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PRACTICAL REVIEW OF COMMON SKIN AND SUBCUTANEOUS TUMOURS IN DOGS AND CATS

Skin and subcutaneous masses are the most common tumours seen in dogs, and second most common malignancy in cats. 20-40% are malignant in dogs and 50-60% are malignant in cats. The top 5 canine cutaneous tumours are mast cell tumours, perianal adenoma, lipoma, sebaceous adenoma and histiocytoma. In the cat it is basal cell tumour, mast cell tumour, fibrosarcoma, squamous cell carcinoma and sebaceous adenoma. The key features of many of these masses will be covered during the lecture.

It is important that the veterinary surgeon be familiar with the individual tumor types as tumor identity impacts many aspects of case management. in general, carcinomas metastasize via the lymphatic system and sarcomas via the haematogenous route. However, the two vascular systems are connected by lymphovenous communications and there are exceptions to these patterns. A strong knowledge base enables the clinician to perform thorough physical examinations and educate the client about tumour behavior, prioritise important staging tests, and choose the type of resection required for cure and long-term prognosis.

In the approach to case management there are two important considerations: 1) whether to obtain a pre-operative biopsy and 2) the extent of pre-operative staging. Staging will vary depending on tumor type but typically consists of thoracic radiographs and aspiration of regional lymph nodes. It is important to understand that a lack of lymph node enlargement does not mean that nodal metastasis has not occurred.

The value of knowing the tumor identity prior to surgical excision cannot be under-estimated, as tumour behavior can influence case management in many ways: degree of local invasion, metastatic potential and biologic activity (eg. release of histamine, heparin with manipulation of a mast cell tumour). However, the decision of whether to obtain a pre-operative (vs. post-operative) biopsy is not always straightforward however and in some locations on the body, excisional biopsy of some masses is an acceptable alternative to pre-operative biopsy. Biopsy remains a priority in the clinical management of most skin and subcutaneous masses.

Incisional biopsy is the removal of a portion of a tumor by sharp incision. This technique is usually performed in cases in which knowing the specific behavior of a tumor may affect an owner’s willingness to treat their pet surgically or when knowing the identity of the tumor would alter the treatment plan. Common methods include:

Wedge incision – Small, wedge-shaped section of tumour tissue removed with a scalpel blade or biopsy punch. For deeper subcutaneous tumours or those under superficial muscle bellies, a short skin incision is necessary to access the mass.

Needle core biopsies – Large bore needles used to sample deeper tumours (eg. Tru-cut for soft tissue). This type of tissue sampling can usually be performed with sedation and local anesthesia.

Disadvantages of the incisional biopsy approach are that it requires that it often requires a second surgical procedure be performed and it creates a direct communication between the tumour tissue and the surrounding normal tissue, possibly increasing the chance of local recurrence. The approach for incisional biopsy must be planned such that the incision site and entire dissection tract can be easily excised during the definitive resection.

In contrast, excisional biopsy is the removal of the entire tumor (usually a small mass) with a surrounding barrier of normal tissue. The main advantage is that biopsy and gross tumour removal are performed in a single procedure. The main disadvantage is that if the tumour is highly invasive and the surgeon does not know the identity of the tumour, they may not plan a wide enough resection to completely remove the tumour. Cytology results and the anatomic location are important factors in the deciding which approach to employ. For example, cytology results may be diagnostic for a mast cell tumor, obviating the need for a tissue biopsy. Tumors in the flank region may allow an excisional biopsy to be performed with wide (ie, 3 cm) margins while the same approach on a distal extremity would result in a large open wound that would not allow primary closure.
All excised tumours should be evaluated histologically. When submitting the specimen the surgeon should provide the pathologist with a concise but accurate history and help the pathologist maintain proper orientation of the tissue. This orientation may be communicated by making a drawing and placement of a suture on a specified margin of the specimen. Knowing the orientation can be very helpful if tumour cells are observed extending to one of the tissue margins and further local therapy is indicated. Alternatively, small tumour bed samples (i.e., small incisional biopsies of the wound bed post-resection) can be harvested from areas of higher concern just prior to closure. Following removal of the mass the surgical margins of the excised specimen should be marked with ink to document the original plane of dissection. Inking the margins can be very valuable, particularly when it is necessary to reevaluate the submitted specimen after the initial sectioning has been performed. The ink is “painted” on with cotton tip applicators by the surgeon and should be allowed to dry for 5-10 minutes before the specimen is placed in formalin. There are multiple colours available; however, some pathologists prefer black or yellow since these colors cannot be confused with the hematoxylin and eosin tissue stains (blue and red). Like suture tags, different ink colours can be used to direct the pathologist to areas of greater concern. The volume ratio of formalin to tumor mass should be 10:1 to insure proper fixing of tissue. With large tumours, near full-thickness fixative incisions should be made 1 cm apart throughout the tumour parenchyma (similar to slicing bread) to allow proper fixation. However, it is critical that the surgeon not allow fixative incisions to connect to the surgical margins as that will lead to confusion when the pathologist examines the tissue.
NEW ADVANCES IN THE MEDICAL AND SURGICAL MANAGEMENT OF MAST CELL TUMOURS IN DOGS

Principles of surgical oncology are driven by ‘what is it, where is it, how bad is it and how can we treat it?’; i.e. diagnosis, staging and therapeutic options. This tenet is very appropriate in the management of mast cell tumours (MCTs) and it is important to remember that more MCTs are cured by surgery alone than any other single or multi-modality plan. This is achieved in the main by planning the appropriate ‘surgical dose’ in order to minimize the need for repeat surgery or post-operative adjunctive therapies.

Fundamental to completely excising MCTs is an understanding of the principles of histological invasion, tumour reactive zones, and decisive curative-intent surgery. Mast cell tumours are typically histologically circumscribed but un-encapsulated, with a poorly defined surrounding reactive zone, consisting of some or all of:

- a vascular response (new blood vessels),
- mesenchymal response (to physical presence of the tumour and abnormal local tissue forces) and,
- inflammatory response (to necrosis / haemorrhage / degranulation).

This reactive zone may be several millimetres in width in smaller low grade tumours, but several centimetres in high grade degrangerating tumours. Within the reactive zone of MCTs will be normal inflammatory mast cells in addition to neoplastic mast cells, and occasionally local extensions of tumour called ‘satellites’, distinct from the main tumour mass. This surrounding zone of predominantly inflammatory cells admixed with neoplastic cells is successfully excised if a surgical margin of ‘normal’ tissue around the borders of the grossly visible cutaneous (or subcutaneous) mass is taken.

Historically a 3cm skin margin laterally around the visible edge of a cutaneous MCT, and a deep tissue margin beneath one fascial plane is described as adequate to completely resect the tumour and reactive zone. When cutaneous MCTs arise on the body the panniculus muscle (platysma, cutaneous trunci, preputialis, supramammarius) is a suitable deep fascial plane, and the thick fibrous fascia is suitable on the limbs. The origin of 3cm is unknown and it seems overly simplistic to suggest this rule equally applies, for example, to both a biologically inactive 5mm MCT present for two years, and also to a rapidly growing 5cm MCT which appeared two weeks previously.

The first reference to the 3cm margin in the literature is unclear and the 3cm preconception was challenged by Simpson and others (2004) who studied 23 grade 1 or grade 2 MCTs excised with 3cm margins. They successfully demonstrated that all grade 1 tumours were completely excised at the 1cm skin margin and all grade 2 tumours were completely excised at the 2cm skin margin, although 2/20 dogs had tumour cells within 1mm of the deep margin (fascial tissue). This was true independent of tumour diameter (range 0.35-5cm). A subsequent prospective study excising all grade 1 or 2 tumours (diameter range 0.4-3.1cm) with a 2cm skin/one fascial plane deep margin achieved complete excision in 91% cases, and avoided the much larger tissue defects seen with 3cm margins (Fulcher, 2006).

Henderson has recently proposed an intriguing ‘proportional margins’ theory for grade 1 or 2 MCTs less than 2 cm in diameter. In brief the width of the lateral skin margin and depth of the deep margin is equal to the tumour diameter. So a 0.5cm diameter MCT is excised with a 0.5cm skin margin and 0.5cm deep margin, whereas a 2cm MCT is resected with a 2cm skin margin and 2cm margin deep (or fascial plane). It would then follow from Fulcher’s work that a constant 2cm would be used in grade 1 or 2 tumours over 2cm in diameter. Henderson’s pilot work was presented at the Veterinary Cancer Society and results of a larger prospective study of grade 1 and grade 2 tumours excised using the proportional margin theory is currently under peer-review. It has not been studied whether a 2cm margin is sufficient to obtain clean margins in MCTs over 5cm in diameter (largest tumour in either Simpson or Fulcher’s papers). It is also not known whether any of these rules described above hold true for grade 3 MCTs.

The phenomenon in dogs of presenting with multiple simultaneous cutaneous MCTs was investigated by Mullins in 2006. 54 dogs with 153 tumours were retrospectively reviewed and it was found that the 1 year and 2-5 year survival rates were 87% and 85% respectively. Rate of metastasis was 15%. The only negative prognostic factor in multi-
variate analysis was the presence of clinical signs at time of presentation (cutaneous ulcers, signs of pain, swelling, or gastro-intestinal signs such as vomiting, melaena or diarrhoea). This study prompted the authors to conclude that multiple cutaneous MCTs in dogs are associated with a low rate of metastasis and a good prognosis for long-term survival with adequate excision. This is useful information for the common clinical scenario of finding 2-10 MCTs on a dog, and finding 5 more whilst clipping. The overall outcome for the patient is favorable, and if the margins on these smaller masses can now be ‘down-staged’ too, then many of these can be removed with conservative surgery.

Mast cell tumours can be successfully removed with the instrumentation available in most general practices. Cautery is recommended to minimize local bleeding and risk of post-operative haematoma. If reconstructive procedures are necessary then skin hooks or using stay sutures to mobilise wound edges are advisable in order to avoid traumatizing the leading wound edges. If a large dead space exists after tumour excision, this should be closed by subcutaneous sutures rather than drains as placing the latter in oncological surgeries widens the potentially contaminated field if the excised tissue is reported as histologically incomplete. Any subsequent adjunctive therapies (e.g. re-excision, radiation) must then also include the path of the drain.

If multiple masses are to be removed under the same anaesthetic, these can all be draped out separately. A new set of instruments should be used for each mass to prevent tumour cells being transferred from one surgical wound to another. Surgery should also include excising any regional lymph nodes found to be cytologically positive for tumour metastases. Removal of the draining lymph node regardless of physical characteristics might be wise as a staging tool.

Following excision, all cut edges of the tissue (skin margin and deep margin) should be stained with India Ink, left to dry, and then placed into 10% formalin to fix, at a ratio at least 1 part mass:10 parts formalin. On processing and interpretation, identifying tumour cells in ‘inked’ tissue represents tumour at the wound edge, and so an incomplete excision. Larger tissue masses may need to be ‘bread-loafed’ prior to fixing, as the formalin cannot diffuse to a depth of greater than 1cm tissue. Alternatively some surgeons prefer to tie small suture knots at locations where concern exists over the width of the normal tissue margin to encourage the pathologist to examine these areas more critically.

Surgical incisions typically heal without complication, although there is an increased risk of wound dehiscence with MCTs due to the local concentration of heparins, histamine and proteases which interfere with the acute inflammatory and proliferative phases of wound healing. Wound breakdown, along with intra-operative hypotension and excessive haemorrhage, is most often seen with large, poorly differentiated MCTs. In one study of grade II MCTs, wound dehiscence was seen in 10% after surgery (Séguin, 2001).

The aim of surgery must be clear prior to starting the resection. A wide excision and reconstruction is the simplest and fastest choice for a cure, but if the mass is not amenable to a wide excision then local excision within the reactive zone to remove gross disease may be performed, with curative-intent adjunctive radiation to follow. Irradiating a flap, or placing a flap into a previously irradiated field however does carry a 77% risk of complications due to poorer wound healing and fibrosis (Séguin 2005).

The reported recurrence rate following complete surgical excision of grade 2 tumours is 11% with time to recurrence of 2-24 months (Weisse, 2002), and the rate following incomplete excision is 23.3% (Séguin, 2006). Although many book chapters, review articles and papers state further surgery, radiation and/or chemotherapy are indicated in the face of incomplete excision, published work shows that most incompletely excised MCTs do NOT recur (18-35% recurrence rate reported). In Séguin’s study, a local recurrence rate of 23.2% (7/28) of incompletely excised cutaneous grade 2 MCTs was identified, with a median follow up of over 800 days. These authors identified that a combination of Ki-67 and PCNA (proliferating cell nuclear antigen) scores was prognostic for local recurrence.

These studies contradict the assumption (just as we are now beginning to appreciate with StS) that most MCTs will locally recur in the dog’s lifetime, following incomplete excision, raising the question of value and efficacy of adjuvant therapies such as radiation or chemotherapy, raising the concern that we are over-treating a number of patients. However, developing local recurrence is typically prognostic for decreased
overall survival however and so until data becomes available regarding the impact of omitting additional treatment following an incomplete excision, adjuvant therapy remains the standard of care.

Radiotherapy is not always available and is associated with increased expense and mild to moderate side effects. Alternatives to radiotherapy, such as hypotonic water, have been investigated. The literature is contradictory on the efficacy of hypotonic water in controlling residual mast cell disease. Surrounding mast cells with deionised or distilled water will cause them to lyse due to the salt content within the cell, but this is also true for most cells (infact hypotonic water used as a RBC lysate in laboratories for exactly that reason) and this helps explain the discomfort associated with hypotonic water injections. Early work (Grier, 1995) demonstrated a significant reduction in local recurrence following incomplete surgical excision when distilled water was injected into the wound (31.6% recurrence) versus surgery alone (63.6% recurrence). In another study using historical controls, 17 incompletely excised cutaneous MCTs were treated with adjunctive deionised water and only 2 (12%) recurred (Neyens, 2004). Jaffe (2000) however published conflicting work showing dogs treated by incomplete excision and deionised water had a worse prognosis with a shorter recurrence free period than those without adjuvant water therapy. Brocks (2008) in an attempt to settle this controversy published results of a randomised, double-blind, placebo-controlled study comparing distilled water to lactated Ringers in dogs with incompletely excised MCTs. They found no significant difference in either local recurrence or survival time between the 2 groups, hopefully laying this subject to rest.

Stanclift and Gilson (2008) published work on neo-adjuvant prednisone prior to surgery to treat MCTs in anatomical locations where achieving wide surgical margins might be problematic. The aim was to use prednisone to consolidate the mass, reduce the volume and so hopefully allow for a smaller surgery to be performed. They studied 49 dogs and had 2 study arms, using doses of either 1mg/kg SID or 2.2mg/kg SID p.o. Dogs received steroids for a median of 10 days (range 3-60 days) and mean reduction in size was 52-78% with either the lower or higher dose of steroids respectively. 87% of masses underwent at least a 25% reduction in size. What was interesting in this study was that 89% of resections were described as clean (classified in this study as at least 1mm of normal tissue histologically between tumour and cut surface), and the tumour excision was taken from the ‘new’ boundary of the mass, i.e. the shrunken mass following steroid therapy. This paper prospectively investigated what was often already done by many clinicians, i.e shrink the MCT with steroids and then excise, but previous discussion centred on whether the pre-treatment or post-treatment mass should be used to plan surgery. One criticism of this paper is that the authors state achieving clean margins with this protocol is very achievable (89%), and yet local recurrence rate following clean excision (17.6%) is higher than most would predict, and may be a consequence of generously describing a 1mm margin as clean without acknowledging that satellite clusters may have been missed during tissue processing.

The ‘rules’ governing surgery of subcutaneous MCTs are poorly defined, and the 3cm margin is still widely advocated. Papers similar to the 1 cm and 2 cm margin studies in cutaneous MCTs have not yet been published with respect to subcutaneous or intestinal MCTs and at this time it seems prudent to maintain the status quo. Inevitably the deep margin for subcutaneous tumours is deeper than for cutaneous MCTs and so volumes of excised tissue are larger, and local reconstruction techniques are more commonplace. When the mass is a discrete gastro-intestinal tumour, intestinal resection-anastomosis is indicated to alleviate intestinal chronic obstructive symptoms. Incisional or excisional biopsies of the draining mesenteric lymph nodes should be acquired for disease staging. Wide (3-5cm) margins of normal intestine should be resected with the mass but the overall prognosis for this tumour location remains poor.

Medical management for non-resectable solitary disease, to treat micro-metastatic disease in higher grade tumours, or to treat distant gross disease. Traditional treatments with such drugs as prednisolone, vinblastine, and lomustine are commonly used in practice with published response rates (measurable disease) ranging from approximately 40-65%, with varying degrees of toxicity. Newer agents such as tyrosine kinase inhibitors are increasingly being used in veterinary oncology, designed to target mast cell tumours with a genetic mutation in the c-kit gene (approximately 15-40% mast cell tumours). Some principles of their action and results will be covered although delayed time to progression and increased survival have been seen in some grade II and grade III tumours.
**SOFT TISSUE SARCOMAS – DIAGNOSIS, TREATMENT AND PROGNOSIS**

Soft tissue sarcoma (STS) is a catch-all classification referring to tumours that arise from the embryonic mesoderm and as such can occur anywhere in the body. Generally they are classified according to cellular lineages (morphology on H and E staining, or immunohistochemistry (IHC)) such as fibrosarcoma, peripheral nerve sheath tumour, myxosarcoma, liposarcoma, or leiomyosarcoma, but sometimes these distinctions are not clear and the generic term soft tissue sarcoma or spindle cell sarcoma are employed. Some tumours of mesoderm behave in a much more aggressive and less predictable fashion and these tend not to be included in STS, examples include lymphangiosarcoma, rhabdomyosarcoma, synovial cell sarcoma, haemangiosarcoma, chondrosarcoma, osteosarcoma. Surgical resection is the principal treatment for primary localised disease as STS are relatively chemo-insensitive and radiotherapy is more of value in a curative context as an adjunct to surgery. The great variation in anatomic location, factored with variable size and grade, can present significant problems when making a treatment plan.

STS are graded into low (I), intermediate (II) and high (III) grade tumours taking into account histological features such as mitotic rate, extent of necrosis and cellular differentiation.

Radiographs may yield some information regarding local behaviour, but may only confirm the mass is of soft tissue density. Ultrasound (esp Doppler) can be useful but cross sectional imaging (CT or MRI) is the imaging of choice and is typically supportive of the diagnosis. Whereas MRI is traditionally regarded as superior for soft tissue detail, CT (esp contrast CT) offers a fast, simple, and accurate solution for all but the most complex STS. It is cheaper, equally as useful as MRI, and it has the advantage that imaging the thorax for metastatic disease can easily be performed at the same time.

In terms of biopsy, fine needle aspirates have an important role in ruling out more likely subcutaneous differentials for example mast cell tumours, lipomas or inflammatory lesions, all of which exfoliate cells well. If lucky enough mesenchymal cells will be aspirated from a STS to make a diagnosis. If an aspirate of a SQ mass fails to yield many cells on the slide, your index of suspicion for a STS should be raised, and prompt a core biopsy. Percutaneous core biopsies (e.g. Trucut) are the best technique for achieving a safe and accurate diagnosis and can easily be performed with local anaesthetic alone or with sedation in nervous patients. Trucut biopsies will reliably differentiate benign from malignant disease and in most cases will also give a good indication of grade. The simplicity and accuracy of core biopsy for STS means incisional biopsies are infrequently indicated and come with the added concerns of location and direction of scar, and tumour dissemination from post-incisional biopsy haematoma.

Surgical resection is the most effective treatment for STS. The aim of curative-intent surgery is to widely excise the primary tumour (dogma; 3cm and/or a fascial plane) and achieve negative histopathological margins. The requirement for a 3cm margin to maximize local control of STS was challenged by Banks and Straw in 2004. In a prospective study, 14 dogs with 15 subcutaneous STS were treated using a standardized protocol. A lateral surgical margin of > 10mm and a single fascial plane deep (or > 10mm of deep tissue) yielded a local disease control rate of 100% with a 93% one year disease-free interval. Banks’ research into what is ‘an appropriate margin for STS’ is relevant, given that these masses can arise more-or-less anywhere, there is a great variety of biological behaviours seen between the grades, and putting the advice of ‘widely excise the primary tumour’ into practice is much more complex than other malignancies with less anatomical variation (e.g. lung, thyroid, intestine, mammary). Radiation has a role if incomplete margins are found, if further surgery is declined, or if the mass is close to important unresectable structures.

This is a different situation in the distal limbs however (typically at/below the stifles, and at/below the elbow) where a wide surgical margin of skin is usually only achievable using free skin grafts or random flaps, and options such as amputation or marginal resection and radiation are considered. Both these options have drawbacks in terms of altered function, morbidity and cost. Whereas it is expected amputation to treat an extremity sarcoma will effect a cure, marginal or incomplete excision of a STS and adjunctive curative-intent (hypofractionated) radiation results in a local recurrence rate of 19-35%.
In both human and veterinary surgical oncology, accepted guidelines on treatment of solid tumours have been difficult to establish. A large stumbling block in creating guidelines on treatment of STS is the uncertainty over what to do with an incomplete surgical margin and its relevance on local recurrence and overall survival. The impact of leaving residual tumour cells in the wound bed of an excised STS is a many fold increase in the rate of local recurrence (Kuntz). Several studies have reported the results of adjunctive radiotherapy in the management of STS with surgically incomplete margins and its success has generally been measured by its ability to provide consistently long overall survival times. The effect on local tumour control however, has been variable, with recurrence rates ranging from 17-60%.

Retrospective investigation into the results of surgery alone (‘primary re-excision’) for the treatment of STS after incomplete resection studied 41 dogs that had undergone aggressive scar revision (attempted wide margins (1-3cm)/1 fascial plane deep) for incompletely excised STS. Complete margins were obtained after re-excision in 90% (37/41) of all the cases with mean margin widths of 2.7cm on the proximal portion of limbs and 1.4cm on the distal portion of limbs. Local tumour recurrence occurred in 15% (6/39) of the dogs at a median time to recurrence of 142 days.

Comparisons of the local control rates achieved with re-excision of the scar compared to radiation therapy of the scar suggest that the outcomes of surgery, when possible, may be equivalent to those achieved with adjunctive radiation therapy. In fact, when the costs and relative morbidity of radiation are factored in, an attempt at surgical excision alone may be a more desirable first line approach. The question then arises, what if the site of recurrence does not afford an extensive re-excision, or the owner declines further treatment after a tumour positive margin is confirmed?

Two recent studies have evaluated the local recurrence rate of canine STS of the distal limbs treated by marginal excision alone (wait-and-see).

- The first (Cavanaugh et al, 2007) followed 26 dogs with tumours of the distal antebrachium or pes, all of whom were determined to have tumour positive margins after marginal excision by a variety of surgeons, some planned, some unplanned. All grades of STS were represented and follow-up intervals were long (median, 781 days, minimum 594 days). The rate of local recurrence was 37% (10/27 tumours) with only 12% (3/26) of the dogs being euthanized for problems relating to local disease.
- The second study (Stefanello 2008) was a retrospective review of planned marginal excisions of low grade distal extremity soft tissue sarcomas by two experienced surgeons. Using this technique, 32% surgeries has clean margins, 34% were ‘clean but close’ and 34% incomplete/dirty margins. Recurrence rate for this study was 11%. Follow up ranged from 210-2202 days.

Both these studies challenge the dogma that local recurrence rate following incomplete resection of STS is high, common, inevitable or guaranteed, depending on your text source. As is the goal of any retrospective study, these two raise questions rather than provide answers. The question which needs to be answered now is not HOW MANY recur, but what can we do to predict WHICH are likely to recur. Ettinger and Scase have shown that AgNORs and possibly Ki67 could be used over and above grade to help predict overall survival in STS, and for a starter, this work needs to be repeated in the context of local recurrence with a similar population of dogs with similar wounds in terms of tumour burden.

Future directions and treatments??

It would be ideal to identify those at risk of local recurrence or metastasis BEFORE surgery based on imaging and better predicting biological behaviour. We could then tailor the dose of surgery and treatment accordingly taking into account the animal’s age, status and prognosis. If we follow human advances, then intra-arterial chemotherapy, interventional chemo-embolisation or isolated limb-perfusion (melphalan/TNFα) are also treatments that may be considered in the future.

The bigger picture here is that STS in humans are relatively uncommon, accounting for <1% of all cancers, with 8500 new cases being diagnosed a year in the US, and 13000 in the EU. Although relatively rare in the dog, STS are seen commonly in secondary and tertiary referral practices. Scope for translational (what would be called pre-clinical trials in the human setting) exists and is likely to benefit both parties.
Bone cancer is a common problem in the middle aged to older dog and needs to be ruled out in any patient whose lameness is unresponsive to symptomatic treatment, or who presents with unexplained bone pain. Amputation and chemotherapy remain the gold-standard for this condition as by far-and-away we have the most experience in predicting outcome following this treatment, and amputation also remains the fastest and most reliable means of eliminating bone pain. However not all clients or all patients go down this route for a variety of financial, orthopedic, neurologic or social reasons. Increasingly owners are considering alternatives such as analgesic protocols, coarse fractionated radiotherapy, chemotherapy options, stereotactic radiosurgery for limb sparing, and conventional allograft or endoprosthesis surgical limb-sparing options.

Canine osteosarcoma can arise in the appendicular skeleton, axial skeleton, in extraosseous tissues (e.g. kidney, subcutaneous tissue, primary lung) or parosteal locations. Appendicular sites are most common and 2/3 tumors arise in the front limbs. It is perhaps no coincidence that 2/3 of a dog’s weight also is supported by the front limbs. The cause of osteosarcoma is not known, but is likely related to an inactivation of the tumour suppressor gene, or amplification of proto-oncogenes.

Radiological features include osteoblastic or osteolytic change, cortical lysis, loss of fine trabecular detail in the metaphyseal area, periosteal reaction (‘Codman’s triangle’), new bone (‘sunburst’), soft tissue swelling, typically no crossing of the joint and a moderate transition zone to normal medulla.

In terms of comparing imaging techniques, radiographs tend to underestimate the length of bone affected, and scintigraphy overestimates the length affected. MRI is the most accurate for determining the medullary cavity invasion.

Following radiographic ‘diagnosis’, a decision must be made as to whether biopsies are performed. Although often cited as a reason to biopsy, finding a fungal disease mimicking osteosarcoma is very unusual. Biopsy options include;

- **Fine needle aspirate** – a needle can be pushed through a defect in the cortex (can be ultrasound guided) into the tumor volume. OSA cells tend to have poor inter-cell binding and so they exfoliate more like a round cell than a true sarcoma. Identifying mesenchymal cells with criteria of malignancy is enough to diagnose a sarcoma (importantly also to r/o round cell, epithelial metastasis, infection etc.).

- **Jamshidi** – a small needle core is likely to provide a diagnosis, although taking at least 3 cores is recommended. Wherever possible, only one hole in a cortex should be made, with three biopsy tracks then running from that hole into the medulla. You should aim for the centre of the lesion to biopsy, rather than the periphery where a diagnosis of reactive bone is more likely to be made.

- **Michel trephine** – a much larger biopsy can be achieved with this ‘coring’ tool. The serrated cylinder removes a thick bone plug which almost invariably provides an answer. It can be useful if there is marked periosteal reaction overlying the tumour, making it difficult to pass a Jamshidi through.

- **Incisional biopsy** – it is rare to perform a surgical incisional biopsy. Indications might include biopsying tissue during fracture repair if the possibility of pathological fracture arose.

- **Excisional biopsy** – this is realistically an amputation. A large number of amputations are performed at UF without having a pre-existing diagnosis if all other signs and tests prove suggestive. Limb-sparing surgery also often proceeds without a definitive diagnosis ahead of time.

When not to biopsy? If there is a real chance the owners may be interested in limb-sparing procedures, either surgical limb sparing, or stereotactic radiosurgery then a biopsy is not always recommended.
For the surgical spare this is because of the risk of tumor spreading down the needle track resulting in local recurrence in the soft tissues. For the radiosurgery it is the risk of pathologic fracture through the biopsy tract that raises most concern.

At presentation, several factors help with decision making; patient assessment, concurrent geriatric diseases, degree of osteoarthritis, organ function (esp. kidneys), presence of myocardial disease (since these are large breed dogs), serum chemistry, alkaline phosphatase (may have prognostic value; high ALKP is associated with a poorer prognosis). The bone affected is also important; OSA is usually found in the metaphyseal regions, whereas diaphyseal tumors (nr nutrient foramen) are often metastatic (urogenital, thyroid, mammary, lung).

Staging is most commonly a three-view chest series. Metastasis to draining lymph nodes is rare (approx 7%) and so palpation for nodes is sensible, but routine aspiration of the nodes is not performed unless enlarged (rare). Staging for bony metastases can be performed by skeletal radiographs, nuclear bone scans, or full body CT/MRI.

The advantage of skeletal survey radiographs is availability, but there is little advantage in cost (need long anesthesia and many exposures), but disadvantages include radiation dose, poor sensitivity, and length of study. Nuclear bone scans use TC-99m-MDP as a radio-isotope which is taken up by bone turnover (osteoclastic activity). It produces a whole body image, and although sensitive (any bone activity identified), it is not very specific (dental disease, osteoarthritis, chronic fractures will all ‘light’ up). Skeletal metastasis is found in approximately 6-8% of OSA cases. Whole body CT/MRIs are becoming increasingly more available (currently world-shortage of technetium) and have added advantages of no quarantine seen with nuclear bone scans. These generate on average 1500 images however which means ruling out a bony secondary cannot be done as easily compared to a bone scan.

Treatment for primary bone tumours include (to be covered in full in lecture);

**Surgery**
- Amputation
- Limb-sparing (metal implant, bone implant, external fixator, no implant needed e.g. ulna, scapula)

**Radiation**
- Palliative
- Hypofractionated curative-intent
- Stereotactic radiosurgery

**Medical**
- Pain management
- Osteoclast inhibitors (bisphosphonates)
- Chemotherapy

Amputation limitations include size, weight, and current orthopedic or neurologic disease. Limb-sparing indications include current orthopedic/neurologic disease, owner reluctance to amputate, and importantly financial means to pursue these options. The commonest limb-sparing site is the distal radius and guidelines include; the tumor should affect less than 50% of the radial length, there should be no joint involvement, minimal soft tissue (and ideally ulnar) involvement, no catastrophic pathologic fractures, and no metastasis (thoracic rads +/- bone scan).

A banked donor bone can be used to fill the defect (allograft). They are fresh frozen once harvested and are secured in the defect using bone plate and screws. Complications include a high rate of infection (50%), mostly likely due to one or more of the following; a large surgical resection, use of non-viable cortical bone, large metallic implants, poor soft tissue coverage so poor vasculature, use of chemotherapy.
Infection if difficult to resolve completely and 25% require additional surgery to remove the implants or amputate. There is however a survival advantage to infection – dogs that get infected live on average 50% longer than those that do not. There is however increased cost to the owner, decreased quality of life, and often continual bandage changes and wound care which can be very time consuming. It was hoped using a metal endoprosthesis to overcome this would eliminate some of these infection issues, but the infection rate unfortunately has remained the same.

Stereotactic radiosurgery (SRS) is the delivery of a single fraction of radiation to the tumor, in an attempt to completely sterilise (and so ultimately kill) the OSA in situ. CT guidance is used to make out the location of the mass, and then a linear accelerator delivers the dose. Advantages include almost any bone (including skull) can be treated, meaning limb-sparing is now possible for other common OSA sites including humerus, femur, tibia etc… Other advantages include no surgery, implants, infection or bandage changes. Disadvantages include that not every dog is suitable (depends on degree of cortical destruction), pathologic fracture can arise in upto 25% of cases, and a high cost (upto $7-7500, Jan 2013).

Chemotherapy protocols used commonly will be described. The expected prognosis remains typically 10-12 months with amputation and chemotherapy, almost regardless of which protocol is followed. Euthanasia following metastasis to the lungs is the typical cause of death in upto 90% patients who undergo chemotherapy for appendicular osteosarcoma.