Strategies for Managing Cancer Pain in Dogs & Cats

PART 2: DEFINITIVE & PALLIATIVE MANAGEMENT OF CANCER PAIN

Controlling cancer pain should always be part of a cancer treatment plan. Pain management should be implemented as soon as possible following diagnosis to address existing pain and prevent onset of new pain.

Even if the patient has no outward, objective clinical signs of pain, the practitioner should assume that any tumor has the potential to cause subclinical pain, and pain management should be considered as part of the therapeutic plan. This is an important concept in the veterinary profession because our patients are unable to communicate their level of pain directly.

TYPES OF CANCER PAIN
Tumors can present in any part of the body, resulting in pain. In the first article of this 2-part series, Pathophysiology & Assessment of Cancer Pain (May/June 2015; available at tvpjournal.com), we described 2 mechanisms for cancer pain:
1. Endogenous chemical irritation
2. Direct tumor invasion with compression of normal tissues.

In addition, cancer pain can result from cancer therapies, such as surgery, radiation therapy, and cytotoxic chemotherapy.

TYPES OF PAIN MANAGEMENT
Optimal cancer pain management is determined by the type of cancer and the owner’s goals for treatment.

Broadly, 2 potential treatment pathways exist in veterinary oncology, both of which may employ analgesic drugs, radiation therapy, surgery, chemotherapy, or a combination of these modalities (Figure 1):
The goal in **definitive treatment** is long-term control of the cancer and potentially long-term, pain-free survival; iatrogenic pain is to be expected as a consequence of definitive treatment.

- **The goal in palliative treatment** is to relieve cancer pain and slow, or minimize, the rate of cancer progression.

Table 1 (page 52) lists pain medications discussed in this article, including dosing and frequency of administration.

**ACUTE/IATROGENIC CANCER PAIN DUE TO DEFINITIVE TREATMENT**

As noted, iatrogenic pain induced by definitive-intent treatments is to be expected. However, the cost of iatrogenic pain in these patients is outweighed by the benefit of longer-term survival. The pain management plan varies depending on the treatment modality used.

**Definitive Surgery**

Surgery is often used to treat localized cancer, and employed with definitive intent in a number of clinical scenarios, including:

- Removal of tumors, such as low- to intermediate-grade soft tissue sarcomas or mast cell tumors in which there is adequate room to remove a wide and deep margin (2 cm lateral + 1 fascial plane)
- Amputation of a limb to remove the anatomic compartment encompassing the tumor (radical surgery).

Pre- and intraoperative pain control for these types of surgeries is similar to pain management used for orthopedic and soft tissue surgeries (eg, fracture repair, amputation due to traumatic injury). For example, the following medications are often administered:

- Opioids and maropitant for anesthetic premedication
- Opioids (with or without ketamine), lidocaine, and dexmedetomidine as intraoperative constant-rate infusions (CRIs)
- Opioids or local anesthetics for regional anesthesia techniques, such as nerve blocks.

Postoperative pain management is also similar, and frequently involves use of nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics, such as opioids.

Acute surgical pain management techniques have been reviewed extensively elsewhere and are not reviewed in detail here. However, see **Consider This Case: Surgical Treatment of Osteosarcoma** (page 50) for a case presentation that demonstrates the use of definitive surgery to treat osteosarcoma.

**Definitive Radiation**

Definitive-intent radiation therapy for residual local neoplastic disease is becoming increasingly common in veterinary medicine. This type of radiation therapy is:

- Frequently indicated for treatment of microscopic cancer left behind following first-attempt surgical excision of tumors, including soft tissue sarcomas and mast cell tumors
- Distinguished by the large size of the total dose delivered and the small size of the dose given at each treatment session (called a fraction).

Treatment is typically delivered Monday through Friday, with breaks on the weekend, for a total of...
New Opioids for Pain Control in Cancer Patients

Recently, a veterinary product with a higher concentration of buprenorphine (1.8 mg/mL; Simbadol, zoetisus.com) and a highly concentrated transdermal fentanyl liquid (50 mg/mL; Recuvyra, elancovet.com) have become available for treating pain in pets. Although these new, long duration, highly concentrated narcotics show promise, they must be administered and handled under the direct supervision of a veterinarian due to the potential for abuse and safety concerns.

Concentrated Buprenorphine
Oral transmucosal (OTM) buprenorphine at a dose of 80 to 120 mcg/kg (highly concentrated preparations, such as Simbadol, may make OTM administration more practical) is effective for analgesic durations of 12 to 24 hours in dogs and cats.6,7 We advise against sending this drug home with clients due to abuse concerns unless no other options are available for adequate pain control.

Transdermal Fentanyl
Transdermal fentanyl liquid is a new method for treating acute pain in dogs (the product is not approved for use in cats and should not be used due to safety concerns). Its advantages include:

- **Efficacy:** Appears to reach bloodstream within 30 minutes of application, attain therapeutic plasma concentrations within 2 to 4 hours of administration, and maintain therapeutic effect for 4 days

- **Safety:** See below
- **Economy:** Less expensive than fentanyl patches and injectable fentanyl
- **Convenience of administration:** One transdermal application provides 4 days of analgesia.

The side effects of transdermal fentanyl liquid are similar to those of injectable fentanyl, including anorexia, sedation, hypothermia, and dysphoria. Our clinical experience suggests that respiratory depression and bradycardia are less frequent than with injectable fentanyl. Remember that once transdermal fentanyl liquid has been applied, its activity cannot be halted unless it is antagonized partially or completely using butorphanol or naloxone, respectively.

To minimize risks when using transdermal fentanyl liquid as a premedication, other tranquilizers and sedatives should be avoided or administered at lower doses. Transdermal fentanyl liquid also has a propofol and inhalant sparing effect8 that should be considered during anesthesia induction and maintenance. For debilitated dogs, ½ to ¾ of the labelled dose may be applied rather than the full dose (2.7 mg/kg). Other opioids may be added if pain is under controlled.

Hospital personnel and owners should be aware of the site of administration of transdermal fentanyl and avoid direct contact with it for 72 hours after application. Any contact with bare skin should be avoided and hand washing should be implemented should anyone touch the area of application before 72 hours.

Levels of Pain
A general understanding of the type of pain induced by definitive radiation treatment is important. Table 2 (page 53) lists some common tumors treated with definitive radiation therapy and expected levels of pain associated with treatment.

In general, definitive treatment of deep-seated tumors, such as brain tumors, is associated with few painful side effects, whereas treatment of superficial tumors, such as those occurring on the skin or oral mucosa, is expected to elicit painful acute side effects. This difference in pain occurs because treatment of deeper tumors deposits most of the radiation energy in deeper tissues, such as the brain, while tissues and organs with more sensitive pain receptors, such as skin, are spared from a significant dose of radiation (paradoxically, the brain itself lacks pain receptors).9

The sensation of a headache or fatigue has been reported in humans with brain tumors, and the same sensation may occur in animals. This sensation is thought to be inflammatory—a result of perilesional edema and potential stretching of the meninges due to the space-occupying mass.10

Acute Effects
The target of radiation-induced damage is the DNA of rapidly proliferating cells, and the most significant side effects of radiation therapy are desquamation of the skin, mucositis, and keratoconjunctivitis sicca of the ocular adnexa. These side effects generally occur in treated areas around a cutaneous, oral, or nasal tumor.

Acute side effects result from depletion of stem

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16 to 24 treatments, with fractions of 2 to 3 Gy, yielding a total dose of 48 to 60 Gy.

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Consider This Case: Surgical Treatment of Osteosarcoma

An 8-year-old, castrated male golden retriever presented for evaluation of a mass on the distal femur. Non–weight-bearing lameness was present and localized to the distal femur. Complete blood count and serum biochemical profile were within normal limits. However, craniocaudal and lateral radiographs revealed a moth-eaten-appearing, lytic region within the distal right femoral metaphysis (Figure 2).

1. Premedication
   Two hours prior to surgery:
   - Transdermal fentanyl liquid (2.7 mg/kg) was applied to the dorsal scapular area; the dog demonstrated mild sedation 2 hours later.
   - Further premedication was achieved with acepromazine (0.01 mg/kg IM), with no other opioids needed to facilitate IV catheter placement.

2. Anesthetic Induction
   Anesthesia was:
   - Induced with propofol (1 mg/kg IV), demonstrating a noticeable propofol-sparing effect due to transdermal fentanyl and acepromazine premedication, and followed by oral tracheal intubation
   - Maintained with isoflurane in oxygen with a circle breathing circuit.

3. Intraoperative Pain Control
   After IV induction, but before surgical incision, an epidural was administered using bupivacaine (0.5 mg/kg) with sterile saline. A coxofemoral disarticulation was then performed.
   
   Intraoperatively:
   - Ketamine (0.5 mg/kg bolus injection followed by 1–2 mcg/kg/min IV CRI) and lidocaine (2 mg/kg IV bolus injection followed by 5–10 mcg/kg/min IV CRI) in crystalloid fluid were administered.
   - Dexmedetomidine diluted in physiologic saline at 0.5 mcg/kg/H was administered as an IV CRI.
   - Two lidocaine patches (5%) were applied to the surgical site after skin closure.

4. Postoperative Pain Control
   The ketamine/lidocaine and dexmedetomidine CRIs were continued for 6 hours postoperatively. The preoperative transdermal fentanyl liquid, which yields 4 days of continuous analgesia, provided additional pain control.
   The patient was ambulating, eating, and drinking normally a day after surgery, and was sent home with:
   - Carprofen (4 mg/kg PO Q 24 H) and tramadol (5–10 mg/kg PO Q 8–12 H) for breakthrough pain
   - Gabapentin (10 mg/kg PO Q 12 H) for potential neuropathic pain.
   If pain is not controlled with the above medications, consider other opioids, such as OTM administration of buprenorphine (120 mcg/kg Q 24 H).

5. Further Definitive Treatment
   The dog was treated with chemotherapy (carboplatin, 300 mg/m2 IV Q 21 days for 4 treatments) beginning 10 days after skin sutures were removed. Five months after completion of carboplatin, thoracic radiographs revealed pulmonary nodules consistent with metastatic disease. The patient began doxorubicin chemotherapy and is currently undergoing treatment.
cells (such as keratinocytic stem cells in the skin) due to radiation damage. As radiation therapy progresses (usually 2 weeks into treatment course), acute side effects begin to appear as mild redness and dry, flaky skin in the treated area, which results from the inability of stem cells to adequately repopulate the keratinocytes that have naturally progressed through their life cycles and shed. As treatment and time continue, these effects become more severe (Figure 3).

Acute side effects due to radiation are best managed proactively, with the knowledge that, although they may appear severe, their occurrence is transient and self-limiting. Cats are generally more resistant to acute side effects than dogs (Figure 4), and their side effects and discomfort tend to be less severe.

**Late Effects**

Deeper-seated tissues, such as muscle, nerve, and bone, are slowly proliferating in adult animals, and the effects of radiation therapy on these tissues may not appear for many years after treatment, if at all. These late effects of radiation therapy, like acute effects, are expected to occur only in the area of normal tissue near the treated tumor. If the smallest area of normal tissue possible is irradiated with small fraction sizes, the potential for late side effects in these tissues is less than 5%. Clinical evidence of late effects includes fibrosis, stricture, necrosis and, potentially, a second cancer in the organs surrounding the irradiated area. Clinically significant late effects are irreversible and potentially life threatening, depending on their locations.

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**FIGURE 3.** Moist desquamation after canine patient received 19 fractions of definitive radiation therapy for soft tissue sarcoma, excised with “dirty” margins from the distal forelimb. The limb is swollen, and several focal areas of redness and edema can be seen (A). One week after completion of definitive radiation therapy, the reaction has become more severe, with radiating redness, edema, crusting, and serum seepage (B). Two weeks after completion, note the near-complete resolution of moist desquamation; the skin is pink and smooth with a few areas of crusts and redness (C). Four weeks after completion, clinical signs have resolved completely (D).

**FIGURE 4.** Cat that has completed fraction 20/20 of definitive radiation therapy for a vaccine-associated sarcoma on the left paralumbar-flank region; dry, flaky skin is present with mild redness (A). Same cat 1 week after finishing definitive radiation therapy; note that dry, flaky redness has progressed and additional alopecia is present. No confluent moist desquamation is present as in the dog in Figure 3 (B). Same cat approximately 2 weeks after finishing definitive radiation therapy; lesions have healed and hair is beginning to grow back (C). This patient was prescribed OTM buprenorphine (80 mcg/kg), as needed.
**TABLE 1.**

**Analgesic Agents & Other Nonpharmaceutical Techniques Commonly Used for Cancer Pain Management**

<table>
<thead>
<tr>
<th>PAIN CATEGORY</th>
<th>APPROPRIATE ANALGESICS</th>
<th>DOSE</th>
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<tbody>
<tr>
<td><strong>Mild</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>NSAIDs</strong></td>
<td></td>
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<tr>
<td></td>
<td>Carprofen (dogs only)</td>
<td>4.4 mg/kg PO or SC Q 24 H or 2 mg/kg PO or SC Q 12 H</td>
</tr>
<tr>
<td></td>
<td>Deracoxib (dogs only)</td>
<td>3–4 mg/kg PO Q 24 H</td>
</tr>
<tr>
<td></td>
<td>Firocoxib (dogs only)</td>
<td>5 mg/kg PO Q 24 H</td>
</tr>
</tbody>
</table>
| | Meloxicam | Dogs: 0.2 mg/kg PO, SC, or IV Q 12 H
Cats: 0.1 mg/kg PO Q 24 H every 2–4 days |
| | Piroxicam | Dogs: 0.3 mg/kg PO Q 24 H
Cats: Up to 0.3 mg/kg PO Q 24 H |
| | Robenacoxib (cats only) | 1 mg/kg PO Q 24 H |
| | **Steroids** | |
| | Prednisone | 0.5–1 mg/kg PO Q 24 H; taper to lowest dose that controls clinical signs |
| | Prednisolone (cats only) | 0.5–1 mg/kg PO Q 24 H; taper to lowest dose that controls clinical signs |
| | **Opioids** | |
| | Tramadol (dogs only) | 5–10 mg/kg PO Q 8–12 H |
| | **Moderate** | | |
| | **Opioids** | |
| | Codeine | 1–2 mg/kg PO Q 8–12 H |
| | Hydrocodone | 0.5 mg/kg PO Q 8–12 H |
| | Morphine | 0.5–2 mg/kg PO Q 6–8 H |
| | Hydromorphone | 0.2–0.4 mg/kg PO Q 8–12 H |
| | Buprenorphine | Dogs: 80–120 mcg/kg OTM Q 12–24 H
Cats: 80–240 mcg/kg OTM Q 12–24 H |
| | Transdermal fentanyl patch | 25, 50, 75, or 100 mcg/H patch |
| | Transdermal fentanyl liquid (dogs only) | 1.3 mg/kg Q 4–7 days on dorsal scapular area |
| | **Severe** | | |
| | **Opioids** | |
| | Morphine (dogs and cats) | Same as above |
| | Hydromorphone | Same as above |
| | Buprenorphine | Same as above |
| | Transdermal fentanyl patch | Same as above |
| | Transdermal fentanyl liquid (dogs only) | 2.7 mg/kg Q 4–7 days on dorsal scapular area |
| | **Can be combined with any other analgesics in different pain categories** | |
| | **Adjuvants** | |
| | Amantadine | 2–5 mg/kg PO Q 12 H |
| | Gabapentin | 5–10 mg/kg PO Q 8–12 H |
| | Oxcarbazepine | 30–60 mg/kg PO Q 8–24 H |
| | Amitriptyline | 1–5 mg/kg PO Q 12–24 H |
| | Lidocaine patches | 1–3 patches depending on size of wound and size of animal, 1 application on the superficial painful site for 5–7 days |
| | **Nonpharmaceutical Modalities** | |
| | Acupuncture | |
| | Physical rehabilitation | |
| | Nutraceutical and nutritional supplemental therapies | |

**a.** Modalities are appropriate for dogs and cats unless otherwise specified.

**b.** Do not administer NSAIDs and corticosteroids concurrently; only administer one NSAID at a time, and provide an appropriate washout period (approximately 5–7 days) when switching from one NSAID to another or to a corticosteroid (and vice versa). Use with caution in cats.

**c.** Highly concentrated formulations, such as Simbadol (zoetisus.com), may be used to help make the volume administered more manageable; however, these products should not be sent home with clients due to safety and abuse concerns unless no other options are available for adequate pain control.

**d.** Combine the opioids with an NSAID and adjuvants for treating severe pain.
### Anatomic Tumor Location, Side Effects, & Expected Pain Scores Associated with Definitive Radiation Therapy in Dogs & Cats

<table>
<thead>
<tr>
<th>ANATOMIC LOCATION</th>
<th>COMMON TUMOR TYPES</th>
<th>EXPECTED SIDE EFFECTS OF RADIATION THERAPY</th>
<th>EXPECTED PAIN SCORE</th>
<th>POTENTIAL DRUG INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
<td>Meningioma&lt;br&gt;Glioma&lt;br&gt;Pituitary macroadenoma</td>
<td>Minimal, if any; many human patients report the sensation of a headache</td>
<td>0–3 (pain difficult to detect)</td>
<td>Prednisone&lt;br&gt;Tramadol&lt;br&gt;Gabapentin&lt;br&gt;Buprenorphine</td>
</tr>
<tr>
<td><strong>Head/neck</strong></td>
<td>Squamous cell carcinoma&lt;br&gt;Oral fibrosarcoma</td>
<td>Mucositis, dry mouth, halitosis and, potentially, moist desquamation (skin of face)</td>
<td>7–10</td>
<td>NSAIDs&lt;br&gt;Tramadol&lt;br&gt;Gabapentin&lt;br&gt;Amantadine&lt;br&gt;OTM buprenorphine&lt;br&gt;Oral hydrocodone, hydromorphone, or morphine</td>
</tr>
<tr>
<td><strong>Nasal</strong></td>
<td>Nasal adenocarcinoma (60% dogs)&lt;br&gt;Sarcoma (40% dogs)&lt;br&gt;Lymphoma (most common nasal tumor in cats)&lt;br&gt;*Acute side effects in cats tend to be less severe than in dogs</td>
<td>Depends heavily on treatment technique employed; pain may range from minimal to nonexistent (modern techniques) to severe desquamation (traditional techniques)</td>
<td>7–10 (traditional radiotherapy)&lt;br&gt;0–3 (advanced conformal radiation therapy)</td>
<td>NSAIDs&lt;br&gt;Tramadol&lt;br&gt;Gabapentin&lt;br&gt;Amantadine&lt;br&gt;OTM buprenorphine&lt;br&gt;Oral hydrocodone, hydromorphone, or morphine&lt;br&gt;Transdermal fentanyl liquid</td>
</tr>
<tr>
<td><strong>Skin/subcutis</strong></td>
<td>Soft tissue sarcoma&lt;br&gt;Mast cell tumor&lt;br&gt;Vaccine-associated sarcoma (cats)&lt;br&gt;*Acute side effects in cats tend to be less severe than in dogs</td>
<td>Moist desquamation and sloughing of pads on digits (depending on location treated)</td>
<td>7–10</td>
<td>NSAIDs&lt;br&gt;Tramadol&lt;br&gt;Gabapentin&lt;br&gt;Amantadine&lt;br&gt;OTM buprenorphine&lt;br&gt;Oral hydrocodone, hydromorphone, or morphine&lt;br&gt;Transdermal fentanyl liquid</td>
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<tr>
<td><strong>Perianal/pelvis</strong></td>
<td>Anal sac adenocarcinoma&lt;br&gt;Transitional cell carcinoma</td>
<td>Depends on treatment site but can range from mild to moderate stranguria/hematuria to diarrhea and severe moist desquamation of perianal skin</td>
<td>7–10</td>
<td>NSAIDs&lt;br&gt;Tramadol&lt;br&gt;Gabapentin&lt;br&gt;OTM buprenorphine&lt;br&gt;Oral hydrocodone, hydromorphone, or morphine&lt;br&gt;Transdermal fentanyl liquid</td>
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### Treating Side Effects

Three general principles apply when treating acute side effects of radiation:

1. Administer pain medication
2. Restrict activity until lesions have healed

It is important to counsel owners that lesions will heal if these recommendations are followed.

First-line treatment for acute side effects is administration of an NSAID, such as carprofen (4 mg/kg PO Q 24 H, given with a meal). In cats, acute side effects in rapidly proliferating normal tissues, such as the skin, are not as severe as those seen in dogs (Figure 3). Recently, a new NSAID for cats, robenacoxib, has become available in both injectable and oral tablet formulations. Robenacoxib is labeled for use Q 24 H for up to 3 days in cats.14

As time and treatment progress, patients undergoing definitive radiation therapy require additional oral pain medications, such as tramadol, buprenorphine, gabapentin, and amantadine.
OTM buprenorphine (80–120 mcg/kg Q 12–24 H) or transdermal fentanyl liquid (2.7 mg/kg, one application) can be used to further alleviate pain when NSAIDs and other analgesics do not provide enough comfort.

De/finite Chemotherapy

Although it is not often recognized as a side effect of chemotherapy in veterinary patients, pain is possible due to:

• Drug extravasation
• Unique drug toxicities.

Extravasation

Severe tissue necrosis and pain occur when vesicant chemotherapy drugs, including doxorubicin, vincristine, and vinblastine, are administered extravascularly (Figure 5). Extravasation of doxorubicin results in severe tissue injury that may result in the need for surgical debridement, amputation, or euthanasia.

Extravasation can be avoided by use of a perfectly placed, one-stick IV catheter and vigilant observation. To reduce the risk of inadvertent catheter dislodgment and extravasation in dogs and cats that are too excited for catheter placement with physical restraint alone, chemical restraint—such as a neuroleptic analgesic technique combining a sedative/tranquilizer (eg, acepromazine, midazolam, dexmedetomidine) with an opioid—should be considered.

Once extravasation is known:

• An attempt to aspirate the drug through the IV catheter and then tissue cooling to induce local vasoconstriction and prevent further spread of the drug is recommended.
• Evidence suggests that intravenous administration of the chelating agent dexrazoxane within 6 hours of doxorubicin extravasation may reduce severity of injury, but ideal dose and timing are unknown.
• Anecdotally, topical 99% dimethyl sulfoxide applied 3 times per day and cold compresses applied up to 4 times per day for up to 2 weeks are recommended.
• Use of the NSAID piroxicam has also been reported anecdotally, and other NSAIDs or opioids may be indicated depending on the severity and extent of tissue injury. NSAIDs and opioids may also be useful to reduce the occurrence of self-trauma following extravasation events that could lead to further local tissue injury.

Although most recommendations for treatment of extravasation injury are anecdotal, it is prudent to manage cases of suspected or confirmed extravasation proactively, with combinations of topical dimethyl sulfoxide, cold compresses, NSAIDs, and opioids to reduce the risk for serious and potentially life-threatening tissue injury.

Sterile Hemorrhagic Cystitis

Acrolein is a metabolite of cyclophosphamide that is concentrated in the urinary bladder and induces sterile hemorrhagic cystitis (SHC), a painful and irritating condition that manifests as hematuria, pollakiuria, and stranguria without evidence of a bacterial infection. When SHC occurs, cyclophosphamide is often discontinued to reduce the risk for worsening clinical signs.

Treatment focuses on supportive care with oral pain medications, including opioids and NSAIDs, as no effective specific therapy for SHC exists. Prevention strategies include:

• Co-administering furosemide at doses up to 2.2 mg/kg IV.
• Splitting a cyclophosphamide bolus dose into an oral dose given over 3 to 4 days\textsuperscript{18}
• Administering cyclophosphamide early in the day (to avoid overnight retention of the metabolite in the bladder)
• Providing large amounts of fresh water, and allowing frequent opportunities to empty the bladder.

**Hand–Foot Syndrome**
Chemotherapy pain due to hand–foot syndrome (HFS) or palmar–plantar dysesthesia is well documented in human patients following administration of chemotherapy drugs, including doxorubicin, capecitabine, and 5-fluorouracil.\textsuperscript{19–22} HFS is characterized by diffuse erythema, swelling, and pain of the palmar and plantar surfaces of the hands, feet, or paws.\textsuperscript{19–23}

While uncommon in veterinary medicine, HFS was reported as the dose-limiting toxicity in dogs treated with a liposomal formulation of doxorubicin.\textsuperscript{20–22} This toxicity was reduced, but not completely eliminated, by co-administration of pyridoxine, which allowed fewer treatment delays and dose reductions and a higher cumulative dose compared with placebo-treated controls.\textsuperscript{23}

**Hand–Foot Skin Reaction**
A similar reaction termed hand–foot skin reaction (HFSR) has been reported in humans following treatment with small molecule inhibitors, including sunitinib.\textsuperscript{19,24–25} HFSR is similar to HFS, but the lesions are histologically distinct and confined to pressure points. HFSR has not been reported in dogs treated with the small molecule inhibitors toceranib (an FDA-approved veterinary drug nearly identical in structure to sunitinib) or masitinib.\textsuperscript{26–29} As liposomal formulations of chemotherapy drugs and novel targeted chemotherapy agents become available in veterinary oncology, this side effect may be detected.

**CHRONIC CANCER PAIN & PALLIATIVE TREATMENT**
Many veterinary patients with cancer are unable to receive definitive treatment; this may be due to metastatic disease at time of diagnosis, other life-limiting comorbidities, or lack of owner finances (Figure 1).

The central focus of palliative treatment is relief of pain and suffering. Although most patients undergoing palliative treatment for their cancer will ultimately succumb to the disease, their quality of life can still be greatly improved for a period of time. Palliative treatment includes administration of pain medications and, potentially, various treatment modalities for the cancer itself.

**Palliative Surgery**
In certain clinical situations, cancer that causes discomfort and/or pain may require surgical palliation. It is important for the practitioner to think about the whole patient and disease process when considering this treatment modality as a method of palliation.

The first dictum of palliative medicine is the overriding goal of decreasing the patient’s pain. In the osteosarcoma case described on page 50, surgical amputation alone could be considered a palliative procedure; within 24 hours the patient felt better than it had prior to surgery. The distinction between palliation and definitive treatment in this case was the pursuit of chemotherapy, which created the potential for more side effects but improved long-term survival.

Gilson provides an excellent review of the indications and pitfalls of surgical cancer palliation.\textsuperscript{30} Continuous pain management using NSAIDs, opioids, gabapentin, and amantadine is necessary in the postoperative period and may be needed for continued palliation when additional therapies are not pursued.

**Palliative Radiation**
What distinguishes palliative-intent from definitive-intent radiation therapy are goals of treatment, total dose of radiation delivered, and size of each fraction delivered. Palliative radiation therapy is designed to relieve clinical signs of pain and discomfort and avoid the potential for adverse side effects.

**Indications**
In patients in which definitive surgery and radiation therapy are not possible, palliative radiation therapy should be considered. Patients with gross soft tissue sarcomas, mast cell tumors, histiocytic sarcomas, and nasal tumors are all viable candidates for palliative radiation therapy.

Palliative radiation therapy is especially helpful for relieving pain that results from tumors that invade bone or other areas of the body. Pain sparing occurs as a result of the release of various anti-inflammatory cytokines at the treatment site.
Nasal Tumors: Advanced Techniques Lead to Fewer Side Effects

Recent advances in cancer treatment delivery have diminished clinically significant acute treatment side effects—effects commonly associated with significant morbidity in dogs and cats—for nasal tumors. Intensity-modulated radiation therapy (IMRT), an advanced treatment delivery system, shapes the radiation beam to nearly any complex shape (Figure 6). The highly conformed shape of the beam allows for sharp “falloff” at the borders of the dose, resulting in diminished occurrence or elimination of side effects, which is possible because the energy from the radiation treatment beam is focused on the tumor, avoiding organs with sensitive pain receptors, such as the skin and oral mucosa.

This advanced therapeutic modality is particularly important in treatment of nasal tumors, which are adjacent to critical structures, such as the eyes and brain, and limits common side effects, such as mucositis, moist desquamation, and keratoconjunctivitis sicca (Figure 7).

FIGURE 6. Axial-slice computed tomography scans of the nasal cavity in 2 dogs receiving definitive radiation therapy for a nasal tumor. Red and yellow areas are receiving 100% of the prescribed dose; blue and green areas are receiving 50% of the prescribed dose. Three-dimensional conformal radiation therapy plan (A); IMRT plan (B). Note that the volume of normal tissue, such as the mandible and skin, receive a significantly reduced dose.

* = tumor; + = tongue; # = lips

FIGURE 7. Patient with nasal tumor one week after definitive radiation therapy (19 fractions) using 3-dimensional conformal radiation therapy plan; note the extensive area of radiating moist desquamation present on the medial canthus and lips and areas of redness and dry desquamation present on the dorsum of the nose and caudal to the eye over the frontal sinuses (A). Patient with nasal tumor one week after definitive radiation therapy using advanced, highly conformal, IMRT plan (19 fractions). Although significant moist desquamation is present, it is limited to a smaller area, radiating rostrally from the medial canthus (B). The patient in B only required NSAID pain medication during treatment, whereas the patient in A required multiple medications to manage painful side effects.
reduced osteolysis, and decreased tumor size.\textsuperscript{32} See Consider This Case: Palliative Radiation for Squamous Cell Carcinoma (page 58) for a case presentation that demonstrates the use of palliative radiation.

Tumors with a favorable long-term prognosis and postoperative microscopic local disease, such as an incompletely resected low- to intermediate-grade soft tissue sarcoma of the distal limb, should never be treated with palliative protocols. Owners who cannot afford definitive therapy should be counseled regarding the probability of recurrence (relatively low) and advised to consider palliative radiation therapy or amputation at a later date should the tumor recur.

The probability of a late side effect in slowly proliferating normal tissues, such as the central nervous system, smooth muscle, or bone, increases exponentially when palliative treatment protocols with large fraction sizes, such as those used in palliative radiation therapy, are employed.\textsuperscript{6}

Differences in Therapy & Side Effects
While definitive treatments are delivered on a daily basis in 16 to 24 treatment sessions, palliative radiation therapy is delivered in 1 to 5 treatment sessions, either daily or once weekly. The fraction is also typically larger in palliative protocols, although the total dose delivered is smaller; definitive treatment fractions range from 2 to 3 Gy (total prescribed dose, 48–60 Gy), while palliative treatment fractions range from 4 to 8 Gy (total prescribed dose, 20–32 Gy).

Higher total doses delivered over a longer period of time are more likely to result in acute side effects in the treated areas, such as mucositis, dry desquamation, and moist desquamation. Lower total doses delivered over a short period of time are less likely to result in acute side effects, while still delivering a high enough dose to have an effect on the tumor, including pain relief, reduced tumor size, and decreased mechanical stretching due to space-occupying masses.

New techniques, such as IMRT, can be used to help minimize the potential for acute side effects in sensitive areas, such as the eye (see Nasal Tumors: Advanced Techniques Lead to Fewer Side Effects).

Palliative Chemotherapy
Chemotherapy is frequently used with palliative intent in veterinary patients. Long-term successful outcomes are still possible when chemotherapy is administered with palliative intent, but a reduction in tumor volume or improvement in overall survival time may not be the ultimate goal.

Indications
Palliative-intent chemotherapy is intended to maximize quality of life by decreasing tumor burden or preventing tumor growth that would impair local function. Even in the face of incurable disease, chemotherapy can:

- Decrease tumor burden, as is often the case with nonresectable or metastatic high-grade mast cell tumors and histiocytic sarcoma
- Reduce the rate of tumor growth, ultimately preventing potentially life-threatening tumor sequelae, as is often the case with transitional cell carcinoma.

Therapeutic Approach
Noncytotoxic drugs, such as pamidronate and other bisphosphonates, may be useful in palliating bone pain or reducing risk for pathologic fractures associated with osteolysis. These drugs are frequently combined with chemotherapy, radiation therapy, or both in the treatment of canine appendicular osteosarcoma.\textsuperscript{33}

IN SUMMARY
Cancer is a complex disease process that requires multimodal treatment, including surgery, radiation, chemotherapy, analgesics, and other nonpharmaceutical therapies. Pain can result not only from the cancer itself but also from the modalities that are employed to treat the cancer. Therefore, multimodal treatment should be used to manage cancer-related pain.

As the demand for, and availability of, veterinary cancer care services increase, veterinary practitioners are likely to encounter many of the clinical scenarios outlined in this article. Veterinarians are also likely to encounter pet owners who are interested in pursuing therapy for pets diagnosed with cancer, which requires an understanding of what treatment options are available, when palliative versus definitive care is indicated, and how to manage pain caused by cancer or its treatment.

CRI = constant rate infusion; CT = computed tomography; HFS = hand-foot syndrome; HFSR = hand-foot skin reaction; IMRT = intensity-modulated radiation therapy; NSAID =
Consider This Case: Palliative Radiation for Squamous Cell Carcinoma

An 11-year-old, castrated male mixed-breed dog presented for evaluation of changes in mentation, anorexia, and mucos hemorrhagic nasal discharge that had been occurring for the previous 3 months. On physical examination, the patient was noted to be circling, and manipulation of the head and nose elicited aggression. The patient had a pain score of 5/5 on the in-clinic scale (See Table 3, Part 1: Pathophysiology & Assessment of Cancer Pain, May/June 2015, available at tvpjournal.com).

Diagnostic Approach
Computed tomography (CT) revealed a heterogeneous, contrast-enhancing mass in the nasal cavity, with destruction of the bones of the medial orbit. The mass invaded the cribriform plate and extended caudally for several centimeters into the forebrain, causing meningeal enhancement and lateral shifting of the falx cerebri (Figure 8). A biopsy of the mass was performed, and squamous cell carcinoma was diagnosed on histopathology.

Therapeutic Approach
1. Palliative radiation therapy (4 weekly treatments with an 8-Gy fraction size) was prescribed, using IMRT to spare the eyes and brain.
2. The patient also started receiving prednisone (0.5 mg/kg PO Q 24 H), OTM buprenorphine (120 mcg/kg Q 24 H), and gabapentin (10 mg/kg PO Q 12 H).

When the patient returned 1 week later for the second dose of radiation therapy, the circling behavior had resolved and pain was no longer elicited when the face and head were touched. OTM buprenorphine was discontinued, and the patient was continued on gabapentin and prednisone for the duration of treatment.

Outcome
The patient was euthanized 3 months after finishing treatment due to acute progression of neurologic signs and seizures.

nonsteroidal anti-inflammatory drug; OTM = oral transmucosal; SHC = sterile hemorrhagic cystitis

References
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