Cancer pain is one of the most common, overlooked, and undertreated comorbidities in human patients. In a recent retrospective study of more than 1000 patients presenting to a radiation oncology service for palliative treatment of bone metastasis, over 25% had pain that was inadequately managed before initiation of radiation therapy.1 Other surveys and systematic reviews of the human literature estimate that the prevalence of inadequate pain management among all humans with cancer approaches 50%.2-4 Although the incidence of untreated or undertreated cancer pain among veterinary patients is unknown, it is most likely similar or even higher.

CHALLENGES OF PAIN MANAGEMENT

No published statistical data specify why veterinary patients are undertreated for cancer pain, but clinical experience suggests several reasons:

1. Cancer pain generally progresses slowly until the patient’s physiologic function is severely affected.

2. As the cancer progresses and becomes more advanced, pain may go undetected for some time before owners notice deficits in function or daily routine.

3. Over time, factors that contribute to the progression of acute pain result in chronic pain (Table 1), which becomes more difficult to treat if no intervention occurs.

The insidious onset of cancer pain is further complicated by the fact that veterinary patients cannot verbally communicate their levels of pain. Attending veterinarians and pet owners must evaluate the patient and categorize the level of pain when, and even before, the patient shows clinical signs because, by the time discomfort is recognized, the animal may already be in severe pain that is difficult or impossible to treat.

Further challenges to managing cancer pain in veterinary patients include the:

- Wide variability in training, experience, and comfort

<table>
<thead>
<tr>
<th>TABLE 1. Factors That Contribute to Progression of Cancer Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncontrolled proliferation of cancer cells</strong> may result in:</td>
</tr>
<tr>
<td>• Bone destruction</td>
</tr>
<tr>
<td>• Impingement on muscle and body cavities</td>
</tr>
<tr>
<td>• Invasion into nerves and other functional structures</td>
</tr>
<tr>
<td><strong>Cancer cells often secrete</strong> growth factors, hormones, cytokines, and other chemotactic factors that can contribute to:</td>
</tr>
<tr>
<td>• Wind-up pain</td>
</tr>
<tr>
<td>• Hyperalgesia (increased sensitivity to pain)</td>
</tr>
<tr>
<td>• Allodynia (painful response to stimuli that are not normally painful)</td>
</tr>
</tbody>
</table>

Unrecognized or undertreated pain that progresses from acute to chronic in oncology patients can lead to treatment failure, death, or premature euthanasia despite treatment of the cancer itself. The longer a cancer patient’s pain is ongoing, the more difficult it becomes to successfully treat both the underlying cancer and the pain.
among practitioners for assessing veterinary oncology patients and treating their disease
• Limited pharmacologic options for managing cancer pain
• Hesitation many practitioners face when considering whether to add pain medications to therapy that already includes multiple drugs
• Lack of a universally agreed-upon standard of care—among general practitioners and even oncology specialty groups—for active management of cancer pain in veterinary medicine.

KEYS TO SUCCESSFUL MANAGEMENT
Successful management of cancer pain in veterinary oncology requires knowledge of the following 3 key areas:
1. Basic understanding of the pathophysiology of cancer pain
2. Early recognition of the clinical signs of cancer pain and understanding of the importance of preventing or delaying chronic pain development
3. Proper concurrent pharmacologic pain management during appropriate treatments for the underlying cancer.

Successful cancer pain management also requires a clear strategy of regular (set intervals during treatment) evaluation of the animal’s pain and quality of life by the veterinarian and client.

PATHOPHYSIOLOGY OF CANCER PAIN
In the early stages of cancer, nerve fibers and nociceptors involved in cancer pain are similar to those involved in acute pain and other types of chronic pain. As the cancer progresses, however, the extent of nerve involvement and the pain mechanisms in abnormal tissues can be quite different from those seen with other types of pain.

Cancer pain can be classified into 2 general categories:
1. Endogenous chemical irritation in the tumor microenvironment
2. Compression and inflammation resulting from direct tumor invasion of normal tissues.

The pain inflicted by abnormal cellular proliferation is very different from chronic pain induced by other conditions, such as osteoarthritis. Table 2 (page 62) summarizes the origin of the sensory nerves associated with certain tumor types, together with levels of pain in dogs and cats.

Endogenous Chemical Irritation
Microenvironment Irritation. In cancer cells, driving mutations that cause unrestrained cellular growth may result in the release of neurotropic growth factors, such as nerve growth factor (NGF). NGF regulates the growth and sensitivity of neurons important for the sensation of pain. Overabundance of peripheral sensory neurons within, and adjacent to, the tumor may result in:
• Increased pain sensitivity
• Decreased pain threshold
• Development of long-lasting chronic pain.

Experimental models of cancer-induced bone pain in animals have found that antibody blocking of NGF results in decreased metastatic bone pain, and a monoclonal anti-NGF antibody developed for dogs is under clinical investigation. Use of canine anti-NGF monoclonal antibody in an experimental model of pain showed significantly reduced lameness scores compared with a placebo. These studies provide evidence that large tumors with rapid rates of growth can also induce pain as a result of abnormal chemical mediators secreted by the tumor into the microenvironment.

Tissue Hypoxia. In addition to chemical mediators in the microenvironment, cancer cells with limitless replicative potential have abnormally rapid growth rates that result in abnormal tissue expansion, innervation, and disorganized tumor vasculature. Disorganized tumor tissues and vasculature result in tissue hypoxia and nutritional deprivation, which trigger further release of various harmful chemicals and chemotactic factors that can lead to peripheral and central pain sensitization.

A tumor need not be large in order to cause regional tissue hypoxia because the maximum
distance oxygen can diffuse is limited to 70 micrometers. This short diffusion distance prevents effective oxygen delivery beyond this radius from often sparse capillaries in the tumor microenvironment. Abnormal tumor vasculature lacks normal physiologic mechanisms of autoregulation; capillaries and arterioles within the tumor vasculature cannot constrict or dilate in response to lowered or altered blood flow, furthering the cycle of localized hypoxia.14

Localized hypoxia of the tumor microenvironment leads to tissue acidosis, which:
- Lowers the sensitivity threshold of peripheral sensory afferents and
- Can lead to allodynia and hyperalgesia.

Increased expression of acid-sensing ion channels in the acidic tumor microenvironment may result in:
- Peripheral pain sensitization and
- Lower pain threshold.

**TABLE 2.**
Common Tumors, Origin of Sensory Nerves, and Pain Levels in Dogs and Cats

<table>
<thead>
<tr>
<th>ANATOMIC LOCATION</th>
<th>SELECTED COMMON TUMOR TYPES</th>
<th>SENSORY NERVES</th>
<th>TISSUE INVOLVEMENT</th>
<th>DEGREE OF PAIN/FUNCTIONAL INTERFERENCE</th>
</tr>
</thead>
</table>
| Head/Neck         | • Oral malignant melanoma<sup>a</sup>  
                   • Squamous cell carcinoma<sup>b</sup> | Cranial nerves (CN V, CN VIII, CN IX) | Invasive tumors that may involve gingiva, soft tissues of tongue/mouth, and bone | • Diminished ability to prehend food  
                   • Tumors may be infected and odiferous  
                   • Tumors that invade bone are exceptionally painful |
| Nasal             | • Nasal adenocarcinoma (60%)<sup>a</sup>  
                   • Sarcomas (40%)<sup>a</sup>  
                   • Lymphoma<sup>b</sup> | CN I (olfactory nerve) involvement may affect patient’s ability to detect food  
                   Cranial nerves (CN V, CN VIII, CN IX) | Localized destruction of nasal turbinate bones  
                   May invade through hard palate or into cribiform plate, frontal bone, or orbit | • Back of oropharynx may be red and irritated on physical examination  
                   • Generally, small, rostral tumors that involve only the nasal turbinates cause mild pain  
                   • Highly invasive masses involving the skull bones or orbit may cause severe pain  
                   • Most clinical signs result from postnasal drip due to secretions from the tumor and inflamed nasopharyngeal tissues |
| Skin/Subcutis     | • Mast cell tumor  
                   • Soft tissue sarcoma  
                   • Vaccine-associated sarcoma<sup>a</sup> | Pain is detected by sensory afferents and transmitted to dorsal horn of spinal cord  
                   Variable—may occur anywhere on the body where there is skin | Mast cell tumors may be very localized to the skin but can directly invade into deeper structures  
                   Soft tissue sarcomas, as a rule, tend to move along fascial planes but do not invade them | • If masses grow to an advanced stage, pressure from the mass may cause severe pain  
                   • Mast cell tumors as a group may secrete histamine and serotonin, which directly cause pain and decrease the pain threshold  
                   • Sarcomas tend to cause mechanical impingement of bones and joints; mild to moderate pain may occur  
                   • Ulcerated sarcomas and mast cell tumors can cause severe pain |
| Bone              | • Osteosarcoma  
                   • Hemangiosarcoma  
                   • Metastatic  
                   • Other | Bone is richly innervated, especially on periosteal and endosteal surfaces  
                   Pain is detected by sensory afferents and transmitted to dorsal horn of spinal cord  
                   Variable—may occur in any bone of the body (limbs are most common) | Medullary cavity, periosteum, endosteum | Primary and metastatic bone tumors may cause severe pain and inhibit mobility of the patient |
| Metastatic        | • Hemangiosarcoma  
                   • Oral malignant melanoma  
                   • Osteosarcoma | Variable—visceral sensory afferents, bone invasion | Viscera, such as lungs/pleura, liver, kidney, and bone | Highly variable—little or no pain to severe, unrelenting pain |

a. Dogs; b. Cats
Examples of Endogenous Chemical Irritation

Mast Cell Tumors
A common canine cancer that releases growth factors, hormones, and cytokines into the tumor microenvironment, which then contribute significantly to localized pain pathology, is the mast cell tumor (MCT).

These tumors are the most common cutaneous cancers in dogs and may secrete serotonin, histamine, and collagenase, all of which contribute to upregulation of pain stimuli locally and systemically. Serotonin, in particular, results in sensitization of peripheral pain fibers, while histamine and collagenase cause localized damage and inflammation in tissues. For these reasons, treatment of canine MCT should routinely include pain management.

When an MCT degranulates (Figure 1), the affected areas become red and edematous circumferential to the primary lesion—this is called Darier’s sign. A red, edematous, and pruritic MCT is evidence of histamine and serotonin release from the MCT into the local microenvironment, which may occur in both low- and high-grade lesions.

Feline MCTs may also release these chemotactic agents into the tumor microenvironment, but the incidence of high-grade tumors that cause significant morbidity is lower in cats than dogs.

Squamous Cell Carcinoma
Oral squamous cell carcinoma (OSCC) is the most common oral tumor in cats. Significant areas of hypoxia have been demonstrated in feline OSCCs through use of multiple hypoxia detection methods. Due to the highly invasive nature of this tumor and its characteristically rapid growth, mechanisms of hypoxic pain sensitization are likely.

Feline OSCCs are highly invasive tumors that can affect the bone and soft tissues of the mouth. This localized destruction of bone and soft tissues directly causes severe pain due to the rich peripheral innervation of periosteal and endosteal surfaces in bone (Figure 2).

FIGURE 1. This high-grade MCT in a dog degranulated after inadequate debulking surgery via mid femoral amputation. Debulking surgery resulted in a significant mass of high-grade tumor being left behind. Initially, the incision healed. However, several weeks later stump recurrence was evident with significant morbidity (star). The red, edematous area radiating from the lesion center represents degranulation of mast cells in the tumor and release of histamine and serotonin—Darier’s sign. The central necrotic cap, with eschar present, in the middle of the red degranulated lesion indicates tissue hypoxia. This lesion is an extreme example of a tumor that simultaneously demonstrates all 3 cancer pain mechanisms (irritation to microenvironment, hypoxia, and inflammation). Right arrow indicates cranial direction; left arrow indicates caudal direction.

FIGURE 2. OSCC is the most common oral tumor of the cat and may cause hypoxia-induced pain. This cat has a highly invasive squamous cell carcinoma of the maxilla, which demonstrates erythema, necrosis, and invasion into the soft tissues of the hard palate. Significant areas of tissue hypoxia may be present in this lesion, leading to pain sensitization. OSCCs are highly invasive and may invade into the bone and soft tissues of the mouth, resulting in severe pain, constant salivation, and loss of normal eating and drinking function.
Direct Tumor Invasion

Tumors act as space-occupying lesions that cause substantial pressure and compression, leading to mechanical and pressure-induced pain. Large tumors are common in veterinary oncology patients because these animals are usually presented when their tumors have reached a noticeable size and advanced stage.

Pain Signal Cycling. Large tumor masses may cause stretching of mechanoreceptors in the skin and muscles, as well as compress nerves in the surrounding tissues. If left untreated, a large tumor mass may result in a vicious cycle of pain signaling. For example, a very large soft tissue sarcoma in a dog (Figure 3) can cause significant pain from the mass protruding outward into the integument and inward toward the abdomen.

Such compressive pressure results in constant stimulation of the sensory receptors due to mechanical stretching and distortion. Chronically distorted mechanoreceptors send continuous pain signals to the dorsal horn of the spinal cord, resulting in chronic pain and central sensitization.

Treatment for this type of pain may include surgical removal of the mass or, if removal is not possible, palliative treatment. Such treatment may include palliative radiation therapy or, in limited situations such as airway obstruction, debulking surgery and must include concurrent pain medications.

Inflammation. Inflammation is an integral part of the uncontrolled proliferation of abnormal cells during the direct invasion of these abnormal cells into normal tissues. Cancer cells may destroy normal tissue surrounding the tumor and trigger the patient's inflammatory response. Inflammatory cytokines and chemokines are released at the site of inflammation, resulting in upregulation of inducible cyclooxygenase-2 and recruitment of more inflammation.

From this perspective, inflammatory cancer pain resembles osteoarthritic pain, although the mechanism is slightly different. Local inflammation around tumors adds an inflammatory component to the patient's pain, beginning with vasodilation, fluid extrusion, and recruitment of neutrophils to the tumor site. Tumors in various locations may also become infected, furthering the cycle of inflammation (Figure 4).

Because inflammatory cancer pain is similar in nature to osteoarthritic inflammation, tumors with such lesions can respond favorably to nonsteroidal anti-inflammatory drugs for pain relief during cancer treatment.

ASSESSMENT OF CANCER PAIN

An ideal cancer pain scoring system should include both:

• An objective in-hospital/clinic pain measurement score
• A score based on the owner’s impression of the animal’s level of pain and quality of life at home.
The veterinarian can use the in-hospital/clinic pain score system upon admission and at follow-up visits to score the patient’s pain initially and evaluate the effectiveness of therapeutic interventions. To achieve this goal, we developed the Purdue Integrated Cancer Pain Score System, which includes the Canine/Feline Brief Pain Inventory for pet owners (page 66) and an in-hospital cancer pain score system for the veterinary team (Table 3).

**Modified Canine/Feline Brief Pain Inventory**

In humans, a rapid and objective pain inventory system called the Brief Pain Inventory (BPI) was developed to validate large, multi-institutional clinical trials. In 2006 researchers at the University of Pennsylvania modified the BPI for use in dogs and called it the Canine BPI (cBPI). At Purdue University, we modified the cBPI (mCBPI) with the intention to designate this system specifically for oncology patients (dogs, cats, and potentially other species) and to exclude patients with osteoarthritis.

Our in-home pain inventory system consists of 3 scored sections, with a total of 10 questions catalogued by dog or cat owners. The first 2 sections are objective and ask owners to score the patient’s pain and function, respectively. The scores can be averaged to help the practitioner gauge the patient’s progress over time. The final question is an overall subjective impression of the client’s perception of the patient’s quality of life.

**TABLE 3. In-Hospital Cancer Pain Score System**

<table>
<thead>
<tr>
<th>PAIN SCORE</th>
<th>BEHAVIOR SIGNS</th>
</tr>
</thead>
</table>
| 1 (minimum pain) | • Relaxed, resting comfortably, not vocalizing, moving freely, calm or asleep  
|               | • Palpation of lesion elicits no reaction from patient |
| 2 (faint pain)  | • Minimal agitation, resting calmly, barely noticeable alteration from signs of minimal pain, some position changes  
|               | • Palpation of lesion elicits minimal response |
| 3 (mild pain)  | • Mild agitation, some position changes, responds to calm voice and stroking, some salivation, occasionally vocalizing  
|               | • Palpation of lesion may cause patient to turn head, lick and/or scratch the lesion |
| 4 (moderate pain) | • Moderate agitation, vocalizing, excessive salivation, muscle trembling, frequent position changes, some thrashing movements  
|               | • Palpation of the lesion may cause the patient to become aggressive or traumatize the lesion further |
| 5 (severe pain) | • Severe agitation, vomiting, vocalizing, excessive salivation, extremely depressed, inactive  
|               | • Palpation of the lesion increases the level of agitation |

The veterinarian can use the in-hospital/clinic pain score system upon admission and at follow-up visits to score the patient’s pain initially and evaluate the effectiveness of therapeutic interventions. To achieve this goal, we developed the Purdue Integrated Cancer Pain Score System, which includes the Canine/Feline Brief Pain Inventory for pet owners (page 66) and an in-hospital cancer pain score system for the veterinary team (Table 3).

**In-Hospital Cancer Pain Score System**

To assess the progress of cancer treatment with pain management, we use the in-hospital cancer pain score system. This system allows for the evaluation of pain intensity and the effectiveness of pain management strategies. It is based on observing the patient’s behavior and responses to pain indicators such as vocalization, movement, and postural changes. The Pain Score, Behavior Signs, and Significance of the Score are categorized into five levels: 1 (minimum pain), 2 (faint pain), 3 (mild pain), 4 (moderate pain), and 5 (severe pain). Each level includes specific signs and behaviors that help in making informed decisions about pain management.

**References**

1. Nicholas Rancilio, DVM, Diplomate ACVR (Radiation Oncology), is a clinical assistant professor at Purdue University College of Veterinary Medicine. He received his DVM from Michigan State University, completed a small animal rotating internship at Washington State University, and completed a residency in veterinary radiation oncology at Purdue University. His interests include oncology patient palliative and hospice care, as well as image guided radiation therapy and stereotactic body radiotherapy.

2. Jean Poulson, DVM, PhD, Diplomate ACVR (Radiation Oncology), is an associate professor at Purdue University College of Veterinary Medicine. She received her DVM and PhD from Colorado State University. Her interests include comparative oncology studies in veterinary cancer patients to benefit both the pets and human patients with similar diseases, intensity modulated radiation therapy (IMRT), and intraoperative radiation therapy.

3. Jeff Ko, DVM, MS, Diplomate ACVAA, is a professor of anesthesiology at Purdue University College of Veterinary Medicine, and is an anesthesiologist at Purdue Veterinary Teaching Hospital. He has taught anesthesiology at Virginia Tech, University of Florida, and Oklahoma State University. Dr. Ko has authored over 100 refereed articles and has recently published the book, Small Animal Anesthesia and Pain Management: A Color Handbook.
### Modified Canine/Feline Brief Pain Inventory (mCBPI)

Nicholas Rancilio, DVM, Diplomate ACVR (Radiation Oncology); Jean Poulson, DVM, PhD, Diplomate ACVR (Radiation Oncology); and Jeff Ko, DVM, MS, Diplomate ACVAA

Purdue University

#### DESCRIPTION OF PAIN

Rate your pet’s pain.

<table>
<thead>
<tr>
<th>CIRCLE THE ONE NUMBER THAT BEST DESCRIBES THE PAIN AT ITS WORST IN THE LAST 7 DAYS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>Not painful</td>
</tr>
</tbody>
</table>

CIRCLE THE ONE NUMBER THAT BEST DESCRIBES THE PAIN AT ITS LEAST IN THE LAST 7 DAYS.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

CIRCLE THE ONE NUMBER THAT BEST DESCRIBES THE PAIN AT ITS AVERAGE IN THE LAST 7 DAYS.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

CIRCLE THE ONE NUMBER THAT BEST DESCRIBES THE PAIN AS IT IS RIGHT NOW.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

#### DESCRIPTION OF FUNCTION

CIRCLE THE ONE NUMBER THAT BEST DESCRIBES HOW DURING THE LAST 7 DAYS PAIN HAS INTERFERED WITH YOUR PET’S:

**GENERAL ACTIVITY**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|
| Does not interfere |

**ENJOYMENT OF LIFE**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

**ABILITY TO ENJOY A PEACEFUL NIGHT SLEEPING**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

**EATING OR DRINKING (APPETITE)**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

**INTERACTION WITH PEOPLE OR OTHER PETS**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

#### OVERALL IMPRESSION

CIRCLE THE ONE RESPONSE THAT BEST DESCRIBES YOUR PET’S OVERALL QUALITY OF LIFE OVER THE LAST 7 DAYS.

| Poor | Fair | Good | Very Good | Excellent |
|---|

Visit [tvpjournal.com](http://tvpjournal.com) to download this form for use in your practice.
pain score system. This modified scoring system was developed previously by one of the authors. The in-hospital cancer pain score system is a 5-point scale on which a pain score is assigned to the dog or cat upon examination when admitted for care. The patient is assessed daily, and the pain score is assigned and recorded.

While the in-home pain inventory score provides a baseline from the perspective of the owner, the in-hospital pain score system provides a progress report for both cancer treatment and concurrent pain management. The clients are asked to continue the in-home pain inventory system when the animal is discharged.

Pain medication is adjusted as required based on the whole Purdue Integrated Pain Score System. The goal of this system is to provide a user-friendly tool that:

• Can be adapted as needed when treating cancer patients
• Tracks the status of pain relief, restoration of function, and quality of life over time.

IN SUMMARY
We hope that this article, and the next article, raise awareness about the all-too-often overlooked problem of cancer pain and help practitioners provide a sound, objective assessment and treatment strategy when managing cancer pain in dogs and cats.

BPI = Brief Pain Inventory; cBPI = Canine Brief Pain Inventory; mCBPI = Modified Canine Brief Pain Inventory; MCT = mast cell tumor; NGF = nerve growth factor; OSCC = oral squamous cell carcinoma

References