An introduction to treating cancer in pets
Dr Angela Frimberger VMD, MANZCVS, Diplomate ACVIM(Onc)
Dr Antony Moore BVSc, MVSc, MANZCVS, Diplomate ACVIM(Onc)
Veterinary Oncology Consultants, Pty Ltd
379 Lake Innes Drive, Wauchope NSW 2446
www.vetoncologyconsults.com

There is never “nothing you can do”
Cancer is not only one of the most common causes of illness and death – as well as sources of client concern - in both dogs and cats, but also one of the most professionally satisfying to treat. Our overriding philosophy is that every pet with cancer and their family can be helped in some way.

In veterinary oncology, quality of life for the patient is always the top priority. Some cancers can be cured by treatments compatible with good quality of life. In other cases, anticancer treatment may significantly extend good quality survival time even if the patient is not permanently cured. However for other patients, palliation may be a more appropriate goal; and because it delays the need for euthanasia, effective palliation can significantly enhance survival time as well as quality of life in veterinary medicine. Even in those cases where hospice care or euthanasia is the best option, performing this with compassion and skill can be one of the most valuable services a veterinarian can provide to help both patient and client.

As a subspecialty, veterinary oncology is increasingly important in veterinary practice as client demand for advanced cancer care increases. To meet that need, the treatment of cancer in pets has evolved to parallel treatment in humans, with certain differences. One of the most important differences is in the goal of therapy. In humans, many cancers are cured, and cancer survivors may enjoy many decades of comfortable life. For this reason, treatment of cancer in humans is aggressive and often associated with severe side effects. On the other hand, most pet owners prefer to avoid severe side effects and prolonged hospitalization for quality of life reasons. In addition, the intense, specialized supportive care units and strategies for human cancer patients are not available for pets even in private practice specialty centers and university veterinary hospitals. Therapies are therefore primarily directed at maximizing quality of life; and the aim is often tumour control, or remission, rather than cure at any cost. “Remission” means partial or complete reduction of any outward evidence of cancer on examination or routine labwork and imaging (i.e. x-rays), and relief of any symptoms, making the pet feel as normal as possible. It is important to recognize that although a pet’s cancer may not be curable, he or she can enjoy a high quality of life. In this sense cancer is similar to other chronic illnesses such as kidney disease or heart disease, which can often be controlled providing a high quality of life, although they may not curable.

It is important to remember that the pet’s primary caregivers are in the best position to know and meet their pet’s needs and desires. The veterinarian’s most important task is to develop a veterinary health care team that is experienced in cancer care and committed to working with the caregivers as members of that team to provide cutting edge treatment and
compassionate care. Compassionate care requires that the patient is as free as possible from the adverse effects of the cancer itself, as well as the treatment.

Some private practice specialty centers and university veterinary hospitals are equipped to provide high levels of care to animals with a wide variety of malignancies. For the primary care veterinarian it is important to have resources to provide information that will allow the caregivers to decide between rational, evidence based treatments that will maximize their pet’s quality of life. It is important to remember that every patient can be helped regardless of finances, time and the underlying diagnosis through supportive care, curative treatment, palliative therapy, hospice care or euthanasia. Furthermore, the veterinarian should provide realistic, honest information in both written form and face-to-face discussions that are not constrained by time.

Within the last 10 years, dramatic advances in veterinary cancer treatment have resulted in improved response rates, disease-free intervals, and survival times. In most situations, dogs undergoing cancer treatment experience limited to no decrease in the quality of their life as a result of the treatment; in fact most pets undergoing treatment for cancer feel significantly better as result of relief of the symptoms of their disease. Advances in palliative therapy and support for canine cancer patients have resulted in good quality of life for these patients while undergoing treatment. Finally, when cure and control is not possible, then the veterinarian can advise on, and provide, hospice care.

Client preparedness

The greatest challenge that the veterinarian faces in using chemotherapy is addressing the preconceptions, biases and negative experiences that owners have about chemotherapy, surgery and radiotherapy. Information regarding side effects of treatment in human patients that may have been experienced by the owner or gleaned from television, the Internet or family and friends are usually inconsistent with the quality of life they want for their pet. It is important for the veterinarian to acknowledge these feelings, and to inform the owner of the differing goals for cancer therapy in cats and dogs with cancer; that is that the treatment (including surgery) should be given to the patient that does not cause what is considered undue toxicity, as defined by the veterinarian and the owner. For some owners this definition may be any loss of quality of life, for others it may be hospitalization. In either situation the veterinarian should establish the goals of therapy in advance of starting treatment. If owners understand that quality of life will take precedence in their pets’ treatment they are more likely to trust the veterinarian and to treat their pets.

Providing accurate information in understandable terms about the type of cancer, prognosis and predictable side effects of treatment is an important responsibility of any veterinarian. Being honest while maintaining a feeling of hope and caring are among the most important aspects of establishing trust with owners of a cancer patient. Encouraging owners to ask questions and to communicate their concerns is equally important. Supplementing verbal instructions with written information about the disease the pet has, and the protocol and the drugs to be used, will greatly assist owners in making their decision. Many of these sheets can be obtained from veterinary oncologists, and the Internet.

It is also important to discuss with the owner not only the potential toxicities of treatment, but also their goals for chemotherapy; in particular, what they would consider a successful outcome.

Palliative intent treatment

For many older veterinary patients, the diagnosis of cancer is obtained at a time when other diseases may limit their survival to a greater extent than does the cancer. For these patients, palliative care may be most appropriate, and the choice of chemotherapy must be weighed against the risk of toxicity. An example would be a Doberman with cardiomyopathy and osteosarcoma. Such a patient may benefit from pain relief for the bone cancer. Cardiac
disease makes doxorubicin a poor choice for chemotherapy, and the diuresis required for cisplatin administration may result in cardiac decompensation. An alternative would therefore be carboplatin. However, if a poor prognosis due to cardiac disease makes it unlikely that the benefits of extended survival due to chemotherapy will be realized, chemotherapy may not be a good choice for such a patient and treatment should focus on pain relief.

**Curative intent treatment**

For younger patients that are in good health, have no concurrent illnesses, and for which chemotherapy holds the possibility of a long tumour control with little risk of toxicity, chemotherapy with curative intent may be undertaken. An example would be an asymptomatic, middle-aged dog with stage 3, B-cell lymphoma, for which the prognosis is guardedly optimistic. Owners of such a patient may even elect to try more aggressive combination chemotherapy to improve the chance of long remission.

**Suitability of the patient**

When evaluating an animal for treatment of cancer it is important not only to obtain a definitive diagnosis, but also to **assess the general health** of the patient by clinical examination and ancillary diagnostics. The prognostic information gained by determining the extent of organ involvement with the tumour as well as identifying unrelated or secondary conditions that need to be treated or controlled before instituting appropriate therapy is mandatory in order to make recommendations as to the suitability of a patient for chemotherapy. This information is also vital for individualizing the type and intensity of a treatment regimen.

**Staging and Health**

Staging is a clinical process that enables the veterinarian to quantitate the extent of cancer involvement in the patient. Staging is sometimes confused with **grading** that characterizes histopathologic features of the tumour. Staging often carries prognostic significance and enables the veterinarian and client to make informed and rational decisions as to the type of therapy best suited for the patient. Most staging systems are based an assessment of three major components of the malignant process (**TNM**);

- the size of the primary tumour (**T**),
- lymph node metastasis (**N**) and
- distant metastasis (**M**).

Most of the information can be obtained from physical examination, but ancillary diagnostics are very important, and often incorporate sophisticated imaging techniques (radiographs, ultrasonography, CT scanning, and MRI). The majority of patients for whom chemotherapy may have therapeutic benefit will have systemic or metastatic disease that is either physically evident, or presumed through historical knowledge of tumour behaviour (osteosarcoma, hemangiosarcoma are examples).

The likelihood of a successful outcome for a patient treated with chemotherapy is as dependent on drug metabolism and elimination (and drug absorption for orally administered chemotherapy) as it is on the sensitivity of the tumour. Consequently, information gained during staging (**CBC, serum chemistry profile and urinalysis**) may identify problems that will impact the type and dosage of chemotherapy to optimize efficacy while limiting toxicity. For example, hepatic dysfunction may lead to delayed drug elimination (examples; vinca alkaloids, doxorubicin) and therefore to greater toxicity such as myelosuppression. In contrast, cyclophosphamide is activated in the liver so hepatic dysfunction may result in poor efficacy.

Similarly renal dysfunction may worsen toxicity for some drugs that are themselves renally toxic. For example, cisplatin and streptozotocin should not be used in patients with renal azotemia. Reduced renal excretion of carboplatin will exacerbate myelosuppression.
Particularly for those breeds with a predisposition to develop cardiomyopathy, treatment with doxorubicin should be accompanied by cardiac evaluation. Pretreatment echocardiography should be performed and dogs with reduction in contractility should not receive doxorubicin. While valvular dysfunction should not be a reason to withhold doxorubicin, mild changes in cardiac muscle function may exacerbate the valvular disease. In these patients, echocardiography should be performed periodically through treatment, ideally prior to each treatment. Treatment should be discontinued if contractility is below normal, and while the patient is still asymptomatic. Cardiac dysfunction due to doxorubicin is irreversible and usually progressive. For this reason, monitoring for signs of early cardiac failure before discontinuing doxorubicin is unacceptable practice.

Describing the Outlook with Statistics

Some terms that are often used when describing the outlook (prognosis) for a patient with cancer follow. These are statistical terms, and provide a guide as how the population of animals with the same cancer type will respond to treatment; such numbers can never tell you how an individual patient will respond to therapy, and how long they will survive.

Definitions of Objective Tumour Remissions and Responses Following Anticancer Therapy

<table>
<thead>
<tr>
<th>Tumour response</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Complete response (CR)*</td>
<td>Disappearance of all evidence of cancer in all sites for a defined period of time (e.g., one inter-treatment interval of 3 weeks).</td>
</tr>
<tr>
<td>Partial response (PR)*</td>
<td>Decrease in size of all tumours by 50% or greater as measured by the sum of the products of two diameters for each tumour. These diameters should be the largest tumour diameter and the diameter perpendicular to it. There should be sustained decrease in tumour size, as defined for CR, and no new tumours should arise.</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Decrease of &lt;50% or an increase of &lt;25% in the sum of the products of the diameters as measured for pr.</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>Increase of 25% or more in the sum of the products of tumour diameters or the appearance of a new tumour.</td>
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*CR + PR = Objective or Overall Response Rate

Kaplan Meier survival curves are one of the most common types of statistical presentations for data in oncology. These curves start with all (100%) of the animals alive (or in remission) and over time, each time a patient dies (or comes out of remission) the curve tracks him/her by reducing the percentage. The result is a series of steps.

From this curve you can calculate the median, mean and survival rates at any time point (usually 1-year and 2-years after treatment starts).
Mean is the average survival time of all the patients in the population being studied. Median is the middle value for the survival times of the population.

An example would be a treatment for 15 dogs with stage 3, T-cell lymphoma where the survival time is measured. The survival times in months for these dogs are: 1, 1, 2, 3, 6, 6, 7, 10, 10, 10, 12, 24, 30, 34, 42. Three of these dogs are still alive at 12, 30 and 34 months. The Kaplan Meier survival curve is seen in Figure 5.1; the cross marks show dogs still alive. For this population the median survival would be 10 months, but the mean would be 13.2 months. The one-year survival rate would be 33.3% and the two-year survival rate would be 26.7%. So when talking to the owner of a dog with a similar disease, at a similar clinical stage (dogs with stage 3, T-cell lymphoma) you could say that there is a 50% chance that their pet would live 10 months or longer, and there is a one-in-three chance they would live more than 1 year. That actual patient may live 1 month, or it may live more than 3 years, but the usual survival numbers are the best information we are able to provide.

**Surgery in Veterinary Oncology**

**Prevention of Cancer**
Prevention of cancer with ovariohysterectomy and orchietomy in the dog is well-defined. These surgical procedures can be critical to preventing in malignant diseases (uterine, ovarian and vaginal neoplasia in the female; testicular neoplasia in the male. Therefore, surgery is important for reducing the risk of cancer development in canine cancer patients.

**Biopsy and Staging**
A surgical biopsy is usually required to make a definitive diagnosis and this information guides the treatment plan and allows an estimate of the prognosis for any given patient. For example, knowing whether a tumour is a benign sebaceous adenoma or a malignant soft tissue sarcoma is extremely important. This is because even though they may have the same outward appearance, the latter requires an extensive surgical resection and additional staging procedures to determine the extent of disease. In contrast, a benign adenoma may need a simple resection. The methods that the surgeon can use to diagnose the malignant condition or the extent of this disease are aspiration biopsy, needle biopsy, punch, incisional biopsy, and excisional biopsy.

1. Needle tracts or biopsy incisions should be placed with careful thought so that the entire biopsy tract (including any drain holes) can be removed when the definitive surgical procedure is performed. When a veterinarian who is unlikely to perform the definitive surgery performs a diagnostic biopsy, the surgeon who will perform the definitive procedure should be consulted prior to the procedure.

2. Care should be taken to not distribute cancer cells into surrounding tissues or through tissue planes during the biopsy procedure. For example, care must be taken to avoid the formation of a hematoma or a seroma, because the hematoma or seroma might spread cancer cells as it dissects between fascial planes, which would require a more extensive definitive resection. When multiple biopsy specimens are taken from different sites, care should be taken to change instruments so that tumour cells are not transplanted from one site to another by the surgeon.

3. Biopsy techniques should be carefully selected to allow the acquisition of sufficient tissue to make a histopathologic diagnosis. Taking multiple biopsy specimens increases the likelihood of an accurate diagnosis if an excisional biopsy is not being planned. Laser surgery can significantly alter the tissue, preventing an adequate evaluation of the margins, and may even hinder a diagnosis.

4. The biopsy specimen should be handled carefully to prevent crushing, artifact, or alteration of the orientation of the tissue specimen. Additionally, tissues should be prepared in such a manner as to allow adequate evaluation of the tissue by different procedures, such as immunohistochemistry. Specimens should be placed in enough
preservative to allow complete fixation (a good rule is 1 part tissue to 10 parts formalin); however, prolonged fixation or storage in formalin may reduce the chances for future successful immunohistochemical staining. Using inked margins or sutures may give the pathologist information regarding orientation of biopsy tissue within the body. Check with your pathologist to determine his or her preferred method of marking tissue.

5. The surgeon should have an understanding of the biologic behaviour of malignant conditions to ensure that all possible sites of metastases are evaluated prior to a definitive procedure being performed.

**Treatment of Cancer**

Surgery is still the modality most likely to cure an animal of cancer if the tumour is localized (not metastasized, and not invading into sensitive structures). However, it is not only with curative intent that surgery is applied to pets with cancer. Biopsy, debulking, and palliation are achieved through surgery, and each needs to be carefully performed so as to minimize the impact on the patient’s quality of life while still achieving the appropriate goal. Careful preparation of the patient, as well as anticipation of complications can be as important as the surgery itself in leading to a good outcome for the patient.

*Intracapsular Surgery*

Also known as debulking or cytoreduction, this technique will never lead to a cure for a cancer, but can have a role in preserving surrounding normal tissues and structures that if damaged could negatively affect the patient’s quality of life. Debulking will often leave behind visible tissue at the site, but can provide palliation when a tumour is causing obstruction (say to the urethra, upper respiratory tract or the gastrointestinal tract) or pain (retrobulbar tumours or spinal tumours). Most debulking surgeries require adjunctive therapy if the patient is to be cured, or have a long-term remission. An example would be a dog with a mast cell tumour of the foot where limb amputation is not possible. Debuling of the tumour, followed by radiation teletherapy could be considered to have a high probability of long term control.

*Marginal Surgery*

By this surgical technique the tumour is removed along the pseudocapsule. The pseudocapsule is formed when the tumour expands, compressing the peripheral tumour cells against the surrounding normal tissue. Grossly, the tumour appears to “shell out”, but microscopic compressed (but viable) tumour cells remain and will regrow if no further treatment is performed. Again radiotherapy is indicated for marginally removed tumours where metastasis has not occurred, and cure is still a possibility with that addition.

*Curative Intent Surgery*

When preparing a patient for curative intent surgery it is important to plan the surgery to include any biopsy needle tracts and incisions as well as drain holes and tracts which will need to be removed as these could be a source of future recurrence. In addition, preparation of sites for skin mobilization or grafting should be considered. Ideally, lymph nodes should be removed and examined histologically for any evidence or tumour metastases. Removal of nodes is not known to improve outcome, but knowledge of node status can direct adjuvant therapy and influence prognosis. Node biopsy and skin grafting may also be considerations when positioning the patient for surgery.

*Wide (Excisional) Surgery*

Excisional surgery removes a “cuff” of normal tissue along with the tumour contained within. Ideally the tumour is removed en bloc, and the lateral or deep margins of the tumour are never exposed. If the margin is wide enough, a cure is possible. However, often what appears to be a wide surgery to the cancer care team may still not be adequate. The nurse can assist in placing ink or sutures at the areas the surgeon feels least confident about, so that the pathologist can specifically section and examine those sites. Most investigators feel a clear histologic margin of 5mm to 10mm (depending on the tumour type) is adequate. It is important to remember that to achieve this, wider surgical margins of macroscopically normal-appearing tissue need to be removed. The published reports
requiring 2-3cm margins are clinical margins, not histologic. However, the pathology report should always be interpreted in light of the clinical impression of the surgery. If the surgeon’s feeling was that he or she was not confident that she achieved margins, the best option is a second, “scar revision” surgery to remove margins around the remaining scar. This is true if the histopathologist does not find tumour cells at the margins, because the pathologist is limited in the amount of tissue they can examine (at 4 micrometer-thick sections); this is why inking the margins at areas of concern is helpful. Thus, if the surgeon feels confident but the pathologist find tumour cells at the margin, the pathology report should take precedence; whereas if the surgeon feels it is unlikely the excision was complete but the pathology report does not find tumour cells at the margins, the surgeon’s impression should take precedence. On the other hand, if the deep margin includes underlying fascia or muscle that has not been penetrated, these may act as a barrier to tumour invasion, particularly early on.

**Radical Excisional Surgery**

Radical surgery removes a complete compartment organ or structure to achieve complete margins. The most commonly seen example is a limb amputation that could cure a mast cell tumour or a low-grade soft tissue sarcoma and be palliative for pain from a bone cancer such as osteosarcoma.

Such aggressive surgical procedures may be viewed as “mutilating” by some owners as they anthropomorphically project their interpretation of their own well-being onto their pets. It is important to remember that animals often have a great quality of life with little regard for the cosmetic changes such surgeries cause.

**Amputation**

Limb amputation is probably the most commonly performed of such surgeries. Although most pet owners initially do not like the idea of amputation, dogs (and particularly cats) respond to the surgery extremely well. In 2 studies in the USA and in Europe, dogs learned to walk well on 3 legs within a month, which exceeded most clients’ expectations. All clients were happy with their decision to amputate. Pets are able to function almost normally on 3 legs: they can go on long walks, play with family members and other pets, swim and go up and down stairs. Most pet owners are pleasantly surprised to see how well their pets adjust to the surgery. The pain associated with the procedure is minimal, and most pets are up and around the next day. Because cats and dogs have no concept of their appearance, amputation is not associated with emotional or psychological difficulties for them. For light, fit animals, amputation is extremely well tolerated. Even very heavy dogs, if they are fit, not obese and without significant orthopedic problems can tolerate the procedure well. Our website has some photos and a video of dogs (including a mastiff-X) that have undergone amputation at www.vetoncologyconsults.com/deciding_about_amputation which may be helpful for some owners to have a look at. Another valuable website for owners of amputee dogs is www.tripawds.com. You should always look at any website yourself before passing the address on to your clients. Finally the book *Without Regret: A Handbook for Owners of Canine Amputees*, by Susan Neal, remains an excellent resource.

**Maxillectomy and Mandibulectomy**

Although most pet owners are understandably initially reluctant to have an aggressive facial surgery such as maxillectomy done for their pet, most who do are satisfied after the procedure, from both cosmetic and functional standpoints. It is important to remember that for pets with most oral tumours, the impact on quality of life caused by the local tumour is the most life-threatening problem; and that complete resection is the best way to alleviate the quality of life problems. In a telephone survey of caregivers for dogs with oral tumours including some treated with partial maxillectomy, satisfaction with the surgical procedure was assessed. Overall 85% of owners were pleased with their decision to treat their dogs, and the longer the dog had lived, the more likely the caregiver was to be satisfied. Although difficulty in eating was noted for 64% of dogs after maxillectomy, pain was felt to be less after surgery for most animals than before surgery. All clients found the cosmetic appearances of their dogs acceptable after facial hair regrew. The quality of the pets’ lives
was perceived by the owners to be most improved after rostral mandibulectomy (100%) and least improved after partial mandibulectomy. Similar good reports came from owners of dogs in another study. A retrospective report of cats treated with mandibulectomy for oral neoplasia (all types) showed that most (~75%) cats were dysphagic or inappetant immediately postoperatively, and 12% never regained the ability to eat. Despite these findings, most (>80%) of the owners were satisfied with the outcome.

Nosectomy

A surgery that is often used to resect a nasal plane squamous cell carcinoma in cats is a “nosectomy”. This aggressive procedure is usually curative, and while the immediate postoperative period is sometimes challenging, cats recover well. Our personal pet underwent this surgery, and lived another 6 years of excellent quality life, similar to the good outcomes seen in other patients.

Brain surgery

Cats treated for meningioma can have rapid recovery from surgery, and more than half the cats live more than 2 years. This would be considered by most owners to be a very aggressive surgery, but the quality of life for cats after surgery is excellent.

Changing Instrument Packs

As the instruments used in the resection of the cancer are potentially contaminated by tumour cells, these have the potential to be seeded into the skin and subcutis as the excision is closed. This has been seen for many cancer types, but is most common with bladder transitional cell carcinomas. Always ensure that a clean pair of gloves and a second “closure” sterile instrument pack is available following removal of the cancer.

Radiation Therapy in Veterinary Oncology

Radiation therapy (or radiotherapy) is effective for controlling a wide range of tumours in pets. Radiation therapy can be used alone or in combination with other cancer therapies, including surgery, and chemotherapy. Radiation therapy is readily available through referral centers in some locations in Australia, in urban areas currently. Dividing cells are most sensitive to the effects of radiation. Tumour cells are controlled in 3 ways: cells damaged by ionizing radiation may be killed directly, or they may later attempt to divide and then die. Some cells remain functional, but do not divide. These cells may be terminally differentiated, or may be sterile. Oxygen is critical to clinical responsiveness of tumours to radiation therapy. Between well-oxygenated and necrotic zones in any tumour are hypoxic cells. Larger tumours are more likely to have abnormal blood supply and therefore more hypoxic cells; for this reason, radiation is most effective when treating small tumours or residual microscopic tumour tissue after surgery.

Treatment Goals in Radiotherapy

One of the most important decisions is whether a patient should be treated with curative or palliative intent. This influences not only the course of treatment, but expectations of the caregiver for their pet. Treatment with curative intent (definitive therapy) is often complicated, requiring frequent travel and multiple anaesthesias. The total dose of radiation is usually higher than that required for palliation and consequently the risk of acute side effects is greater. Such treatment is likely to be prolonged and expensive; however, for many tumours the chance of long-term tumour-free survival (> 3 years) is high. In contrast, palliative radiation therapy has a short-term goal, to relieve pain or symptoms of cancer when a specific site is causing a problem to the patient, but the rest of the cancer is unlikely to respond to any treatment (e.g. a painful digital metastasis from a pulmonary tumour that is not causing signs at any other site). For this reason, palliative therapy should minimize...
cost, inconvenience, discomfort and risk of side effects, and should be completed in the shortest reasonable time. It is often given weekly for 3 to 4 weeks.

**Types of Radiation Therapy**

Radiation therapy can be broadly subcategorized into teletherapy, brachytherapy, and systemic radiation therapy. With the exception of a few radiopharmaceuticals (radioiodine, samarium), radiation therapy is a local treatment; meaning that its effect is limited to the area it is directed (as a radiograph images only the field of interest); therefore care should be taken to ensure that the animal is staged properly to delineate the extent of the primary cancer, and that no metastases are present. Dogs with metastatic disease may not be good candidates for an intensive course of radiation therapy. The area to be irradiated should include margins similar to those that would be removed at wide excisional surgery. Consultation with an oncologist is essential to determine whether a particular patient with a malignancy is likely to benefit from radiation therapy.

**Teletherapy**

The delivery of radiation therapy from a machine to the patient is called teletherapy or external beam radiation therapy. External beam radiation therapy primarily is delivered by linear accelerators, radioactive cobalt ($^{60}$Co) or cesium ($^{137}$Cs) source units, or orthovoltage radiation therapy machines. Because the source of radiation is external to the patient, teletherapy does not make the patient radioactive. Therefore there is no period of isolation or quarantine required for patients treated with teletherapy.

When describing teletherapy, the dose of radiation absorbed is the most biologically relevant to tumour control and toxicity. The unit of measurement of radiation absorbed dose is the Gray (Gy). A course of radiation therapy is described in terms of the total dose, the number of fractions in which the total dose is delivered and the time course over which it is delivered. For example; 60 Gy, given in 3 Gy fractions, five days a week for four weeks. Most tumours in veterinary medicine receive a total dose of 40 to 60 Gy delivered in 9 to 20 treatments over 3 to 6 weeks.

**Orthovoltage Teletherapy**

Orthovoltage machines produce radiation of an energy that has penetration limited to superficial tissues (about 4 cm), and the maximum dose is delivered to the skin. This means that deep seated tumours will not receive an adequate dose when orthovoltage is used. In addition, tumours that are surrounding or surrounded by bone may have areas of the tumour “protected” due to absorption of radiation dose (bone blocks the radiation, just like X-rays are blocked from reaching a film). Orthovoltage, however, is valuable for treating superficial soft tissue tumours such as squamous cell carcinomas, mast cell tumours or soft tissue sarcomas, and tumours within air-filled cavities, such as nasal tumours. Acute side effects are seen mostly in the superficial tissues where the highest dose is delivered, and because bone absorbs higher radiation doses than surrounding tissues, late side effects are more common in bone when orthovoltage, rather than megavoltage, is the source of radiation.

**Megavoltage Teletherapy**

Radiation produced by megavoltage machines (cobalt-60 and linear accelerator) is not affected by tissue density, and deeper structures can be irradiated than when using an orthovoltage source. Maximum dose in tissues is not achieved until a depth of approximately 0.5cm below the surface; therefore megavoltage radiation can be “skin-sparing”. Because megavoltage radiation is skin-sparing, irradiation of superficial tumours is achieved by placing a layer of tissue equivalent bolus material over the tumour that allows build up of dose so the tumour is no longer "spared".

**Electron Beam Teletherapy**

Electron beam therapy is available using certain linear accelerators. Electrons can be given different energies so the distance they travel varies, but then the energy reduces very rapidly. Lower energy electrons are very useful for superficial tumours because deeper tissue is spared by a prompt fall in radiation dose; for example a sarcoma on the thoracic
wall of a cat where underlying lung must be spared. One disadvantage of electron beam therapy is the same as for orthovoltage; bone may shield underlying tissues.

**Brachytherapy**

Radiation therapy can be administered from implanted radiation sources (“seeds” or “straws”) within or around the tumour (brachytherapy). Brachytherapy radiation has a rapid drop off in intensity with increasing distance from the source and is therefore very effective for delivering extremely high doses very specifically to a local site, with normal tissue damage usually being restricted to immediate surrounding tissues. Because the source of radiation is implanted in the patient, interstitial brachytherapy makes the patient radioactive. Therefore there is a period of isolation or quarantine required for patients treated with interstitial brachytherapy, until their implants are removed.

Another form of brachytherapy uses an external radioactive strontium source applied to the tumour for a short period of time. This technique is most useful for shallow (<3mm) small tumours, such as squamous cell carcinoma on a cat's eyelid.

**Systemic Therapy**

Radiation can be targeted to a specific tissue by use of a radionuclide with special affinity for the tumour cells. Examples in veterinary medicine include $^{131}$Iodine for treatment of thyroid carcinoma and $^{153}$Samarium targeted to bone for treatment of bone tumours in dogs. Because the source of radiation is targeted to tissue within the patient, systemic radiotherapy makes the patient radioactive. Therefore there is a period of isolation or quarantine required for patients treated with systemic radiotherapy, until the radioactivity is reduced to a safe level (usually less than a week).

**Chemotherapy in Veterinary Oncology**

Where does chemotherapy fit in?

Chemotherapy is the principal modality used to treat systemic cancers such as haematologic malignancies, as well as metastatic solid tumours (carcinomas and sarcomas). Because of the focus on quality of life over quantity, the drug dosages and schedules used in veterinary chemotherapy are more conservative and less likely to result in side effects than those in human cancer patients. When discussing chemotherapy, communication and sharing of information between the veterinarian and the owner is essential, and should be gentle but honest. Options should never be limited by the veterinarian’s impression of the owner’s finances or preferences. Rather, a veterinarian should be well-informed and offer all the medically feasible options, and be able to discuss their potential benefit, side effects, and cost in order to allow a pet owner to make an informed decision.

Treat the patient, not the pathology report

Although it is tempting to think of chemotherapy protocols as a “recipe” for treating particular types of cancer, in fact they are a guide. Just because a treatment has shown the best efficacy for a particular type of cancer does not necessarily mean it is the best treatment for the individual patient. Just as every patient - and their metabolism and excretion of drugs - is individual, every cancer is also an individual. Complete evaluation of the cancer and the patient is therefore important both in prognosis and making an initial treatment plan, and continuing to tailor the plan in response to the patient’s condition. It may also be necessary to consider other medical factors that may pose an increased toxicity risk (more below) and nonmedical factors, as well as owner factors such as finance, scheduling constraints or owner pregnancy, in deciding what course is best for a particular patient.

**Chemotherapeutic strategies**
As a general rule of thumb, chemotherapy drugs are most active against cells that are actively cycling or in specific phases of the cell cycle. Tumours grow most rapidly when they are small. As they grow larger, the growth rate decreases. Poor perfusion also means chemotherapy drugs may not be delivered to cancer cells at cytotoxic levels, and hypoxia may decrease the tumour cell response to treatment. In addition, cellular heterogeneity increases as tumours grow, leading to a higher level of spontaneous drug resistance. So in general, chemotherapy will be most active against small tumours, following either early detection or a “debulking” procedure such as surgery or radiation therapy (more below).

Combination chemotherapy can avoid some drug resistance problems by affecting different metabolic pathways in cells that are resistant to other drugs. While combination chemotherapy could potentially be more toxic to normal cells, judicious scheduling of agents so that their toxicities do not overlap can be exploited to improve tumour kill without compounding toxicity.

While combination chemotherapy may circumvent individual drug resistance, it does not completely avoid the problem of cross-resistance to multiple unrelated chemotherapy drugs. The transmembrane pump protein (P-glycoprotein) is present at increased levels in some tumour cells, and both the level and prevalence increases with exposure to chemotherapy. This phenomenon of multiple drug resistance (mdr) occurs between natural product drugs such as anthracyclines (e.g. doxorubicin), and vinca alkaloids (e.g. vincristine). In practical terms this means that a lymphoma that is resistant to the combination of vincristine, cyclophosphamide and prednisone (COP) may also be resistant to doxorubicin even if it has never been used, so drugs that are not mdr substrates should be used in preference (e.g. alkylating agents).

Multimodality therapy
Adjuvant chemotherapy is used following resection of a primary tumour, where the patient is at significant risk of recurrence or metastasis but before recurrence or metastasis is clinically detectable, the classic example being canine osteosarcoma. The advantage is that when a primary tumour is resected, micrometastases have a high growth fraction and a low number of resistant cells, so the chemotherapy can have greatest efficacy. The disadvantage of adjuvant chemotherapy is that those patients cured by surgery are exposed to needless risks of toxicity. For tumours such as canine osteosarcoma and haemangiosarcoma, and feline mammary tumours, this percentage is small; but in other situations the decision whether to use adjuvant chemotherapy may be less clear.

Less commonly used, neoadjuvant chemotherapy is given before localized treatment modalities such as surgery or radiation therapy, with the objective of reducing the size of the primary tumour and reducing the scope and side effects of other definitive treatment.

Chemotherapy dosing
Most chemotherapy drugs have a narrow therapeutic margin, so doses must be chosen and calculated with utmost care to provide minimum toxicity risk and maximum efficacy. Although imperfect, current dosage recommendations are often based on body surface area (BSA, m²). Overall, using the BSA formula means that smaller dogs receive a higher dosage than larger dogs (in proportion to body weight), supposedly compensating for more rapid drug distribution, metabolism and excretion. If this is true, then drug exposure, and efficacy and toxicity, should be relatively uniform across a species. If fact, this is not so, and for veterinary use, dosage based on BSA for many drugs is imperfect; and small dogs and cats should be dosed at a lower rate than larger dogs.

The problems with the BSA formula have been evaluated in studies. In the formula, the constant (K) is supposed to be a shape constant for a given species. K was derived from
studies with very small sample sizes, and the highly variable shape of dogs probably means that the constant is NOT constant for different breeds of dogs.

Despite these limitations, until further guidelines are available, the veterinarian should use a BSA conversion table as the best practical solution, and become familiar with the individual drugs that require lower dosage for small pets. BSA can be determined using a conversion table, in textbooks and on our website at http://www.vetoncologyconsults.com.

**Dose intensity**

Dose intensity is defined as the amount of drug administered per unit time (mg/m²/wk) and can be increased by increasing the drug dosage or by shortening the intertreatment interval. Optimal dose intensity improves the outcome for chemotherapy, and dose intensity should be the highest tolerated by the patient with minimal toxicity.

The other benefit of maximizing dose intensity is to reduce the risk of drug resistance developing. It is important not to administer drugs at sub-therapeutic dosages. On the other hand, if there is tumour growth, it is not good practice to continue the same treatment protocol at the same dosages.

**Effects of the body on chemotherapy drugs**

There are four major factors that affect how chemotherapeutics are handled in the body and therefore its toxicity or efficacy. These need to be considered in chemotherapy dosing for each individual patient, particularly in geriatric oncology patients.

**Absorption**

Oral chemotherapeutics may have reduced absorption in a pet with malabsorption, for example GI lymphoma, leading to decreased efficacy of the drug.

**Distribution**

Drugs affected by protein binding such as vinca alkaloids or mitoxantrone may be affected when an animal is hypoproteinaemic; a larger proportion of the drug may remain pharmacologically active, or may be more rapidly cleared from the body. The effect of other protein-bound drugs should also be considered.

**Excretion**

The concentration of drug in blood over time is a function of total clearance by all eliminating organs. For example, decreases in glomerular filtration rate may affect drugs such as carboplatin; and bile transport disruption could reduce clearance of vincristine or doxorubicin.

**Metabolism**

Hepatic dysfunction may affect reductase metabolism of doxorubicin, thereby increasing toxicity. Cyclophosphamide and DTIC require hepatic activation, so reduced metabolism may reduce toxicity but also efficacy.

Although most tumour cells are in active phases of the cell cycle and susceptible to chemotherapy, most normal cells are not. Chemotherapy toxicity is most common in renewing tissues - haematopoietic cells, mucosa, epidermis, gametes, and foetal tissues. This is important for both patient side effects and for client and practice staff safety.

**Chemotherapy toxicity**

Many clients are concerned about side effects in their pets. Taking a proactive approach is important in both preventing side effects and managing them when they occur. The first step in preventing chemotherapy side effects is careful dosing, discussed in Part 1. Prophylactic
measures prevent many side effects. When side effects occur, they usually resolve with supportive care; and dose reductions in future cycles of the same treatment will usually avoid repeat occurrences.

**Myelosuppression** is bone marrow toxicity. The nadir of peripheral counts occurs about 5-10 days post-treatment. Haematopoietic stem cells are also largely non-proliferating and so are relatively chemoresistant, but are stimulated to divide by myelosuppression; so further chemotherapy during this time can cause stem cell destruction. The usual interval between myelosuppressive drug administrations is every 2 to 3 weeks, but some drugs may have delayed or prolonged nadirs, and their intertreatment intervals are longer.

A complete blood count (CBC) including platelet count should be checked at the expected neutrophil nadir, usually 7 days after administration. The absolute neutrophil count (not the percentage, or the total leukocyte count) should be evaluated. A count of <1.0 x 10^9/L indicates dose reduction of that myelosuppressive drug by 25% even if no complications occur.

In addition, a CBC should be evaluated immediately prior to each potentially myelosuppressive chemotherapy, and treatment delayed if the neutrophil count is <3.0 x 10^9/L.

Neutropenia itself is asymptomatic and poses no quality of life problem. The potential complication of concern is sepsis / febrile neutropenia, as this is potentially life-threatening if untreated. Nonetheless, most neutropenia in veterinary chemotherapy patients is self-limiting and uncomplicated. Giving prophylactic antibiotics after the first administration of a potentially myelosuppressive treatment (and with every doxorubicin) reduces the risk further. However animals with an absolute neutrophil count of <1.0 x 10^9/L are considered at risk and these animals should be treated aggressively if signs occur. A fever or any other sign of sepsis after chemotherapy should be treated as an emergency and the veterinarian should provide aggressive support including intravenous fluids and parenteral broad-spectrum antibiotics.

Thrombocytopenia rarely causes clinical signs, however at counts of <50 x 10^9/L the risk of bleeding increases. Myelosuppressive chemotherapy should not be administered if the platelet count is < 100 x 10^9/L.

**Gastrointestinal** toxicity may cause inappetance, nausea, vomiting or diarrhoea, with management depending on the severity of signs. Significant vomiting requires hospitalization for supportive care, but mild nausea can usually be managed at home with antiemetics. Significant vomiting is not acceptable and is largely preventable. Mild diarrhoea is usually manageable with dietary modifications but severe or haemorrhagic diarrhoea may require hospitalization for supportive care.

**Cardiotoxicity** in veterinary oncology is only a clinical problem for dogs receiving doxorubicin. Chronic cardiotoxicity is related to lifetime cumulative dose of doxorubicin, and the end result resembles dilated cardiomyopathy. Cardiotoxicity is most frequent above 180 mg/m^2, and doxorubicin should not be given above this level without extreme caution and careful consideration of relative risks. Breeds susceptible to dilated cardiomyopathy, particularly Dobermans, are more sensitive to this toxicity and some clinicians will not administer doxorubicin to these dogs even with pre-screening.

**Nephrotoxicity** is the primary dose-limiting toxicity of cisplatin. It is partially ameliorated by administering with appropriate diuresis. Cisplatin should not be administered if the serum
creatinine is above the normal range or the dog is otherwise at risk for renal disease (and should never be administered to cats under any circumstances).

Doxorubicin has been associated with cumulative nephrotoxicity in cats and should not be administered to cats with pre-existing renal disease. It is important to check the serum creatinine level before each doxorubicin treatment in cats.

**Urothelial toxicity** (sterile hemorrhagic cystitis) is mainly associated with cyclophosphamide administration. Clinical signs vary in severity but can be severe and prolonged. Secondary urinary tract infection can occur, so culture and sensitivity should be performed.

**Hypersensitivity reactions** may occur during rapid doxorubicin administration, but rarely if the drug is given over 15 to 20 minutes. True *anaphylaxis* may follow L-asparaginase administration, but very rarely following intramuscular or subcutaneous administration. If anaphylaxis occurs, treatment with corticosteroids and antihistamines plus other supportive measures as necessary should be instituted immediately, and the patient should never receive further L-asparaginase.

**Summary**
Chemotherapy in veterinary private practice can provide patients with extended survival time and excellent quality of life, and can be very rewarding. Chemotherapy can be performed successfully in veterinary private practice. To achieve this, one needs to consider all individual patient- and tumour-specific variables in choosing chemotherapy schedules and doses.