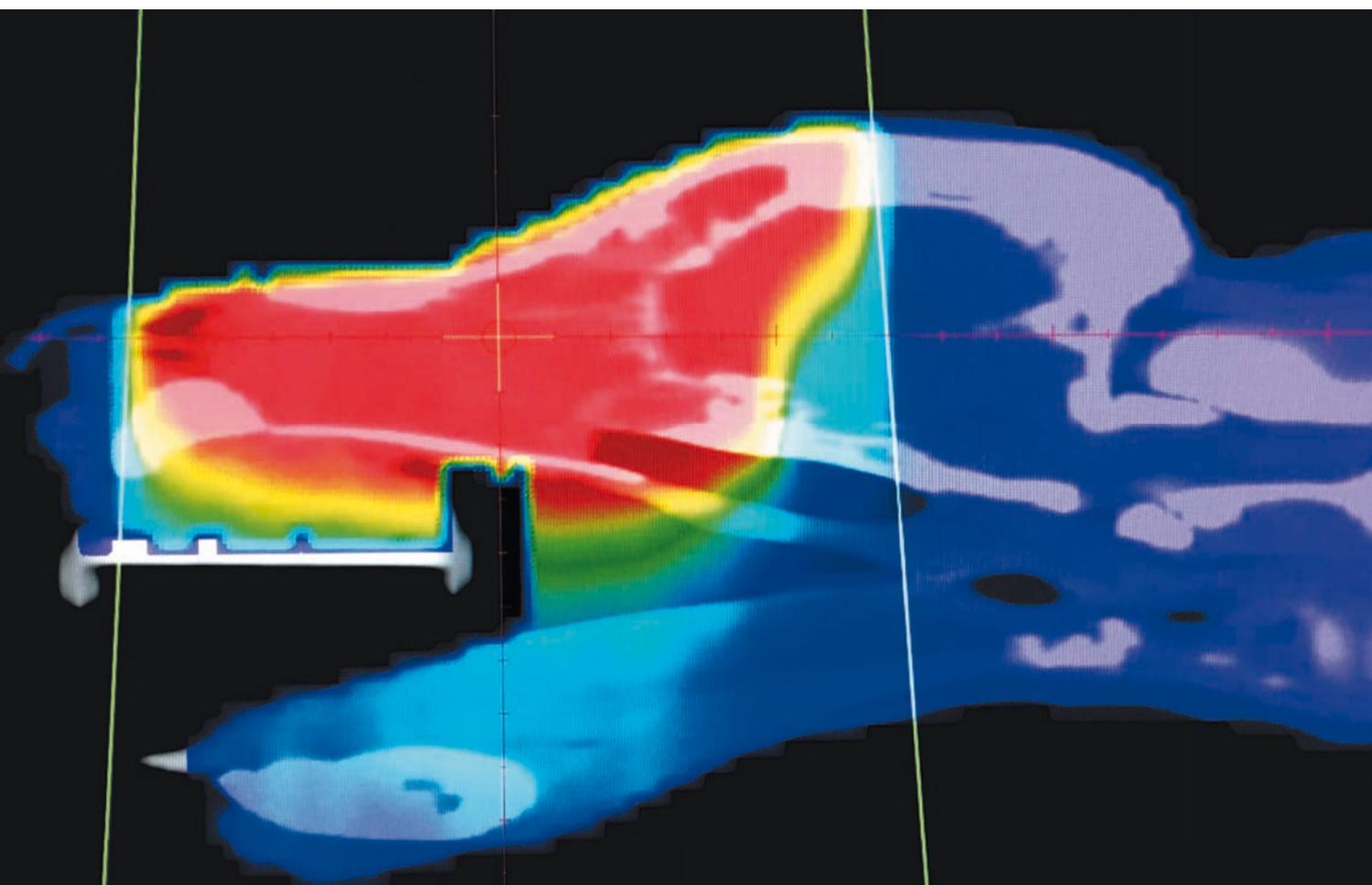


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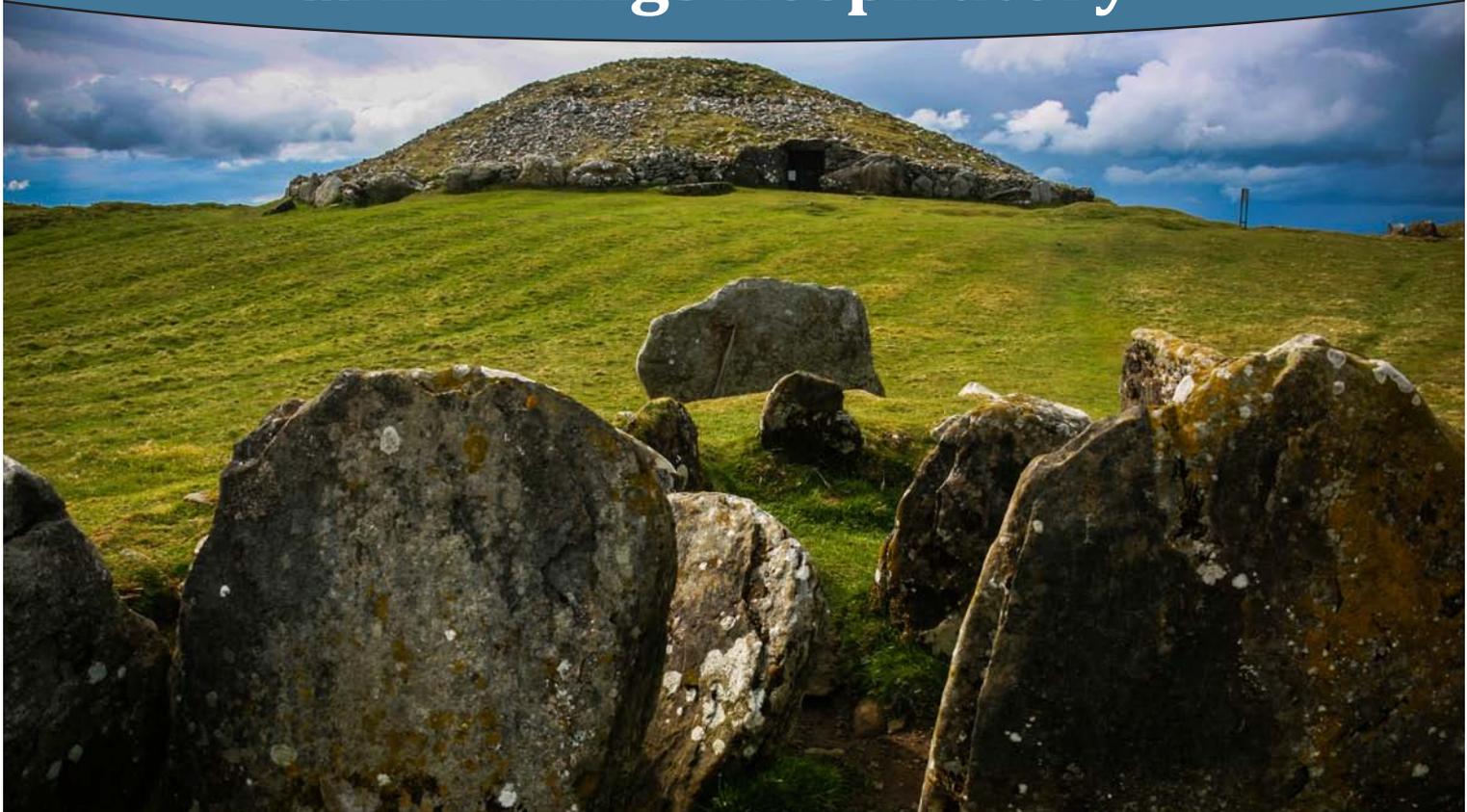


Oncology

Targeted therapies for canine and feline cancer • Managing the feline cancer patient • Adrenal tumors in cats and dogs • Epidemiology of canine mast cell tumors • Cutaneous tumors... The essentials for successful surgery • Radiotherapy in veterinary medicine • A brief guide to... Linear accelerators • Nutritional management of the cancer patient


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Ancient Egyptian records offer a fascinating glimpse as to how medicine and disease were viewed many centuries ago, and none more than the one known as the Edwin Smith Papyrus. Widely regarded as the world's oldest known surgical document, it was written around 1600 BC (and named after the collector who once owned it), and contains various case studies, including a

report on a patient with cancer. As well as noting wryly that the disease had no treatment or cure, the papyrus demonstrates that the Egyptians' medical knowledge considerably exceeded that of Hippocrates, who lived 1,000 years later. But it was the Greek father of medicine who first used the word *carcin* (crab) to describe tumors, whilst the physician Galen later refined the definition, applying the term *oncos* (swelling) to any neoplastic growth (hence the term oncology), and restricting *carcin* for malignancies.

Hippocrates was restricted in his investigations – as it was forbidden to perform dissections – so he only described tumors visible to the naked eye, whilst therapies were rudimentary and often limited to blood-letting and laxatives. Gradually, it was realized that cancer could develop anywhere within the body, but scientific discoveries battled with myth and superstition for many years, and primitive treatments remained popular for centuries. Only in 1902 did the brilliant zoologist Theodor Boveri propose that changes in a cell's characteristics could result in it developing the potential for unlimited, unregulated growth. He went on to speculate that cancers might be linked to radiation, physical damage or chemical insults, and even predicted the existence of what are now known as tumor suppressor genes and oncogenes.

Time moves on; whilst there are still many fallacies and unknowns associated with cancer, this edition of *Veterinary Focus* helps dispel the ancients' belief that the disease has no known treatment or cure, and that a multi-disciplinary approach, coupled with new therapies and knowledge, now offers hope for many pets afflicted with cancer – and hence hope for their owners too.

Ewan McNeill – Editor-in-chief

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The licensing arrangements for therapeutic agents intended for use in small animal species vary greatly worldwide. In the absence of a specific license, consideration should be given to issuing an appropriate cautionary warning prior to administration of any such drug.

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Targeted therapies for canine and feline cancer



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KEY POINTS

- **Cancer is primarily a genetic disease, and changes in cancer cells that cause protein dysregulation are targets for therapeutic intervention.**
- **Small molecule inhibitors and monoclonal antibodies are the two most common clinical approaches used to block cellular processes necessary for growth and survival.**
- **The goal of targeted therapies is to inhibit crucial cell signaling pathways or strengthen immune effector-mechanisms.**
- **Further investigation of the molecular drivers in tumor cells will contribute to the development of novel targeted agents in both human and veterinary medicine.**

■ Introduction

Improvements in our understanding of the distinguishing molecular and immunologic features of cancer cells over the past twenty years has led to the development of numerous innovative cancer therapies, culminating in a paradigm shift in the fundamental approach to cancer treatment. For example, targeting tumor reliance on signaling pathways for growth and metastasis has led to substantial improvements in cancer therapies that transcend species and tumor histology. Dysregulation of a class of cellular proteins, known as kinases, has been identified as an important molecular driver of many tumors, and targeting these kinases has revolutionized the treatment of many cancers in humans and animals. Another major target for therapy that has generated substantial impact in the outcome of human cancer patients is the immune system, with monoclonal antibodies capable of breaking tolerance resulting in dramatic anti-tumor responses, although immunotherapy will not be addressed in this review. Understanding the role of targeted therapies in both human and veterinary oncology, and the complexities that underlie therapeutic responses, is paramount for continued successful incorporation of

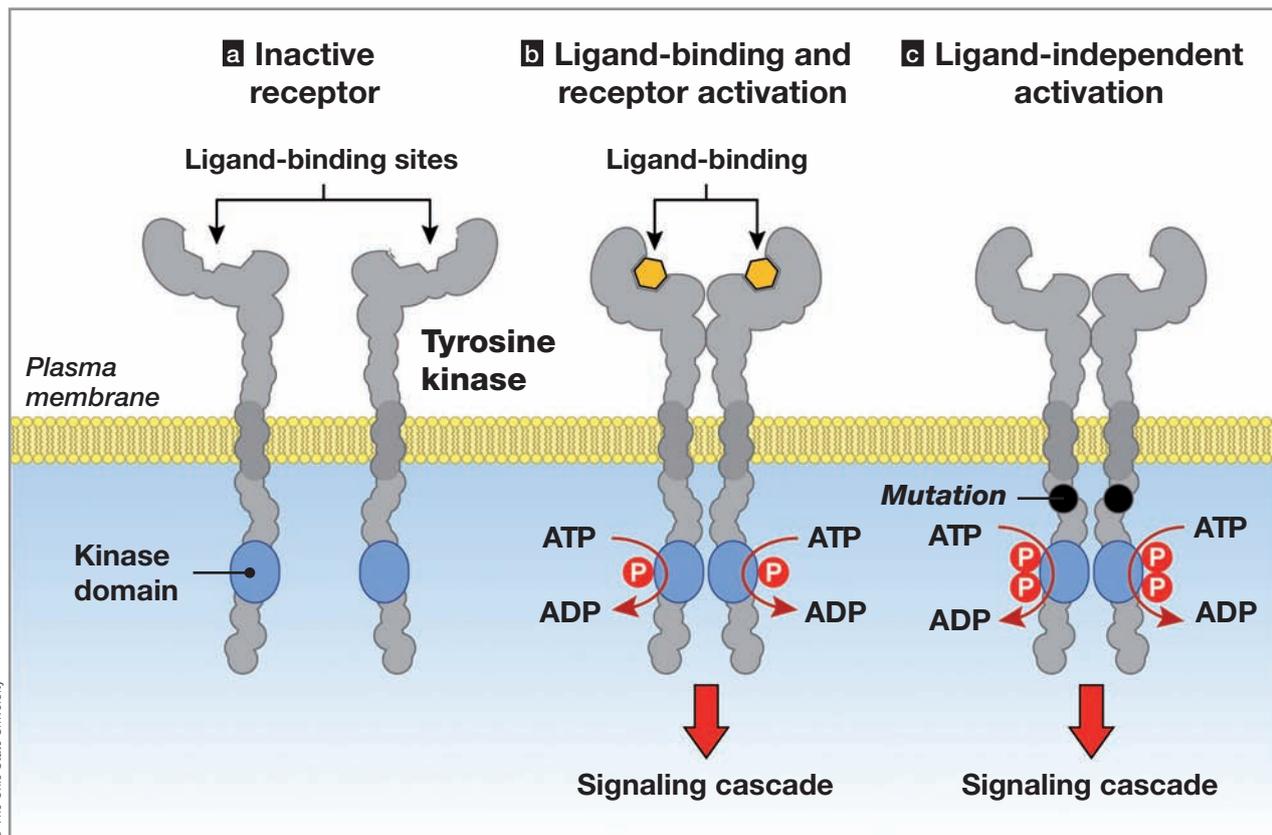
such therapies into comprehensive cancer treatment plans. This paper considers the concept of small molecule inhibitors and their potential for treating small animal cancers.

■ Kinase dysregulation in cancer

Kinases are proteins that regulate signaling pathways crucial for cell processes, such as growth, survival and differentiation. They promote signal transduction within the cell by binding ATP and catalyzing the transfer of phosphate groups from ATP to target amino acid residues (serine, threonine or tyrosine) (1). Kinases can be found on the cell surface (receptor tyrosine kinases, RTKs), in the cytoplasm, and in the nucleus. Typically, signaling is initiated when a growth factor (ligand) binds to a kinase on the cell surface, creating a cascade of downstream effects that ultimately affect gene expression (1). Kinase dysregulation is a primary mechanism used by cancer cells to promote uncontrolled growth and survival, and is thus an attractive therapeutic

target. Multiple mechanisms of kinase dysfunction have been identified in cancer cells, including mutations, chromosomal translocations, gene overexpression, and co-expression of growth factor and receptor kinase (an “autocrine loop”), all resulting in continuous activation of the kinase (**Figure 1**). For example, mutations consisting of internal tandem duplications and point mutations have been identified in the receptor kinase *KIT*¹ in approximately 30% of canine mast cell tumors (MCT), resulting in constitutive activation of the kinase in the absence of growth factor binding, thereby promoting uncontrolled growth and survival of tumor cells. Similarly, point mutations have been found in *KIT*² in feline MCT, resulting in activation of the protein (2). More recently, activating point mutations in the cytoplasmic kinase BRAF were identified in over 80% of transitional cell carcinoma tumor samples evaluated (3). Identical BRAF mutations are found in human melanoma, thyroid cancer, and colon cancer, and these are known to contribute to tumor growth.

Figure 1. Tyrosine kinase receptor signaling. Tyrosine kinase receptors are found in an inactive state as monomers at the plasma membrane (**a**). Ligand binding induces receptor dimerization, autophosphorylation and downstream signaling (**b**). Activating mutations in the kinase result in constitutive autophosphorylation of the receptor in the absence of ligand binding, leading to unregulated downstream signaling and promotion of uncontrolled growth and survival of tumor cells (**c**).



Advances in the understanding of aberrant signaling pathways in cancer cells has aided recognition of pivotal kinases that are key oncogenic drivers, and therefore promising candidates for therapeutic intervention. Targeting these fundamental alterations in tumor signaling pathways has led to the successful development of several small molecule inhibitors in human medicine. While this approach has only recently been applied to veterinary medicine, it has impacted how cancer is treated in both dogs and cats.

■ Small molecule inhibitors in canine cancer

Toceranib phosphate

Toceranib phosphate is an orally bioavailable small molecule inhibitor that blocks signaling of the receptor tyrosine kinases VEGFR2, PDGFR α/β , KIT, Flt3 and CSF1R. It has significant activity against MCTs that possess activating *KIT* mutations, due to its ability to block KIT signaling. However, it was initially developed as an anti-angiogenic agent due to its ability to inhibit VEGFR (vascular endothelial growth factor receptor) and PDGFR (platelet derived growth factor receptor), thus giving it broader activity against several solid tumors such as thyroid carcinoma and apocrine gland anal sac adenocarcinoma.

The initial phase 1 clinical trial of toceranib included 57 dogs with a variety of different cancers (4). The overall biologic activity in this study was 54% (6 complete responses (CR), 10 partial responses (PR) and 15 stable disease (SD)), with the highest response rates observed in dogs with MCT bearing *KIT* mutations. Subsequently, a placebo-controlled randomized clinical trial in dogs with unresectable grade 2 and 3 MCT demonstrated high single agent (*i.e.*, administration of only one therapeutic agent) activity, with an objective response rate (ORR) of 42.8% (21 CR, 41 PR) (5). An additional 16 dogs experienced SD, such that 60% of dogs on study experienced clinical benefit from the toceranib. Consistent with

the notion that *KIT* mutations are a driver in canine MCT, responses were twice as high in dogs with *KIT* mutations compared to those without.

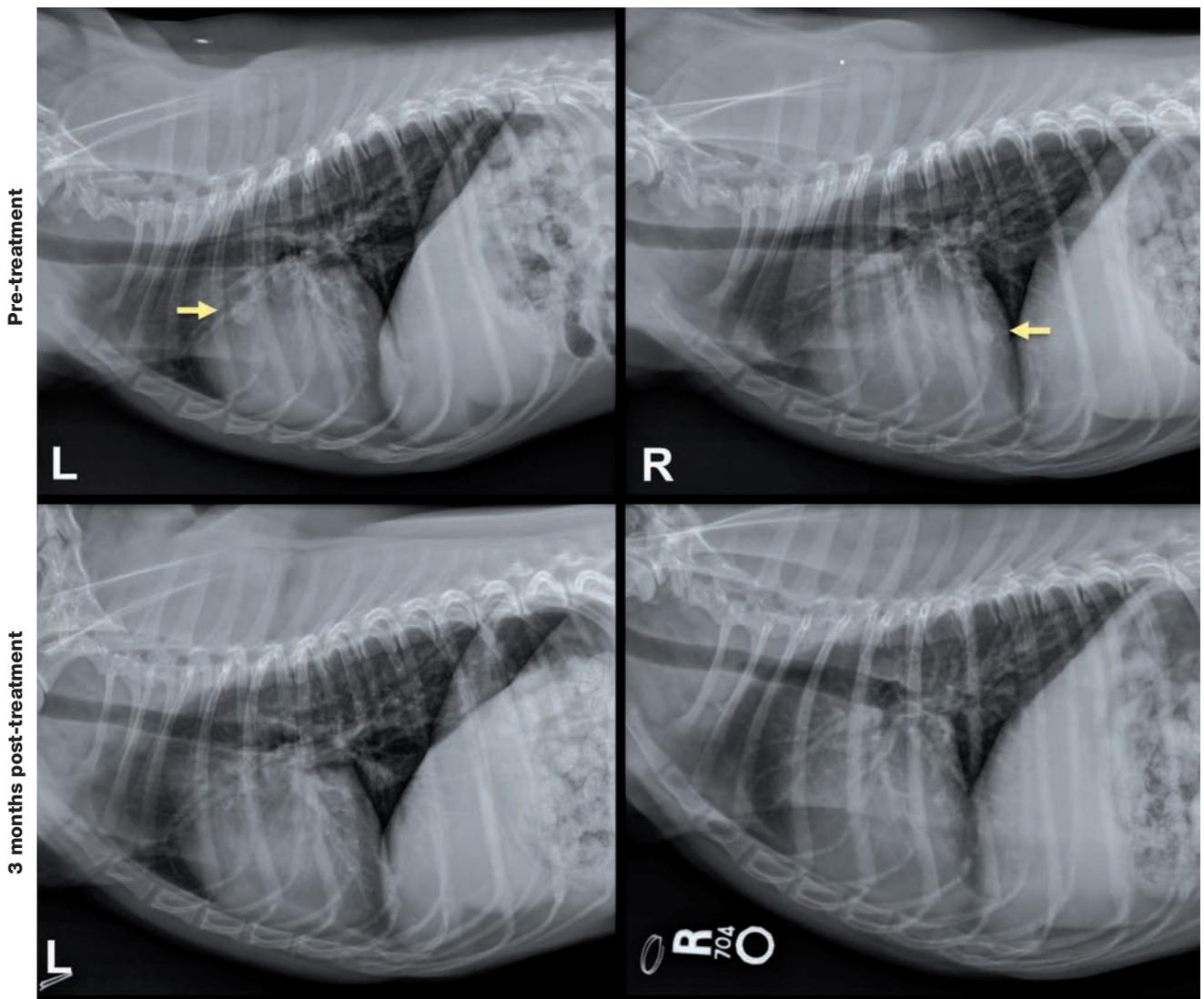
Toceranib has now been used to treat various solid tumors in dogs. Clinical benefit (SD + CR + PR) was observed in 74% of dogs in one retrospective analysis (6). Tumor histologies that responded to toceranib included apocrine gland adenocarcinoma of the anal sac (28/32), metastatic osteosarcoma (11/23), thyroid carcinoma (12/15), head and neck carcinoma (7/8) and nasal carcinoma (5/7) (**Figure 2**). This is significant when one considers that the response rate of traditional cytotoxic chemotherapy with metastatic neoplasia is generally less than 20% and of short duration. Research is ongoing to determine the role of toceranib targets in different tumor histologies, as well as to identify biomarkers of response to therapy. For example, while PDGFR α/β and VEGFR2 are expressed in canine anal sac adenocarcinoma and thyroid carcinoma, they do not appear to be constitutively activated, and thus are unlikely to be targets for toceranib in these cancers (7).

Toceranib has been primarily evaluated in the setting of gross disease, but the response rates in this setting are thought to reflect potential for activity in microscopic metastatic disease. However, two recent studies did not find evidence of clinical benefit using this approach. A clinical trial was undertaken in dogs with appendicular osteosarcoma (OSA), whereby all dogs underwent amputation and carboplatin chemotherapy, and were then randomized to receive toceranib/piroxicam/cyclophosphamide or piroxicam/cyclophosphamide. The median disease free interval (DFI) for control and toceranib-treated dogs was 215 and 233 days, respectively ($p = 0.274$); the median overall survival (OS) for control and toceranib-treated dogs was 242 and 318 days, respectively ($p = 0.08$). The one-year survival rate for control dogs was 35% compared to 38% for dogs receiving toceranib (8). The conclusion was that adding toceranib to metronomic

Typical definitions of common terms*.

Disease-free interval (DFI)	The period of time between the start of treatment and disease progression
Overall survival (OS)	The period of time from the date of diagnosis until death
Maximum tolerated dose (MTD)	The highest dose of a drug that does not result in unacceptable side effects
Time to progression (TTP)	The period of time from the first date of treatment to the date of progression of disease

*Note that different studies may define these terms in different ways; the reader should refer to each paper for the specific definition.



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Figure 2. Response to toceranib therapy in a mixed breed dog with metastatic thyroid carcinoma. Lateral thoracic radiographs demonstrating pulmonary metastatic nodules (arrows) prior to treatment and three months after commencing toceranib therapy.

piroxicam and cyclophosphamide therapy following amputation and carboplatin chemotherapy did not improve median DFI, OS or the one-year survival rate in dogs with OSA, nor did it improve these endpoints over carboplatin alone. Similarly, a clinical trial evaluating the impact of toceranib in dogs with splenic hemangiosarcoma following splenectomy and doxorubicin chemotherapy found no survival benefit with the addition of toceranib (9).

Toceranib has also been evaluated in combination with other therapies to treat canine cancers. A phase 1 trial was performed in tumor-bearing (non-mast cell tumor) dogs to establish the safety of co-administration of toceranib and

piroxicam (10). Dose escalation continued up to and including the approved label dosage for toceranib and standard dosage for piroxicam without noting an increase in the frequency of dose-limiting side effects that required discontinuation of therapy. Additionally, several anti-tumor responses were observed during the clinical trial. While the combination of standard dosages of both drugs was found to be generally safe, the dogs were not monitored to assess whether gastrointestinal side effects occurred after several months of administration, but the conclusion was that piroxicam and toceranib can be administered on an alternate daily basis to help mitigate any toxicity risk (*i.e.*, piroxicam day 1, toceranib day 2, piroxicam day 3, etc.).

The combination of toceranib with standard chemotherapeutics administered at the maximum tolerated dose (MTD) often necessitates dose reductions due to neutropenia. A phase 1 study of vinblastine and toceranib in canine MCT determined the MTD to be 1.6 mg/m² vinblastine and 3.25 mg/kg Q48 h toceranib (11). The dose-limiting toxicity (DLT) of this combination was neutropenia, suggesting sensitization of the myeloid compartment. Despite a 50% reduction in dose intensity of vinblastine, the ORR was 71%, suggesting additive or synergistic activity. Similarly, the DLT of simultaneous administration of lomustine and toceranib is neutropenia, with the MTD of lomustine determined to be 50 mg/m² every 3 weeks when given in combination with toceranib (12). While not a primary objective of this study, objective responses (38.4%) were seen in multiple hematologic malignancies and solid tumors. More recently pulse-administered toceranib (given on days 1, 3 and 5 of a 21-day cycle) in combination with lomustine at 50 mg/m² given on day 3 of each cycle was associated with an ORR of 46% (4 CR, 15 PR) in unresectable MCT (13). As in other combination studies, neutropenia was the DLT.

Toceranib has also been evaluated in combination with radiotherapy in dogs with non-resectable MCT (14). Toceranib was administered at 2.75 mg/kg Monday, Wednesday and Friday, in combination with omeprazole, diphenhydramine and prednisone (1 mg/kg Q24 h) for 1 week, after which coarsely fractionated radiation therapy began (4 Fx of 6 Gy Q7 d). The ORR was 76.4% (58.8% CR, 17.6% PR), and the overall median survival time (MST) was not reached. Importantly, there were no enhanced radiation side effects with this protocol. Another clinical trial investigated the biologic activity of combined toceranib and radiation with nasal carcinoma. In this study, dogs that received radiation alone had a median survival time of 371 days compared to 615 days for those that also received toceranib, suggesting that combination therapy provides an advantage for dogs with this tumor (15).

Masitinib mesylate

Masitinib is a small molecule inhibitor that blocks KIT, PDGFR and the cytoplasmic kinase Lyn. The biologic activity of masitinib was demonstrated in a randomized, double-blind placebo-controlled phase 3 clinical trial of 202 dogs with non-resectable grade 2 and 3 MCT (16). While significant increases in response rates in dogs with and without *KIT* mutations were not observed after masitinib administration compared to placebo, the time to progression (TTP) was significantly longer in dogs

receiving masitinib (118 days vs. 75 days). In addition, a subsequent study of 139 dogs with unresectable grade 2 and 3 MCT demonstrated long-term disease control was significantly higher in dogs receiving masitinib, with 36% of treated animals alive at 2 years, compared to 15% of dogs not receiving masitinib (17). The drug has also been reported to have activity against T cell lymphoma in dogs, but as yet there is a paucity of published data as to its efficacy.

Imatinib mesylate

Imatinib is a small molecule inhibitor with activity against Bcr-Abl, KIT and PDGFR. Imatinib was developed to treat chronic myelogenous leukemia (CML) in people, with response rates up to 90% reported (18) and is used off-label in veterinary medicine; although it has not been evaluated in prospective clinical trials, anti-tumor activity has been demonstrated in both dogs and cats. Objective responses have been observed after imatinib therapy in canine MCT (both with and without *KIT* mutations); in one study, 10/21 dogs with MCT treated with imatinib had their tumors shrink, with all dogs that possessed *KIT* internal tandem duplications responding (4 CR, 1 PR) (19). Additionally, one dog with a non-resectable gastrointestinal stromal tumor bearing *KIT* exon 11 mutation responded to imatinib (20).

Based on the reported usage of imatinib in dogs and cats, it is likely that clinical responses will be most strongly associated with *KIT* mutation status. However, responses are also noted where the mutation is absent, suggesting other mechanisms of kinase dysregulation. For example, mutations in PDGFR α/β have been documented in imatinib-responsive systemic mastocytosis and gastrointestinal stromal tumors in the absence of concurrent *KIT* mutations (21,22).

■ Small molecule inhibitors in feline cancer

Kinase dysregulation is ill-defined in feline cancers, although *KIT* mutations have been demonstrated in feline MCT (2,23). As such, only a few studies have evaluated the efficacy of small molecule inhibitors in cats with cancer. A retrospective study was conducted to evaluate the activity of toceranib in cats with oral squamous cell carcinoma. Forty-six cats were included; 23 received treatment with toceranib (group 1) and 23 did not (group 2). The overall biological response rate in group 1 was 56.5%. Median survival time of toceranib-treated cats was significantly longer at 123 days compared with 45 days in untreated cats ($P = 0.01$). Cats achieving

stable disease or better on toceranib therapy had significantly longer progression-free survival ($P < 0.0001$) and median survival ($P = 0.0042$) times than those with progressive disease on toceranib (24). In contrast, a study evaluating toceranib for cats with injection site sarcoma (ISS) demonstrated no clinical response, although the drug was well tolerated (25).

The safety profile of masitinib has been assessed in a phase 1 study performed in healthy cats (26). Reversible proteinuria (2/20 cats) and neutropenia (3/20 cats) was observed, along with weight loss during the second week of administration. A phase 1 clinical trial of imatinib in 9 cats with various solid tumors determined that it could be safely administered at 10 mg/kg Q24 h, with the primary adverse event being mild gastrointestinal toxicity (27). Activity of imatinib has been reported in cats with MCT possessing exon 8 or 9 *KIT* mutations, with one study demonstrating objective responses in 7/8 cats (2,23).

Strong PDGFR staining has been identified in feline ISS tissues, and PDGFR β phosphorylation has been demonstrated in feline ISS cell lines after PDGF exposure (28). PDGFR phosphorylation in feline ISS cell lines was inhibited by masitinib (29). Four cats with ISS in a phase 1 clinical trial demonstrated disease stabilization with imatinib therapy (27). While driver mutations in feline ISS have not been identified, imatinib inhibits PDGF/PDGFR signaling in feline ISS and tumor growth in a murine xenograft model of the disease, supporting the notion that it may be a relevant therapeutic target (28). Ultimately, additional research is needed to more accurately define the role of kinase inhibitors in feline cancers.

■ Approach to therapy

Despite the targeted nature of many kinase inhibitors, the therapeutic window of these drugs is narrow, and without close monitoring and evaluation of patients prior to initiating therapy, toxicities can be observed. In addition, side effects can be exacerbated by disease-related comorbidities, so management and prevention of side effects is a critical component of therapy.

Toceranib has a significant adverse event profile at the label dose of 3.25 mg/kg given every other day. Several studies have now shown that lower doses are associated with meaningful clinical benefit and adequate drug exposure, with an enhanced safety profile permitting more continuous dosing without the need for drug holidays (4,6,30). When toceranib was given at doses between

2.4-2.9 mg/kg Q48 h, low-grade gastrointestinal, hematologic and musculoskeletal adverse events were the primary clinical toxicities observed, and these were readily managed with concomitant medications (30). Based on this study, the current recommendation for toceranib dosing is 2.5-2.75 mg/kg given every other day or on a Monday/Wednesday/Friday schedule.

Clinical toxicities reported with both toceranib and masitinib include gastrointestinal (GI) toxicity (anorexia, vomiting, diarrhea), renal toxicity (protein-losing nephropathy, PLN), hypertension, and less commonly hepatotoxicity, muscle pain and pancreatitis. While GI toxicity secondary to kinase inhibitor therapy is readily manageable, early intervention is important. A proton pump inhibitor such as omeprazole can be used in conjunction with toceranib, as this helps prevent GI irritation/ulceration. Mild anorexia and diarrhea can be treated with antiemetics (maropitant, ondansetron), prednisone, and anti-diarrheals (metronidazole, probiotics, loperamide) respectively. A temporary discontinuation of the drug with subsequent re-institution of therapy at a lower dose should be undertaken in cases of any grade 2 GI toxicity.

Hepatotoxicity with imatinib administration has been reported in dogs at very high doses (100 mg/kg) experimentally, and anecdotally at therapeutic doses (10 mg/kg) (31). Hepatotoxicity associated with toceranib administration has also been reported and is generally responsive to temporary drug discontinuation and hepatoprotectants (SAME plus silymarin). Reinstitution of therapy is typically considered with dosage and/or schedule modification.

The incidence of PLN is ill-defined in the veterinary literature, but may be recognized as a relatively frequent sequel to kinase inhibitors administration now patients are more closely monitored for this side effect, although the cause is unknown. Severe protein loss (albumin, globulin) and bicavitary effusion necessitating drug discontinuation has been reported with masitinib administration. Imatinib is generally well tolerated, although one case of PLN was reported in a cat with hypereosinophilic syndrome treated at 9.6 mg/kg/day (32). Hypertension has also been reported following toceranib administration in dogs, although the actual incidence is not known. For toceranib-induced PLN, therapy with an ACE inhibitor is typically instituted, in concert with a drug holiday. The duration of the drug holiday is dependent on the animal's health status, but wherever possible the adverse clinical signs should have disappeared prior to restarting toceranib. Close monitoring of the urine protein/creatinine ratio is

warranted once the drug is re-initiated to ensure that the PLN is not worsening. Hypertension is often observed in conjunction with PLN and therapy with amlodipine is often utilized to manage this toxicity.

■ Conclusions

Small molecule inhibitors are being rigorously pursued in

veterinary and human oncology, and the unprecedented early successes have markedly accelerated the determination to define the complexities driving neoplastic processes. It is likely that more of these will make their way into veterinary medicine, providing a substantial new resource that ultimately will impact on how many dogs and cats with cancer are treated successfully.

^{1,2} KIT¹ is a receptor tyrosine kinase encoded by the *KIT²* gene.

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Challenges specific to the feline cancer patient



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■ Introduction

Cancer treatment of both cats and dogs has been on the rise in both specialty and primary care practices. For example, a survey of UK veterinary practices showed that 70.8% had used cytotoxic therapy in the past year, and 39.6% had referred a patient to another practice for such treatment (1). The most commonly prescribed drugs were cyclophosphamide (92.4% of practices) and vincristine

(89.6%), followed by chlorambucil (42.8%) and doxorubicin (30.1%), and given the frequency of lymphoma in animals, it is not surprising that these drugs are the most often prescribed.

When compared to other domestic animals (and humans), cats are unique in many ways – they are obligate carnivores, they are predators, many bear a striking resemblance to their larger, wilder relatives in both appearance and behavior, and for the most part their body size is relatively uniform across breeds. Their cancers are unique as well, which must be taken into account when considering treatment options. One example is feline lymphoma, which can manifest in several different forms; unlike other species, cats rarely develop multicentric lymphoma, but frequently develop the intestinal form of the disease. The treatment options and prognostic expectations vary depending on the type of lymphoma. Other examples are appendicular osteosarcoma, which (in contrast to dogs) rarely metastasizes in the cat, and splenic mast cell disease, which is quite treatable. However, this article does not focus on specific feline cancers, but rather will review the challenges that can arise when treating a cat with cancer.

KEY POINTS

- Many cancers in cats differ in their clinical behavior, treatment recommendations, and prognosis when compared to similar cancers in other species. The approach to feline neoplasia should therefore be based on species-specific information.
- Clear communication with an owner regarding treatment options and their feasibility, and careful management of the owner's expectations, will result in improved adherence to clinical recommendations.
- Cats with lymphoma are often ill at the time of diagnosis, and maintaining a good quality of life during treatment depends on supportive care as well as cytotoxic therapy.
- The hallmark of cachexia is loss of muscle mass, while loss of adipose tissue is indicative of inadequate caloric intake; both body muscle and body fat should be assessed in the feline cancer patient.

■ Diagnosis and staging

The process of diagnosing cancer in cats is similar to other species, and the staging tests are similar as well. Depending on the type of cancer and the clinical status of the patient, cytology or biopsy may be the recommended procedure, and there are several options for obtaining samples (2), depending on the location of the organ or mass in question (*i.e.*, fine-needle aspiration, incisional/excisional biopsy, endoscopy, laparoscopy, or exploratory abdominal surgery). Other diagnostic investigations depend on the differential diagnoses, findings

on physical examination, the results of any initial tests performed, and the patient's status.

As with other species, the recommended staging tests for feline cancer depend on the diagnosis. For cats who are clinically ill and ultimately diagnosed with cancer, this may have already been performed as part of the diagnostic work-up, and no additional staging may be necessary. It is, however, recommended to perform feline leukemia virus testing on cats with lymphoma. In addition, the majority of cats with small cell lymphoma are cobalamin-deficient, so measurement of serum cobalamin is recommended, with subsequent supplementation if indicated (3).

■ Treatment challenges

Drug delivery

The primary options available for treating cats with cancer are similar to those for other species. Cats, however, can present some unique challenges regarding drug administration, and it is important to take into account the ability of an owner to medicate their cat (and also transport their cat to the surgery) when developing a treatment plan; this can result in more consistent therapy and less anxiety for the client. Some cats are intolerant of remaining still for intravenous (IV) injections or infusions, and may require sedation for safe administration of the chemotherapy drugs that are tissue irritants or vesicants, such as the vinca alkaloids and doxorubicin. Sedation adds time and cost to the visit, and sedating a patient weekly for treatments is not ideal. One possible solution is to administer the drugs intraperitoneally (IP), which may be better tolerated and safer for both the cat and the personnel administering the chemotherapy. When IP administration of vincristine and cyclophosphamide to 26 cats receiving a COP-based protocol (cyclophosphamide, vincristine, prednisone) for lymphoma was retrospectively reported, no adverse effects related to the injections were noted (4). The response rate in the study was 76.9%, (the partial response rate was 19.2%, with only one cat unresponsive to treatment), which is similar to or better than other reports of COP protocols for feline lymphoma. The median disease-free interval was 421 days, which again compares favorably to other reports. The cats tolerated the IP injections well, and the authors noted that no handler was injured during treatment. It should be noted that ten of the cats had nasal lymphoma, which may skew the results towards a more favorable outcome compared to other studies. However, the study shows that IP chemotherapy administration appears to be well tolerated and may be an effective

substitute for sedation and IV injection. The bioavailability of IP vincristine and cyclophosphamide in healthy cats is 100% and 76% respectively, so it would appear to be a reasonable method of drug delivery in this species (5).

Some cats are extremely resistant to oral dosing, which can be a significant source of stress for clients and can damage the pet-owner bond. If a cat requires several medications, the owner may be able to combine them in a gelatin capsule, so that only one pill is administered. Another option offered by some pharmacies is to compound two drugs together. Liquid formulations of many oral medications can also be formulated, and it may be possible for the concentration (and flavor) to be tailored to the cat, to minimize the volume of medicine required. **(Figure 1)**. However, compounding chemotherapy drugs as a liquid is not recommended; this increases the risk that people in the household are exposed to the drugs, particularly if the cat spits out the liquid or hypersalivates after dosing.

Transdermal formulations of some drugs such as prednisolone and supportive care medications can be attempted, but the bioavailability of drugs applied by this method is unknown **(Figure 2)**. Therefore, if a cat does not respond to transdermal medication, it could be because the medication is not working, or that it is not being absorbed. Again, it should be emphasized that some drugs such as chemotherapeutic agents should not be

Figure 1. A cat voluntarily accepting prednisolone compounded as an oral suspension.



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given transdermally, as the human exposure risk is extremely high.

Some cats tolerate subcutaneous injections better than oral medication, and if the owner is competent then this option can be used at home for glucocorticoids (dexamethasone) and some supportive care medications (e.g., maropitant). Again, the author does not recommend allowing owners to administer chemotherapy in this fashion.

Supportive care

Improving quality of life is a primary goal when treating cancer in cats, and this is particularly important when presented with a cat which already has clinical signs at the time of diagnosis. Adequate analgesia should be used wherever appropriate, but it can be challenging to improve the quality of life while balancing potential side effects from chemotherapy. Fortunately, there are a host of supportive care medications available, assuming that the client can administer them. The most common clinical signs seen with cancer and the chemotherapy side effects that impact on quality of life are nausea/vomiting, decreased appetite, and weight loss. The author most commonly uses ondansetron and maropitant to treat nausea, while prednisolone and/or mirtazapine can be used if the cat's appetite remains poor despite administration of anti-emetics. Treatment with megestrol acetate may also be considered if appetite does not improve with other medication, although this drug has many potential side effects (including diabetes mellitus and mammary carcinoma) and the author prefers to use it only for end-stage palliative care and only in carefully selected patients (6). Megestrol acetate is a potent suppressor of the hypothalamic-pituitary-adrenal axis; changes in post-ACTH cortisol levels were seen as quickly as one week after starting treatment in healthy cats given megestrol acetate (7), so it is essential to inform clients that the medication should not be withdrawn abruptly. It is worth noting that other healthy cats in this study received prednisolone, which did not suppress the axis to the same degree.

Assisted enteral nutrition with feeding tubes is a controversial issue in feline oncology. A tube ensures that the owner can get an adequate amount of nutrition and water into the cat, and it is easier to measure calorie consumption than with free feeding. It is often possible to give medications via the feeding tube, which reduces stress for both owner and cat. The downside is that a feeding tube can enable an owner to keep their cat alive



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Figure 2. Transdermal medication can be applied to the inner aspect of the pinna. Owners should wear gloves when applying medication in this way to avoid exposing themselves to the drug.

in the face of extreme discomfort, and thus prolong, rather than minimize, suffering. It is therefore important to communicate effectively with the client about the purpose of the feeding tube, and to ensure that both clinician and client have the same goals and expectations for the cat's clinical situation.

Two studies have examined the outcome of feeding tube placement in cats, and found that most owners were comfortable using them. One study (8) compared the placement and usage of 21 percutaneous endoscopic gastrostomy (PEG) versus 46 esophagostomy (E) tubes in feline patients. Liver disease (most commonly hepatic lipidosis) and cancer were the most common diseases included in the study. All of the owners of cats with PEG tubes surveyed stated that they were comfortable using the tube, and only one owner was uncomfortable with their cat's E tube. There were no significant differences between PEG and E tubes according to number and severity of complications, owner comfort level, owner difficulty (or lack thereof) with initial feedings, and weight change while the tube was in place. The number of days the tube was in place was significantly shorter for E tubes versus PEG tubes. Another study (9) specifically evaluated E tube placement in 60 cats and found that most patients either gained or had stable weight while being tube fed, and the mean

duration of tube placement was 23 days. Noted complications included vomiting (including vomiting the tube), swelling of the head, and inflammation or infection at the tube site, with complications occurring in about 1/3 of patients. It is worth noting that both studies were published 12-18 years ago, and it is reasonable to think that skill level with tube placement, owner communication regarding tube usage, and suitable diets for enteral tube feeding have improved in the past two decades. To the author's knowledge, no more recent studies showing clinical effects on body weight and owner satisfaction with E tubes in cats have been published, although a recent study evaluating the prognostic impact of weight changes during treatment of lymphoma in cats included 21 cats that had enteral feeding tubes placed (10). The tubes were more likely to be placed in cats with small cell lymphoma, and tube feeding was not significantly associated with weight change.

For inappetent or anorexic cats, a feeding tube may help to improve their nutritional state while cancer treatment is started. Not every patient will gain weight despite achieving adequate caloric consumption. Persistent weight loss in the face of adequate caloric intake is a hallmark of cancer cachexia syndrome.

■ Cancer cachexia

Cancer cachexia is well described in human medicine, but it is such a complex and multi-factorial syndrome that no standard-of-care treatment currently exists for it. Common aspects of cancer cachexia include weight loss despite adequate caloric intake, loss of muscle mass, early satiety, decreased appetite, increased serum levels of inflammatory cytokines, and poor tolerance of and response to cancer treatment (11-16). Cancer cachexia is estimated to affect up to 80% of human patients with some cancers (17,18) and is an independent negative prognostic factor for survival (12,13).

Table 1. Clinical scoring system to assess muscle mass in cats. The temporal muscles, scapulae, and hind limbs were the areas assessed by the investigators (20).

Score	Description of muscle mass loss
0	Severe (substantial muscle loss)
1	Moderate (noticeable muscle loss)
2	Mild (slight muscle loss)
3	Normal (no muscle loss)

A fair number of feline cancer patients struggle with weight loss and food consumption. Owners also often note signs of early satiety – the cat goes to the food bowl and seems interested, but stops eating after just a few bites. The weight loss experienced by these patients may be due to inadequate caloric intake because they are feeling ill from their cancer, their treatment, or both. This scenario would not explain the specific muscle loss seen in many cats with cancer. In starvation (inadequate caloric intake), the body works to conserve muscle, so fat tissue is primarily lost. In cachexia, the opposite occurs – the body preferentially breaks down muscle, with or without loss of fat mass. Because current body condition scoring (BCS) systems for cats incorporate adipose tissue mass, not specifically muscle mass, it is important to assess both adipose tissue and muscle mass in feline cancer patients (**Tables 1 and 2, Figures 3 and 4**). Relying solely on BCS may prevent clinicians from identifying cats that have moderate to severe muscle mass loss despite being overweight or obese (**Figure 5**).

One prospective study examined the effect of body weight and BCS in cats with cancer, with the vast majority (91%) of cats exhibiting clinically evident loss of muscle mass (muscle mass score of 0 or 1) while most (60%) cats had clinically evident loss of adipose tissue (score of 0 or 1) (19). Cats with lower body weight or BCS had shorter survival times and both factors were associated with remission status as well; cats in remission from their cancer had significantly higher body weights and BCS compared to those that were not in remission. Other studies have demonstrated that cats that have lost weight prior to starting chemotherapy or that weigh less than the median weight for cats in the study at the beginning of chemotherapy have a shorter survival time (20,21).

A recent retrospective study compared survival of cats that were undergoing chemotherapy for lymphoma

Table 2. Clinical scoring system to assess fat mass in cats. The area over the ribs and abdominal fat pad were the areas assessed by the investigators (20).

Score	Description of fat mass
0	Absent
1	Decreased
2	Normal
3	Increased

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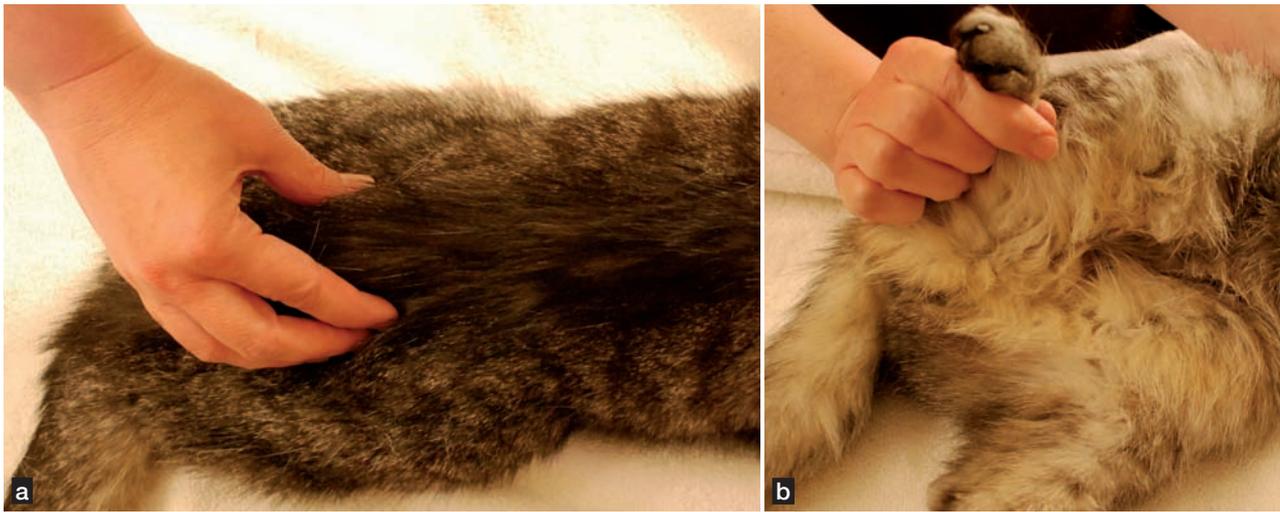


Figure 3. A cat with significant muscle mass loss over the scapulae and spine (a) as well as absence of the abdominal fat pad (b). This cat received a muscle mass score of 0 and an adipose tissue mass score of 0.

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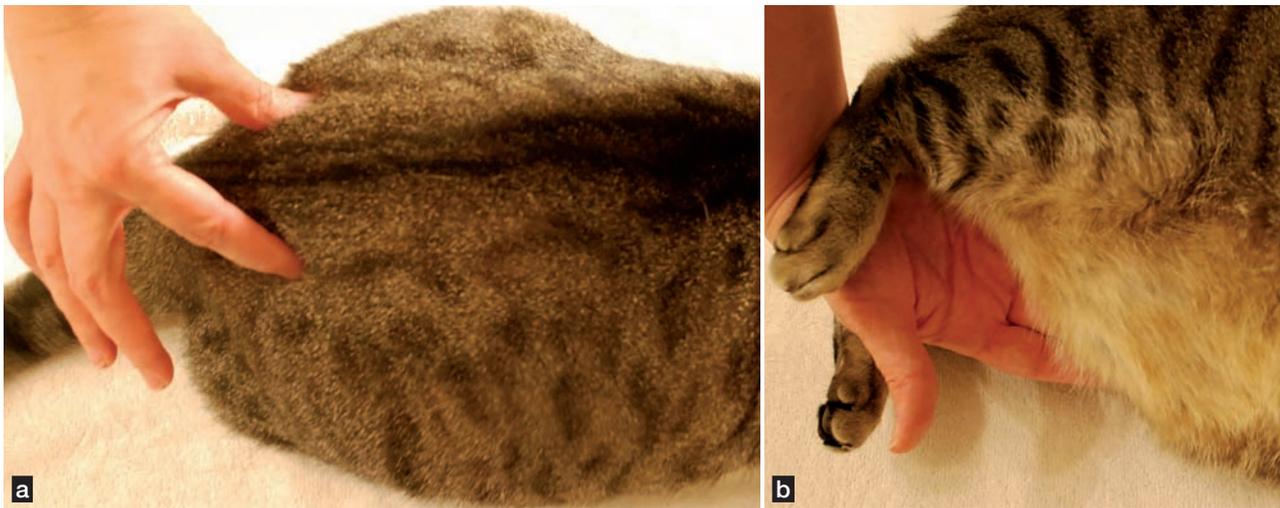


Figure 4. In contrast to the cat in Figure 3, this cat has normal muscle mass which is scored 3 (a), and a large abdominal fat pad (b) consistent with an adipose tissue mass score of 3.

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Figure 5. A cat with significant muscle mass loss, with visibly prominent ilial wings and lumbar spine (a) but increased fat mass, as evidenced by the large abdominal fat pad (b). This is indicative of both obesity and cachexia. Although this cat is not in a state of starvation, the decreased muscle mass is consistent with a metabolic process (in this case cancer) which is causing breakdown and loss of muscle.

according to how their weight changed during treatment (10). Cats with small cell and large cell lymphoma were included in this study, and weight data from baseline and months 1, 2 and 3 were recorded and compared. Cats were grouped as gained, lost, or stable weight, based on whether their weight at the specified time points was at least 5% more, at least 5% less, or less than 5% changed compared to baseline. No differences in survival were noted according to weight change for cats with small cell lymphoma, but a difference was noted in cats with large cell lymphoma one month into treatment. Specifically, cats that lost at least 5% of their body weight had a significantly shorter survival compared to the other cats. The same trend was seen at the two-month time point, but statistical significance was not achieved.

These studies confirm that baseline body weight and changes in weight during treatment are prognostic for survival in cats with cancer, specifically lymphoma. When added to the finding that the majority of cats with cancer have clinically evident loss of muscle mass, one can make the argument that some cats with cancer exhibit clinical aspects of cancer cachexia. Additional research is needed to evaluate treatment strategies aimed at reversing the cachectic state.

■ Quality of life

Only one study has specifically examined clients' perceptions of the quality of life of their cat during chemotherapy (22). Overall, most clients (83%) were happy with their decision to treat their cat using chemotherapy, and 87% said that they would treat another cat in future if necessary. Owners also identified markers of quality of life in their cats. The most commonly cited indicator was appetite (92% of owners), followed by playing/having fun, being interactive, general demeanor, and having energy. Owners were also asked about their cat's quality of life at different time points. Not surprisingly, mean quality of life scores were highest prior to cancer diagnosis and chemotherapy. Scores were higher after starting chemotherapy compared to after the diagnosis was obtained but before chemotherapy was started. Owners of cats who had died by the time of the survey were significantly less likely to report being happy that they opted for chemotherapy, and owners of cats who experienced side effects from the chemotherapy were more likely to regret their decision to opt for this treatment. Note that participants in this study were surveyed just once during the course of their cat's treatment, and the timing of the survey varied from cat to cat, so there is a high risk of recall bias. It would be

interesting to survey cat owners in real time at multiple points during treatment for lymphoma to better determine how they think their cats are feeling during treatment and before they know the outcome of the therapy. The fact that almost all owners selected "appetite" as a quality of life indicator shows that an owner is as likely to be concerned with their cat's appetite as the veterinarian is by their cat's weight, and the two factors are certainly related.

■ Communication

Effective communication is essential to any veterinarian-client interaction. This is especially important when treating feline patients, because cats often act very differently at home compared to how they behave in clinic. It is therefore essential to learn as much as possible from the owner about the cat's behavior at home to gauge its quality of life. For example, if a client says a cat is eating, but is persistently losing weight, it is helpful to find out what the cat's feeding behavior is at home. The cat may actually be consuming an adequate amount of food, or may be going to the food bowl frequently but consuming only a very small amount. Making this distinction may change the diagnostic and/or treatment plan.

Medication adherence can be particularly challenging for cat owners. If the cat resists being medicated, the struggle can impact on the bond between the owner and cat. If not specifically asked about it in an empathetic and non-judgmental way, some owners may not tell the veterinarian that they are struggling to medicate, or that they are unable (or unwilling) to administer some medications. Such information will affect treatment recommendations going forward, and can encourage discussing alternatives to the current medications and formulations. Studies that have surveyed clients regarding their expectations for communication from veterinarians show that clients expect to receive the truth (*i.e.*, accurate information about what is going on with their pet) in an empathetic, compassionate, non-rushed, non-judgmental way (23-25). Similarly, another study found that clients were significantly more likely to adhere to surgical and dental care instructions when the veterinarian's recommendations were clear (26). It is therefore important not only to give clients clear options and recommendations, but to deliver that information in a way that promotes understanding and retention. For example, giving information in multiple forms (written, oral, charts/pictures) is preferred by clients (23,25). Pausing often to minimize "information overload", and asking for the client's feedback about the recommendations and the information shared, gives the clinician the opportunity to check that the owner has both heard and understood what is being said.

■ Conclusion

Treating cancer in a cat can be a roller-coaster ride with both good and bad days, and it is important to build trust from the beginning to ensure quality patient care, client care, and veterinarian self-care. Treating affected cats presents a series of challenges – from owner difficulty in medicating and transporting the pet to the veterinarian, to patients with refractory weight and muscle

loss – that require creativity, compassion, and clear communication from the veterinarian. As research into different aspects of feline oncology continues, more information about prognostic factors, supportive care, and more effective cytotoxic treatment strategies will emerge to help tackle current challenges and discover new ones.

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Adrenal tumors in cats and dogs



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KEY POINTS

- **Increased clinical expertise, combined with better availability of higher-resolution diagnostic imaging techniques, has resulted in adrenal neoplasia being diagnosed more frequently over the last few years.**
- **Cushing's disease is the most readily recognized clinical disease resulting from adrenal neoplasia, but various other tumors can arise in the adrenal gland and these can be functional or non-functional in nature.**
- **Abdominal ultrasound is the most frequent diagnostic modality used to assess the adrenal glands, although it cannot identify tumor type.**
- **The diagnostic and therapeutic approach should always be based on the clinical signs, laboratory abnormalities and characteristics of the adrenal mass, as some of these will be benign and non-functional in nature.**

■ Introduction

Adrenal tumors are relatively uncommon in small animals, with a reported incidence of approximately 0.17-0.76% in dogs and 0.03% in cats (1). However, increased clinical expertise, combined with better availability of higher-resolution diagnostic imaging techniques, has meant that these neoplasms are diagnosed more frequently in recent years, and this article reviews the more common adrenal tumors, their clinical signs and diagnostic tests.

Adrenal tumors can be surprisingly diverse. One study reviewed neoplastic adrenal lesions found in dogs and cats following complete necropsy evaluation over a 20-year period; in dogs, 41% were adrenocortical tumors, 32% were neuroendocrine medullary tumors and 27% were metastatic lesions. In cats, around 30% were adrenocortical neoplasms, 10% were medullary tumors and as many as 60% were metastatic lesions (1,2). The most common metastasis was lymphoma, although many other secondary tumors, such as carcinoma of the lung, stomach and pancreas, can develop in the adrenal glands.

A tumor may be identified during investigation for a suspected adrenal disease (hyperadrenocorticism, pheochromocytoma, hyperaldosteronism), but can also

be found incidentally whilst investigating an unrelated illness (1,3,4). It is important to note that non-neoplastic adrenal lesions (e.g., nodular hyperplasia, granulomas, hematomas, abscesses or cysts) can also occur (**Table 1**). If an adrenal mass or nodule has been identified, the diagnostic and therapeutic approach should always be based on the clinical signs, laboratory abnormalities and characteristics of the adrenal mass, as some of these lesions will be non-functional and benign in nature, with no clinical signs. In humans, the majority of incidental adrenal masses are benign and non-hypersecretory and do not warrant surgery, due to the attendant risk of morbidity and mortality. A similar approach is recommended in dogs and cats with adrenal masses, as not all will require therapeutic intervention.

■ Clinical signs

Adrenal neoplasia may be functional or non-functional in nature; functional tumors can secrete cortisol, sex hormones, aldosterone or catecholamines. The clinical signs can vary greatly and will depend on the tumor characteristics, including any excess secretion of hormone. **Table 2** offers a summary of the clinical and laboratory findings in animals with functional adrenal tumors.

Cortisol-secreting adrenocortical tumors cause adrenal-dependent hyperadrenocorticism (ADH) and are the most common functional neoplasms of the adrenal glands. Adenomas and carcinomas occur with approximately equal frequency in dogs, whereas in cats approximately 2/3 are adenomas. These tumors secrete cortisol autonomously, independent of pituitary ACTH control, resulting in the classical signs of Cushing's disease, which

Table 1. Differential diagnosis of adrenal gland masses/nodules.

Adrenal cortex	Adrenal medulla
Cortisol-secreting tumors	Pheochromocytoma
Aldosterone-secreting tumors	Neuroblastomas
Sex hormone-secreting tumors	Ganglioneuromas
Nodular hyperplasia	
Non-functional tumors	
Myelolipoma	
Metastatic lesions	Other type
Lymphoma	Granulomatous disease
Lung carcinoma	Cyst
Mammary carcinoma	Hematoma
Gastric carcinoma	Abscess
Pancreatic carcinoma	
Histiocytic sarcoma	
Melanoma	
Prostatic carcinoma	

include polyuria and polydipsia (PU/PD), polyphagia, lethargy, abdominal distension (a “potbellied” appearance), panting and muscle weakness. Obesity is also regularly seen. Many owners will consider the early signs as part of a pet's normal aging process. Dermatological signs (**Figure 1**) are also frequently noted, including bilateral truncal alopecia and comedones, pyoderma, and seborrhea. Cats in particular often have fragile, easily traumatized skin, along with alopecia, seborrhea and an unkempt hair coat (**Figure 2**), although, in fact, most cats will present due to uncontrolled diabetes mellitus (5,6).

Figure 1. Focal areas of alopecia and diffuse calcinosis cutis involving the dorsal aspect of the neck and trunk in a Rottweiler with adrenal-dependent hyperadrenocorticism.



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Figure 2. A 13-year-old domestic shorthair cat with hyperadrenocorticism. Note the bilateral alopecia and unkempt hair coat (**a**) and abdominal distension (**b**).



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Table 2. Clinical and laboratory findings in animals with functional adrenal tumors.

Hyperadrenocorticism (HAC)	Pheochromocytoma	Hyperaldosteronism	Sex hormone-secreting tumor
Common signs			
PU/PD Polyphagia Abdominal distension Panting Lethargy Weakness Alopecia Skin abnormalities Obesity	Lethargy Weakness Weight loss Anorexia Collapse Panting/tachypnea PU/PD	Weakness Polymyopathy Hypertension Ocular signs of hypertension PU/PD Lethargy	Similar to HAC
Less common signs			
Thin skin Calcinosis cutis Myotonia Neurological signs Reproductive abnormalities	Vomiting Diarrhea Coughing Epistaxis Seizures Paraparesis Rear limb edema	Polyphagia Muscle pain	Urine spraying Aggression Estrous behavior
Hematology findings			
Neutrophilia Lymphopenia Eosinopenia Monocytosis Thrombocytosis Polycythemia	Anemia Neutrophilia		
Biochemistry findings			
Increased ALT/ALP Hypercholesterolemia Hypertriglyceridemia Hyperglycemia Low urea	Azotemia Hypercholesterolemia Hypoalbuminemia Increased ALT/ALP	Hypokalemia Hypertatremia Metabolic alkalosis Hypophosphatemia Hypomagnesemia Increased ALP (dogs) Increased CK Azotemia	

Pheochromocytomas (PHEOs) are catecholamine-secreting neuroendocrine tumors arising from the adrenal medulla. They are rare in dogs and even more uncommon in cats, with only a few cases reported in the literature, and should always be considered as malignant. Epinephrine (E) and norepinephrine (NE) are the most commonly produced chemicals, with dopamine produced less frequently. The presenting signs are often non-specific and intermittent, but the owner may report lethargy, weakness or collapse, weight loss and anorexia, and PU/PD. Most of the signs are related to hypertension and arrhythmias caused by excess catecholamine release, which is often random in nature. There

may be no obvious clinical abnormality on examination; however, the mucosae can be hyperemic (as a result of flushing from catecholamine release) or pale (due to either vasoconstriction or hemorrhage). Tachypnea, tachyarrhythmia (**Figure 3**) and cardiac collapse can occur, and ascites may develop due to thromboembolism within the caudal vena cava and other vessels. Ophthalmological examination may reveal hypertensive retinal hemorrhages. Neurological findings are often non-specific but may indicate focal central nervous system lesions secondary to hemorrhage or metastasis. Hind limb paraparesis can develop secondary to vascular compromise or local tumor extension (3,7).

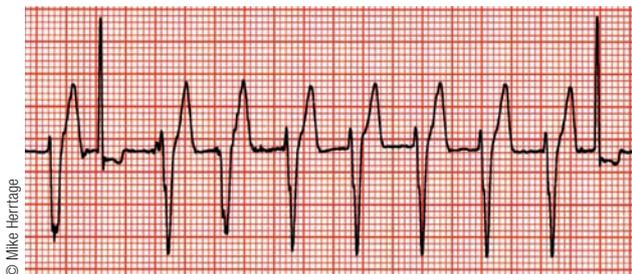
Aldosterone-secreting tumors (primary hyperaldosteronism or Conn's syndrome) are also infrequent in small animals, but are less rare in cats than in dogs. Hyperaldosteronism is caused by a uni- or bilateral functional tumor within the zona glomerulosa of the adrenal cortex, with both adenomas and carcinomas reported. The mineralocorticoid excess results in sodium and water retention by the kidneys, along with increased potassium excretion; the resulting systemic arterial hypertension and hypokalemia lead to the main clinical signs, which can include weakness (sometimes episodic), ventroflexion of the neck (**Figure 4**), PU/PD, lethargy, depression, stiffness, and muscle pain (8,9).

Sex hormone-secreting tumors of the adrenal cortex can produce excessive amounts of several sex hormones, including progestogens, estrogens and androgens. Progesterone has potentially direct glucocorticoid effects, and high concentrations may also result in clinical signs of hypercortisolemia by displacing cortisol from cortisol-binding protein. Some reports record dogs with sex hormone-secreting tumors that presented with signs similar to hyperadrenocorticism (HAC) despite suppressed serum cortisol concentrations (10-12). There are also a few reports of neutered cats with adrenal neoplasia that develop signs typically associated with unneutered animals. These include urine spraying with strong odor, detectable spines in the penis, aggressive behavior (males and females), and cyclic (intermittent) estrous behavior (posturing, vulva licking, vocalizing, rolling on the ground and head rubbing) (13,14).

Figure 4. Hypokalemic polymyopathy in a cat with primary hyperaldosteronism. Note the cervical ventroflexion and plantigrade position.



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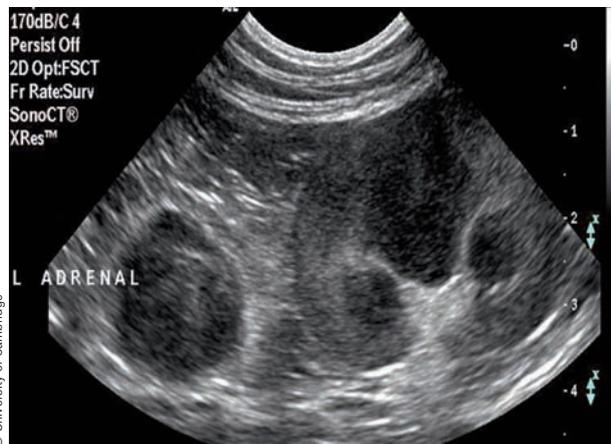
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Figure 3. Electrocardiography of a dog with ventricular tachycardia. Clinical signs in dogs with pheochromocytoma, such as lethargy, intermittent weakness and collapse, are usually related to hypertension and arrhythmias caused by catecholamine secretion.

■ Diagnostic imaging

Ultrasound is the most frequent diagnostic modality used to assess the adrenal glands (**Figure 5**). The normal adrenal glands are uniformly hypoechoic, flattened, bi-lobed organs located craniomedial to the kidneys. The most reliable indicator for adrenal size is the diameter (thickness) with a proposed normal maximal diameter of 0.74 cm for dogs; however, there is an overlap between normal and hyperplastic adrenal gland measurements, and up to 9% of dogs with non-adrenal disease can have adrenal enlargement based on this value. Interpretation of gland size should therefore always be based on the clinical signs and laboratory abnormalities. If an adrenal mass has been detected, the contralateral adrenal gland should always be evaluated. In cases of ADH, the excess cortisol secreted suppresses endogenous ACTH secretion, resulting in atrophy of the

Figure 5. Ultrasonographic image of the left adrenal gland of a 13-year-old domestic shorthair cat with primary hyperaldosteronism due to a unilateral adrenocortical adenoma.



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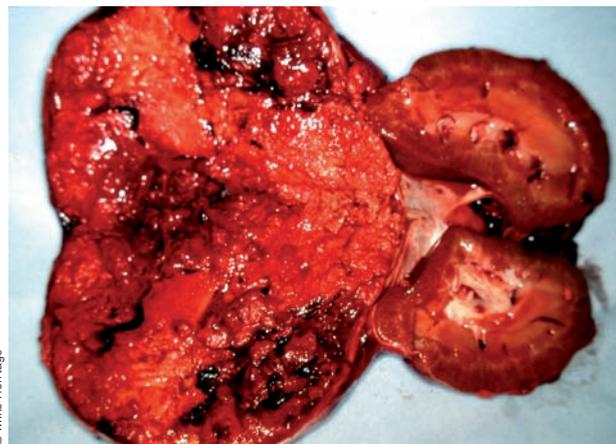
contralateral adrenal cortex. If a dog has an adrenal mass and the contralateral gland is small, ADH is therefore the most likely diagnosis, and PHEO or other causes less likely, although some animals with ADH have a normal-sized contralateral adrenal gland. Although rare, it is also important to note that bilateral adrenal tumors can occur and concurrent ADH and PHEO, or PHEO and aldosteronoma have been reported (5,15,16).

Adrenal tumors cannot be typed by ultrasonography, but carcinomas tend to be larger than adenomas, and some studies report that adrenal masses > 20 mm are significantly related to carcinomas. One report noted that incidental malignant adrenal tumors ranged in size from 20-46 mm, whereas all benign lesions had a maximum dimension < 20 mm. However, small tumors can also be malignant, and large non-neoplastic adrenal masses cannot be differentiated from tumor by ultrasonography (4,15).

Ultrasound is also useful in detecting invasion of surrounding structures, most commonly adjacent blood vessels and the kidneys (**Figure 6**). Direct extension into the spinal canal has also been described in cases of PHEO (17). Although ultrasonography is a fast and easy tool to detect vascular invasion, it is not always possible to differentiate vascular involvement from compression or a blood clot (15).

Radiography may help to identify adrenal masses, especially if they are calcified. Unilateral mineralization in the region of an adrenal gland also suggests the possibility of a tumor, although offers no differentiation between benign and malignant growths. Thoracic radiography is highly recommended whenever an adrenal mass is discovered; pulmonary metastasis can develop in around 10% of HAC and PHEO cases, and also with some non-functional adrenal masses (4,5).

Advanced imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI) can be invaluable to help delineate the size of the mass, its location, and any invasion of adjacent structures (with 92% sensitivity and 100% specificity in some reports). Metastasis to various sites – including local lymph nodes, viscera, bones, heart and spinal canal – may be identified (4). More specific techniques, such as nuclear scintigraphy utilizing radioisotopes, have been used in human medicine to help identify neuroendocrine tumors, but these methods are in the early stages in the veterinary field (18).



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Figure 6. Post-mortem examination of a dog with hyperadrenocorticism revealed an adrenocortical carcinoma invading the kidney.

■ Cytology

Cytology can be used to distinguish between cortical and medullary neoplasia, with a reported accuracy of 90-100%, but is not reliable in distinguishing benign from malignant neoplasms; however, it can be useful to identify metastatic lesions in the adrenal glands. In human medicine, cytology is not recommended if there is suspicion of PHEO, as sampling can precipitate potentially severe side effects such as pain, uncontrolled hemorrhage and a severe hypertensive crisis due to sudden release of catecholamines, or even death (19).

■ Specific diagnostic tests

Adrenal-dependent hyperadrenocorticism

The preferred test for ADH is the low-dose dexamethasone suppression test (LDDST). It is the most sensitive test for diagnosis of HAC if an adrenal mass has been identified, and will identify virtually all dogs with cortisol-secreting adrenal tumors. However, the test can have low specificity, especially when measured in a population of sick dogs. Dexamethasone (0.01 mg/kg IV) is administered after a sample for basal cortisol is taken, with a repeat sample taken 8 hours later; note that in cats a ten-fold higher dose of dexamethasone (*i.e.*, 0.1 mg/kg IV) is required (6). If the dexamethasone fails to adequately suppress circulating cortisol concentrations, and there are compatible clinical signs, this is consistent with a diagnosis of HAC. A blood sample taken at an intermediate time point (*e.g.*, 3 or 4 hours) will only help if pituitary-dependent hyperadrenocorticism (PDH) is suspected; suppressed or near-normal plasma cortisol levels at this stage, or marked suppression (> 50% of baseline concentrations) followed by a rise in cortisol

concentration 8 hours after dexamethasone administration, allows a diagnosis of PDH to be made. Failure to suppress cortisol at an intermediate time point will however happen in virtually all cases of ADH, as well as around 65% of PDH cases (3,5).

An alternative method, the ACTH stimulation test, is based on the fact that animals with HAC have the capacity to secrete excessive amounts of cortisol. The test involves administration of synthetic ACTH (5 µg/kg IV or IM, although in cats IV administration is recommended) with samples for cortisol levels taken before and one hour after injection. Affected animals tend to have an exaggerated response to the test, but the sensitivity is only 60% in dogs with ADH, so a negative result does not exclude the diagnosis (5).

A combined LDDST and ACTH stimulation test may be considered, especially in cats, but it offers no advantage over separate LDDST and ACTH tests and can be more difficult to interpret. Again, a blood sample for basal serum cortisol is collected and dexamethasone administered at 0.1 mg/kg IV, with a second blood sample collected 4 hours later. Immediately after this, synthetic ACTH is administered (5 µg/kg or 125 µg IV) and another sample collected for cortisol determination an hour later (*i.e.*, 5 hours after starting the test). Almost all cats with HAC will fail to show serum cortisol suppression after dexamethasone administration, and about 50% have a clearly exaggerated response to ACTH administration (6).

Basal endogenous ACTH concentrations are of no value in diagnosing HAC for two reasons; ACTH has an episodic secretion in healthy animals, and there is an overlap in ACTH levels when comparing normal animals to dogs with HAC. However, animals with ADH usually have undetectable endogenous ACTH concentrations. The main limitation is that careful sample handling is essential, and the clinician must explicitly follow the instructions from the testing laboratory (5,6).

Pheochromocytoma

Definitive diagnosis of PHEO is made on histopathology. However, in human medicine, the standard diagnostic tests for PHEO require detection of increased concentrations of catecholamines (E, NE, and their breakdown products metanephrine [MN] and normetanephrine [NMN]) in urine collected over a 24-h period, or in plasma. The concentrations of urine catecholamines and its metabolites-to-creatinine ratios have been evaluated in

dogs with PHEOs using a single morning urine sample. Affected dogs have a significant increase in E, NE and NMN:creatinine ratios when compared with healthy dogs, and the least overlap is seen with the NMN:creatinine ratio. When comparing dogs with PHEO and dogs with HAC, only the NMN:creatinine ratio was significantly higher in dogs with PHEOs. Using a cut-off value of 4 times the highest NMN:creatinine ratio for healthy dogs (with a reported range of 14.0-91.0), the specificity is nearly 100%, although the sensitivity is low, so some dogs with PHEOs will be missed using this value. The results are less reliable using serum catecholamine levels or the MN:creatinine ratio, as there is overlap between normal and affected animals, and again sample handling is critical (20).

A recent study evaluated the plasma-free MN and NMN concentrations in dogs with PHEOs, reporting that fNMN concentrations are significantly higher in affected dogs when compared to healthy dogs, dogs with HAC, and dogs with non-adrenal illness. They also found that dogs with PHEOs have a high concentration of fMN in comparison with healthy dogs and dogs with HAC, but the levels did not differ from dogs with non-adrenal illness (21).

Primary hyperaldosteronism

Plasma aldosterone concentration (PAC) is widely available and is the initial test for primary hyperaldosteronism, although the clinician should observe the reference ranges provided by the specific laboratory. Affected animals will have a characteristically high PAC, but this should be interpreted in combination with serum potassium levels. As hypokalemia is a predominant stimulus for lowering PAC, the presence of hypokalemia with moderately elevated PAC is regarded as significant. A high PAC in a cat with hypertension, hypokalemia and an adrenal mass is diagnostic for primary hyperaldosteronism. However, remember that elevated PAC is not pathognomonic for primary hyperaldosteronism, and anything that stimulates the renin-angiotensin-aldosterone system (RAAS), such as chronic renal failure and congestive heart failure, can also increase PAC, *i.e.*, secondary hyperaldosteronism (8,9).

The ratio between PAC and plasma renin activity (PRA), known as the aldosterone-to-renin ratio (ARR), is a better screening test than PAC alone for the reasons stated above. In primary hyperaldosteronism, PAC is characteristically high and the PRA is undetectably low. The combination of a high-normal or elevated PAC and a

low PRA indicates persistent aldosterone synthesis in the presence of little or no stimulation by the RAAS. Many veterinary laboratories do not perform PRA, but the human laboratory assay is suitable for use in cats. In humans, cessation of any anti-hypertensive medication is recommended at least two weeks before diagnosis of hyperaldosteronism is attempted, but this could be potentially harmful in hypertensive cats (8,9,22).

Although the ARR is currently the gold standard when screening for feline primary hyperaldosteronism, it has some limitations. A large blood sample (up to 4 mL) is required and it should be separated immediately before freezing for storage and transport. False-negative results are still possible because aldosterone levels will fluctuate during the day, and false positives are also possible, as renin is not the only regulator of aldosterone secretion (8,9,22).

A fludrocortisone test can also be useful for diagnosis of primary hyperaldosteronism. The test is performed as follows: a first morning urine sample is collected by the owner to determine the basal urinary aldosterone-to-creatinine ratio (UACR). Fludrocortisone acetate is then administered (0.05 mg/kg Q12h PO) for 4 days and a second urine sample collected the morning after the last dose is given. A basal UACR $< 7.5 \times 10^{-9}$ excludes primary hyperaldosteronism, whilst a value $> 46.5 \times 10^{-9}$ confirms it. In cats with primary hyperaldosteronism, fludrocortisone administration induces $< 50\%$ suppression of the UACR (22).

Sex hormone-secreting tumors

Elevated sex hormone concentrations (*i.e.*, androstenedione, estradiol, progesterone, and 17-hydroxyprogesterone (17OHP)) have been reported in dogs with adrenal tumors. Overproduction can be identified by an ACTH stimulation test, measuring serum sex hormone levels before and after ACTH. However, these hormones are also commonly increased (pre- and/or post-ACTH) in dogs with pituitary-dependent HAC; this should therefore always be ruled out before testing for sex hormone excess (11,12).

One study reported two dogs with adrenal tumors which had clinical signs of HAC despite markedly suppressed serum cortisol concentrations on the ACTH stimulation test and a LDDST which did not support HAC. One tumor secreted progesterone, 17OHP, testosterone, and dehydroepiandrosterone, while the other secreted progesterone, 17OHP, androstenedione, and

estradiol. In another study that included non-cortisol-secreting tumors, 4/6 dogs secreted 17OHP, 4/6 secreted androstenedione and 1/6 secreted progesterone (10,12).

Non-secreting adrenal tumors

As noted above, in humans, the majority of adrenal masses discovered incidentally are benign and non-hypersecretory. To be categorized as such, imaging of the adrenal mass is routinely performed, along with appropriate endocrine tests.

Adrenalectomy in these cases is only indicated if the mass is found to be functional, or if it has a diameter greater than 4-6 cm, or where there is vascular invasion. If a patient does not meet these criteria, due to the low risk of developing malignancy and the increased morbidity and mortality risks from surgery, resection of the mass is not indicated and diagnostic imaging is repeated every 3-6 months for 2-5 years.

In animals, a diagnosis of ADH can usually be easily established using the tests described above; however, diagnosis of PHEO or hyperaldosteronism can sometimes be challenging, as the necessary endocrine function tests are not always readily available. One study evaluated the clinical features and prognosis associated with non-cortisol-secreting adrenal gland masses, a common situation in general practice, and noted that such masses tend to present in older dogs, with a low (5%) frequency of radiological evidence of pulmonary metastases at diagnosis.

The adrenal masses were found on investigation or follow-up of other non-related diseases in 50% of cases, during evaluation for PU/PD (35%), increased liver enzymes (10%) or lethargy (5%). The vast majority of the masses (80%) remained stable over the course of a year, with a median survival time without surgical management of 18 months. Factors inversely associated with survival were body weight, radiological metastases at diagnosis, and tumor size. The authors also suggested adrenalectomy as a reasonable option when any adrenal mass is greater than 20 mm, as these are significantly related to carcinomas (3,4).

Conclusions

There is an increased frequency in the diagnosis of adrenal neoplasms in recent years. The clinical signs in affected animals vary greatly, depending on the hormones secreted (if any) by the tumor and its characteristics, and

the history and physical examination is crucial to determine which diagnostic tests are most appropriate in each case. The veterinarian should also bear in mind that no endocrine function test is 100% sensitive or specific.

Diagnostic imaging should include abdominal ultrasound – to determine the tumor characteristics and the potential for invasion of surrounding tissues – and thoracic imaging, to investigate for radiologically evident metastasis.

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Epidemiology of canine mast cell tumors



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■ Introduction

Mast cell tumors (MCT) or mastocytomas are the most common skin tumor of the dog (1), but an increased risk has been reported in several breeds, including Boxers, Boston Terriers, Labrador and Golden Retrievers, and Bulldogs (1-2), and several studies have also reported an association between the risk of MCT and neutering (gonadectomy), including age at neutering (2-6). This study reviews some basic variables regarding canine MCT, including breed and age prevalence, and the gender/neuter status of affected animals.

■ Methods of analysis

The records of all dogs presented at Banfield Pet Hospital from June 1996 through December 2015 were screened to identify those with MCT, with a diagnosis based on in-house needle biopsy and/or histopathology and/or diagnosis by an external specialist. Basic descriptive statistics on signalment (age at diagnosis, gender, neuter status, and age at neutering) and prevalence estimates were calculated. Age at neutering was available for animals where the surgical procedure was performed at a Banfield hospital, but this parameter could not be determined if the surgery had been performed elsewhere. Overall prevalence, and the top affected breeds, were determined for 2015, with only commonly seen breeds included.

■ Results

During the selected period, over 12.5 million dogs were seen at Banfield hospitals, of which around 60% were gonadectomized and 40% were entire – only a small number of dogs had an unknown spay/castrate status. MCT was diagnosed in 19,470 animals during this period, with the tumor being less prevalent in entire dogs than in gonadectomized animals (**Table 1**). Only a slight

difference in age at diagnosis was seen when comparing castrated and intact males, while the difference was more noticeable in females, with spayed females diagnosed approximately one year later in life.

Age at neutering was available for around 27% of the gonadectomized dogs seen in the period studied, with a median age of 0.5 years in both genders. Age at neutering was available for less than 25% of the gonadectomized MCT cases, with a median age at surgery of 0.5 years for females and 0.6 years for males.

In 2015, 2,556 MCT cases were seen at Banfield, an overall prevalence of 13.5 cases per 10,000 dogs, with the highest occurrence in spayed females, followed by castrated males (**Table 2**). The most commonly affected breeds were calculated (**Table 3**), with Boxers (81.6 per 10,000) and Pugs (47.6 per 10,000) being the two most affected.

■ Discussion

Although MCT is the most common canine skin tumor, the disease prevalence in the population is relatively low (3-6). A recent UK-based study examined canine MCT prevalence and found approximately 27 per 10,000 dogs were affected (2) (about double the prevalence estimated from this review) and the at-risk breeds identified here are similar to other studies (1-4).

These results support the notion that neutering is associated with increased risk of MCT. In addition, the results suggest that MCT is diagnosed at a later age if the animal has been neutered. Future research into risk factors for MCT should employ multivariate models that control for factors such as age, sex, and neuter status, and with the increased interest in age at neutering as a risk factor

Table 1. Descriptive statistics of canine mast cell tumors (MCT).

Gender	Total number of dogs seen	Number of MCT cases	Prevalence (per 10,000)	Median age in years at diagnosis
Intact female	2,222,301	803	3.6	7.1
Intact male	2,774,144	1,273	4.6	7.3
Spayed female	3,816,231	9,778	25.6	8.1
Neutered male	3,711,838	7,616	20.5	7.5
Unknown status	15,254	0	0	0
Total	12,539,768	19,470	15.5	7.8

Table 2. Canine MCT prevalence, by gender and neuter status, in 2015.

Gender	Total number of dogs seen	Number of MCT cases	Prevalence (per 10,000)
Intact female	329,016	139	4.2
Intact male	240,932	100	4.2
Spayed female	938,562	1,346	14.3
Castrated male	950,926	971	10.2
Unknown	393	0	0.0
Total	1,889,881	2,556	13.5

Table 3. Top canine breeds with MCT in 2015.

Breed	Total number of dogs seen	% of all dogs seen	Number (%) of MCT cases	Prevalence (per 10,000)	Lower limit, 95% CI (per 10,000)	Upper limit, 95% CI (per 10,000)
Boxer	44,864	2.4	366 (14.3)	81.6	73.3	89.9
Pug	29,818	1.6	142 (5.6)	47.6	39.8	55.4
French Bulldog	10,360	0.5	36 (1.4)	34.7	23.4	46.1
Boston Terrier	20,975	0.6	66 (1.4)	31.5	23.9	39.0
American Bulldog	11,239	1.1	35 (2.6)	31.1	20.8	41.4
Pit Bull Terrier	98,079	5.2	204 (8.0)	20.8	17.9	23.7
Labrador Retriever	115,005	6.1	226 (8.8)	19.7	17.1	22.2
Miniature Pinscher	17,460	0.9	26 (1.0)	14.9	9.2	20.6
Golden Retriever	42,588	2.3	60 (2.3)	14.1	10.5	17.7
Jack Russell Terrier	24,123	1.3	30 (1.2)	12.4	8.0	16.9

for both development of MCT and other diseases, it would be useful to also include this variable in future studies. Evidence from population-based research can

enhance our understanding of risk for this important canine skin tumor, and ultimately enable better communication with pet owners.

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CUTANEOUS TUMORS

The essentials for successful surgery



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■ Introduction

Surgery is the oldest technique for cancer therapy and is still the most important strategy when treating a localized cancer. When clearly indicated, carefully planned and correctly executed, surgery is the treatment modality which gives the patient the highest chance for a cure (1). However, before deciding that surgery is the most appropriate treatment, suitable diagnostic measures have to be implemented to evaluate the nature and extent of the tumor (2,3), and a tissue sample (obtained by

the least invasive method) is critical. In most cases, a cytologic fine-needle aspiration biopsy or a histologic sample via biopsy needle is sufficient to obtain a diagnosis. Excisional biopsy (*i.e.*, “complete” removal of a neoplasia without prior knowledge of the tumor type) is only indicated in those (few) cases where the extent of surgery (width and depth of the resection) is not influenced by the type of neoplasia. Once a cancer diagnosis has been established, a thorough work-up is performed to determine the extent of the disease. This work-up, or staging, is directed by the expected biological behavior of the tumor, and includes determining the degree to which the tumor has extended into the tissues, searching for metastatic spread to lymph nodes, lungs or other organs, and examining the patient for paraneoplastic signs (**Figure 1**) (4). Only once a satisfactory diagnosis and staging has been achieved is it possible to plan a surgical therapy and discuss it with the owners.

In some cases, a complete evaluation of the tumor is only possible by excisional biopsy; canine mammary tumors are a classic example of the exception to the rule that pre-surgical biopsy is essential. With these tumors, a pre-operative minimal biopsy is neither sensitive nor specific enough to define tumor malignancy and grade, so excisional biopsy must be performed and the entire tumor submitted for pathologic evaluation.

It is vital to emphasize that ignorance of the tumor type and stage can lead to sub-optimal surgery, with the result that a potentially curable cancer can become incurable or even fatal for the patient. Most mistakes in the field of tumor surgery are made before the scalpel is actually in the surgeon’s hand!

KEY POINTS

- **Once a cutaneous cancer diagnosis has been established, a thorough work-up of the patient is required to evaluate the extent of the disease.**
- **Surgery may aim to be curative, to achieve cyto-reduction, or be palliative in nature, and the goal should be defined before the operation and discussed with the owner.**
- **When planning a surgical intervention, the type of tumor will determine the extent of the resection; modern diagnostic imaging techniques can assist with the planning process.**
- **There are various options for closure and reconstruction of the surgical defect; more sophisticated techniques are required if the resection is large and/or the tumor is at a critical anatomical site.**



Figure 1. An ulcerated grade 2 mast cell tumor on a Doberman's pinna. Staging revealed a large metastasis in the ipsilateral prescapular lymph node (arrowed) which would influence the surgical approach and the prognosis for the patient.

■ Planning the operation

In a non-metastatic resectable solid tumor, surgery is usually the only therapy required and is frequently curative. If the tumor cannot be adequately resected, has already metastasized at the time of diagnosis, or has a high potential for late metastasis, surgery is frequently combined with additional “adjuvant” treatments such as radiation or chemotherapy (1). In such situations, surgery is only a part of a multimodality approach, and the entire treatment plan, including all adjuvant therapies, should be discussed with the owner before surgery is undertaken. In some cases, surgical intervention is not

indicated or (due to the advanced stage of the illness) is no longer an option, and a “heroic” attempt to “help” the patient surgically may only lead to a decreased quality of life. Bear in mind that extensive surgery is difficult to justify if the chances for local tumor recurrence remain similar should more conservative resection techniques be employed, or if the patient may ultimately die from metastatic disease. In human medicine, there is considerable debate concerning the balance between the surgical aggression needed for effective local tumor control, patient morbidity, and the risk of death from tumor metastasis. Any potential therapy for advanced cancer cases should always be weighed critically against the expected gain for the patient.

The pre-operative planning includes defining the goal of the therapy, deciding on the width and depth of the resection, and considering reconstruction of the surgical defect (2,3). There are three possible aims for surgery, namely a cure, cyto-reduction, or palliation, and this should be defined before the operation and discussed with the owner to avoid the danger of false hope.

I) Curative resection (*i.e.*, complete surgical removal) is usually possible only for circumscribed tumors without metastasis, and, in general, the first operation has the highest chance of success. Although understandable, the desire to use a “low-risk” quick, conservative surgical approach often leads to the opposite result. The impact on the patient is in any case increased when a recurrence of the tumor requires further, more extensive surgical intervention (**Figure 2**). Frequently, however, a curative resection on “second try” is no longer possible.

Figure 2. (a) An incomplete resection of a soft tissue sarcoma in a dog resulting in tumor recurrence at the surgical site. In this location, a correctly performed first surgery should have been curative. **(b)** For the second resection to be curative, extremely wide margins have to be taken around the entire previous scar.



II) A cytoreductive operation is defined as incomplete removal of a tumor, with macroscopic or microscopic tumor remnants left in place. It is, however, only sensible and worthwhile in terms of prolonging the patient's life if it is accompanied by effective adjuvant therapy (**Figure 3**). For invasive tumors (e.g., sarcomas, mast cell tumors) the microscopic extent of the tumor is often underestimated, so that even when a curative operation is intended, only a cytoreduction is achieved due to remaining microscopic neoplastic tissue.

III) The intention behind **palliative surgery** is that the operation should primarily allow improvement in the patient's quality of life (reduced pain and improved function), with the secondary aim of prolonging the animal's actual survival time (e.g., through delaying the necessity of euthanasia) (**Figure 4**) (5).

When planning the surgical intervention, the nature of the tumor, or rather the expected extent of its invasive growth, define the extent of the resection. In regions with complex anatomy (e.g., the head), modern diagnostic imaging techniques such as CT and MRI are favored above radiography for planning purposes (6). Fundamental considerations for the surgeon when planning an operation are the extent of the resection (marginal, wide or radical), and the measures necessary to reconstruct the surgical defect. An extensive operation site must therefore be adequately prepared so that resection, reconstruction and closure of the wound can be achieved aseptically.

■ Carrying out the resection

Benign tumors are usually cured by an intracapsular

Figure 3. A subcutaneous soft tissue sarcoma in a mixed breed dog. Due to the lack of skin and the inability to obtain tumor-free deep margins in this location, the preferred strategy in this case will be surgical cytoreduction followed by a “curative” course of radiation therapy.



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excision or, if there is no capsule, with a safety margin of a few millimeters (“marginal resection”). In subcutaneous benign neoplasias (e.g., lipomas), it is not necessary to resect the covering skin; rather, the tumor is usually approached through a skin incision midline over the mass.

The margin of safety around a malignant neoplasm depends on the type and grade of the tumor, its stage, and the anatomic location (2,7). Authorities will often make a generalized statement such as “always take 3-cm margins in all directions” but these are of little practical value; such extensive margins are not always indicated nor, depending on the tumor location, are they always possible. In some malignant tumors, a 1-cm margin from the palpable tumor is quite adequate for a curative resection, while for others the minimum margin should be kept at 3 cm or even more. In addition, there is also a difference in the peripheral margin and the deep margin required for adequate tumor resection. As a general rule, the dermis covering subcutaneous malignant tumors should be resected *en bloc* with the tumor.

As a first step when aiming for a curative resection of a malignant tumor, the primary anatomic compartment in which the neoplasia resides should be defined. In a skin tumor, this is the dermis and/or the subcutaneous tissue, and from this compartment the neoplasia will extend in a three-dimensional fashion. This initially manifests as microscopic, non-palpable invasion beyond the palpable tumor margins. As this invasion progresses, visible macroscopic extension into neighboring tissues will follow, leading to changes in the texture of the overlying skin and reduced mobility of underlying tissue (**Figure 5a**).

Figure 4. A large ulcerative injection site sarcoma on the lateral aspect of a cat's neck. Tumor resection in this situation is palliative; removal of the mass will improve the patient's quality of life.



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Figure 5. A large grade 2 mast cell tumor on the thoracic wall of a West Highland White Terrier. Note the structural changes to the skin, indicating infiltration of the dermis (a). Due to the size of the tumor and its obvious capacity for invasion a 3-cm peripheral margin has been chosen at resection (b). The deep margin underneath the tumor is defined by the latissimus dorsi muscle, which serves as a potent barrier against deep invasion. The muscle is resected *en bloc* together with the tumor. No functional deficits are to be expected from this procedure, and primary wound closure is possible due to ample loose skin over the thorax (c).

Lateral (peripheral) margins

Loose subcutaneous tissue does not pose much of a barrier to tumor invasion, which results in current recommendations regarding the lateral distance that should be kept from the palpable margin of the tumor. This constitutes the lateral (peripheral) excision margin. For malignant tumor types with a low tendency for invasive growth (such as canine subcutaneous grade 1 soft tissue sarcomas or low-grade mast cell tumors), a peripheral margin of 1-2 cm is adequate. Some authors advocate that, for low-grade tumors, the minimum peripheral margin should equal the diameter of the tumor (e.g., 2-cm margin for a 2-cm tumor, etc.) (Figure 5b).

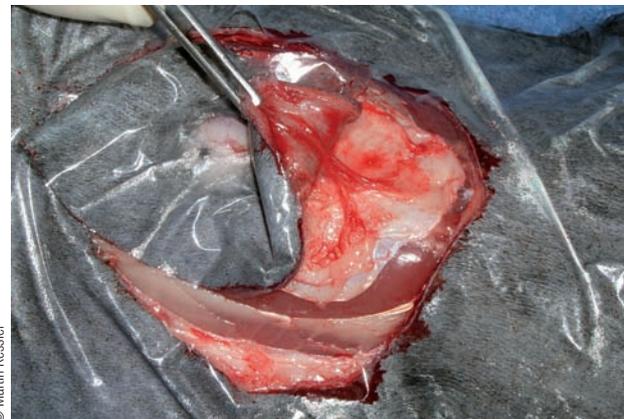
Highly infiltrative tumors (such as feline injection site sarcomas, canine high-grade soft tissue sarcomas or high-grade mast cell tumors) should be removed with a lateral margin of at least 3 cm, even if small and apparently circumscribed. For feline injection site sarcomas, which are considered the most invasive subcutaneous tumors in small animals, up to 5-cm lateral margins have been recommended. Such proposals have to be considered the minimum distance for the peripheral margin from the tumor, and can be increased if anatomically possible at the surgeon's discretion to maximize the level of safety (2,8-11).

Deep resection margin

Since tumors are three-dimensional growths, the depth of the excision must also allow for an appropriate safety margin. The excision depth is determined by the anatomic properties of the underlying tissue and thus by the competence of the barrier that the tumor encounters at the deep margin (2,8-11). Fascias and muscle layers provide an effective initial barrier against tumor invasion,

and the stronger the fascia the less the tumor is able to penetrate. For invasive tumors, it is necessary to at least remove the underlying fascia, even if the tumor clinically appears encapsulated and movable. Higher-grade sarcomas or mast cell tumors have a tendency to form a "pseudo capsule" from compressed tumor cells, which may give a false impression of an encapsulated benign growth. If the tumor is palpably connected to the underlying tissue, removal down to the second layer of muscle or fascia, and in some cases resection of the entire depth of the chest or abdominal wall, is necessary. Muscles that extend across the resection boundary, as well as nerves or blood vessels that enter the resection field, should be cut at the measured border of the surgical

Figure 6. Curative tumor surgery. Note the wide lateral margins and the resection of the fascia for adequate deep margins. Since deep infiltration of the tumor is limited in this case by a strong fascia, it is sufficient to resect only the fascia and not the underlying muscle, as the fascia defines the anatomic border of the compartment. By taking the fascia *en bloc* with the tumor a clean resection is possible, despite the fact that the actual deep margin is only a few millimeters.



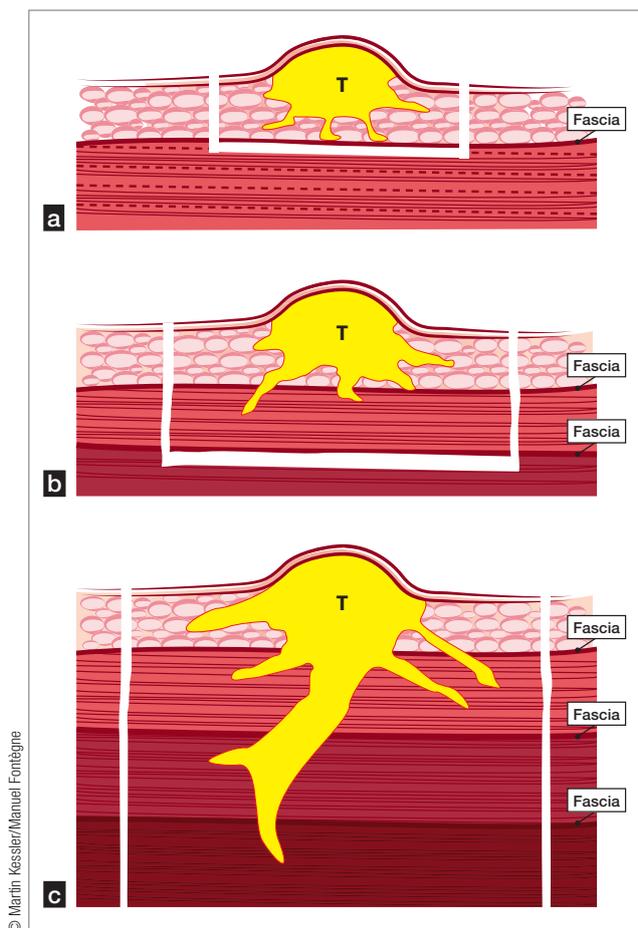


Figure 7. Tumor resection for different types of invasive tumors over the abdominal wall.

(a) Correct resection for a grade 1 malignant tumor. The lateral margins correspond to the tumor diameter. The incision is straight down and runs underneath the fascia.

(b) Correct resection for a grade 2 malignant tumor. The lateral margins are wider than in **(a)**, the deep margin includes the external abdominal oblique muscle.

(c) Correct resection for a grade 3 malignant tumor. The lateral margins are at least 3 cm, the deep margin includes full thickness of the abdominal wall.

margin (**Figure 5c**). All biopsy tracts, plus scars from any previous operations, must be removed along with the tumor (12,13). With this “compartmental” method of resection, where surgery penetrates into the next body compartment, the chances of the patient remaining free of tumor recurrence are much higher (**Figure 6**).

Any interference and surgical manipulation of neoplastic tissue should be kept to a minimum whenever possible, and it is contraindicated to cut into the tumor; neoplastic

tissue should be considered as “contaminated” and handled as such. The use of holding sutures and instruments in the tumor-free margins is preferable to manual manipulation. Careful hemostasis is important to provide optimal visualization during surgery and to minimize post-operative complications.

Curative surgery can only be successful if a clean resection is achieved in all directions of infiltration (*i.e.*, lateral and deep) (**Figure 7**). Obtaining sufficient lateral margins whilst leaving the fascia in place results in an inadequate deep resection and thus remains a cytoreductive surgery at best. This is especially true for tumors in critical locations such as the distal limbs, where the width and depth of the resection is limited by the lack of skin, and especially by the lack of a competent fascia preventing deep invasion. If satisfactory lateral or deep safety margins cannot be achieved, the entire operation should be planned as a cytoreductive procedure and elaborate measures to close the defect (such as flaps, grafts and drains) should be avoided. Cytoreductive surgery results in a less extensive resection and a shorter scar, and requires a smaller radiation field when adjuvant therapy starts. In general, radiation should commence as soon as possible after wound healing.

■ Surgical reconstruction

The degree of sophistication required to close a surgical defect is directly related to the size of the resection and the location of the tumor (14). The ample amount and mobility of the skin on the neck, chest wall, trunk and proximal limbs helps closure of even large skin defects, and surgery in these areas can usually be completed by primary wound closure, simply by undermining adjacent skin. However, where only limited skin is available (*e.g.*, distal limbs and head) reconstructive techniques are frequently necessary, and, in many cases, the most demanding part of the surgery is not the removal of the tumor itself, but reconstruction of the ensuing defect. Thorough knowledge of reconstructive techniques is of great importance for tumor surgeons. In small animals, the anatomy of the skin and its blood supply allows for large skin flaps to be elevated from the underlying tissue and to be transposed into new locations in order to fill skin defects.

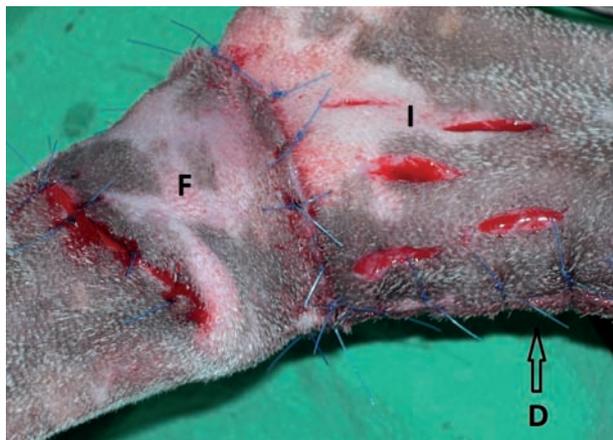
Random skin flaps

The blood supply of these skin flaps is based on the direct cutaneous arteries and veins of the subdermal plexus. On the trunk, the neck and the proximal limbs this blood supply lies in the hypodermis at the level of the panniculus



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Figure 8. Preparation of a random skin flap. When manipulating a flap, stay sutures rather than “grasping” instruments can be used to minimize trauma along the free edge of the flap. Note the “random” cutaneous vessel that forms the subdermal plexus (arrow).



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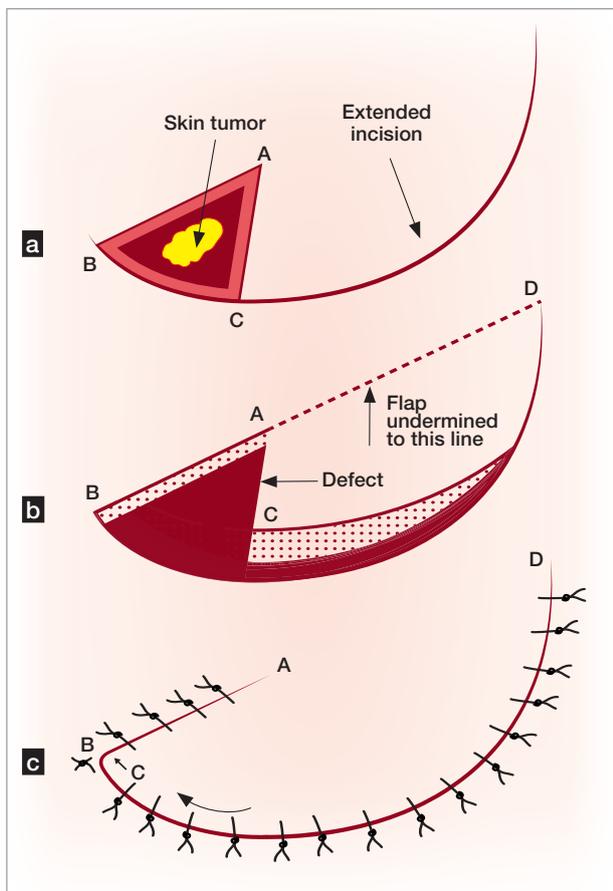
Figure 9. A transposition flap to cover a resection defect distal to the hock in a dog. The flap (F) has been turned 90° into the defect and the donor bed (D) has been closed by using small relieving incisions (I).

muscle. On the distal limbs, where there is no panniculus muscle, it can be found deep to the dermis at the level of the limb fascia. Since these indiscriminate blood vessels are utilized to support the detached skin area, such flaps are referred to as “random” skin flaps (**Figure 8**). Depending on the shape of the flap and orientation of reattachment, several types of random flaps are possible.

A simple advancement flap can be used to cover rectangular or round defects in locations where sufficient skin is available only in one direction; after mobilization, the flap is extended into the defect without any rotation. Typical examples would be defects under the chin (advancement flap rostral from the ventral neck area) or defects over the origin of the tail (advancement flap from the caudal dorsum). If sufficient skin is available on both sides of a (rectangular or round) defect, a double advancement flap (H-plasty) can be used, whereby two opposing advancement flaps are prepared and drawn together to cover a central defect.

If a rectangular flap is rotated by up to 180° into a defect, it is called a transposition flap. Rotations beyond 90° are unusual, because the flap will lose considerable length when rotated (**Figure 9**). Transposition flaps are used to cover skin areas ventral to the eye (using skin from the cranial and lateral neck region), perineal area (skin from the dorsum) and the head (skin from the dorsal neck).

A rotation flap is especially useful for covering triangular defects (**Figure 10**), whereby a semicircular skin area is



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Figure 10. A rotation flap is especially useful for covering triangular defects. When planning this reconstruction, the triangular defect is considered to be part of a circle, and a respective semicircular skin area is undermined and rotated into the defect. It is important to make the circle large enough to avoid tension.

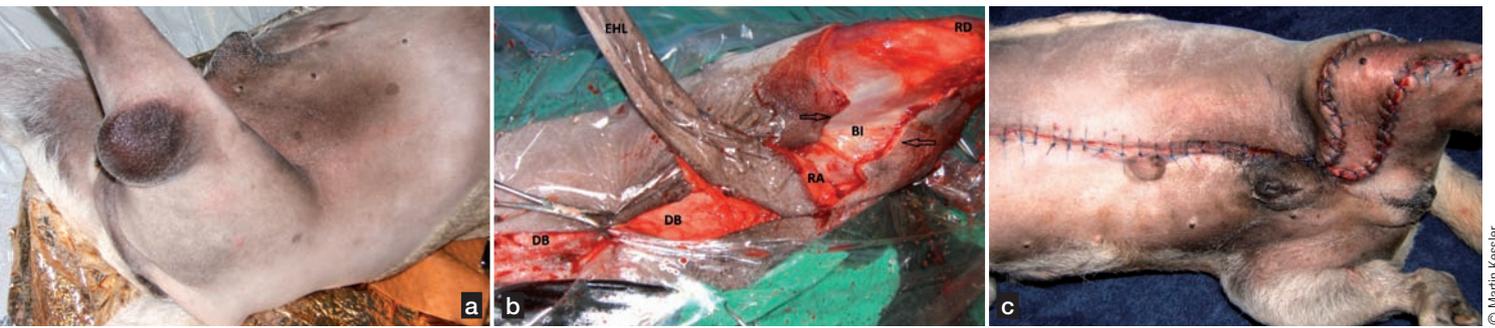


Figure 11. (a-c) The superficial epigastric axial flap is based on the epigastrica caudalis superficialis vessels. In the bitch, the flap includes the caudal mammary glands. In male dogs, the lateral aspect of the prepuce is included but note the epigastric vessels are smaller in diameter in the male compared to females. In the cat, epigastric flaps include the caudal three mammary glands and can be used to cover defects as far distally as the tarsus.

(a) A grade 2 mast cell tumor on the lateral aspect of the distal thigh.

(b) Flap preparation is similar to a regional mastectomy. The first incision is along the abdominal midline, the

second runs parallel beyond the lateral margin of the mammary chain and is connected with the first incision cranially and the flap dissected from cranial to caudal. The donor bed (**DB**) is held apposed with towel claps until closure. Care is taken to preserve the epigastric blood vessels. The flap (**EHL**) is rotated 180° around the vessel pedicle (rotation axis; **RA**) and a bridging incision (**BI**) is performed separating (arrows) the skin between the donor bed and the resection defect (**RD**). The flap is sutured without tension and a suction drain placed to prevent seroma formation underneath the flap.

(c) The completed surgery.

undermined and rotated into the defect. It is important to make the circle large enough to avoid tension. Measuring and drawing the incisions on the skin with a surgical marker is recommended. Lateral defects on the proximal aspect of the front or hind limb can be covered with a rotational flap from the lateral thoracic or abdominal wall respectively. Such flaps can also be used bilaterally to cover a central defect by rotating two opposite semicircles (e.g., defects on the caudal aspect of the dorsum/tail head using bilateral rotation flaps from the upper thigh).

Axial pattern flaps

Axial pattern flaps are supported by a direct blood supply from a defined (“axial”) blood vessel. If the skin remains attached at the base and only the free end of the flap is placed into the defect it is called an “axial rotation flap”. An “island flap” is a skin flap with a defined blood supply which is completely dissected free and remains attached only to the vessel. Axial pattern flaps are especially useful in covering defects in some critical skin areas of the body and are frequently used to cover large resection defects in the proximal limbs and head. Good knowledge of the vascular anatomy and meticulous dissection techniques are a prerequisite for successful flap preparation. The most important axial flaps are:

1) superficial epigastric flap (covering defects of the caudal abdomen, inguinal and perineal region, and medial and lateral hind limb, reaching down as far as the hock) (**Figure 11**)

- 2) thoracodorsal flap (for defects on the proximal aspects of the forelimb and thorax)
- 3) omocervical-flap (for shoulder and axilla defects, and also head and neck defects if a dog has a short neck)
- 4) circumflex ilium profundum flap (for defects on the caudal thorax, abdominal wall and flank, thigh and pelvis)
- 5) genicular flap (for medially and laterally thigh defects)
- 6) brachial flap (for proximal and medial foreleg defects)

Defects distal to the carpus or tarsus are difficult to cover with skin flaps, and free skin grafts may be required. Where compartmental resections result in full thickness abdominal or chest wall defects, muscle flaps from the latissimus dorsi, abdominal oblique or medial thigh muscles can be used to reconstruct the body wall, followed by skin advancement (**Figure 12**). If these muscles have to be resected along with the tumor, synthetic mesh can be used to reconstruct the body wall.

■ Post-surgical considerations

Evaluating the completeness of a tumor excision is very important for further clinical management (15). There is no standardized system for submission of tissue to a veterinary pathology laboratory for margin assessment, and thus no standardization among pathology institutions on how to examine samples and how to report on the surgery quality (16-18). Radical tumor surgery often results in large specimens of resected tissue, and submitting the entire resection *en bloc* for pathologic examination carries major disadvantages. Firstly, a thorough fixation of large

tissue samples is not possible, since formalin only penetrates about 1 cm into tissue. Additionally, it is purely coincidental whether the histological sections will be taken at actual “critical” margins of a large specimen. It is the surgeon, not the pathologist, who knows which areas of the specimen correspond to the areas of the tumor with the highest chance for residual tumor. For this reason, to determine if a tumor has been completely removed, the surgeon should send a representative specimen of the tumor itself as well as sufficient tissue biopsies obtained during surgery from the tumor bed and margins of the resected area. These “tumor bed” biopsies are very helpful in assessing completeness of excision, since both the location and number of sampled sites can be determined by the surgeon. Alternatively, surgical ink can be used to mark the most critical areas of the margins before sample submission, but this does not predict the number of sections taken by the pathologist.

Finally, although beyond the scope of this paper, it is worth noting that after an extensive surgical intervention, good nursing and supportive care is essential. Insufficient fluid volume and/or blood replacement, poor perioperative pain

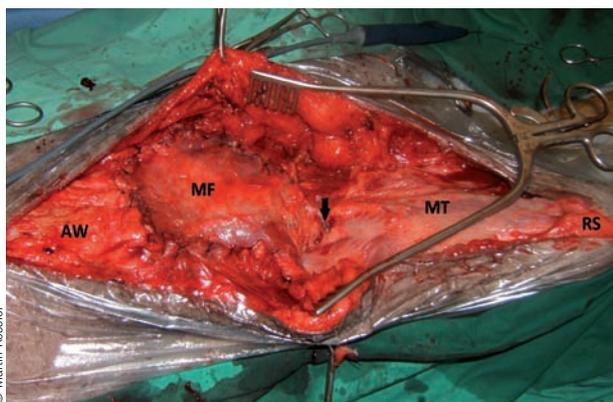


Figure 12. Reconstruction of the abdominal wall after resection of a highly invasive sarcoma. The sartorius muscle on the medial thigh (MT) is cut at the medial aspect of the right stifle (RS) and the ensuing muscle flap (MF), which receives its blood supply at the base in the inguinal area (arrow), is turned onto the abdominal wall (AW) and sutured to the defect border. Subcutaneous tissue and skin are closed by simple apposition.

management, and inadequate postoperative supervision can dramatically increase the complication rate or even the risk of fatality.

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Radiotherapy in veterinary medicine



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Dr Necova graduated from the University of Veterinary Medicine in Kosice, Slovakia, and spent some time in general practice before undergoing a one-year rotating internship at VRCC referrals in the UK. During this time, she developed a major interest in oncology and went on to complete a specialized Oncology internship. She is currently following an Oncology residency at the same institution, which provides specialist facilities for medical and radiation oncology.



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Dr North obtained her PhD in 1982 from the University of London Royal Marsden Hospital and went on to become assistant professor in the department of Tumor Biology in Houston, Texas, before deciding to move into veterinary medicine. She received her DVM from Texas A&M and completed a residency in Oncology at the New York Animal Medical Center. She is a RCVS recognized specialist in Oncology and a European specialist in Medicine and Oncology, and is boarded in Medical and Radiation Oncology. In 2002, Dr North established VRCC, the first private center in Europe to install a Linear Accelerator for radiotherapy treatment.

KEY POINTS

- With the recent significant advances in veterinary oncology and increasing demand and interest from pet owners, radiation has become a vital discipline.
- Radiotherapy produces free radicals which causes biological damage to cells. This damage is non-specific, affecting neoplastic and normal cells alike, and both acute and late-stage side effects may be seen.
- Before initiating radiotherapy, a treatment goal – tailored to the individual animal – must be determined. The clinician should contact the radiotherapy center to discuss the best approach for the patient prior to referral.
- Radiotherapy is a valuable treatment modality for multiple oncologic conditions, and can also be used as a palliative treatment to improve quality of life for patients where other modalities are not indicated.

■ Introduction

Veterinary medicine and care for companion animals have advanced rapidly over recent years. With improved life expectancy, the risk of a pet developing cancer at some point in its lifetime also increases. This, in turn, means more demand for advanced veterinary care, as owners will seek the best treatment for their pets with cancer. Radiation therapy is an effective treatment for many animal cancers, but until recently its use was limited by the sparse availability of treatment centers. However, with greater accessibility to radiotherapy facilities, the number of veterinary patients treated with this modality is growing rapidly, and an understanding of the indications and principles for treating small animal cancer patients is now essential for the general practitioner. This article provides a practical overview on radiotherapy to help the clinician when advising clients on treatment options available for cancer patients.

■ What is radiation therapy?

For both human and animal cancer patients, a multimodal approach is frequently indicated. This involves various combinations of surgery, chemotherapy and radiotherapy to improve patient survival times. Surgery and radiotherapy are modalities indicated for solid tumors

where loco-regional control is the main aim. Chemotherapy is used for the treatment of systemic and/or metastatic disease.

Ionizing radiation can be administered by an external source (teletherapy), through placement of radioactive sources interstitially (brachytherapy), or by systemic or cavitory administration of radioisotopes, *e.g.*, iodine-131 (¹³¹I) (1). External-beam radiation, the most commonly used method, may be classified as orthovoltage or megavoltage in nature, depending on the energy of the delivered particles. Orthovoltage produces X-rays of low to medium energy (150-500 kVp), whereas megavoltage emits high-energy photons (greater than 1 million volts (1MV)) (2).

Most oncology centers use megavoltage radiation, with the most commonly used machines being linear accelerators (LINACs) (see paper on page 40). Penetration of orthovoltage radiation is low, with maximum dose delivered to the skin and increased absorption by bone; as well as being unsuitable for treating deep-seated tumors, it carries an increased risk of late-onset side effects. The advantage of megavoltage equipment is the skin-sparing effect, whereby the maximum dose is attained at some distance below the skin surface, enabling the optimal dose to be delivered to deeply seated tumors without causing severe side effects to the skin (1,2). The absorption of megavoltage radiation is not dependent on tissue composition and density, permitting even distribution of the dose throughout all tissues within the field.

■ How does radiation work?

Radiation damages critical cell structures, especially DNA, either directly or indirectly. The major effect is indirect; a cell consists of approximately 85% water, which is targeted by the ionizing radiation, producing free radicals which result in biological damage, either cell death or by preventing the cell from further reproduction. However, the radiation effects are not specific for cancer cells, and normal cells are also susceptible to damage. Rapidly proliferating tissues (known as acutely or early-responding tissues) can show side effects during radiation treatment, whereas changes in slowly dividing cells such as bone (known as late-responding tissues) can take months or years to become apparent.

■ Goals of radiation therapy

Radiotherapy is usually considered a local treatment, as it is aimed at a specific area of the body where the tumor appears. Only cells within the treatment field are affected,

and cell death is limited to the treated area (3). Curative intent radiotherapy protocols as a definitive treatment are rare in veterinary patients; radiation is more typically used as adjunctive or neoadjuvant therapy. Adjunctive therapy is the more common application, usually when dealing with incompletely resected tumors to sterilize microscopic neoplastic cells potentially left behind in situations where further surgery is not feasible due to the anatomical location of the tumor or sometimes client preference. This situation usually arises with tumors of distal extremities or facial/oral areas. Neoadjuvant therapy, where radiation is used to shrink the mass before surgical excision is attempted, may be employed if the tumor is initially too large for surgical excision or is too deeply attached to underlying structures.

Palliative radiation, to improve quality of life, has also become more commonplace in recent years. Such therapy can offer pain relief in patients with inoperable tumors (especially with primary or metastatic bone tumors (*e.g.*, mammary carcinoma or prostatic tumors), or to relieve a physical obstruction by shrinking the tumor in size. In many cases, it is the only treatment modality for large, inoperable brain tumors and for patients with granulomatous meningoencephalitis which is non-responsive to medical management (1). Palliative treatment protocols consist of fewer fractions administered in larger doses per fraction compared to curative (definitive) treatment protocols.

A typical definitive radiation protocol consists of 16-20 treatment fractions administered on a Monday-Friday basis, whereas hypo-fractionated (palliative) protocols involve once weekly treatments for 4-6 weeks in total. Calculating the actual fractionated dose depends on various factors that take into account the biologic principles of radiation therapy, the radiosensitivity of the tumor, the tolerance of surrounding tissue, the treatment goal for the patient, the owner's financial limitations, and the ease of access to the treatment center (4).

As the reproducibility of the treatment needs to be guaranteed to best address the tumor, the patient must remain absolutely still during each treatment; this requires general anesthetic, and an owner should be made aware of this before referral. However, the actual treatment time is fairly short and the anesthetic lasts only 10-15 minutes, depending on the complexity of the protocol.

■ Biologic principles of radiotherapy

Not all tumors respond equally to radiation, primarily due to the differences in tumor biology. A treatment protocol is

therefore designed to promote the death of neoplastic cells whilst minimizing the consequences of ionizing radiation to normal cells (5). The sensitivity of a cell population to radiation depends on its ability to repair DNA damage caused by the treatment. The response of both normal and neoplastic tissues following a radiotherapy session has been described as the “four Rs” of radiation: repair of the DNA damage, repopulation, redistribution and re-oxygenation (6). Division of the radiation dose (fractionation) allows healthy cells to repair, while proliferating, quickly dividing neoplastic cells do not have sufficient time between fractions to repair. Cell regeneration also depends on recruitment of stem cells, which takes longer in tumor tissues.

When the therapy is initiated, many of the cells are in a phase of the cell cycle which is sensitive to radiation, resulting in cell death. During the interval between the treatment fractions, cells progress from one phase of the cycle to another, which affects their sensitivity to radiation; this is known as redistribution. It is known that hypoxic cells are resistant to radiation, so a reduction in the number of oxic cells results in previously hypoxic cells receiving a better supply of oxygen (re-oxygenation), which makes them more susceptible to radiation.

The chosen fraction size and the interval between treatments are very important considerations and both depend on the therapy goal. Curative intent protocols, with lower doses per fraction and a higher total dose, are designed to maximize delivery to the tumor tissue while minimizing side effects to normal tissues within the radiation field. Smaller doses per fraction allow a larger total dose to be given, while sparing the late-responding tissues, as shown in one study where the late complications of irradiating the pelvic canal in dogs were examined. Animals that received a lower dose per fraction (2.7Gy instead of 3.3Gy) developed fewer late side effects, although the overall rate of complications was low (7).

■ Radiotherapy side effects

Reactions from radiotherapy treatment are classified as acute/early and late/delayed. Acute side effects are seen at the time of treatment or shortly (2-3 weeks) after completion of radiotherapy. These side effects involve quickly proliferating tissues, such as skin, mucosa and intestinal epithelium, and the most common signs include moist desquamation, alopecia (**Figure 1**), mucositis, conjunctivitis and depigmentation, depending on the area treated. Acute side effects are usually self-limiting and can be treated symptomatically as necessary. It is important to



Figure 1. Dermatitis (**a**) and alopecia (**b**) are two acute side effects commonly seen during or shortly after radiotherapy.

prevent self-trauma to the radiation site by the patient to allow adequate healing. With appropriate treatment, recovery from such side effects is usually rapid, typically 2-4 weeks (8). Palliative treatment protocols are designed to cause fewer acute side effects, as the goal is to maintain a good quality of life despite the expected short survival time.

Late side effects involve tissues that are slowly proliferating, most commonly bone, heart and nervous system. The total dose of administered radiation is restricted by the maximal tolerance of tissues included within the radiotherapy field. When delayed side effects occur, these can be severe and difficult to treat, as they result in necrosis, fibrosis and therefore loss of function or sometimes death. However, late side effects usually occur months or years after completion of radiotherapy (**Figure 2**). Radiotherapy is not a benign treatment and ionizing radiation itself is a carcinogen. It is therefore possible to see radiation-induced tumors develop within previously treated radiation fields; however, the overall incidence of radiation-induced tumors in veterinary medicine is thought to be extremely low (< 1-2% of treated patients) and occurs many years after the initial treatment (9).

■ What types of tumor can be treated?

Every veterinary oncology patient must be evaluated for local disease as well as systemic (staging) spread. Radiation therapy can be considered for a number of tumors.

Oral tumors

These may arise in the areas where aggressive surgery with wide margins is not feasible, as it could leave functional or

cosmetic abnormalities. Therefore, for many tumors a multimodal approach combining surgery and radiotherapy can provide improved local control rates and prolong survival time. Most of the canine oral tumors are responsive to radiation therapy, including melanoma (**Figure 3**), acanthomatous ameloblastoma, oral sarcomas, epitheliotropic lymphoma (**Figure 4**) and squamous cell carcinoma. In cats, the latter tumor type has proven to be poorly responsive to radiotherapy; even though an initial response (*i.e.*, reduction in tumor size) may occur, rapid recurrence is very common.

Nasal tumors

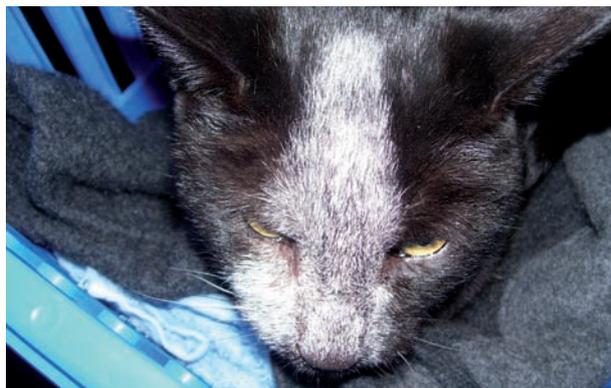
It can be difficult to achieve good local control of these tumors due to their anatomical location, which is very challenging for surgical intervention. Several studies have showed no benefit with survival times when nasal tumors were treated by surgical excision alone (10,11). Radiotherapy offers the best reported outcome for these tumors and is the treatment of choice; curative or palliative intent therapy can provide prolonged survival with improved quality of life for patients, bearing in mind that histologic type and stage are prognostic indicators (**Figure 5**). Two published studies evaluating curative intent radiotherapy protocols in nasal tumors showed survival times of 446 and 420 days respectively (12,13).

Brain and pituitary tumors

Most treatments for brain tumors are based on an imaging diagnosis and therefore the role of histological type for prognosis is lacking. However, as many brain tumors are not amenable to resection, or clients decline surgery, radiotherapy is frequently used alone, and as such will often result in good response and survival times; one study reported a median survival time for dogs with brain tumors treated with radiotherapy at 23.3 months (14). In general, pituitary tumors are also radiation-sensitive, and radiotherapy should be considered as a treatment modality; affected dogs have been reported to have median survival times between 1-2 years (**Figure 6**). Feline pituitary tumors have shown marked clinical improvement of associated endocrinopathies (insulin-resistant diabetes, acromegaly) with radiotherapy.

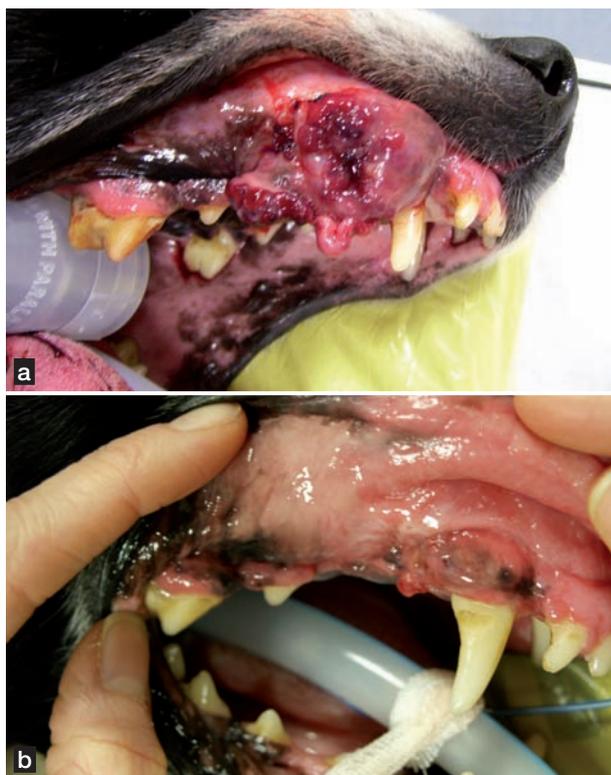
Tumors of the extremities

Radiotherapy can be a very good tool to “mop-up” neoplastic cells in locations where complete excision is not feasible. The tumors most commonly amenable to adjuvant radiotherapy are incompletely excised soft tissue sarcomas and mast cell tumors, which demonstrate good response rates and long-term tumor control (**Figure 7**). When removing these types of tumors surgically, general



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Figure 2. Late side effects can develop many months after radiotherapy, including leukotrichia (whitening of the hair).



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Figure 3. A dog with oral melanoma before (a) and after (b) completing radiotherapy treatment.

practitioners often fail to achieve complete excision, and further surgery may not be feasible due to the tumor location (*e.g.*, the distal extremities). If radiotherapy is advised by the referral center, and has not been previously factored into the treatment plan, good quality photographs of the tumor location before surgical removal can be an essential tool for the oncologist when planning the radiotherapy field. Knowing the previous boundaries of the tumor can be very useful, as the surgical scar may

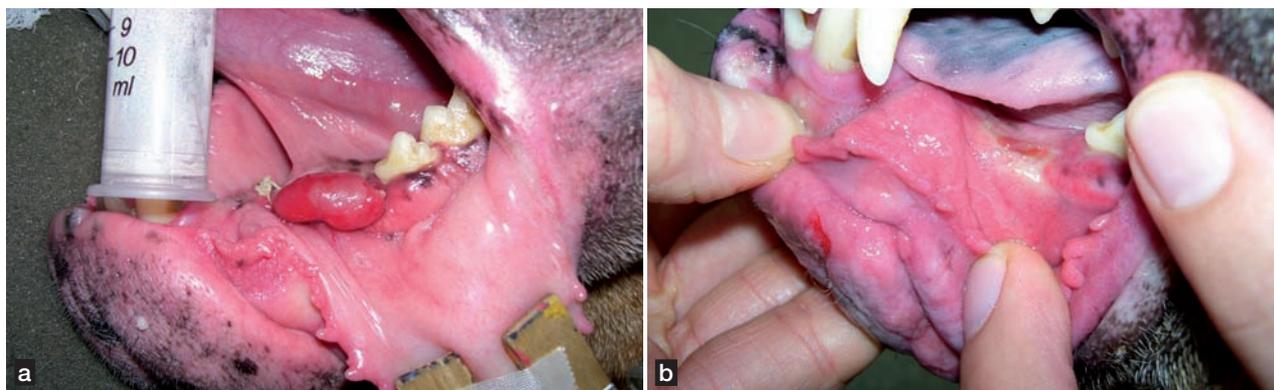


Figure 4. An oral epitheliotropic lymphoma in a dog before (a) and after (b) completion of radiotherapy treatment.

not be in the center of the excised mass and offers no guarantee for positioning at radiotherapy. With pre-planned radiotherapy (e.g., as an adjunct to surgical debulking), the oncologist should assess the patient prior to surgery wherever possible to help optimize the treatment plan. Remember that one of the principles of radiotherapy planning is to spare the skin (i.e., irradiation of the entire circumference of the limb risks later complications), especially when a tumor is located in a distal extremity. Therefore, assessing the tumor *in situ* will help prevent missing neoplastic cells with the radiotherapy; obviously, if neoplastic cells are outwith the radiation target this risks recurrence of the tumor and disappointment for both client and clinician. Special attention should be paid to feline injection site sarcomas; these tumors pose a significant challenge for adequate local

control due to their locally infiltrative nature and high-recurrence rates following surgery or radiotherapy alone. In many cases, a combination of these two modalities offers the best control, with median survival times reported to be 600-1,300 days (15, 16).

Bone tumors

Radiation can be used as a palliative treatment option in cases of appendicular osteosarcoma where amputation is not appropriate for the patient or is declined by the owner. The main aim is pain relief (seen in up to 92% of cases) and improved quality of life. The reported median survival times are between 3-6 months (17-19).

Radiotherapy should also be considered for patients with tumors of the thoracic and abdominal cavities, and where

Figure 5. CT scans of a dog with nasal carcinoma before (a) and 3 months after (b) radiotherapy treatment.

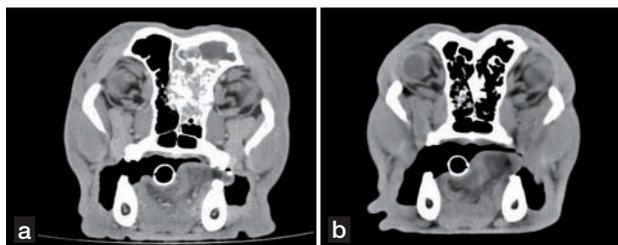


Figure 6. CT scans of a canine pituitary tumor before (a) treatment and 13 months after (b) completion of radiotherapy treatment.

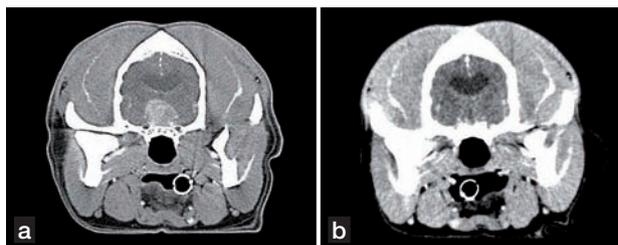
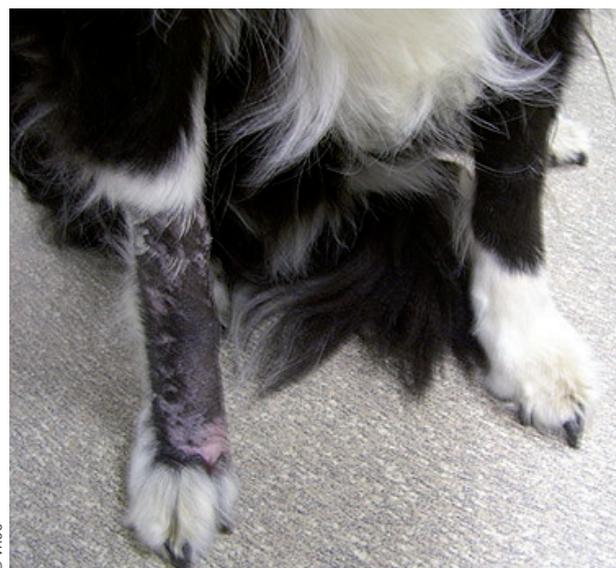


Figure 7. A dog with hyperpigmentation and alopecia within the radiotherapy field after treatment for an incompletely resected mast cell tumor.



surgical resection is not an option. Thyroid carcinomas and thymomas are both responsive to radiation therapy, and as a sole modality survival times can be greater than one year (20). Radiation should also be considered for urinary tract tumors, anal sac adenocarcinoma with regional metastasis, and mediastinal lymphoma; however, appropriate case selection is warranted.

■ Conclusion

Radiotherapy is a very valuable treatment in veterinary oncology, but each case should be carefully assessed whenever it is considered to be an option. The patient's overall health and ability to tolerate multiple repeated general anesthetics should be evaluated. Histopathological

diagnosis and tumor grade and stage are also essential when determining if radiotherapy is appropriate and which protocol should be considered (definitive vs. hypofractionated). For many cancer patients, radiotherapy can significantly improve quality of life and prolong survival, but understanding the principles of radiation and its indications is essential for case selection and multimodal therapy approach. Although this article provides the basic principles and tumor types that can be treated, it is beyond its scope to discuss all the oncologic conditions amenable to radiation; it is therefore both essential and advisable to contact a radiotherapy facility for specific advice when considering any case that may be deemed appropriate for referral.

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A BRIEF GUIDE TO...

Linear accelerators



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Figure 1. A Varian 2100 EX Linear Accelerator used for radiation therapy in veterinary medicine.

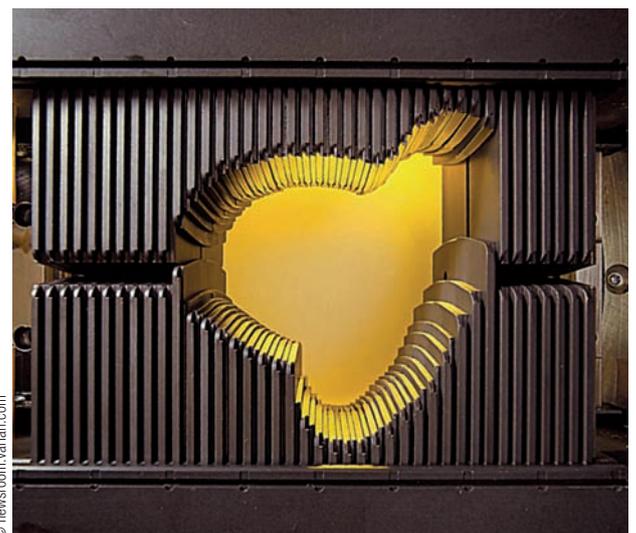
■ What is a LINAC?

A Medical Linear Accelerator (LINAC) is the device most commonly used for external beam radiation when treating cancer; nowadays, LINACs account for most of the operational megavoltage treatment units employed in clinical veterinary medicine (**Figure 1**) as they can treat all parts of the body. Megavoltage radiation has excellent tissue-penetrating capabilities, enabling radiation therapy to be utilized for both superficial and deep-seated tumors.

■ How does a LINAC work?

A LINAC uses high-frequency electromagnetic waves to accelerate electrons which then collide with a heavy metal target to produce high-energy x-rays in the megavoltage range. The high-energy x-rays are then shaped as they exit the LINAC to conform to the borders of the tumor. This shaping may be achieved with blocks and/or wedges, or a sophisticated computer-controlled

Figure 2. A 120 leaf MLC designed to shape the radiation field and limit dose to the surrounding normal structures.



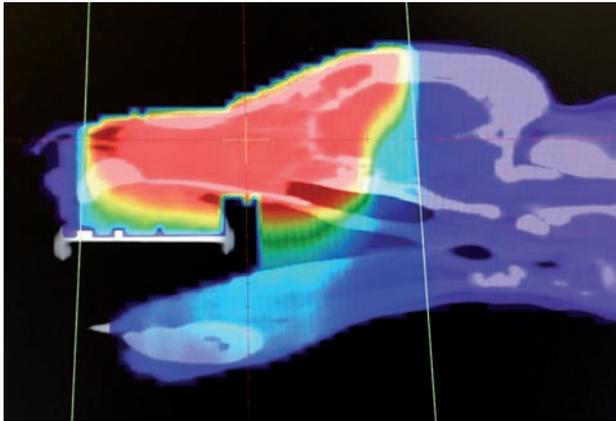


Figure 3. A color wash from a radiation therapy plan designed to treat a nasal tumor. The red areas indicate high-dose regions, with the blue areas representing low-dose regions.

multi-leaf collimator (MLC) (1). Many LINACs now come equipped with an MLC incorporated into the head of the machine, and this has contributed to many of the advancements in the delivery of radiation for cancer patients. The MLC is made up of individual leaves, each approximately 0.5-1.0 cm thick (**Figure 2**); the leaves can be moved in or out as required, allowing excellent conformal shaping of the LINAC's treatment beam to the tumor borders. This ultimately decreases the radiation dose to the healthy tissue surrounding the tumor and limits negative side effects.

Computerized therapy planning systems are also commonly used when treating with a LINAC (**Figure 3**). This system uses computed tomography (CT) images to generate beam shapes and dose distributions that maximize the dose to the tumor and thus improve tumor control (2).

■ What are the indications for LINAC treatment?

Radiation therapy with a LINAC should be considered for a patient when local control of a solid tumor cannot be obtained surgically without excessively compromising the animal's function, appearance, or quality of life. A combination of surgery and radiation therapy will often allow a more conservative surgical intervention and yield comparable or better tumor control and/or functional



Figure 4. (a and b) Patient setup showing immobilization equipment employed for radiation treatment of a nasal tumor. The use of a bite block and thermoplastic mask helps to “lock” the dog's head in place, and ensures that the patient is set up in the exact same position every day for the treatment.

outcome than either surgery or radiation alone. Radiation therapy can also be used alone when surgery is not a viable treatment option.

Radiation therapy has a wide range of applications, for example in many oral and nasal tumors (**Figure 4**), brain tumors, bone tumors, thyroid tumors, mast cell tumors, and soft tissue sarcomas. These tumors can be treated either with curative intent protocols or with palliative protocols (where the primary goal is to improve the patient's quality of life) as appropriate (2).

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Nutritional management of the cancer patient



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■ Introduction

It is believed by many that nutrition plays a role in cancer prevention, development, and treatment. Processed and red meats have been linked to cancer development while broccoli, green tea, and berries are reported to help prevent cancer. Many foods and diet strategies are touted as being critical to cancer treatment for both people and animals. Hundreds of dietary supplements are sold with the (unsubstantiated) promise or suggestion that they may have anti-neoplastic effects. It is no surprise that

many owners whose pets are being treated for cancer are interested in potential benefits from nutritional modifications. Some pet owners blame a diet for causing the cancer, while others want to home cook so they can feel that they are actively contributing to their pet's care. Overall, many owners opt to modify or supplement their pet's diet in the hope that these changes will improve survival time or help cure their pet.

Despite large volumes of information in lay sources – books, magazines and the Internet – touting various nutrients, diets, or supplements for treating cancer in pets and humans, there remains little strong evidence to support the majority of nutritional strategies commonly suggested for pets or people with cancer. Sadly, there is little published research addressing nutrition or specific nutrients for cancer in dogs and virtually none in cats. The lack of good data on dietary strategies is likely related to the complexity and heterogeneity of cancer, as well as the difficulty in designing and implementing clinical trials investigating nutritional strategies.

Based on the current evidence, the most important nutritional goals for dogs and cats with cancer are to ensure an appropriate caloric intake to maintain body weight and preserve muscle mass (**Figure 1**), and to ensure that all essential nutrient needs are met. While many owners feel the need to change the diet of a pet after a cancer diagnosis, it is important to emphasize that diet change may not have any benefit. There is absolutely nothing wrong with simply continuing patients on the diet that they have been doing well on, provided they will eat an appropriate amount to maintain weight and that the diet is properly cooked, nutritionally adequate,

KEY POINTS

- **There is little strong evidence to support the majority of nutritional strategies commonly suggested for pets with cancer; this is likely related to the complexity and heterogeneity of cancer as well as the difficulty in designing and implementing clinical trials to investigate such strategies.**
- **On current evidence, the most important nutritional goals for pets with cancer are to ensure an appropriate caloric intake to maintain body weight and preserve muscle mass, and to safeguard that all essential nutrient needs are met.**
- **Low-carbohydrate diets remain unproven for pets with cancer, as do anti-oxidants, but supplementation with omega-3 fatty acids should be considered.**

and made by a reputable company with a history of good quality control.

■ Diet types

There is no one diet that is ideal for all dogs or cats with cancer, nor is there any evidence to suggest that any specific commercial or home-prepared diet is best for the typical veterinary cancer patient. Calorie and nutrient needs can be met with a commercial diet, a home-cooked diet, or a combination, but a home-cooked diet requires much more careful planning and institution on behalf of the owner to ensure nutritional balance. Several studies have reported that the vast majority of readily available diet recipes (from lay books, veterinary textbooks, and Internet sites) designed for healthy dogs and cats, as well as those intended for pets with cancer and other serious illnesses, do not meet established nutrient recommendations (1-3). Moreover, even with the most nutritionally balanced recipe, it is important to prepare the diet as directed, as owners (86% in one study) frequently modify or substitute ingredients which can alter the nutritional profile of the diet greatly (4). Owners interested in home cooking should ideally work with a board-certified nutritionist* to ensure that the recipe is nutritionally appropriate and optimized to the pet's individual needs.

Many lay resources and a few veterinarians recommend the feeding of raw diets – either commercial or home-prepared – for pets with cancer. This practice is based on the goals of providing a diet that is thought to be appropriate to the evolution of dogs and cats, and it is often suggested that this kind of diet provides the best nutritional support for a pet with cancer. The biggest concern with this strategy is the high prevalence of bacterial contamination in both home-made and commercial raw diets (5). While healthy dogs and cats may be somewhat more resistant to serious illnesses from food-borne pathogens than people, the immune changes associated with cancer – not to mention immunosuppressive medications used as therapy – present a real danger of serious infection in pets with cancer. Most raw advocates downplay these risks and suggest that concerns should be similar with commercial diets, but the fact remains that there were over a dozen recalls of commercial raw foods and treats for bacterial contamination in the United States in 2015, compared to only one recall of cooked pet food for contamination. One large-scale study demonstrated that 15/196 and 32/196 raw

*see www.acvn.org or www.esvcn.eu/college



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Figure 1. It is important to monitor a pet's body weight, body condition, and muscle condition to ensure that nutritional needs are being met.

pet food samples tested were positive for *Salmonella* and *Listeria* contamination, respectively (6). Home-prepared raw diets do not fare any better – meat sold for human consumption is regularly recalled due to bacterial contamination, and it has been suggested that most raw chicken, turkey, and pork purchased from grocery stores is contaminated with potentially pathogenic bacteria (7). Owners should be clearly informed of the risks of feeding raw meat (to both their pets and their human family) and should be strongly encouraged to feed properly cooked commercial diets or cook all animal products to a safe internal temperature.

■ Maintenance of body condition

Maintenance of an ideal body condition during cancer treatment can be important to ensure the best prognosis. While some resources report that pets with cancer have higher energy needs than normal animals, this has not been a consistent finding – studies in dogs with various cancers have reported lower, similar, and higher energy needs compared to healthy dogs (8,9,10). Therefore, it is best to treat every animal as an individual and adjust calorie intake to maintain an appropriate body condition.

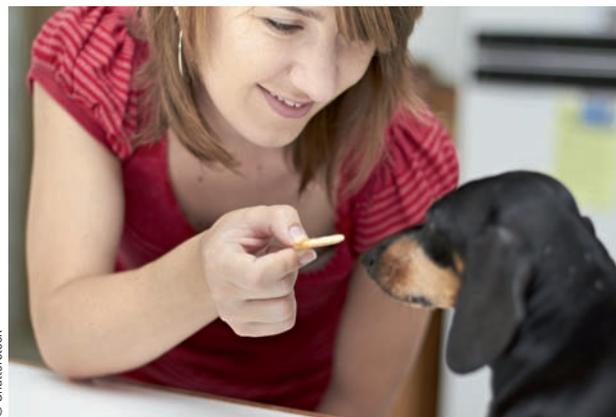
While obesity has been linked to cancer development and even a worse prognosis in some human cancers, there are few known associations so far in dogs or cats, and it is unclear at this time whether being overweight confers a worse prognosis for pets with common cancers. For pets that are overweight (> 7/9 body condition

score) such that it poses quality of life or mobility issues, or exacerbates comorbidities (e.g., hyperlipidemia, hip dysplasia), it may be beneficial to institute a weight loss plan geared towards a modest decrease in body fat weight (10-15% loss) without loss of muscle, rather than focusing on obtaining an ideal body condition score. It is the author's experience that many dogs actually gain substantial amounts of weight during cancer treatment, likely due to the use of drugs such as prednisone and somewhat reduced activity, coupled with increased treats ("spoiling") provided by owners because they feel bad that their pet has cancer or has to undergo treatment (**Figure 2**). This kind of weight gain is unlikely to benefit the dog and can cause other problems.

For underweight dogs and cats, the emphasis should be on distinguishing muscle loss due to the cancer (cachexia), which is not necessarily easily reversed, from fat loss, which may respond more reliably to increasing the daily calorie intake. Cachexia and being generally underweight is quite common in people with advanced cancer, but is much less common in dogs. One recent retrospective study found that only 6% of dogs diagnosed with lymphoma were underweight; muscle loss was unable to be assessed in this study (11). Being underweight was associated with decreased survival time when compared to normal or overweight dogs in the study.

Weight and muscle loss is much more common in cats with cancer than dogs and is associated with a worse prognosis (12). Generalized muscle loss associated with aging (sarcopenia) is common in older cats, so it can sometimes be challenging to distinguish "normal" muscle loss from cancer cachexia (**Figure 3**). It is very important to assess the diet and calorie intake of underweight and muscle-wasted pets as early as possible, preferably while these changes in body composition are still subtle. Feeding diets high in protein and calories may help reduce weight loss in a pet with good appetite, provided there are no other medical contraindications to such diets, but may not be very helpful in a pet with poor appetite.

Sometimes pets lose weight during treatment for reasons unrelated to appetite or the disease itself. A good example are animals undergoing radiation treatments that require daily anesthetic sessions. These pets may spend much of their day fasting prior to anesthesia, under anesthesia, and recovering, and may not have enough time to eat adequate amounts of calories (**Figure 4**).



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Figure 2. Many dogs actually gain substantial amounts of weight during cancer treatment; owners may offer treats because they feel bad that their pet has cancer or has to undergo treatment.

They may also be hospitalized during treatment, which can lead to increased anxiety. It is very important to ensure that these pets are not fasted longer than required and that they are given adequate time and a conducive environment in which to eat (**Figure 5**). This may mean removing food in the middle of the night rather than the previous evening, and offering food as soon as the pet is recovered enough to eat safely. Utilizing higher calorie diets (4,000-5,000 kcal/kg dry matter) may also be helpful so that less volume needs to be eaten to meet energy needs. Feeding amounts should be adjusted to maintain body weight.

■ Specific nutrient considerations for pets with cancer

It is worthwhile evaluating some of the more common claims for specific nutritional ingredients put forward for pets with cancer; comments on the more pertinent factors follow.

Carbohydrates

One of the most prevalent recommendations, online and within the veterinary community, is that pets with cancer should be fed as low a carbohydrate diet as possible because carbohydrates "feed" the cancer. It has been known for over 50 years that cancer cells obtain most of their energy via anaerobic fermentation of glucose to lactate – rather than via aerobic respiration as in most normal cells (13) – and it has been reported that dogs with lymphoma have higher insulin and lactate levels than normal dogs (14). Thus, the suggestion has been made that dogs and cats with cancer may do better on lower carbohydrate diets. However, this theory has not been confirmed with any *in vivo* study.



Figure 3. Generalized muscle loss associated with aging is common in older cats, so it can sometimes be challenging to distinguish “normal” muscle loss from cancer cachexia.

The only published study that has addressed this question investigated the use of high-carbohydrate (55% of calories) versus low-carbohydrate (7.5% of calories) diets in dogs with lymphoma. The data did not show a benefit for the low-carbohydrate diet in terms of remission times (survival time was not assessed and statistics were not performed) or energy requirements (15). The author is unaware of any other published studies in dogs or cats. There continues to be a need for well-designed controlled clinical trials to further investigate the role of dietary carbohydrates in cancer treatment of pets. Despite the current lack of evidence to support the benefits of low-carbohydrate diets, this recommendation continues to be enthusiastically embraced by clients and veterinarians alike.

Fortunately, for many pets, there appears to be little harm to trying a low-carbohydrate diet (here defined as < 20% of calories from carbohydrates). Any owner wishing to try this strategy should be assisted to select a diet from a reputable manufacturer that is formulated to be complete and balanced. Many commercial canned high-meat/low-carbohydrate diets (“95% meat” or “100% meat”) are not designed to be fed as the majority of the diet and will result in nutrient deficiencies if fed alone; it is essential to check the statement on the label to ensure the diet has undergone feeding trials or is formulated to meet national or internationally agreed nutrient profiles. Home-cooked low-carbohydrate diets can also be utilized, but they must be properly supplemented and balanced.

As a whole, low-carbohydrate diets (not to be confused with “grain-free” diets, some of which can be quite high in simple carbohydrates) are generally quite high in fat

and calories and may lead to weight gain if calories are not closely monitored. Pancreatitis in dogs or gastrointestinal disturbance can also be seen in sensitive animals; a slow transition from the current diet may be helpful. Low-carbohydrate diets are typically contraindicated in pets with kidney disease, severe liver dysfunction (signs or suspicion of hepatic encephalopathy), hyperlipidemia, and urate or cystine uroliths.

In summary, if low-carbohydrate diets are well tolerated, there is no evidence to suggest that they are harmful to otherwise healthy animals; however, nothing at this point suggests there is a clinical benefit in switching a pet with cancer to a low-carbohydrate diet.

Protein/amino acids

Many sources recommend a higher protein diet for pets with cancer. These diets are often quite palatable, allow for lower carbohydrate contents, and, theoretically, may have some benefits in reducing cancer cachexia. Independent of total protein, many individual amino acids have roles in the body other than as the building blocks of protein. For example, the role of leucine in cancer metabolism is an intriguing area of research. Leucine, a branched-chain amino acid, has a regulatory role in protein synthesis as it activates the mammalian target of rapamycin (mTOR) pathway which increases protein

Figure 4. Some animals with cancer undergo radiation treatments that require daily anesthetic sessions. These pets may spend much of their day fasting prior to anesthesia, under anesthesia, and recovering, and may not have enough time to ingest adequate amounts of calories.

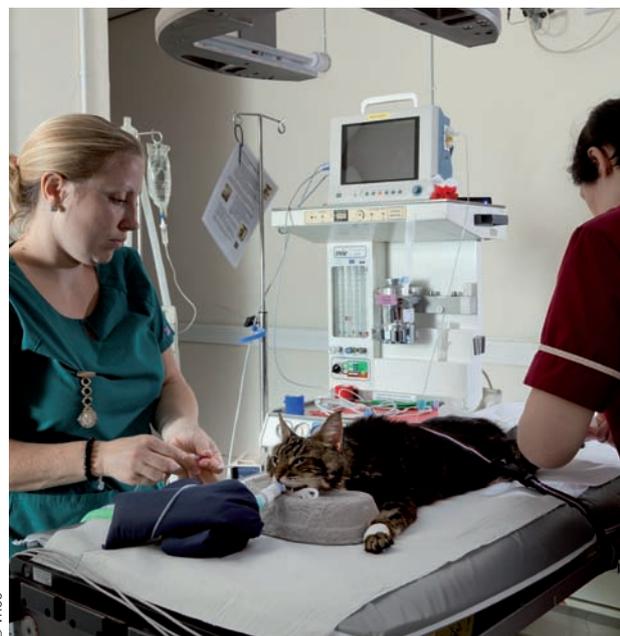




Figure 5. It is very important to monitor an animal's food intake whilst the pet is hospitalized.

synthesis in the muscle. These effects have been suggested to help maintain muscle mass in aging rodent models (16), which is appealing for potential prevention of cachexia as well. However, the mTOR pathway is also being studied because of its suspected role in carcinogenesis, as it regulates cell proliferation and cell survival in addition to protein synthesis (**Figure 6**). Compounds that upregulate this pathway are thought to contribute to tumorigenesis and many novel anti-tumor compounds and strategies are now targeting this pathway. In theory, high leucine could contribute to carcinogenesis, and indeed increased tumor growth has been shown in leucine-supplemented rodents with pancreatic tumors (17).

Another commonly discussed amino acid is arginine, which (via its conversion into nitric oxide) has been shown to have both pro-neoplastic and anti-neoplastic properties at the molecular level. *In vivo* data from humans and animals with neoplasia are still inconclusive; one study (18) in dogs with presumed stage III lymphoma, but not stage IV, showed that animals fed a diet supplemented with arginine and omega-3 fatty acids had a longer disease-free interval and survival times compared to dogs on a similar diet without either addition. However, many aspects of this study have been criticized, including the *post hoc* subgroup analysis and the method of initial staging, and any potential benefits of arginine cannot be separated from those of omega-3 fatty acids.

In summary, more data are needed before educated recommendations can be made regarding the optimal

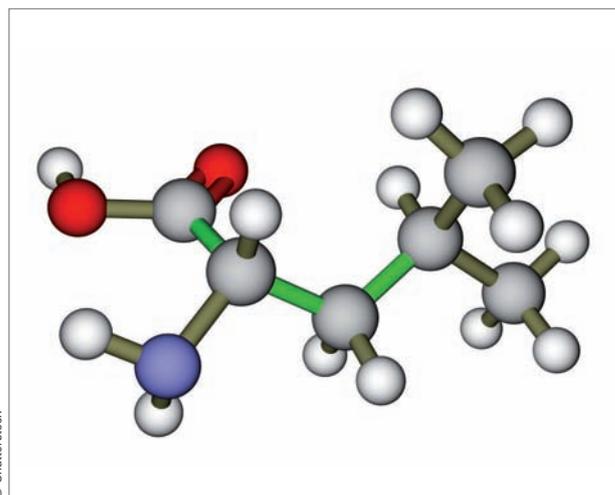


Figure 6. Leucine may help maintain muscle mass, but it also activates a pathway that could be involved in carcinogenesis.

dietary protein amounts and amino acid composition for pets (or people) with cancer. Until then, the most important concern is ensuring that adequate protein is fed to meet nutritional requirements and then adapting this to fit in with other nutritional goals that the veterinarian and owner have for the pet.

Fats

Most of the research looking at fat and cancer has focused on omega-3 fatty acids. Omega-3 polyunsaturated fatty acids (PUFAs) have been demonstrated to have anti-inflammatory effects in numerous species, including dogs. In rodents, they have been shown to help reduce muscle loss associated with cancer cachexia. They are increasingly being investigated for potential anti-neoplastic activity as well, and owners may well be interested in supplementing various omega-3s when their pet is diagnosed with cancer.

There are two main sources of omega-3 fatty acids: terrestrial plants, and marine algae and fish. Flaxseed is an excellent source of alpha-linolenic acid (ALA), a polyunsaturated omega-3 fatty acid. The two well-known long chain omega-3s, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are only found in marine algae and the cold water marine fish that eat the algae. Although ALA can theoretically be converted to EPA and then DHA through enzymatic means, a sizable percentage of dietary ALA intake is oxidized for energy (19) and the conversion rates in mammals are generally poor. Cats are not thought to have clinically relevant conversion of ALA to EPA.

The literature is ambiguous when it comes to benefits of ALA for neoplasia, despite the enthusiastic Internet endorsement of this fatty acid. Research in human breast and prostate cancers, mostly correlation studies, has suggested both positive and negative associations between ALA intake and tissue concentration and cancer.

The evidence for potential benefits for EPA, and especially DHA, is more impressive in humans and animal models, although not strong enough to make supplementation the standard of care in human oncology. Many studies are currently ongoing to more accurately discern the potential anti-neoplastic effects of long chain omega-3 fatty acids in humans and animals, as well as to determine the appropriate doses to optimize these effects *in vivo*.

Only one controlled study has investigated a diet high in EPA and DHA on outcome in dogs with cancer (18). This study, mentioned above, did not show an improvement in the overall disease free interval or survival time, but increasing serum DHA concentrations were associated with increased survival time in stage 3 dogs only.

Despite the very limited supportive evidence for benefit of EPA and DHA supplementation in pets with cancer and the lack of a defined appropriate dose, the sum total of the human and animal literature is suggestive of a benefit, and it is therefore very reasonable to feed a diet high in EPA and DHA, or to supplement a low-omega-3 commercial diet with these fatty acids. Although appropriate doses have yet to be determined, the author generally starts with a total daily dose of ~300 mg EPA and DHA (1 regular strength human fish oil capsule) per 10 lb/4.5 kg body weight. There is minimal evidence at this point to support a benefit of flax (ALA) supplementation as a source of omega-3 fatty acids in dogs with cancer, and it should not be used as a source of omega-3 fatty acids for cats. Clinicians should keep in mind that there is an upper limit to how much omega-3 can be safely supplemented, because adverse events can be seen (20), although this ceiling remains rather ill-defined.

Antioxidants

Antioxidant supplementation is controversial in cancer patients, both human and animal. While there is evidence that some antioxidants may help prevent certain types of cancers, there is also evidence that some antioxidants increase the risk of certain cancers (*e.g.*, beta carotene and lung cancer). Studies in humans with active tumors have shown variable results from high-dose antioxidant

supplements, including beneficial, no observable, and detrimental effects. Common recommendations in humans include avoiding antioxidant supplements within a few days of chemotherapy and throughout a course of radiation. These recommendations apply to antioxidant supplements, rather than antioxidants naturally occurring in whole foods (or commercial diets for pets). The author certainly recommends avoiding unnecessary concentrated supplementation of antioxidants during active cancer treatment with chemotherapy or radiation.

■ Assisted feeding

For pets whose calorie intake is below expected needs (hyporexia or anorexia), more aggressive nutritional support may be required. Orexigenic (appetite-stimulating) drugs such as mirtazapine (3.75-30 mg/dog PO Q24 h, 1.88 mg/cat PO Q48 h), cyproheptadine (1-2 mg/cat PO Q12-24 h), or steroids can be considered (off-license), depending on the patient. The potential for drug interactions needs to be considered and it should be kept in mind that appetite stimulants rarely result in full energy needs being consumed by patients that were previously eating only a small portion of their daily needs. A more detailed discussion of these drugs is beyond the scope of this review.

Some pets with cancer (such as those with oral masses) may require assisted feeding utilizing a feeding tube to maintain an appropriate body weight (**Figure 7**). Feeding tubes should be instituted early on, when weight loss or reduced appetite is anticipated or first noted and may be more easily reversed, rather than as a last ditch attempt in an emaciated or cachexic animal. Nasoesophageal

Figure 7. Nasoesophageal tubes are easy to place in the conscious animal and can be used with liquid diets for hospitalized pets requiring short-term nutritional support.



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tubes can be used with liquid diets for hospitalized pets requiring short-term nutritional support. Esophageal tubes can be easily placed for most dogs and cats and have the advantage of low rates of serious complications and easy removal if there are problems or they are no longer needed. Gastric tubes can be valuable for longer-term support, but require a longer anesthetic period and have the risk of more serious complications, especially if the tube is inadvertently removed prior to the formation of a proper stoma. Ethically, feeding tubes are best used when quality of life other than appetite is judged to be reasonable, or when feeding support is expected to be only temporary (e.g., radiation-induced oral mucositis).

■ Summary

The best evidence supports feeding pets with cancer commercial or home-cooked diets designed to meet both their energy and essential nutrient requirements. There is no “magic cancer diet”, despite passionate claims to the contrary. Low-carbohydrate diets remain unproven; supplementation with EPA and DHA should be considered. Supplementation of arginine remains equivocal. Antioxidant supplementation is controversial and until it becomes less ambiguous, it is likely best to avoid exogenous supplementation outside of the levels provided by a well-balanced diet, especially during chemotherapy or radiation. Some pets may require assisted feeding to maintain an optimal body weight and condition.

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