine grade and evaluate margins. The majority of low and intermediate grade tumors are cured with adequate surgical excision. Occasionally, external beam radiation therapy (RT) may be used as a primary treatment in cases of non-resectable tumors. Approaching the dog with multiple mast cell tumors can be challenging and primary therapy should be considered on a case by case basis.

**Adjuvant local therapy**

Adjuvant local therapy should be discussed with pet owners when adequate margins cannot be achieved due to location or histologic assessment reveals incomplete or narrow excision. Unfortunately, confusion exists regarding which tumors require additional treatment due to varied reports of local recurrence rate in incompletely and narrowly resected tumors (ranging anywhere from about 12-60%). When local therapy is being considered, grade, proliferation indices and c-kit status may be helpful in determining which cases would benefit. The implication of regrowth based on location may also play a factor in discussion with owners regarding the importance of adjuvant therapy. Standard of care options include primary re-excision and radiation therapy, both of which have been found to reduce local recurrence rates and increase survival times. MCTs are radiosensitive and 75-96% of dogs will have a local cure with adjuvant radiation therapy. An alternative option is electrochemotherapy (when available) which shows initial promise in improving local control for incompletely removed tumors.

**Systemic therapy**

Chemotherapy or tyrosine kinase inhibitors (TKIs) should be offered following excision of tumors in dogs with poor prognostic indicators (grade III, high mitotic index, metastasis, poor location, etc.). High grade and metastatic mast cell tumors are unlikely to be cured, but adjuvant therapy may improve disease free intervals and survival times. Vinblastine and lomustine are commonly used traditional chemotherapeutic agents. Response rates range from 11-64% when used against bulky disease; however, chemotherapy is more successful against microscopic disease. A variety of chemotherapy protocols exist. A combination vinblastine/prednisone protocol is preferred as a first-line protocol for adjuvant therapy in the author’s practice (weekly therapy for 4 treatments and then biweekly therapy for 4 treatments). If the initial vinblastine dose is well tolerated (2 mg/m2), dose escalations (increases of 0.25 mg/m2 at a time up to 3.5 mg/m2) should be considered in an attempt to improve efficacy. Lomustine (CCNU) is typically dosed every 2-3 weeks.
and requires close monitoring due to potential for myelosuppression and hepatotoxicity. Denamarin is recommended as supportive therapy for any dog treated with lomustine. Paclitaxel (Paccal Vet) has also recently been evaluated and appears to be safe and clinically effective for gross disease (complete or partial response 59%). However, the role of this agent in the adjuvant setting has not yet been defined. Metronomic chlorambucil may also be a consideration in cases where dogs have failed other therapies or a lower cost alternative is desired.

Toceiranib phosphate (Palladia) and masitinib (Kinavet) are orally administered TKIs that have efficacy against gross disease. While these drugs can be considered as adjuvant treatment, there is no data currently to define the efficacy of TKIs alone in the adjuvant setting. In the author’s practice, toceiranib is discussed as an option for primary adjuvant therapy in cases when an owner declines intravenous treatment for their pet or subsequent to traditional chemotherapy when the presence of a c-kit mutation is known. In the treatment of bulky disease, Toceranib has a response rate of about 40% (~60% if stable disease is included). While dogs with KIT mutations were more likely to have a response than those without (69% vs. 37%), routine testing prior to toceiranib therapy is probably not indicated for bulky disease as tumor response will guide therapy. Adverse effects include GI toxicity, mild to moderate leukopenia, and occasional muscle pain or mild PLN. Tolerability of toceiranib improves when doses lower than the label dosage are used (2.5-2.75 mg/kg EOD or M,W,F). Combination of toceiranib with vinblastine chemotherapy and palliative radiation therapy has also been studied.

Masitinib is conditionally approved for the treatment of nonresectable grade II or III cutaneous MCTs as a first-line therapy. Treatment with masitinib (12.5 mg/kg daily) has been shown to improve time to progression and survival rates at 12 and 24 months for dogs harboring activating c-kit mutations. Thus, this drug can provide the potential for long-term disease stabilization in some dogs. Adverse effects include mild GI toxicity, mild myelosuppression, occasionally PLN, and rarely hemolytic anemia. An appropriate monitoring schedule is important when treatment with oral TKIs is employed. When significant adverse effects are noted, treatment is typically discontinued for a period of time. In the author’s experience, it can often be restarted at a lower dose.

**Ancillary therapy**

Histamine blockers (H1 and H2) are indicated for cases when gross disease is present, either preoperatively or in the palliative setting for nonresectable masses/ metastatic disease. Diphenhydramine (2 mg/kg BID-TID) and famotidine (0.5 mg/kg QD-BID) are common choices.

Clinical management of mast cell tumors can be challenging due to the wide range of biologic behavior. Although many cases are cured with adequate local therapy, the use of prognostic indicators discussed can help guide the clinician in determining which tumors are more likely to behave aggressively, and thus, become life-threatening for the dog. When clear poor prognostic factors exist, complete staging and adjuvant therapy is strongly advised. However, uncertainty regarding prognosis may remain in some cases despite our best efforts to define tumor behavior. This highlights the importance of owner education and clinical judgment in selecting appropriate diagnostic and therapeutic options.
Transitional cell carcinoma and prostate carcinoma continue to be problematic diseases in our canine patients. Tumors are often locally advanced at diagnosis and the location of disease frequently limits surgical options and results in dysuria or obstruction of the urinary tract. Additionally, as advancements in primary tumor control are made, the rate and impact of distant metastases becomes greater. Despite these challenges, treatment options are available that may afford dogs improved quality of life and extended survival time.

Transitional cell carcinoma (TCC) is the most common tumor of the urinary bladder and affects tens of thousands of dogs each year. Risk factors for development of TCC include both heritable genetic factors and environmental exposures. Breeds at an increased risk of developing TCC include Scottish Terriers, Eskimo dogs, Shetland Sheepdogs, West Highland White Terriers, Keeshonds, Samoyeds, and Beagles. Owners of such breeds should be educated on the risk of TCC and informed of concerning clinical signs related to the urinary tract.

Prostatic cancer may be either TCC or prostatic carcinoma (PC). Prostatic carcinomas are less common, representing less than 1% of canine tumors. The etiology of prostatic carcinoma is unknown although high grade prostatic intraepithelial neoplasia (PIN) has been detected in dogs with and without prostatic carcinoma. Breeds at an increased risk include Bouvier des Flandres, Doberman pinscher, Shetland sheepdog, Scottish terrier, beagle, miniature poodle, German shorthaired pointer, Airedale, and Norwegian elkhound. The risk of both TCC and prostatic adenocarcinoma may be increased in neutered dogs. Both TCC and prostatic carcinoma are of particular interest due to similarities between dogs and humans and the potential for translation of research between species.

**Presentation and diagnosis**

Dogs with both TCC and prostate carcinoma commonly present with hematuria, stranguria and pollakyuria. In addition, tenesmus and dyschezia may occur secondary to prostate tumors or enlarged regional lymph nodes. Since these tumors predispose dogs to bacterial infections of the urinary tract, temporary improvement or resolution of clinical signs may occur with antibiotic therapy. When evaluating dogs with signs related to the urinary tract, neoplasia should be considered and further investigation pursued if no bacterial infection is present, response to therapy is transient or incomplete, or if the breed is at high risk for TCC or prostatic carcinoma. Clinical signs of local invasion and distant metastatic disease may also be present.

Evaluation of dogs with suspected TCC or prostate carcinoma often begins with a thorough physical examination including a rectal exam, urinalysis, and imaging of the abdomen. Thickening and/or a mass of the bladder wall or urinary tract or an enlarged, irregular prostate increases suspicion for TCC or prostatic carcinoma, respectively. Finding abnormal epithelial cells in urine also increases suspicion. Cytology may be able to provide a diagnosis of carcinoma. However, histopathology is ultimately needed for definitive diagnosis. Samples may be obtained via surgical routes, cystoscopy, traumatic catheterization, FNA or prostatic wash depending on tumor type. Tumor seeding is a risk of percutaneous biopsy/FNA. Samples may be obtained from the primary tumor or metastatic lesions. The value of urine antigen testing for TCC has limited value due to false-positive results.

**Staging**

Canine TCC is most commonly located in the trigone region of the urinary bladder. Urethral involvement occurs in 56% of dogs and prostatic involvement occurs in 29% of male dogs. Almost 80% are invading the bladder wall (T2) and 20% invade nearby organs (T3). Metastasis is present in about 20% of patients at diagnosis but more than half of dogs at death. Canine prostatic tumors are both locally invasive and have a high rate of regional and distant metastasis (~80%). Lymph node and lungs are the most common sites but skeletal metastasis (especially lumbar vertebrae and pelvis) occurs in 22-42% of patients. Staging should include CBC, serum chemistry profile, urinalysis and culture, thoracic radiographs, abdominal radiographs and/or abdominal ultrasound, +/- urinary tract imaging. Abdominal ultrasound is most often employed to monitor tumor response; however, a standardized protocol is often necessary for this to be accurate.

**Treatment**

**Systemic medical therapy**

The mainstay of TCC and prostate carcinoma treatment is systemic medical therapy with chemotherapy, COX inhibitors, and a combination of these. The goal of therapy is remission or disease stabilization and improvement in clinical signs. The typical chemotherapy drugs employed are generally well tolerated and include mitoxantrone, vinblastine, gemcitabine, and platinum agents.
Doxorubicin and metronomic chlorambucil have also been investigated for TCC. The best outcomes are seen when COX inhibitors (such as piroxicam) are combined with chemotherapy agents. Mitoxantrone is most commonly used as a first line agent in the author’s practice; vinblastine is also commonly used for TCC. However, many drugs are often employed sequentially throughout the disease course guided by tumor and clinical response as well as tolerability of therapy. With combination therapy for TCC, survival times can extend beyond a year with good quality of life. When chemotherapy is declined piroxicam used as a sole agent can provide palliation of clinical signs and a median survival time of about 6-8 months. In cases where piroxicam is not well tolerated, evidence supports deracoxib as a reasonable alternative. For prostate carcinoma, evidence supports a survival benefit with piroxicam or carprofen (~7 vs. 1 month) whereas the benefit of systemic chemotherapy is less clear.

Treatment of secondary urinary tract infections should be guided by culture and sensitivity results to minimize antibacterial resistance.

Surgery
Curative intent surgery has a limited role in dogs with TCC due to the typical trigonal location, extensive bladder wall invasion, multifocal lesions, or the presence of metastatic disease. It may be indicated for cytoreduction when small tumors are located away from the trigone; however, it is unclear if cytoreductive surgery augments the benefit of adjuvant therapy. Transurethral approaches (tumor removal via cystoscopy) including laser ablation are possible but less beneficial in canine patients compared to humans since disease is rarely superficial. The benefit of including this type of therapy in a multi-modal approach is unknown but may be considered in select cases when owners are highly motivated. Surgery is also generally palliative for prostatic carcinoma and prostatectomy or electrosurgical transurethral resection is generally recommended only for dogs with early stage disease. Importantly, complications are common and survival benefit is limited; careful case selection is necessary.

Palliative surgical procedures to maintain urine flow are possible for both tumors and include prepubic cystotomy catheters and placement of urethral stents. Placement of urethral stents is preferred since there are no external components or owner maintenance. Complications can occur and the median survival time after stent placement is limited (about 1-2 months) but owners are generally satisfied with the outcome.

Radiation therapy
The use of radiation therapy (RT) to treat TCC and prostate carcinoma is challenging due to change in bladder location and shape. Because of this, large fields are needed and complications in surrounding normal tissues are common. Advances in RT technology (IM-IGRT/ SRT) may allow more targeted and controlled delivery to local disease and preliminary information shows promise for increased survival times when combined with chemotherapy and NSAIDs. Currently, the benefit of adding coarse-fraction external beam RT to systemic therapy is questionable but there may be a place for palliation of urinary tract obstruction or clinical signs relating to local disease or skeletal metastases in select cases.

Intravesicular therapy for TCC
Partial remission and stable disease have been documented in dogs treated with chemotherapy delivered directly into the bladder. Significant systemic absorption occurred in some dogs and response was not superior to systemic therapy. However, this treatment may be considered for select cases or dogs that have failed other therapies.

Emerging therapies
New strategies currently under investigation include folate targeted therapy; a bladder cancer specific peptide (PLZ4) targeted therapy, and demethylating agents.
The plasma cell is of lymphoid lineage and specifically a terminally differentiated B-lymphocyte. Based upon its origin, plasma cells have the capacity to produce immunoglobulins, which under physiologic conditions preserve immune competence and protect the host organism from extracellular pathogens. Like any normal cell, malignant transformation can occur and give rise to a cancerous population of plasma cells. There are a number of disease conditions comprised of malignant plasma cells and include multiple myeloma (MM), solitary osseous plasmacytoma (SOP), extramedullary plasmacytoma, and in felines a syndrome known as myeloma-related disorder in which cancerous plasma cells infiltrate visceral organs.

In dogs and cats, the cause of plasma cell cancers is largely undetermined; however, given the role of plasma cells in mucosal immunity, there has been some speculation that chronic antigen stimulation might promote the development of these malignancies. Anecdotal and clinical support for this speculation would be the common anatomic regions affected by plasma cell tumors including the interdigital regions, oral cavity, and gastrointestinal tract, which are systems commonly in contact with environmental antigens. Multiple myeloma is the most common plasma cell malignancies to cause systemic signs of illness, and will be the focus of this review.

Pathology and natural behavior
Clonal origin plasma cell proliferating systemically (usually within multiple bone marrow sites) producing immunoglobulin. Neoplastic cell of origin is the terminally differentiated B-lymphocyte (plasma cell), which normal function is to produce specific immunoglobulin to recognize pathogenic antigens (neutralization, agglutination, and opsonization).

Physical appearance of the cells varies markedly between patients (can be very bizarre). Immunoglobulin produced in excess (a.k.a. M component or paraprotein), usually complete immunoglobulin but sometimes just a portion of the molecule (light chains only = Bence Jones protein, heavy chains only = heavy chain disease). Remember that fully function immunoglobulin is a heterodimer (2 light chains binding with 2 heavy chains).

The M component is usually IgG or IgA. If the M component is IgM, it is called macroglobulinemia or Waldenstrom’s macroglobulinemia. Cryoglobulins are paraproteins that precipitate at temperatures <37º C, causing cutaneous lesions in extremities (colder areas). The M component can cause multiple problems for the patient. Infection is a major problem, and arises because excessive production of the paraprotein inhibits production of normal immunoglobulin, patients are considered to be ‘immunologic cripples’. Hyperviscosity syndrome arises secondary to the massive amounts of paraprotein present. The severity of the serum hyperviscosity is related to the type, size, shape and concentration of the M component. Hyperviscosity necessitates increased perfusion pressure to maintain vascular flow and also causes hypervolemia both of which increase the cardiac workload and can cause cardiomegaly. Combine this with myocardial hypoxia secondary to poor vascular perfusion and heart failure may result. Neurologic abnormalities including lethargy, ataxia and seizures occur because of poor perfusion. Bleeding problems (hemorrhagic diathesis) occur in about 1/3 of dogs with myeloma.

Bleeding may be caused by M-components 1) inhibiting platelet aggregation and release of activating factors 2) adsorbing minor clotting proteins 3) generating abnormal fibrin polymerization 4) producing a functional decrease in calcium. Thrombocytopenia will play a role in bleeding also. Renal failure can be caused by the high protein content in the glomerular filtrate, as a consequence of tubular obstruction by proteinaceous casts, amyloidosis, ascending pyelonephritis, tumor
infiltration, and decreased perfusion secondary to hyperviscosity. Retinal lesions are another sequelae of hyperviscosity. Changes include dilated and tortuous retinal vessels and retinal hemorrhages.

**History and physical examination**

Animals may present with nonspecific signs of weakness, PU/PD, pain, lethargy, or inappetance. More specific signs include epistaxis and gingival bleeding or signs due to a compressive lesion or fracture. Rarely, dogs will present with neurologic signs. PE is often nonspecific, try to localize pain if possible (palpate along limbs and spine).

- CBC may reveal anemia (secondary to either anemia of chronic disease, blood loss, or red blood cell destruction secondary to high serum viscosity, or myelophthisis).
  - Neutropenia and thrombocytopenia will be seen first if myelophthisis is present.
  - Thrombocytopenia may also be immune-mediated.
- Serum chemistry will show hyperglobulinemia (> 90%) and hypercalcemia (15 - 20%). Renal failure is seen in 33-50% of dogs (secondary to poor perfusion).
- Serum electrophoresis should be performed to characterize the globulinemia as monoclonal or polyclonal.
- Urine can be evaluated for Bence-Jones proteins. This requires heat precipitation or electrophoresis, as commercial urine dipstick methods will not detect these proteins.
- Bone marrow aspirate reveals > 10% infiltration of plasma cells.
- Survey skeletal radiographs evaluating specifically for osteolytic (punched out) lesions. Sites most commonly affected include the vertebral bodies, ribs, pelvis, skull, and proximal long bones.
  - Biopsy or fine needle aspirate of osteolytic lesions may be needed for diagnosis.

**Demonstration of two or more of the following strongly supports the diagnosis:**

1. Bone marrow plasmacytosis
2. Presence of osteolytic bone lesions (No osteoproliferation)
3. Hyperglobulinemia with monoclonal gammopathy
4. Bence-Jones proteinuria

**Prognostic factors**

Negative prognostic factors are somewhat intuitive and include:

- Hypercalcemia
- Bence-Jones proteinuria
- Extensive osteolytic bone lesions
- Renal Failure
- Severe hyperviscosity

**Treatments options and long term prognosis**

- Fluid therapy
  - Intravenous fluid therapy is often needed initially to correct dehydration, improve cardiovascular status, and manage hypercalcemia and azotemia. Treatment with isotonic saline solution is preferred over other fluids in the initial management of hypercalcemic patients.
- Antibiotics
  - Antibiotic therapy may be needed to treat concurrent infections, such as urinary tract infection or bacterial pyoderma, as these can progress to life-threatening infections if left untreated.
- Palliative radiation
  - Neoplastic plasma cells are sensitive to irradiation, and radiation therapy is a highly effective palliative treatment for MM since it can relieve discomfort and quickly decrease the tumor burden. Indications for radiation therapy include painful bone lesions, spinal cord compression, pathologic fracture (after fracture stabilization), or a large soft tissue mass.
- Bisphosphonates
  - Bisphosphonates, such as pamidronate, may be useful in managing hypercalcemia as well as decreasing osteoclastic bone resorption and bone pain. The recommended dose of pamidronate is 1 to 2 mg/kg given intravenously in dogs and, anecdotally, 1 mg/kg given intravenously in cats every 21 to 28 days. Prior to administration, evaluate renal function; dilute the pamidronate in saline solution (amount based on the size of
the patient) and administer as a slow infusion over two hours to minimize renal toxicities. Aminobisphosphonates are an essential component of therapy for MM in people, and their use is associated with significantly reduced skeletal-related events and improved survival in some studies.

- Analgesics
  - Dogs and cats with MM may experience moderate to severe pain; treating for this pain is a priority. Pain may be relieved by treating the underlying cancer and providing various analgesic therapies and supportive care.

- Chemotherapy
  - Although a cure is unlikely, MM can be a rewarding disease to treat since chemotherapy can greatly extend the quality and duration of life. The chemotherapy drugs most often used are alkylating agents, usually melphalan, combined with corticosteroids. However, eventual relapse during therapy is anticipated.
  - The overall response rate for dogs treated with melphalan and prednisone chemotherapy is 92%, with 43% of dogs achieving a complete response and 49% achieving a partial response. The median survival time of dogs treated with this drug combination is 540 days, which is significantly longer than the survival time of 220 days in dogs treated with prednisone alone.
The nasal cavity is comprised of various cell types which provide secretory and structural functions. As such, the malignant transformation of cells within the nasal passage often gives rise to tumors of epithelial or mesenchymal origin. Primary tumors of the nasal cavity account for approximately 1-2% of all neoplasms in dogs. In the majority of cases, nasal neoplasms are histologically malignant and are capable of regionally invasive and expansive growth patterns which invade into the nasal passages, frontal sinuses, and cranial vault cavity. With lower frequency, nasal tumors can eventually spread to regional and distant sites, which include the draining lymph nodes and lungs, respectively. Histologically, carcinomas are more common than sarcomas, and account for 60% to 78% of all nasal tumors. In the majority of descriptive studies, adenocarcinoma was most common (45%) histologic subtype, followed by squamous cell carcinoma (20%), chondrosarcoma (14%), undifferentiated or anaplastic carcinoma (11%), and unspecified carcinoma (10%). Nasal tumors are less commonly diagnosed in felines than dogs, but nonetheless are malignant in greater than 90% of affected cats. Lymphoma and carcinoma are the most common types of nasal tumor diagnosed in cats.

Pathology and clinical symptoms
Nasal tumors are characterized by rapid and progressive local tissue invasion, but a low metastatic rate. Humane euthanasia of dogs diagnosed with nasal tumors is the result of local tumor progression rather than development of metastatic disease. Although the incidence of regional and distant metastases for nasal tumors is relatively low (less than 30%), the histologic subtype may influence both localized and metastatic behaviors. Carcinomas may be subcategorized as being less or more aggressive. In general, highly undifferentiated and anaplastic carcinomas, as well as squamous cell carcinomas, prove more difficult to treat in dogs. Consequently, dogs suffering from anaplastic carcinoma or squamous cell carcinoma generally survive for shorter periods of time in comparison with dogs diagnosed with nasal adenocarcinoma. Median survival time of dogs with aggressive carcinomas and less aggressive carcinomas has been reported to be 7.2 and 11.9 months, respectively. Nasal tumors arising from mesenchymal origin, in particular chondrosarcoma appear to be less aggressive, with dogs achieving median survival durations approaching 2 years.

Given their growth within the nasal passage, many dogs remain asymptomatic for many months until tumor burden is substantial and occludes airflow or erodes through bone and blood vessels. The most common clinical signs seen in animals with nasal tumors include epistaxis, facial asymmetry, non-hemorrhagic nasal discharge, and sneezing. Physical examination findings may include stertorous breathing, enlarged mandibular lymph nodes, neurologic signs, decreased retropulsion of the eye(s), exophthalmus, ocular discharge resulting from nasolacrimal duct obstruction, and overt facial bone deformation. Although the presence of facial deformity is highly suggestive of a cancerous process, other differential diagnoses should include fungal or bacterial rhinitis, foreign body, trauma, developmental abnormalities, and dental pathology. Epistaxis is a common clinical sign in dogs and cats diagnosed with nasal tumors. The majority of dogs (~85%) with nasal neoplasia will manifest with frank hemorrhagic or serosanguinous nasal discharge, which correlates with a poorer prognosis.

Diagnosis and staging
Presumptive diagnosis of nasal passage cancer can be made based upon multiple clinical and physical findings, as well as patient signalment. However, baseline diagnostics which should be considered in any patient with presumed nasal tumor might include the following:

- Complete blood count
  - Anemia: secondary to hemorrhage
    - Uncommon to have severe blood loss
- Serum chemistry panel
  - Usually unremarkable
- Coagulation panel and buccal mucosal bleeding time
  - Rule out systemic coagulopathy for epistaxis
- Systemic blood pressure and fundoscopic examination
  - Rule out systemic hypertension for epistaxis
- Regional lymph node aspiration and cytology
Determine if malignant population of cells have regionally spread to dependent lymph node (uncommon)

- Thoracic radiography
  - Determine if malignant population of cells have distantly metastases to the pulmonary parenchyma (uncommon)

- Skull radiography
  - Evaluate for asymmetry
    - Filling defect on affected side, contrary to findings with fungal rhinitis (lysis)
    - Insensitive measure for identifying nasal pathology

- Computed tomography
  - Identification of mass effect
  - Identification of associated bony lysis and proliferation
  - Highly sensitive imaging modality for detecting nasal pathology

- Cytology
  - Feasibility is dependent upon location of primary tumor and ability to sample with needle

- Biopsy
  - Preferred method of definitive diagnosis
  - Several different methodologies for sample retrieval
    - Blind intranasal sample collection with forceps or curette
    - Rhinoscopic assisted biopsy (space and visual constraints)
    - Otoscopic transilluminator guided biopsy for rostral lesions
    - Open rhinotomy biopsy (not generally performed, high morbidity)
    - Hydropulsion with nasal flushing and dislodgment of tissue fragments

Nasal tumor treatment options

Radiation Therapy
The delivery of ionizing radiation with megavoltage therapy machines have been used for curative intent and palliative therapy for nasal tumors. Radiation therapy has the advantage of treating the entire nasal cavity, including bone, and its use has been associated with the greatest improvement in survival when compared to non-radiation treatment options. Despite the inability to cure the majority of dogs treated with radiation therapy, many patients enjoy relatively long durations of local disease control, improved clinical symptoms, and increased quality of life scores.

Definitive Treatment
Radiation therapy with curative intent has been previously described as a sole treatment option of nasal tumors in dogs. Conventional protocols require the administration of small fractions (3-4.2 Gy) repeatedly (10-19 treatments) on a daily or every other day basis for a total radiation dosage of 40 to 57 Gy. With the advancement in radiation technologies, it has become possible to “sculp” the radiation field to the contours of tumors within the nasal passages, thereby minimizing adverse effects to surrounding normal tissues. Advanced radiation units which allow for conformal targeting of tumor tissues include stereotactic radiosurgery and intensity-modulated radiation therapy. The use of stereotactic radiosurgery and intensity-modulated radiation therapy have not definitively proven improvements in survival time for treated patients, however, their remarkable precision with depositing radiation lessens undesirable acute and late radiation side effects, thereby attenuating unnecessary patient treatment-related morbidity.

Radiation therapy with surgery
Some debate exists over the utility of combining radiation therapy with surgical resection for the management of canine nasal tumors. For the majority of patients diagnosed with nasal cancer, cytoreductive surgery is not deemed possible or favorable for improved outcome, given the highly invasive properties of nasal tumors and the confined anatomic region of involvement. The vast majority of studies do not demonstrate any added benefit when surgery is combined with radiation therapy for the localized management of nasal tumors. However, in patients with small and ventrally confined nasal tumors which can be surgically approached through the soft palate, the combination of radiation therapy with surgery might be an option which improves overall disease control durations without and unacceptable increase in patient morbidity.

Radiation therapy with chemotherapy
Systemic chemotherapy has been classically indicated for the treatment of disseminated metastatic disease. However, the achievement of high local concentrations within the primary tumor microenvironment may allow for systemic chemotherapy to exert direct anticancer activities, which may contribute to the localized control of various cancers, including nasal tumors. However, given the paramount role of ionizing radiation for the management of nasal tumors, the inclusion of systemic chemotherapy for the treatment of nasal cancer has been as a radiosensitizer, rather than a direct cytotoxic agent. Various small descriptive studies have been conducted in veterinary medicine to support the potential benefit of combining radiation therapy with a radiosensitizing chemotherapeutic agent such as cisplatin or carboplatin. Collectively, the anecdotal evidence would suggest the feasibility of combining platinum agents with
radiation therapy, without unacceptable toxicity; however, historical studies have been inadequately designed to determine if any therapeutic benefit is achieved with this rational combination approach.

**Palliative radiation therapy**
The goal of palliative radiation therapy is to reduce tumor burden and improve quality of life. Most commonly, palliative radiation protocols deliver large fractions of radiation (6-8 Gy fractions) once to twice weekly for a total of 4-6 treatments. This palliative dosing strategy typically ameliorates clinical symptoms associated with disease, however is insufficient to dramatically reduce tumor burden for prolonged periods of time.