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Vinay Puttanniah
Brian M. Bruel
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Editors

Essentials of Interventional Cancer Pain Management

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Preface

The writing of this manuscript has been a remarkable experience that started 4 years ago and has now finally reached its completion phase. My decision to pursue this project was not only to share my thoughts in the field of interventional cancer pain medicine but also to educate myself on how various disciplines both encounter and treat their cancer pain patients. The manuscript is not meant to diminish the incredible work, education, and research that have improved pharmacotherapeutic options for our patients, but rather serve as a supplement to these therapies.

All too often, it is easy to assess one problem and quickly “Google” it for a searchable solution. We find ourselves piecing together answers from a handful of incomplete resources. These fragmented answers don’t tell the complete story. Thus, I do believe that a larger compendium, a “textbook,” can be quite helpful. Our many specialties – radiation oncology, neurosurgery, rehabilitation, supportive care, oncologists, radiologists, psychiatrists, integrative medicine, and anesthesiologists, among others – address only a part of the cancer pain story. But as far as I have seen, we have been missing one collective resource that surveys the broad knowledge of these fields. I pursued this project specifically because I wanted to help create something meaningful for all of us struggling to successfully treat cancer pain.

The first part of the book addresses the lack of consistency seen in the literature regarding interventional treatment options for specific cancer pain syndromes. Initially, we discuss both primary cancer and treatment-related cancer pain syndromes that we may encounter as physicians managing cancer patients. What follows is our initial attempt to implement paradigms we can use in treating specific groups of cancer, such as breast cancer. This is a daunting task made even more difficult as new treatment options emerged during the writing of the textbook. I hope this will be a starting point for future paradigms to develop for our patients.

The remainder of the text divides into a more common approach to addressing interventional cancer pain medicine. After discussing interventional options that are commonly employed by physicians, we begin to investigate how our surgical colleagues may address some of our more severe pain syndromes. We continue with an extended section on perhaps the most important interventional available for our patients, intrathecal drug delivery.

Next, an emerging field of interventional oncology has led to many therapeutic advances in treating focal cancer lesions. We highlight radiologic options in targeted neurolysis and ablative techniques, specifically for bone metastasis. Furthermore, with newer modalities in radiation delivery, I feel that it is important to develop collaboration with our radiation oncology colleagues to develop paradigms involving radiation therapies.

As we begin to see how cancer pain affects our patient’s quality of life and function, we introduce our rehabilitation section to address these concerns. The effects of exercise and physical therapy should not be underappreciated especially when addressing fatigue and oncologic outcomes. I have personally seen the improvements of our bracing and manipulation techniques in improving our patient’s mobility and pain. I think this section’s significance is highlighted in the care the subject is given in our text. The final section echoes this sentiment as we introduce our integrative and psychological therapies. Taken together, we can globally assess and address our patient’s needs throughout the cancer journey.

I hope this reference will serve as a special guide for our readers. The large breadth and scope of this project exemplifies our need to coalesce knowledge to truly deliver a multispecialty approach for managing our cancer pain patients. This is our first step in this field and hopefully will expand ideas for our patients on this foundation we present to you.

In the end, I hope this manuscript serves to help and guide many future physicians, as it has helped me, establish a better framework to manage our complex patients.

New York, NY, USA

Amitabh Gulati

Acknowledgments

From Amitabh Gulati:

Throughout this journey, I have been fortunate to have the support of many people but none more important than my wife, Rati, and my two young children, Ariya and Taran (both of whom were born during this project).

Furthermore, I would like to take a moment to commend my mentors during my journey as a cancer pain physician. As a resident, I was exposed to the caring and compassion required to support our cancer patient's journey. Under Dr. Michael Byas-Smith's tutelage, I came to realize that for patients suffering from cancer-related pain, their fight is surviving and beating cancer, but this pain is a constant reminder of their struggle. While "treating the cancer will treat the pain" works, lessening suffering during the process should be both an admirable goal and a necessity. While I was a fellow, Dr. Kenneth Cubert exemplified this as a mentor and friend. We play a small, yet vital role to help our fellow patients overcome their disease. I want to personally thank both and many of my other esteemed colleagues for their inspiration and everlasting knowledge.

Furthermore, in the last few years, I have cherished the exchange of ideas with the Cancer Pain Resource Consortium. This may very well be the first group of people with the diversity of experiences allowing all of us to collaborate and treat our patients with a new sense of completeness. Many of the authors are eager members who share the same passion as I do. I hope that this project is a testament to the group's ideals in pursuing the best care for all of our patients.

While I hope we have contributed to this field, I feel that this project is just the beginning of our goal to improve our patient's care. Our patient's lives are changing because of newer oncologic treatments and promise. Maybe we will be lucky one day, and cancer will be treated quickly and without suffering. Until then, I hope all of us in this field adapt and treat our patients with the best of our abilities, using the growing collaboration among us.

From Vinay Puttanniah:

To my mentors and teachers in science and medicine who encouraged me to ask the difficult questions and pursue profound answers.

To my father who instilled in me the value of hard work and dedication entirely through his actions.

To my mother who showed me what it meant to practice compassionate medicine.

To my children, Arun, Devan, and Vera, whose curiosity and persistence inspire me daily to be the best father and teacher I can be.

And most of all, to my wife, Lukshmi, for believing in me. Your relentless encouragement, guidance, and unconditional love have allowed, inspired, and motivated all of my actions.

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Part I

Perspectives on Cancer Pain Medicine

Perspectives on Interventional Cancer Pain Management

1

Arvider Gill and Oscar A. de Leon-Casasola

As of January 2012, approximately 13.7 million Americans with a history of cancer were alive [1]. It is unclear how many of these individuals were cancer-free and how many had evidence of cancer and may have been undergoing treatment. Regardless, the burden of disease is significant; about 1,665,540 new cancer cases, not including cancer in situ, are expected to be diagnosed in 2014 [1]. If 30–50% of individuals with advanced cancer experience significant pain, then one can understand the high prevalence of pain affecting this population. Moreover, the 5-year relative survival rate for all cancers diagnosed between 2003 and 2009 is 68%, up from 49% in 1975–1977 [1]. These numbers explain the high number of patients experiencing pain due to their cancer treatments, including chemotherapy-induced peripheral neuropathy, postradiation visceral and neuropathic pain, and postsurgical pain syndromes. These survivors have increased the need for resources to treat these patients at cancer centers, as they have complex pain syndromes that are not managed by community physicians.

Despite advances in the understanding of the neurobiology of pain in cancer, the translation of this information to multimodal pharmacologic analgesic therapy and the advent of new interventional techniques for the management of cancer pain have not shown a dramatic reduction in the prevalence of patients experiencing cancer pain. Recently, a group in the Netherlands reported that 55% of the 1429 respondents with a diagnosis of cancer had experienced moderate to severe pain in the week prior to the

survey and that 42% of patients were experiencing pain despite receiving pharmacological treatment for it [2]. In the United States, 3,123 ambulatory patients with breast, prostate, colorectal, or lung cancer were evaluated for pain at their first visit and then 4–5 weeks later. Of those patients, 67% had pain and ongoing pharmacological treatment with opioids at the first visit. However, 33% did not have adequate pain control at that time despite their treatment with opioids [3]. At the follow-up visit, though they continued treatment with opioids, there was no reduction in the number of patients experiencing inadequate pain control [3]. This study also showed that the prevalence of pain due to solid tumors has not changed in the United States in more than 20 years, despite the wide availability and increased consumption of opioids [3]. In contrast, a randomized clinical trial comparing intrathecal therapy (IT) to comprehensive medical management (CMM) in the treatment of refractory cancer pain showed that once the patients were enrolled into the study, and then treated by a pain specialist, there was a further 39% pain reduction in patients allocated to the CMM group versus a 51% in those receiving IT therapy [4]. The difference was not statistically significant illustrating the power of pharmacological therapy in the hands of pain specialists.

These findings suggest that the involvement of a pain specialist may have a significant impact in the quality of pain control experienced by cancer patients. This difference may be the result of the implementation of multimodal therapy with topical analgesics [5], judicious opioid use [6], anticonvulsants with modulating capabilities of the voltage-gated calcium channel [7], tricyclic antidepressants [7], and titration to doses associated with therapeutic effects [8]. The importance of adequate pain management in cancer patients needs to be underscored because there is evidence in the oncology literature that survival rates are proportionally related to symptom control and that pain management contributes to better psychosocial functioning and quality of life [9]. Because of the interactions of psychosocial issues and

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pain, care for these patients is best provided in a multidisciplinary environment where psychological support includes emotional support, coping skills training, and cognitive behavioral therapy [10].

As noted, evaluation of pain is critically important in the oncology patient. Pain intensity must be quantified, and quality must be characterized by the patient (whenever possible based on patient communication capacity). The brief pain inventory is an appropriate tool for this purpose [11], while the short form McGill Pain Questionnaire may be used in cancer patient to evaluate the multidimensionality of pain [12]. A comprehensive pain assessment should be performed if new pain is present and regularly performed for persisting pain. Moreover, the quality of pain must be evaluated to determine if there is a neuropathic pain component. There are several neuropathic pain scales that may be implemented for this purpose, including the Douleur Neuropathique (DN4) [13] and the Leeds assessment of neuropathic symptoms and signs (LANSS) [14], which are easy to use, and may be applied in a short period of time. The patient impression of adequate pain relief and the healthcare provider assessment of adequacy of function, and any special issues for the patient relevant to pain treatment, is also necessary to have a complete evaluation of the success of therapy. Because patients with cancer pain will likely need opioid therapy, it is also important to evaluate the patient for the risk of abuse and diversion. Several tools have been created for this purpose and can be easily implemented [15, 16].

Pharmacological pain therapy is very successful in cancer pain [6, 17]. However, invasive techniques are sometimes needed because patients cannot tolerate pharmacologic titration to therapeutic levels or because inadequate analgesia is achieved despite maximum doses of these agents. In these individuals, there are several options. These include neurolytic blocks of the sympathetic axis for those patients with a visceral pain component [18, 19], intrathecal therapy for both somatic and neuropathic pain components [20–22], peripheral and spinal cord stimulation [23], and other interventional procedures performed in the non-cancer population, as non-cancer-related pain may also occur in this population.

In summary, the use of pharmacological multimodal therapy and interventional procedures may result in successful pain control in the great majority of patients afflicted by cancer-related pain when implemented by practitioners well versed in the use of these alternative therapies.

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The Practice of Cancer Pain: A Case Series

2

Sana Shaikh

Introduction

Surviving cancer is just the beginning. Often the struggle for many patients is thriving after treatment which may be limited by pain. While strategies to treat pain in the chronic pain population exist, implementing pharmacologic and interventional therapies for the cancer pain patient may be challenging. The following case series illustrate a framework that chronic pain physicians may use to treat cancer pain syndromes.

The clinical practice of pain management can vary from one practice to another based on patient population and referrals. In community-based practices, practitioners may have a consistent population base with similar anatomy and pathophysiology. A distinct challenge to the practice of cancer pain medicine is that each patient's tumor pathology and metastatic disease leads to evolving sources of pain. It is important to consistently reevaluate imaging as the primary and secondary diseases result in changing pain syndromes. Choosing interventions is often balanced with oncologic treatment protocols and life expectancy.

Case 1: Oncologic Diagnosis in the Community Setting The incidence of cancer is 454.8 cases per 100,000 men and women per year (based on 2008–2012 cases) [1]. The epidemiology of cancer pain among diagnosed cases of cancer is variable depending on the source. A systematic review of 52 articles showed that pain was prevalent in 64% of patients with metastatic or advanced-stage disease, 59% in patients on anticancer treatment, and 33% in patients after curative treatment [2]. Another study estimated the prevalence of pain in cancer at 25% for those newly diagnosed, 33% for those undergoing active treatment, and greater than 75% for those with advanced-stage disease [3, 4]. Due to the

high prevalence of pain as a symptom in cancer patients, it is important to consider an underlying oncologic process in the differential diagnosis when evaluating the initial presentation of pain.

Case 1: A 75-year-old female with a distant history of non-small cell lung cancer presents with right shoulder pain. The pain in the right-sided shoulder is a constant, sharp pain with radiation to the lateral aspect of the deltoid, elbow, and anterior chest wall over the right pectoralis muscle. She denies any numbness or tingling in the arm. Upon initial presentation of pain, the patient was evaluated at a community-based pain practice where she was given a prescription for physical therapy for the right shoulder and an intraarticular steroid injection.

The patient noted that physical therapy exacerbated her shoulder pain and that the injection resulted in minimal improvement of her symptoms. Multiple opioid regimens were tried with dose-limiting nausea noted and a lack of adequate pain relief achieved. Despite the addition of steroids, nerve pain-modulating medications, and muscle relaxants, the pain progressively worsened at which time she presented to the hospital with severe pain and limited ability to move the right shoulder.

CT examination of the right shoulder revealed a lytic lesion in the glenoid process of the right scapula along with a complete supraspinatus tear (Fig. 2.1). A PET scan showed a large lytic lesion within the right coracoid process extending into the glenoid process. She was started on a regimen of steroids and radiation therapy to the right glenoid process. After 2 weeks of radiation with minimal improvement in symptoms, both the interventional pain service and orthopedic surgery were consulted for possible interventions to improve patient's shoulder pain.

Given her the anatomy and location of her pathology, the patient would unlikely benefit from an additional intraarticular shoulder joint injection. A consultation and discussion with orthopedic surgery led to a recommendation of

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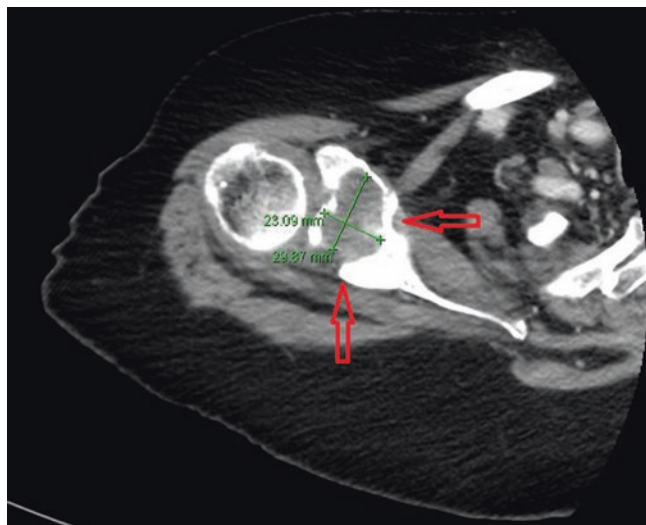


Fig. 2.1 CT scan of the right upper extremity is demonstrating a lytic metastasis in the superior glenoid (arrows) with new cortical breakthrough and an extraosseous soft tissue component and new probable nondisplaced, pathologic fracture

surgical resection of the coracoid and scapula fracture along with rotator cuff tendon repairs. After pain management, anesthesia, and surgical discussion, it was decided to proceed with the surgery with preoperative nerve blocks to help with postoperative pain control and rehabilitation. Ultrasound guidance was used to target right cervical C5 and C6 for neural blockade in combination with the PECSII nerve block. Perioperatively, the patient was noted to have excellent pain relief with regional analgesia leading to an overall perceived decrease in oral opioid regimen requirements.

Patients undergoing orthopedic surgery for tumor resection often have anatomical considerations unique to their tumor location. Surgical incisions and planning can often be unpredictable and cross multiple dermatomes in comparison with orthopedic surgery for nonmalignant pain. Careful planning between the acute pain specialist, anesthesiologist, and surgical teams is important to ensure adequate perioperative pain relief.

Case 2: Symptom Management in Oncologic Pain Treatment A systematic review of palliative symptoms in cancer patients showed that their most prevalent symptoms were fatigue, excretory symptoms, urinary incontinence, asthenia, pain, constipation, and anxiety which occurred in at least 50% of patients [5]. In a comparison between palliative care in cancer and non-cancer geriatric patients, cancer patients were found to have more pain, digestive symptoms, psychological symptoms, and fatigue than non-cancer patients. The study also found that the prevalence of digestive symptoms, pain, and psychological symptoms was higher in younger and in cancer patients than in the elderly

and the non-cancer patients [6]. A systematic review demonstrated that home, hospital, and inpatient specialist palliative care significantly improved patient outcomes in the domains of pain and symptom control, anxiety, and reduced hospital admissions [7]. Overall the treatment of palliative and pain symptoms is crucial to the quality of life patients experience as part of their cancer treatment.

Case 2: A 57-year-old male with metastatic colon cancer involving the liver and lungs presents with intractable hiccups. His hiccups started after a CT scan and have occurred every few minutes consistently with some periods of pause not lasting longer than 20 min. As an outpatient, his oncologist tried a regimen of baclofen twice a day dosing with no change in symptoms. He was also given a single dose of fluconazole to empirically treat esophageal candidiasis. As part of the workup for this patient's new onset of hiccups, the patient had reimaging of the body including CT of the chest, abdomen, and pelvis (Fig. 2.2). This imaging showed an increase in size and number of multiple bilateral pulmonary metastases and persistent splenomegaly, with portal venous hypertension. It was suspected that diaphragmatic irritation secondary to pulmonary metastatic disease was the likely etiology of the patient's persistent hiccups.

A trial of bilateral sphenopalatine ganglion blocks was performed which resulted in only a 20 min resolution of the hiccups. A trial of gabapentin 300 milligrams daily was initiated and titrated to three times a day dosing along with a regimen of oral viscous lidocaine to be swallowed instead of rinsed three times a day. The patient had complete resolution of hiccups after therapeutic titration of oral viscous lidocaine and Neurontin at three times a day. The patient was discharged on maintenance gabapentin therapy and oral viscous lidocaine on an as-needed basis.

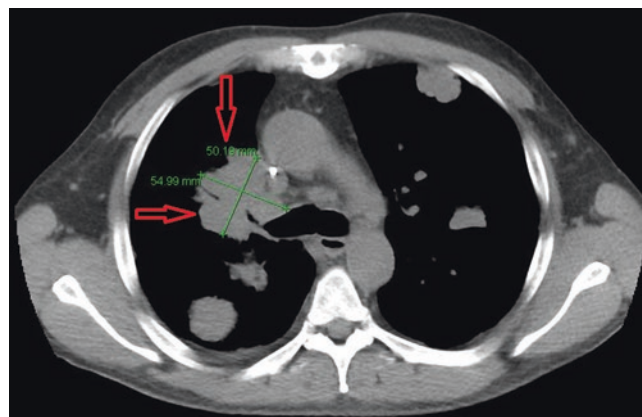


Fig. 2.2 CT of the chest, abdomen, and pelvis with contrast showed slightly increased size of bilateral pulmonary metastases in the right upper and lower lobes. The picture above showed the right peri-hilar mass increased marked narrowing of the right upper lobe bronchus (arrows)

Localized treatments for pain including directed topical treatments can often be helpful to treat novel causes of pain.

Case 3: Changing Pain States in Oncologic Patients The symptoms of cancer often change over time, and there is a need for practitioners to have a low threshold for reevaluation of the underlying disease process. New symptoms can manifest from treatment or from progression of cancer, either locally or to distant sites. Diagnostic workup of these possibilities is important in determining the treatment plan. Collaboration between interventional pain and other service may offer patients a wide variety of options to treat different pain and non-pain symptoms during cancer treatment. Ultimately, it is most important to consider a wide array of therapies to optimize symptom manage and quality of life.

Case 3: A 41-year-old male with multifocal peripheral schwannoma involving the pleura and liver presents with right-sided chest wall pain. Interventional radiology recommended cryoablation of this lesion on the anterior aspect of the seventh rib. The patient was also referred for consultation with the pain service for possible interventional options for pain relief.

On initial assessment, patient noted pain as a sharp, tingling, and burning in the right upper quadrant of the abdomen. Despite the use of opioids, the patient found the pain to cause significant daily disability. Upon physical exam, there was tenderness to palpation across the right seventh and eighth rib in an anterolateral location. This correlated with a seventh rib schwannoma (Fig. 2.3). A right-sided intercostal nerve block of the seventh and eighth ribs under ultrasound guidance was performed.

The patient's noted significant improvement from baseline and that relief lasted for 11 weeks. At that time, pain



Fig. 2.3 CT of the chest and abdomen with contrast showing right-sided chest wall mass responsible for patient's first onset of chest wall pain (arrows)

returned with the same presentation and severity. Given the positive response from first procedure, the intercostal nerve blocks were repeated; however the patient had minimal relief from this procedure. Given this response, imaging with an MRI of the thoracolumbar spine was repeated to evaluate for extension of disease into the spinal cord. MRI of the spine revealed paraspinal masses abutting exiting nerve roots at the right T7–T8 level. A thoracic epidural was performed with significant relief of the patient's pain. Patient's pain relief lasted for 6 weeks with significant progression of the original disease. Due to the rate of disease growth, we planned for intrathecal pump placement to treat the neuraxial source of the pain.

Though various nerve blocks can make sense clinically based on the history and physical exam, it is often necessary to correlate these findings with relevant and up-to-date imaging in order to optimize efficacy and safety of a planned intervention. It's important to consider the possibility that an initial intervention that was helpful may not be possible given changes in anatomy related to progression of disease. It is crucial to always reassess patients given the aggressive nature of some of the baseline etiologies.

Case 4 and 5: Considerations for Intrathecal Drug Delivery in the Oncologic Population The goal of interventional pain physician is to consider intervening in someone's pain outcome as early as possible to treat a patient's pain and improve their quality of life and function. The intrathecal delivery of opioids and other adjuvant medications is an effective way to treat refractory cancer pain while minimizing systemic side effects and allowing for a greater ability to address increased pain medication requirements. A randomized clinical trial of implantable drug systems showed better clinical pain relief, less systemic side effects, and a tendency toward increased survival in the treatment of cancer pain [8].

The following two cases describe clinical scenarios where directed drug delivery via an intrathecal pump would be indicated and how the progression of disease ultimately was the reason to proceed or the reason to not proceed with an intrathecal pump placement. Intrathecal drug delivery is an especially useful method to very quickly adjust and meet increasing opioid requirements while minimizing side effects.

Case 4: A 35-year-old woman who was recently diagnosed with adenocarcinoma of the rectum in the setting of Crohn's disease presents for consultation with the interventional pain team 6 months after being diagnosed. The patient's pain first started with increasing perineal discomfort and pain. She underwent imaging studies with MRI of the abdomen and pelvis which showed enlarged perirectal lymph nodes and three irregular hypodense masses in the

liver which were suspicious for metastatic disease. Liver biopsy would confirm metastatic disease and rectal cancer. Further imaging showed perirectal nodal disease and distant mets to the liver, pleura, left adrenal, and bone.

The patient's perirectal pain progressed to include saddle anesthesia, with pain in the right buttock radiating around laterally into the right groin and intermittent right first toe paresthesia. Additional workup was consistent with extensive disease from T12 through the sacrum, an L5 fracture, left foraminal narrowing due to metastasis at L4–L5 and L5–S1, and presacral extraosseous disease with right S2–S3 sacral nerve root impingement (Fig. 2.4a and b). She denies bowel or bladder incontinence and noted no weakness in the lower extremities. Interventional radiology and the pain service were consulted for on input on symptomatic treatment of the pain in conjunction with ongoing chemotherapy. Radiation therapy to the sacral spine was started along with an oral steroid regimen.

The patient and pain practitioner's initial goal was to alleviate as much of the patient's perineal paresthesias and radicular pain as possible. Review of the MRI showed no disease at the sacral hiatus, and a caudal epidural steroid injection was planned. The patient's INR was elevated likely due to hepatic involvement and was treated with vitamin K. Once the coagulopathy improved, a caudal epidural steroid injection was performed with moderate relief of radicular pain. She continued to have midline sacral pain. Directed drug delivery via an intrathecal pump was discussed given the fast progression of the disease after completion of radiation therapy. Unfortunately, the patient's disease would continue to progress aggressively and left her with a limited prognosis affecting her risk and benefit profile for intrathecal pump placement. The benefits of the procedure did not outweigh the risks and costs for placement of an intrathecal pump. Further goals of care were discussed with the patient, and a plan for hospice initiation was determined. The patient's pain was managed with hydromorphone PCA.

Patient's may often have pain that is amenable to directed drug delivery via intrathecal pump; however it is important to reconcile the patient's wishes and beliefs regarding palliation with the risks and benefits of the procedure. An intrathecal pump placement can improve patient's ability to be functional, and often pain is a short-term setback before the benefits are achieved.

Case 5: A 36-year-old male with a history of sacral spindle cell sarcoma metastatic to the pelvis presented to the inpatient pain service after having had a left-sided hind-quarter amputation (Fig. 2.5). The consultation is called for acutely worsened pain in the left groin and pelvis on an inpatient basis. An epidural catheter had been placed perioperatively for acute pain control, but a plan for intrathecal drug delivery had simultaneously been discussed with the patient. The epidural was dosed with a combination of hydromorphone and bupivacaine solution. An epidural trial of medica-

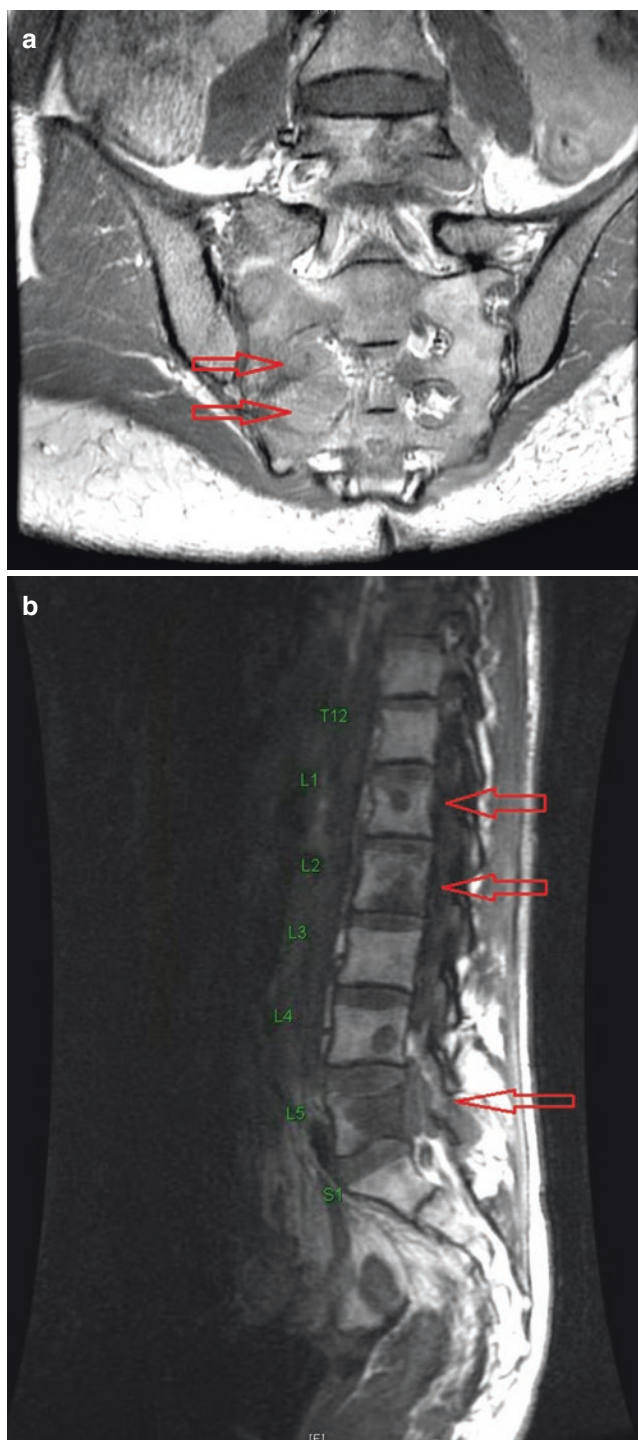


Fig. 2.4 (a) Left MRI sacrum showing bilateral sacral metastases have increased with bilateral presacral extraosseous disease. The right sacral ala with metastasis infiltrates into the S2 and to a greater extent the S3 neural foramina (arrows). (b) Right MRI lumbar spine consistent with osseous metastases involving almost every level throughout the cervical, thoracic, and lumbar spine (arrows at L1, L2, and L5 vertebral disease with epidural extension at L5)

tion can often be considered when considering the efficacy of neuraxial medicine prior to intrathecal pump placement. The patient noted improved pain control and side effect pro-

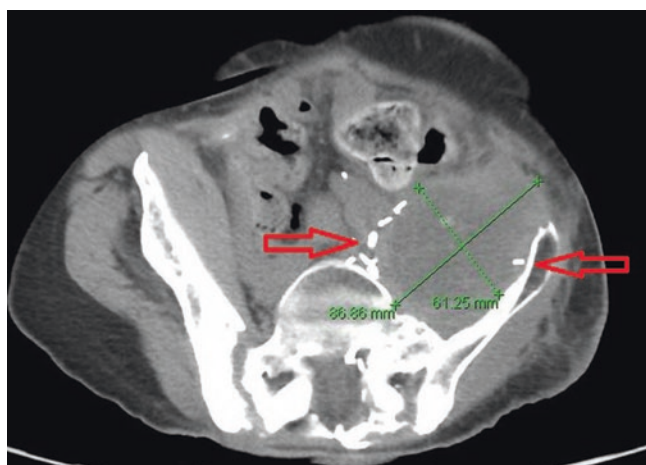


Fig. 2.5 CT of the chest, abdomen, and pelvis shows necrotic left pelvic mass centered at the left iliopsoas muscle and extending into the peritoneum (arrows)

file from decrease in systemic opioid treatment. An intrathecal pump was placed without any side effects or complications, and the patient returned for subsequent outpatient visits and for adjustment of dose over the next few months. Ultimately the cancer progressed, and various combinations and doses of intrathecal medications were titrated to alleviate the pain.

A retrospective case study of 46 cancer patients who had an epidural trial discussed how to use a patient's pre-pump systemic opioid requirements to calculate an appropriate intrathecal dose without having to do an epidural trial [8]. There are several ways to trial a patient for neuraxial directed drug delivery, but epidural trial can be a reasonable option for patients who are in the hospital.

Conclusion

This chapter highlights several different cases that can represent challenges to interventional pain physicians when treating cancer patients. It is crucial to continuously challenge

and adjust the therapeutic plan as patients' underlying pathology, treatments, and goals of care change. Most important is having a low threshold to consider that an initial underlying pathology has changed and may require new diagnostics or a change in management. Ultimately the goal is optimal pain relief and to give patients a chance to enhance their quality of life and functionality. Each patient has personal goals, and it is these benchmarks that should guide therapy. Each patient's case provides an opportunity for reflection and reminds pain practitioners to learn, advance, and develop algorithms to best treat each patient.

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Part II

Cancer Pain Syndromes

Pathophysiology of Cancer Pain

3

Stephen Lawrence Thorp

Introduction

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. Pain is prevalent among patients with cancer, with a systematic review finding pain prevalence to be 66.4% in advanced metastatic or terminal disease, 55% during anticancer treatment, 39.3% after curative treatment, and moderate to severe pain being reported in 38.0% of all patients [2]. Adequate control of pain can improve patient’s quality of life through improved mood, functional status, and rest, among other things. Pain may even be related to survival [3]. Cancer-related pain is unique and may be related to the anatomic location of the tumor, pathophysiology of the tumor, or treatment of the tumor. Similarly, the origin of the pain itself can be somatic, visceral, neuropathic, or mixed in nature. Given the complexity of cancer pain and its multiple etiologies, it is critical to assess the pathophysiology of the cancer and its role in creating a pain syndrome.

Anatomic Location of Tumors

Pathophysiology of Bone Tumor Pain

The location of a tumor is often the direct cause of significant pain for patients. As an example, tumors in the bone are one of the most common sources of pain in patients with cancer. There are multiple types of primary benign and malignant bone tumors, and metastasis to bone is common [4]. When tumors metastasize to the bone, the route is most commonly hematogenous but can also be due to contiguous spread or

via lymphatics. The vertebrate is the most common site of metastasis; however the pelvis, ribs, femur, and skull are also common sites. Patients typically present with well-localized pain that worsens with weight bearing and activity and is tender to palpation on physical examination.

The etiology of bone pain is complex and not fully understood [5]. The periosteum and marrow cavity are both innervated by peripheral nociceptors capable of causing pain. In animal studies, it has been shown that sensory and sympathetic neurons innervate the bone, with the periosteum having the densest innervation followed by the bone marrow [6]. The sensory fibers that innervate the bone differ from more well-characterized afferents that innervate the skin. Bone is innervated primarily by A-delta fibers, and there is very little innervation by either C-fibers or A-β fibers [7]. Sharp nociceptive bone pain is likely transmitted by the A-δ fibers, and the dull ache is transmitted from the C-fibers that become sensitized. Bone pain likely has a neuropathic component as well, as invading tumor cells injure sensory fibers [8].

When bone is invaded by cancer cells, a release of inflammatory mediators such as prostaglandin E₂ (PGE₂) sensitizes the peripheral nociceptors. This mechanism underlies the role for nonsteroidal anti-inflammatory (NSAIDs) agents in treating bone pain. Metastasis and primary tumors can be lytic, due to increased osteoclastic activity, or sclerotic, due to increased osteoblastic activity, both of which induce mechanical instability in the bone [9]. The instability in the bone may eventually manifest as a vertebral compression fractures (VCF) if the tumor is located in the vertebral body. Fractures localized within the vertebral body may be treated with vertebral augmentation techniques such as kyphoplasty; however, more severe fractures resulting in neurological dysfunction and severe pain may require surgical stabilization.

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Etiologies of Neuropathic Pain

Accordingly, tumor location in close proximity to neural structures can lead to neurological impairment and neuropathic pain. Neoplastic plexopathy represents a severe and difficult to treat form of cancer pain. Neoplastic plexopathy arises when a tumor progresses to involve one of the main plexuses; the cervical, brachial, or lumbosacral plexus. Treatment for tumor-induced plexopathies may involve surgical or radiation therapy, in addition to neuropathic pain medications.

The cervical plexus contains contributions from the C1, C2, C3, and C4 spinal nerves and provides innervation for the muscles of the neck as well as the prevertebral muscles. Impingement upon this plexus by tumor can result in cervical plexopathy, which typically presents with pain in the neck, shoulder, or throat. Weakness in the shoulder is related to weakness in the trapezius and sternocleidomastoid muscles, which are innervated by the spinal accessory nerve. The patient may also have shortness of breath, particularly if there is underlying pulmonary pathology, due to involvement of the phrenic nerve and hemidiaphragmatic paralysis. Cervical plexopathy is most commonly associated with head and neck tumors and lymphomas but may also be due to lung and breast cancers [10]. The cervical plexus can be blocked superficially resulting in cutaneous analgesia, or by anesthetizing the C2, C3, and C4 spinal nerves as they exit their respective cervical foramina, or the deep cervical plexus.

Far more common than tumors impacting the cervical plexus are tumors compressing the brachial plexus. The brachial plexus is composed of the ventral rami of C5–T1 in most individuals, with occasional contributions from C4 and T2 spinal nerves. The nerve roots exit the foramina and travel anterolateral between the anterior and middle scalene muscles, where they combine to form superior, middle, and inferior trunks. At approximately the level of the first rib, these trunks again divide into an anterior and posterior division, which then form the lateral, medial, and posterior cords, so-named for their relation to the axillary artery. The three cords then divide into the peripheral nerves which supply innervation to the upper extremities.

Brachial plexopathy is most commonly associated with lung and breast cancer. Superior sulcus, or Pancoast, tumors are located at the apex of the lung and may impinge upon the brachial plexus. The clinical presentation of the plexopathy is related to where the plexus is impacted. The most commonly affected portion of the brachial plexus is the lower roots, and patients often present with radicular pain and radiculopathies in an ulnar nerve distribution. When head and neck neoplasms impact the brachial plexus, they typically affect the upper cervical roots and superior trunk, causing pain more commonly in a median or radial nerve distribution.

The lumbar and sacral plexus provide innervation to the lower extremity. The lumbar plexus is comprised of the ven-

tral rami of the L1–L4 spinal nerves, with variable contributions from the T12 and L5 spinal nerves. The plexus lies in the psoas compartment located between the quadratus lumborum and psoas muscles and is composed of dorsal and ventral divisions. The main branches of the lumbar plexus include the femoral, obturator, and lateral femoral cutaneous nerves as well as the iliohypogastric, ilioinguinal, and genitofemoral nerves. The sacral plexus arises from S1–S3 giving rise to the sciatic nerve posteriorly, which then forms the common peroneal and tibial nerves, as well as the pudendal nerve which provides sensation to the perineal area.

The most common tumors invading this plexus are colorectal, sarcomas, and genito-ureteral tumors, with the sacral plexus being involved more commonly than the lumbar plexus. When the lumbar plexus is involved, the most common presenting symptom is leg pain, followed by numbness and weakness [11]. As the plexus lies in the psoas compartment, tumors affecting the psoas muscle can cause significant pain, termed malignant psoas syndrome [12]. When the sacral plexus is involved, the clinical picture can present with pain down the posterior aspect of the leg and weakness in the foot, similar to an S1 radiculopathy. The patient may also present with perineal pain and incontinence in later stages. Diagnosis of neoplastic plexopathy is confirmed with magnetic resonance imaging (MRI) and positron emission tomography (PET) to identify areas of active neoplasm in or abutting the plexus. Electromyography (EMG) can be used to further elucidate which nerves are most affected and guide treatment.

Other Associated Pathophysiology for Anatomic Cancer-Related Pain

While pain related to tumor in the bone and nervous system structures is the most common cause of anatomical pain, other anatomical locations may generate pain as well. Tumors in the brain are well known to cause headaches, as are metastasis to the spinal meninges [13]. Distension of capsular organs is another well-known cause of tumor-related pain as occurs when liver tumors distend Glisson's capsule causing abdominal pain [14]. In all of these examples, the primary treatment of cancer pain is treatment of the cancer and any therapies that remove or reduce the size of the tumor.

Chemical Mediators of Pain

The tumor microenvironment (TME) is composed of tumor cells and stromal cells and has a substantial role in tumor progression and cancer-mediated pain [15]. Tumor and stromal cells communicate with each other, their microenviron-

ment, as well as the tissue they are invading by secreting multiple noxious chemical factors, inflammatory mediators, and immunomodulators. These stimuli are transduced at peripheral nociceptors and transmitted via an action potential to the spinal cord and travel via ascending tracts to the supraspinal processing centers. While this likely plays a role in all cancers, the details of a few specific examples have been elucidated.

Pathophysiology of Pain in Patients with Multiple Myeloma

Multiple myeloma is a malignant cancer of plasma cells that results in a unique pain syndrome referred to as myeloma bone disease. Bone pain is the most common symptom reported at presentation, in more than two-thirds of patients, and 80–90% of patients with multiple myeloma will develop bone lesions during their disease [16]. The etiology of this bone pain is likely dysregulation in bone remodeling. Normal bone remodeling is a continuous process of old bone resorption stimulated by osteoclasts and new bone formation through collagen synthesis and mineralization by osteoblasts. When multiple myeloma metastasizes to the bone, it induces bone resorption by activating osteoclasts. The myeloma cells release and stimulate cells in the bone marrow microenvironment to release osteoclastogenic activating factors such as RANKL, MIP-1 α , TNF- α , interleukin 3 (IL-3), and IL-6 [17]. In addition to the stimulation of osteoclast formation and activity, many of these factors are also involved in the inhibition of osteoblastic activity as well as a supportive role for myeloma cells themselves.

Pathophysiology of Cancer Pain in Patients with Breast Cancer

Breast cancer, in addition to causing pain with metastasis to sites such as the bone and compressing neural structures as discussed previously, causes pain through the release of chemical mediators as well. The tumor and stromal cells release and induce host release of numerous mediators of pain. The amount and content of circulating cytokines have been shown to be not only distinct to subtype of breast cancer but potentially to the amount of pain suffered by patients as well. Luminal type A and B breast cancers exhibit higher levels of TGF- β 1 and TNF- α than healthy controls, and TGF- β 1 levels are higher in HER2-amplified tumors than luminal types [18]. In contradistinction, triple-negative tumors have lower circulating levels of TGF- β 1 when compared with other subtypes and healthy volunteers. While the different cytokine profiles of tumors are currently under investigation, the direct relationship with pain is still being elucidated.

In addition to inflammatory cytokines inducing inflammation and sensitization of peripheral nociceptors, cytokines may also be involved in noninflammatory pain. TGF- β is a cytokine that has been implicated in regulating osteoclasts and mediating bone resorption, as occurs with metastasis to bone. TGF- β is released by chondrocytes during bone injury and may mediate the production of nerve growth factor (NGF) in chondrocytes as well [19]. Further, TGF- β has been shown to be inhibited by proinflammatory cytokines and, as such, may be a noninflammatory mediator of pain in metastatic bone pain. The stimulation of osteoclastogenesis may also lead to the release of growth factors and other mediators that may cause the growth of the invading tumor cells.

Novel Therapies for Cancer-Related Pain

The treatment of cancer pain is multifaceted and discussed throughout this text. The most important treatment of cancer pain is treatment of the cancer itself. Treatments in the form of surgery, radiation therapy, chemotherapy, interventional treatments, and medication management are at the forefront of treatment. These treatments may be the cause of, or contribute to, the patient's pain as well, as with chronic postsurgical pain, radiation-induced neuritis, or chemotherapy-induced peripheral neuropathy, to name a few examples. In recent years there has been increased interest in treatments that target the pathophysiology of the cancer. These same molecular targets are also potential targets for the treatment of pain, as these therapies that target the cytokine and inflammatory mediators released by tumors and inhibit tumor growth also decrease tumor-related pain.

Bone-related pain and the molecular causes of the pain are now being targeted as pain therapies. One such molecule is Src, a protein tyrosine kinase non-receptor that is associated with the N-methyl-D-aspartate (NMDA) receptor complex. Found in neurons, Src has been shown to be associated with pain and maintaining inflammatory hyperalgesia [20]. Further, Src has a vital role in osteoclast activity. By targeting this molecule involved in bone resorption, there is potential to decrease the breakdown of bone and thus one aspect of the bone pain itself. Bisphosphates are another well-known treatment that inhibits osteoclast-mediated bone resorption by reducing osteoclast activity [21]. While effective in reducing osteoclastic activity, bisphosphonates do not impact osteoblastic activity and have numerous potential side effects including renal impairment and osteonecrosis of the jaw. Further, bisphosphonates have been shown to inhibit the ability of the metastasis to interact with the osteoblasts and inhibit their secretion of chemokine CCL2 [22].

The treatment of myeloma bone disease is multifaceted and involves medication management, radiation therapy, chemotherapy, vertebral augmentation, and surgery. The under-

Table 3.1 Potential targets for the treatment of myeloma bone disease

Osteoclast mediators	Osteoblast mediators
OPG	WIF-1
RANK	SFRPs
MIP-1 alpha	Dkk
VEGF	Runx2
SDF-1 alpha	TGF-beta

OPG osteoprotegerin, *RANK* receptor activator of nuclear factor kappa-B, *MIP-1 alpha* macrophage inflammatory protein-1 alpha, *VEGF* vascular endothelial growth factor, *SDF-1 alpha* stromal-derived factor-1 alpha, *WIF-1* wnt inhibitory factor-1, *SFRPs* secreted frizzled-related proteins, *Dkk* Dickkopf family of secreted proteins, *Runx2* runt-related transcription factor 2, *TGF-beta* transforming growth factor-beta

lying pathophysiology discussed previously has also become a target for therapy. Bisphosphonates, discussed previously, are a mainstay of therapy for multiple myeloma. In addition to bisphosphonates, a number of mediators known to be involved in the pathogenesis of myeloma bone pain are currently being investigated as potential therapeutic targets, and there is tremendous potential for such agents (Table 3.1). One such agent, bortezomib, is a proteasome inhibitor that has been found to improve the survival of patients with multiple myeloma [23].

Pain related to breast cancer may be related to many of the topics discussed previously, including compression of neural structures and metastasis to bone. As in the treatment of myeloma bone pain, there are many potential novel therapies being investigated that may be used to not only treat the cancer but the pain it causes as well. It has been shown that altered glutamatergic signaling can disrupt the normal cycle of bone remodeling and cause significant pain [24]. Utilizing inhibitors of glutamate release from the cancer cells is one such novel therapeutic approach. Sulfasalazine is an inhibitor of glutamate release that has been shown to reduce nociceptive behavior in a mouse model of breast cancer bone pain [25]. The continued investigation of further treatments related to the pathophysiology of breast cancer pain will continue to change the management of the cancer itself and the pain it causes.

Conclusion

Cancer pain is difficult to treat and a terrible malady for those suffering from cancer. Traditional therapies continue to be the standard of care and involve medication management, radiation therapy, chemotherapy, vertebral augmentation, and surgery, among other therapies. New studies that elucidate the pathophysiology of individual cancers open the door for novel therapies that may target the cancers as never done before. As new therapies evolve, the treatment of cancer-related pain will evolve as well, ushering in a new paradigm of treatment for our patients.

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