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Fundamentals of Cancer Pain Management

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Fundamentals of Cancer Pain Management

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In remembrance of Dr. Lisa Stearns, a pioneer in cancer pain management and relentless advocate for care to enhance quality of life.

This book is dedicated to our patients, for whom we strive to ease suffering, and to our families, who support us steadfastly in this work.

Andrew Leitner
Christine Chang

Preface

Those of us privileged to work in the care of cancer patients have seen significant treatment advances over the past several years. The utilization of targeted interventions for cancer pain has also gained more acceptance over time. Unfortunately, despite these advances, pain remains the most common, and the most feared, symptom of patients with cancer. As medicine and oncologic care become more specialized, we increasingly need to address areas, such as pain management, that cut across disciplines. This book is one such effort, from a group of experts who share the challenges and rewards of caring for the cancer patient in pain.

The founder of the hospice movement, Cicely Saunders, developed the phrase "total pain" to describe the suffering that patients may experience across the entire biopsychosocial spectrum. If pain is a multifactorial experience, so must be its management. Though opioid therapy has relieved the suffering of countless patients, the opioid epidemic—and the regulatory response to it—has meant a re-evaluation of monotherapy approaches to pain. This is particularly relevant for cancer survivors. Indeed, those of us who practice in the field of cancer pain management recognize that few patients are helped by a single pill or needle alone. For this reason, a primer on a spectrum of treatment modalities is offered here.

This text is intended as both a reference for the oncology professional and an introduction for those who may be interested in specializing in this patient population. The first part explores the history and epidemiology of cancer pain and introduces the common presentations of pain from cancer or its treatments. Special attention is given to the fortunately growing proportion of long-term cancer survivors. The remainder of the text focuses on therapeutic areas, with an understanding that many, if not all, may come to bear on the treatment of our most complex patients. There are several excellent texts with broader coverage of these modalities—here we focus on their specific application to patients with cancer. The part on pharmacologic therapies devotes considerable attention to opioid analgesia, which remains a core treatment modality in cancer pain. Of key importance as well are the non-opioid analgesics, which are addressed alongside a growing list of emerging therapies. Interventional and locoregional therapies continue to expand in scope, and the coverage in this part is intended to be an advanced primer, particularly in understanding patient selection for these therapies. Finally, we conclude

with the recognition that pain is a biopsychosocial experience requiring a holistic approach to rehabilitation. Topics include psycho-oncology, physical medicine, and integrative therapies.

We are fortunate to have the contribution of North American as well as European authors, providing valuable perspective on the practice of cancer pain management in various healthcare systems. Finally, it should be noted that this project was brought to completion during the international COVID-19 pandemic, with many of the authors finding themselves on the front lines of care. It would seem that the same sense of urgency that has driven us to care for the cancer patient in pain has called many of us to take on pandemic roles as well. We remain inspired by the efforts of our colleagues and the collaboration that resulted in this book.

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Part I
Background and Assessment of Cancer Pain

History and Epidemiology of Cancer Pain

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David J. Copenhaver, Ming Huang, Jasmine Singh, and Scott M. Fishman

1.1 Cancer Pain Prevalence and Etiology

Pain is indelibly associated with the cancer experience. A systematic review and meta-analysis indicate that the prevalence of cancer pain is 55% during anticancer treatment, 66.4% in advanced, metastatic, or terminal disease, and 39.3% after curative treatment [1]. Further, moderate to severe pain is present in 38% of all patients afflicted with cancer, highlighting the broad need for safe and efficient pain care [1]. Those who have been treated for cancer and continue to survive are estimated to be 12 million in the USA [2]. Therefore, as cancer treatment becomes more efficacious and quantity of life extended, one can observe a perceptible shift. Cancer has become in many instances a chronic illness that is often associated with pain.

Etiologies of cancer-related pain appear to be multifactorial. Sources of pain include the tumor itself including metastatic lesions directly causing nociceptive pain, visceral pain, and/or neuropathic pain. Anticancer treatments themselves may cause various specified pain conditions secondary to chemotherapeutics, radiotherapy, and surgery.

It is important to note that tumors can secrete noxious chemical irritants, inflammatory mediators, and immunomodulators that act upon peripheral nociceptors [3]. Nociceptive pain is due to mechanical, thermal, or chemical stimulation of nociceptors that are located in skin, connective tissue, muscles, and bones [3].

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As we review our current understanding of cancer-related pain, it can only be placed into perspective by assessing the historical context of how humanity has qualified pain and cancer.

1.1.1 The Early Greeks

Pain is a complex human experience that has been well documented since ancient times. Since the beginning, there has always been an attempt to find the origin, mechanism, and treatment of pain. According to the ancient Greek philosophers, pain is punishment from the gods; it is a necessity for the development of self-control and a testament to one's character. Enduring severe pain allowed one to demonstrate courage and wisdom [4].

Plato, like many Greek philosophers, believed pain originated from the center of the heart. He viewed pain and pleasure as opposite to each other and as a product of an interaction with the soul. The experiences of pain and pleasure can cloud one's judgment and prevent one from knowing what was real [4]. Aristotle believed that the heart was the center of the five senses including sight, hearing, smell, taste, and touch. Pain was not included in his five senses; rather, it was believed to be a part of one's emotions and not a function of one's sensory experiences [5].

Hippocrates, wildly recognized as the father of medicine, used the word pain for the first time as a medical condition. He believed the nature of the body to be made up of four humors or liquids (blood, black bile, yellow bile, and phlegm). Imbalance in these humors was thought to be the source of pain. In his own words, "pain is felt when one of these elements is in deficit or excess, or is isolated in the body without being compounded with all the others" [6].

1.1.2 Rene Descartes

One of the lasting legacies of Descartes is his concept of mind–body dualism. He reached the conclusion that the mind is a non-physical entity with self-awareness that is separated from the body, a physical entity. Different from his predecessors, he believed pain originated from the brain instead of the heart. He is also credited as being one of the first philosophers to describe the detailed somatosensory pathway and attempted to make the distinction between sensory transduction and perception of pain [7]. In *Treatise of Man*, he described nerves as hollow tubes that connect and deliver sensory and motor information [8].

1.1.3 Early Twentieth Century

The early twentieth century was filled with advances in the treatment of cancer. The first use of radiation therapy to cure cancer was reported in 1903 by Goldberg and London for the eradication of basal cell carcinoma of the skin. Halsted's surgical

approach to radical dissection of breast tumor, which was developed in late nineteenth century, continued to gain wider use in the early twentieth century. Radiation and surgical therapy gradually became mainstream treatment options for cancer patients. However, there was inadequate attention directed toward the control of pain in cancer patients by the medical community. Hospital facilities or medical clinics specialized in the treatment of pain were nonexistent. Physicians who were involved in the care of dying patients were often hesitant and unwilling to use opioids to treat even advanced cancer pain due to fears of addiction and euphoria [9]. Instead, cancer patients who suffered from severe pain were praised for their heroic efforts in not using opioids. The use of morphine as a painkiller was further restricted with governmental regulations with the passing of Harrison Narcotics Act of 1914.

1.1.4 Post-World War II

By the end of World War II, cancer had become the second leading cause of death in the USA. Government establishments, major pharmaceutical companies, elite universities, and research institutes started waging war on cancer as public attention turned to treating cancer as a potential curable disease. When the federal government established the National Cancer Institute in 1937, the initial annual research fund was approximately $700,000, but that number had increased substantially in the next two decades after World War II. By 1968, its annual research budget had exceeded over 185 million [10].

The National Cancer Act of 1971 signed by President Nixon continued government-organized efforts to fight cancer. The act helped create new cancer centers and training programs, and award contracts for research, increased collaboration between public agencies and private industry, established an international cancer research data bank, and improved public understanding of cancer as a biological disease [11].

1.1.5 Cancer Patients' Autonomous Voice

Government-led organized efforts to fight cancer partly stemmed from the change of public opinions about cancer treatment. Starting in the 1960s, there was an increase in the publication of narratives from the cancer patient perspective. These narratives focused on the frustration surrounding inadequate pain control and lack of patient autonomy. Prominent writers and journalists frequently published stories of the struggle they encountered in managing the cancer pain of their dying friends and family members. Stewart Alsop, a renowned journalist, frequently wrote columns and books to describe his battle with leukemia and death and dying from the patient perspective. He called for patient autonomy and spoke to how patients should have a voice and choice regarding their analgesia. In his own words, "a terminal patient in full command of his faculties should be permitted to ask a

committee of experienced doctors about his future, and if he is told it holds nothing but suffering, and death at the end, he should have the right to demand, and to receive, a pill or some other painless means of ending his life" [12].

1.1.6 1950–1960s

Progress and development of cancer treatment with chemotherapy drugs were significant in the 1950–1960s. Prior to this, treatment of cancer was by either surgical resection or radiotherapy. In 1956, methotrexate was successfully used to cure gestational choriocarcinoma. This marked the first time that cancer could be eradicated by a pharmacological agent. In the next decade, patients with Hodgkin disease and acute lymphoblastic leukemia were also first reported to be cured or put into remission with chemotherapy [13]. By the late 1960s, chemotherapy had become one of three major treatment modalities along with surgery and radiotherapy.

1.1.7 Ray Houde Memorial Sloan Kettering

Shortly after World War II, the search for an ideal powerful analgesic (but also non-addictive) medication began. Research programs and laboratories, created under the Committee on Drug Addiction and Narcotics (a subdivision of the US National Research Council), had developed over hundreds of morphine derivatives awaiting testing [14]. The need for a standardized approach to the testing of the pharmacological agents became apparent. Ray Houde, with colleagues Ada Rogers and Kathleen Foley at Memorial Sloan Kettering, developed methods and research programs to assess pain and the efficacy of analgesic therapy for cancer patients. The methods they used continue to serve as models for standard analgesic trials for many decades [14].

1.1.8 John Bonica

John Bonica is often considered as the founding father of pain medicine. Before his time, there was little mention of the evaluation and treatment of patients with pain in medical textbooks. With his firsthand experiences of treating wounded soldiers who suffered severe pain in the Madigan Army Hospital during World War II, he recognized pain as a complex condition and called for the integration of opinions from multiple disciplines including, but not limited to, neurosurgery, neurology, orthopedics, and psychiatry for treatment of acute and chronic pain [15, 16]. The book *The Management of Pain*, which he wrote in 1953, was considered the first comprehensive medical textbook devoted entirely to practice of pain medicine. He pushed for pain to be recognized and treated as a medical condition and brought awareness to the medical world. By transforming the way pain was perceived,

evaluated, and treated, he created a framework for pain medicine that accounts for psychological, biological, and social aspects of the disease. This biopsychosocial model continues to be influential in the modern practice of pain medicine.

1.1.9 Ren Leriche and Other Neurosurgical Approaches to Cancer Pain

The French surgeon Rene Leriche was a pioneer in inventing surgical procedures that provided pain relief for soldiers who suffered from pain related to reflex sympathetic dystrophy or causalgia. It was well documented that he performed the first periarticular sympathectomy on a patient who developed painful paresthesia after a gunshot wound to the axilla and resulted in patient getting pain relief 15 days later [17].

Other neurosurgical approaches were also developed to interrupt the transmission of pain in the early twentieth century. Neurosurgeons Edward Martin performed the first division of the anterior lateral column for treatment of severe intolerable cancer pain related to tumor invasion of cauda equina in the early twentieth century. The procedure achieved pain relief of the lower extremities after surgery [18]. The first use of neurolysis of the celiac plexus (transcutaneous splanchnic nerve block) was described in 1914 by Kappis and colleagues. He was able to demonstrate that abdominal pain can be blocked via nerve block of the splanchnic nerves [19].

1.1.10 Latter Twentieth Century

1.1.10.1 Increasing Call for Improved Pain Control

The latter half of the twentieth century saw major advances in understanding, identification, and pharmaceutical management of pain in a patient suffering with cancer. Despite the advancement in therapeutic approaches, including the development of various opioids, most cancer pain patients in the 1970s still died in severe pain [20]. There were not sufficient guidelines and systematic treatment approaches for management of cancer pain. As part of an international effort to address the under-treatment of cancer pain, the World Health Organization (WHO) in 1986 released the concept of a simple "three-step analgesic ladder" to standardize the management of cancer pain in a stepwise fashion depending on severity of pain. The template was not perfect. However, it marked the first time a simple rule could be applied to the treatment of cancer pain. It helped guide new and inexperienced clinicians to make practical decisions for their patients in treatment of pain. This template also legitimized the use of opioids in treatment of pain and led to a wider adaptation throughout the world.

1.1.10.2 The Discipline of Hospice and Palliative Care

Palliative care is a relatively young discipline. The modern concept of palliative care started out as a form of hospice care at St. Joseph's Hospice in the 1950s where Dr. Cicely Saunders based her observations of patients dying of cancer. She recognized there was little known about pain management of cancer patients and introduced the idea of "total pain" in an attempt to provide a holistic approach to meet the physical, psychological, and spiritual distress of her dying cancer patients [21]. Psychological and spiritual aspects of pain experiences were taken into account with focus on improving overall comfort and quality of life. Gradually, palliative care as a discipline started to take shape and offered a wider range of services. It helped to manage the side effects arising from treatment of cancer in addition to cancer pain. The term palliative care was invented by Dr. Balfour Mount, a surgical oncologist in Canada to distinguish it from hospice care [22]. The field continued to evolve and served a unique role in the multi-disciplinary treatment of cancer pain.

1.1.10.3 The Discipline of Pain Medicine

Under the leadership of John Bonica, the International Association for the Study of Pain was created in 1973 to help promote research, educate, and advance the understanding of the treatment of pain. The association served as platform for researchers, clinicians, and policy makers to gather together to share the latest scientific knowledge in pain medicine and translated that into the clinical practice of pain management. The organization also helps promote education and training in the field of pain management worldwide. One of its biggest contributions was bringing clinicians from various different disciplines together and adopting a uniform definition and classification of pain diseases and conditions. Despite the fact that the field of pain medicine is relatively new compared to other fields in medicine, it has made significant progress in last few decades of twentieth century. From the specificity theory of pain to a multi-disciplinary approach, the pain community has come to understand that pain is complex, multi-dimensional with not just sensory-discriminative, rather with affective–motivational and cognitive–evaluative components. Treatment of pain gradually changed from a single dimension involving pharmacologic treatments to include other treatment approaches such as specialized injections and implants coupled with guided imagery and cognitive behavioral therapy. Pain medicine has continued to evolve and has slowly emerged as unique field of its own. Cancer pain management is a natural extension of the evolution of pain medicine as a discipline.

1.2 Cancer Pain: Historical Perspectives and Current Thoughts

Recent studies have demonstrated specialized communication between cancer cells and those of the host's immune system, peripheral nervous system, and central nervous system [23]. The intersection of the immune system and the nervous system has become a fundamental framework for understanding cancer-related pain. By way of example, precancerous head and neck tumors that are benign usually do not cause pain; however, once the cells become malignant they do tend to involve neurological structures and cause pain [23]. Furthermore, squamous cell cancers release high levels of nerve growth factor (NGF), and the treatment of these factors with specific antibodies or nerve growth factor inhibitors have been shown to decrease pain [23]. The extent that the nervous system plays in the development of cancer pain continues to be studied. More research is needed to elucidate the unique relationship of the immune system and nervous system in the development of cancer-associated pain.

1.3 Cancer Pain Guidelines, Paradigm Shifts in Opioid Management, and the Development of Interventional Approaches and Targeted Analgesic Therapies

Traditionally, the gold standard in managing pain associated with cancer follows a stepwise plan in accordance with the World Health Organization's ladder of analgesia. These guidelines were developed by clinicians that were largely experts in pain medicine and palliative care from the 1950s to the 1980s and finally with updates completed into the late 1990s [3]. Opioids have served as the mainstay of treatment when it comes to cancer pain care. Nonetheless, current studies suggest that patients with cancer have similar rates of risk for misuse, abuse, and addiction as the general public [24]. When coupling this information with the graded increase in survivorship and the perspective of cancer as a chronic illness, there has been a perceptible paradigm shift. The prescription drug abuse crisis in the USA is a complex topic, but perhaps one of the most important learning points from the crisis is the view that clinicians who prescribe opioid therapy should consider themselves as risk managers. The treatment of pain from cancer has been given a pass in most contemporary opioid prescribing guidelines. However, cancer patients also suffer from substance use disorders [24]. The new paradigm suggests that clinicians must manage pain and risk, harnessing opioids when the benefits outweigh the risks, and otherwise sparing opioid therapy when it is not the optimal choice. Essentially, clinicians must remain vigilant of looming risks and always able to assess the risk of pain versus the risk of treatment.

Non-opioid adjuvant treatments include Tylenol, NSAIDs, neuropathic agents, NMDA receptor blockers, injections, and surgical procedures. For those patients with cancer, these classes of medications and interventions were typically

recommended to be initiated once opioid titration therapy had been optimized—balancing relief with side effects [23, 25].History has dictated a shift in cancer pain treatment, as advanced cancer pain management has now relied on various interventions and medication strategies that are opioid sparing. In many cases, malignant bone pain may not respond to opioid medications, and as such the following may be used: NSAID, corticosteroids, bisphosphonates, radiopharmacologic drugs, oral ketamine therapy, and calcitonin [23, 25]. We are learning cancer-related bone pain has a direct correlation between the immune system and nervous system leading to novel therapies such as nerve growth factor inhibitor [26]. Pain due to malignant bowel obstruction may be reduced with the use of anticholinergic agents, octreotide, and corticosteroids, which all may reduce pain and other symptoms such as emesis [23, 25].

Plant-derived cannabinoids include THC and CBD [23]. These agents are currently under study and have been noted to both be analgesic and have anti-tumor effects. Nabiximols (Sativex) is an oromucosal spray with a 50:50 ratio of THC: CBD that has been shown to have some effect in relieving cancer-related pain [23].

The history of cancer pain treatment has demonstrated that although opioids may be a necessary part of pain management in patients with cancer who are at the end of life, not all will need them, and in some instances, pain may not be responsive to opioid therapy. In such cases, there may be more effective alternatives to opioids. For instance, pain from bone metastases is often more responsive to steroids or NSAIDs than to opioids. Similarly, chest wall pain from a rib fracture, or pleural tumor, is often more responsive to steroids or NSAIDs than to opioids. At times, pain may be amplified by psychological etiologies, social stresses, or spiritual/existential angst. Addressing these pain amplifiers may offer pain reduction. These biopsychosocial considerations are important to highlight even as the literature may suggest that 70–90% of cancer-related pain is responsive to the use of opioids [25]. As such, evaluation and treatment of such type of issues should be directed to the appropriate experts.

When opioid therapy is prescribed, it is important to consider the use of urine drug screens and to be particularly astute for results that do not show the opioid that is being prescribed, as this may suggest an issue with the test or potential diversion. Clinicians must also be cautious with frequent requests by the patient to increase opioid dosage as this might indicate worsening pain, opioid tolerance, or potentially drug abuse. Likewise, frequent prescriptions that are lost or misplaced, concurrent use of other psychoactive substances, or failure to follow the recommended treatment, may suggest aberrant drug use that needs further investigation.

For those patients who do not benefit in pain reduction with the use of opioid medications, Davis et al. recommend the following: to those that have never responded to the use of opioid medications [27], a taper should be instituted and the sole use of non-opioid medications should be implemented. Furthermore, such patients should be evaluated for spiritual and existential crises that may be contributing to lack of improvement, as somatization may be present. Pain that, by its very nature, does not respond to opioid analgesics will require adjuvant therapies early in the course of treatment, in addition to non-pharmacologic options. Davis

et al. went on to explain that those patients who may have initially responded to the use of opioids, but who no longer do, should be evaluated for other comorbid conditions, including poor compliance, anxiety, delirium, and depression. It is important to distinguish between addiction and patients who may appear to display drug-seeking behaviors; however, the underlying reason may truly be inadequate control of pain. In such cases, drug-seeking behaviors diminish as medications are titrated to adequate relief, and if there is concern over diversion of medications or of truly assessing responses to various doses, an inpatient hospitalization may be warranted in order to attain close observation in a controlled setting [25].

1.4 The Future Portends a Sophisticated Approach of Treating Cancer Pain

Cancer continues to plague humanity as a prevalent and frightening source of suffering. Pain is common and often interwoven with varying levels of nociception, fear, anxiety, and angst. Each of these elements can contribute to a perfect storm that too often results in profound suffering. The multifaceted contributors to cancer-related pain and suffering span the mind–body spectrum and require an equally broad therapeutic approach to re-establishing comfort and quality of life.

Patients with cancer are living longer, given early detection and improved treatment regimens, and many types of cancer are more curable than ever or managed in remission for long periods, to the point that they are now thought of as a chronic disease [28]. As such, psychosocial factors often influence the long-term sequelae [28]. Meta-analysis reviews indicate that stressful life events and depression are correlated with shorter survival time and increased mortality among various types of cancer [28]. One meta-analysis concluded that an absence of social relationships has the same effect on mortality as tobacco and alcohol and that this effect has an even stronger effect on survival time than the effects from physical inactivity and obesity [28].

As we expand our knowledge of, and experience with cancer and pain, therapies will become increasingly targeted to the site of pain generation, while limiting unnecessary toxic exposure to the remaining parts of the body and brain. This shift began many decades ago and is continuing to evolve in the twenty-first century. These approaches are well exemplified by the various interventional techniques that are currently used to treat cancer pain. These techniques are beneficial when the side effects of oral pain medications outweigh their benefits, or increasing amounts of medications are required for attaining sufficient pain relief.

Subsequent chapters devote considerable attention to these techniques, which we describe briefly here. In determining which methods may be most helpful in minimizing pain, the patients' estimated survival time may be taken into account [29, 30]. For example, neurolytic blocks may last for several months and intrathecal therapy may provide relief for several years [29, 30]. Regional anesthesia techniques are often first line as they are less invasive and minimize the risk of nerve

injury [29, 30]. Ablative techniques have narrow risk-to-benefit ratios and as such are reserved until less invasive techniques become less efficacious [29, 30]. The celiac plexus block (CPB) is an example of a procedure that poses significant risks, with most of the risk front loaded at the time of the procedure. Nonetheless, these risks may be acceptable relative to the substantial benefits of CPB, in well-selected patients with pancreatic cancer, particularly as these benefits may be amplified if the treatment is implemented early. Older recommendations stressed that the need for an initial diagnostic block with local anesthetic should be completed in order to determine the potential usefulness of a neurolytic procedure as well as to predict the potential neurological deficits from neurolysis [29, 30]. However, the high yield of this procedure in well-chosen patients relative to risks of two procedures (a separate diagnostic injection and therapeutic neurolytic injection) has led some clinicians to start with, and provide only the single neurolytic injection. The advantages of neurolytic techniques include longer-lasting relief and reduced cost over time; however, it is essential that patients are aware that potential adverse outcomes from neurolysis include permanent motor loss, paresthesias, and dysesthesias [30].

Other interventional techniques also access the neuraxis for managing pain in cancer patient. These advanced approaches involve delivering medications directly into the spine via the epidural or intrathecal spaces. Effective patient selection for these types of drug delivery interventions relies on social support for engaging in a relatively complex process for collaboration with the medical system, as well as the expectation of adherence to visits for timely follow-up for assessing relief of pain, medication adjustment, and refills of medications [30]. Advantages of intrathecal delivery over epidural route are the decreased frequency requirement for refills, and a 10:1 conversion factor may be used when converting doses from epidural to intrathecal; this amounts to decreased doses and volumes and as such accounts for less frequent requirements for refilling medications [30].

Intrathecal neurolysis is an older technique for managing cancer pain for those with somatic pain, as opposed to neuropathic or visceral pain. Neuroablative agents placed into the subarachnoid space include alcohol and phenol, with a goal of a pure sensory blockade as opposed to a motor one. This method may be a choice for patients with localized, severe, intractable pain whose life expectancy is under 1 year [30]. Side effects include short duration of pain relief, weakness of the lower extremities, and bladder/rectal dysfunction [30].

Sympathetic blockade at various levels may be administered for cancer-related pain with an etiology from visceral organs [30]. Neurolysis is often performed at the sympathetic chain of the associated level due to the impractical nature of catheters at these locations. Examples include the use of a celiac plexus block for upper abdominal cancers, superior hypogastric plexus block for pelvic cancers including ovarian, bladder, and prostate, as well as ganglion impar blocks for anal or vaginal cancer-related pain. Celiac plexus blocks are estimated to achieve relief for 70–90% of patients who undergo the procedure, and complications include postural hypotension, diarrhea, pneumothorax, retroperitoneal hematoma, neuropathic pain syndrome, and paraplegia [30].

Peripheral nerve blocks may be used and have achieved improved outcomes with the use of advanced technology, such as ultrasound guided imaging to ensure medication is infiltrating the appropriate nerves/plexuses, as well as for an improved safety margin of performing such procedures with visualization of neurovascular structures. Examples of nerve blocks include: femoral nerve, sciatic nerve, brachial plexus, suprascapular nerve, psoas compartment, distal lumbar plexus, paravertebral, and intrapleural blocks [30].

Spinal vertebral body fractures may be treated with percutaneous techniques. Vertebroplasty and balloon kyphoplasty help to restore the height of the bony vertebral body and minimize kyphosis with an additional goal of stabilization of the fracture [30]. The primary adverse effects include: infection, paraplegia, and embolization of the cement. Recently, medial branch radiofrequency neurotomy has been used to treat the pain from vertebral compression fractures. This technique addresses the pain caused by the biomechanical strain placed on the spinal facet joints due to the change in the vertebral body architecture due to fracture [31].

Neurosurgical interventions have historically been used to treat cancer pain largely in the trunk, pelvis, and lower limbs [29]. From the available evidence, largely nonrandomized case series, the most promising types of procedures have included those with nociceptive cancer pain that had received dorsal rhizotomy, spinothalamic cordotomy, and myelotomy [29]. The goal was to maintain pain relief for 9–12 months, and the main risks involved: intra-operative death, post-lesion dysesthesias, and altered motor, sensory, and sphincter control [29]. It is also important to note that the types of patients deemed to be candidates for such procedures had life expectancies of under 1 year and were also receiving opioid administration, hospice care, and possibly intrathecal drug delivery; as such, performing these procedures was not necessarily considered to be superior to the aforementioned modes of care involved rather complements to the multi-disciplinary care. Due to advances in image guidance, the use of cordotomy and myelotomy has seen an increase in procedure rates. Dorsal root entry zone lesioning involves heat application to the nociceptive fibers of the lateral portion of dorsal rootlets and medial portions of Lissauer's tract. It is estimated that there is an 80% long-term success rate if used in those with intractable upper extremity limb pain due to brachial plexus avulsions [29]. What is more, the intra-operative mortality rate and complication rate are low [29].

Deep brain stimulation, medial thalamotomy, and anterior cingulotomy have all been employed for the treatment of intractable pain [29]. Procedures once considered more destructive with significant side effect have improved in precision and sophistication secondary to technological advancement.

1.5 Conclusion

"*Cure sometimes, treat often, comfort always*" is a guiding Hippocratic principle of medicine and driving force behind pain management. The history of pain management in the treatment of patients with cancer closely parallels mankind's age-old

quest for analgesia. This pursuit is undoubtedly tied to the earliest evolution of humanity itself, with substantial consequences for survival, adaptation, and advancing the species. Although the term humanity relates to the collective human race, it is also defined in terms of compassion, empathy, and generosity, essential needs of patients in pain, particularly those at the end of life.

From the time of Plato and Aristotle, pain has been defined in the context of the mind and body. However, throughout the expansive growth of health knowledge and the metamorphosis of medicine from a high-touch art to a high-tech science, reductionism has shifted the focus of health care from symptoms to cure. Pain management has emerged as a well-accepted specialty that is focused on curing when possible, but always treating suffering and endeavoring to improve function and quality of life. Throughout the history of medicine, patients with cancer and those at the end of life have not always received the attention to suffering that they deserve. However, they have raised awareness of pain management as a human right and have spurred a movement in health care that has helped our field return not only to its core Hippocratic roots, but also to the ancient Aristotelian understanding of pain and suffering as an inextricably linked union of the mind and body.

As we continue to understand the existential concerns regarding pain and cancer, we learn from our history. The discipline of pain medicine has evolved to encompass a biopsychosocial model with thoughtful risk/benefit stratification for patients. Understanding our patient's needs and incorporating a customized treatment plan informed from these needs will always be paramount. The advancement of novel therapeutic techniques and technology that improves the safety and efficacy of our current pain care strategies portends a bright legacy to the future of treating those individuals suffering with the malady of pain and cancer.

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Cancer Pain Syndromes

2

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2.1 Introduction

Pain from cancer can present in a multitude of ways. In this chapter, we will identify the types of cancer pain and their etiologies. Following this, we will explore how cancer pain can present as somatic pain, visceral pain, and neuropathic pain. We will explore the aspects of the history and physical examination that point to specific diagnoses of pain and how to appropriately treat each diagnosis appropriately. Finally, we will touch upon a phenomenon known as opioid neurotoxicity.

Like other forms of pain, cancer pain is classified as being nociceptive or neuropathic. Nociceptive pain occurs when nociceptors at the ends of axons react to a noxious stimuli. This noxious stimuli can be mechanical or chemical. This can occur, for example, with the bony destruction involved with metastatic cancer pain. In such a case, bony metastasis results in local inflammation and release of inflammatory mediators, which trigger nociceptive sensors. This trigger travels from the periphery to the central nervous system and ultimately enters the cortex where the pain signal is processed. Nociceptive pain can be further categorized into visceral or somatic pain. Somatic pain occurs due to more superficial structures, such as bone, ligament, or subcutaneous tissue. Visceral pain comes from internal organs, such as in the case of a primary pancreatic tumor. The two types of pain can

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be distinguished by the quality of their presentation. Visceral pain is often described as dull and poorly localized, whereas somatic pain is described as sharp and easily localized. Somatic pain can be further categorized into superficial and deep. Superficial somatic pain involves superficial structures like skin and subcutaneous tissues, whereas deep somatic pain involves deeper, non-visceral structures such as bone. Deep somatic pain can often mimic visceral pain and can be described as dull or achy.

Neuropathic pain differs in that it involves direct injury to the nerve itself. The most common cause of neuropathic pain in the general population is diabetes, in which a state of hyperglycemia induces direct nerve injury. This results in the perception of neuropathic pain. It is important to note that both neuropathic and nociceptive pain typically result in differences in qualitative pain for the patient. Neuropathic pain is often described as burning, or electrical pain, whereas nociceptive pain can be described as sharp, aching or throbbing. Neuropathic pain in cancer patients can be triggered by tumor compression or infiltration of nerves, surgical injury, or nerve damage from radiation and chemotherapies. The large majority of cancer patients present with an overlapping picture of neuropathic and nociceptive pain, particularly as their disease progresses.

2.2 Assessment of Cancer Pain

The history and subjective experience of the cancer patient plays a critical role in determining treatment options for the patient. The patient's location of disease should be noted, as visceral pain can correlate to specific regions of the body. For example, renal cell carcinoma typically presents with flank pain, while pancreatic cancer typically presents with epigastric pain radiating to the back. In addition, the quality of the pain should be ascertained, so as to determine whether the pain is nociceptive or neuropathic in nature. While opioids are the mainstay for moderate-to-severe cancer pain, the addition of adjuvants should be considered whenever neuropathic pain is suspected. Alleviating and aggravating factors should be documented, as well as temporal patterns of pain. Pain that is constant may require implementation of long-acting opioids, whereas intermittent pain may require breakthrough doses of short acting opioids.

The physical exam should be documented, and any changes in the physical exam should be properly worked up. Many forms of cancer can present with metastases. Early detection may reduce morbidity. The most common site of cancer metastases is the bone. While all bony metastases can cause pain, the most morbidity for the patient is often experienced with spinal column metastases. Growing metastases near the spine can lead to cord compression, nerve root compression, or cauda equina syndrome, which presents with neurologic symptoms in the lower body, bladder or bowel incontinence, and saddle anesthesia.

Laboratory and radiographic examination for cancer pain can be important in targeting interventional therapy for cancer patients. If intervention such as a continuous peripheral nerve catheter or epidural catheter is considered, a platelet count should be verified. Platelets >100,000/uL are required before placement of any continuous catheter due to the risk of hematoma formation [1]. The risks and benefits of long-term catheter placement should also be evaluated in any patient with severe leukopenia, due to increased risk for infection. In patients with new onset extremity or back pain, radiographic evaluation is important to evaluate for bony metastasis. Radiation therapy is the gold standard for pain due to bony metastasis, which can be confirmed by radiography. When imaging studies are inconclusive as to the source of new pain in a patient, electromyography and nerve conduction studies can be performed together to further delineate sources of pain. When combined, the technique is useful for evaluating etiology of pain, the type of fibers involved, the pathology, and the time course of the injury.

2.3 Psychosocial Assessment of Cancer Pain

Recent advancements in our understanding of pain management have led to the evolution from the biomedical model to the biopsychosocial model of pain management. This model has been adopted by most large pain organizations including the World Health Organization and the American Pain Society. The implication of this model is that pain is no longer thought of as a diagnosis that can simply be treated with medical management. The biopsychosocial model understands pain as a biological process with heavy influences from psychological and social factors [2]. Together, these factors help explain the wide variation in pain experienced by patients with similar medical conditions. Traditionally, much of cancer pain management has revolved around medical management of pain. This is demonstrated by the fact that most pain evaluation systems do not incorporate psychosocial factors into measuring pain. Our new understanding of pain implies that we should be paying careful attention to the psychosocial aspects of pain if we hope to adequately treat a patient's pain. Depression and anxiety related to the uncertainty of a cancer diagnosis can cause severe distress in a patient. Ignoring these aspects of a patient's care inevitably leads to under-treatment of pain. Chronic cancer pain is associated with high levels of emotional distress that correlates to the degree of pain experienced by the patient. An association between pain levels, social support groups, and coping mechanisms has also been established [3]. Patients with limited access to social support groups, and patients with poor coping mechanisms, such as catastrophizing, have been shown to have higher levels of pain. As such, psychological and behavioral treatments should be implemented to help cancer pain patients. Psychological treatments with strong evidence for their efficacy include hypnosis, relaxation with imagery, and cognitive behavioral therapy [3]. Cognitive behavioral therapy can be combined with relaxation imagery and seeks to restructure the cognitive processes that worsen pain, such as catastrophizing. Behavioral

techniques can be taught to the patient, so that they may better identify pain triggers and also improve communication between the patient and caregivers. Many of these techniques deal with improving the patient's sense of self-efficacy, which in turn improves their ability to cope with their diagnosis.

2.4 Symptom Assessment Tools

Treating pain appropriately in cancer patients requires that practitioners be well versed in dealing with palliative care issues as well. Palliative care differs from pain management in that it hopes to treat the patient as a whole, addressing issues ranging from pain to the emotional and spiritual needs of the patient. Although the term palliative care often deals with issues regarding end of life care, in reality it applies to any situation in which a patient suffers from a serious, prolonged illness that affects their quality of life. This includes the large majority of cancer patients. Cancer treatment deals with an array of symptoms both physical and psychosocial, only one of which is pain management. As such, early implementation of palliative care should be considered in any patient with a cancer diagnosis. Due to the severity of their disease, patients with terminal illnesses often experience difficulty in communicating the array of symptoms that they are experiencing. Multiple assessment scales have been developed as a way of communicating symptoms to physicians. This in turn boosts the quality of patients' lives. Importantly, better assessment of patient symptoms can improve patient survival rates [4].

The Edmonton Symptom Assessment Scale assesses a patient's subjective experience of symptoms as rated on a scale from 0 to 10, in the categories of pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, well-being, and other problems [5]. The MD Anderson Symptom Inventory evaluates a larger array of symptoms that includes 13 different cancer-related symptoms, each rated on a scale of 0–10. It then evaluates the impact of these symptoms on six quality of life issues. Lastly, the Memorial Symptom Assessment Scale Short Form uses a 0–4 scale to assess 32 symptoms and the amount of distress the patient experienced as a result of the symptoms. The goal of many of these assessment scales is to identify symptoms that would otherwise go unreported to the physician, which in turn facilitates treatment of these symptoms.

2.5 Cancer Pain Types

2.5.1 Somatic Pain

As described earlier in the chapter, somatic pain, which can be further divided into deep and superficial, is a common source of pain in cancer patients. Determining whether a patient's pain is somatic or visceral in origin is largely a by-product of the

history and physical examination of the patient, as well as an understanding of the staging of the patient's cancer. Most commonly, a cancer patient's pain etiology is a combination of nociceptive and neuropathic pain. While opioids are the mainstay for moderate-to-severe cancer pain [6], neuropathic adjunctive medication should be added to a patient's regimen when neuropathic pain is thought to contribute to the patient's pain. The term tumor burden was coined to describe the amount of cancer in the body, or the size of a tumor. Multiple studies have shown that a higher tumor burdens correlates to a poorer prognosis. Likewise, higher tumor burden conveys an increased risk of having a mixed nociceptive and neuropathic pain picture. These patients often have associated higher pain scores for patients, due to the increased likelihood of nerve or end organ damage.

2.5.2 Malignant Bone Pain

Malignant bone pain is a somatic pain and is the most common cause of cancer pain [7]. The pain from bony metastasis can present from local metastasis or pathologic fracture. The cornerstone of bone cancer pain treatment is radiotherapy [8]. Radiation applied directly to the bone results in tumor shrinkage and reduction of pain scores. It is most useful in patients who have isolated tumors in order to limit extensive radiation dosing and the associated side effects. While the pathophysiology of pain with bony metastasis is still poorly understood, it is thought that a part of the pain pathway is mediated by the conversion of arachidonic acid to prostaglandins by cyclooxygenase (COX). Non-steroidal anti-inflammatory drugs (NSAIDs), by means of COX inhibition, prevent the formation of prostaglandins and are particularly effective at controlling bone pain [8]. Steroids also reduce bone pain by a similar mechanism of anti-inflammation and may be considered as a co-analgesic with opioids. NSAIDs are typically started as first-line medical management for bone pain, with addition of a weak opioid analgesic if necessary. Opioids may be escalated in situations where pain control is inadequate. Caution with NSAIDs must be taken in patients with underlying renal, cardiovascular, or gastrointestinal disease. In cases in which extensive long bone fractures are involved, orthopedic surgery may be required to improve mobility, pain, and the patient's quality of life.

2.5.3 Visceral Pain

2.5.3.1 Malignant Intestinal Obstruction

Visceral pain occurs when organs become distended, inflamed, or ischemic. A classic example of this process occurs with malignant intestinal obstruction. Patients with abdominal or pelvic cancer have the potential for recurrent gastrointestinal obstructions. This most commonly occurs with ovarian and colorectal cancer, due to their proximity to the gastrointestinal (GI) tract [9]. Malignant intestinal obstructions (MIO) cause distension of the affected region, triggering

visceral pain in the patient. Symptoms can range from intestinal colic pain, to constant abdominal pain depending on the degree of obstruction. Symptoms are usually accompanied by nausea and vomiting. Abdominal radiographs typically show dilated loops of bowel or air fluid levels, indicative of an ongoing bowel obstruction. Adequate treatment of the patient's pain in this situation is dependent on relieving the distension within the affected organ. Palliative surgical removal of the surgical lesion is an option, but has an associated high morbidity and mortality especially in the terminally ill population [9]. For these reasons, other modalities are usually attempted first. Drugs are often used as first-line therapy with opioids still the gold standard for treatment of pain related to malignant intestinal obstruction. Besides their direct analgesia, they also reduce peristalsis, which helps with the pain. Patients are often unable to tolerate oral medication, so medications should be administered by intravenous or alternative routes. Scopolamine and other anticholingerics also reduce gastrointestinal peristalsis thus reducing pain. Importantly, many anticholingerics also have useful antinausea effects. Octreotide, a somatostatin analog, can be used to reduce secretions in the GI tract, and thus pain related to gastric distension. Metoclopramide, a dopamine antagonist, is a medication used to increase gastric motility and thereby decrease nausea and vomiting. Caution should be used when administering metoclopramide for MIO, as it can worsen conditions in the presence of complete gastrointestinal obstruction. Metoclopramide should only be administered in cases of partial GI obstruction. When medical management is no longer effective for the patient, invasive methods should be attempted. A nasogastric tube can be placed to decompress the stomach and reduce nausea or vomiting. NG tubes should ideally be in place for less than 7 days due to the risk for complications including nasal alar necrosis, gastric perforation, and pulmonary aspiration. A percutaneous gastric tube is another technique used to reduce pain and nausea related to MIO. A tube is inserted into the stomach through the abdominal wall and vented to the outside, thus reducing distension. This procedure has fewer complications than NG tube insertion and is the preferred intervention in MIO. In patients not responsive to these modalities of treatment, the risks and benefits of palliative surgery should be discussed with the patient.

2.5.4 Neuropathic Pain

Neuropathic pain involves the peripheral or central nervous system. Growing tumors or metastatic lesions can damage nerves leading to the development of neuropathic pain. Additionally, chemotherapy, radiation and surgery can cause neuropathic pain by means of causing direct injury or inflammation to nerves. Neuropathic pain can be distinguished from nociceptive pain based on the quality and distribution of the pain perceived by the patient. Neuropathic pain can follow dermatomes, as in the case of lumbar radiculopathy in which impingement of a lumbar nerve root causes shooting pain in the distribution of the affected nerve. The quality is often described as burning, tingling, electrical, shock-like, or numb. The resulting pain is important to distinguish from nociceptive pain, as the quality of

pain and the medication regimen to treat neuropathic pain are distinct from nociceptive pain. Neuropathic pain is typically treated with tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, and antiseizure medications. While cancer pain is most often correlated to the inflammatory, invasive, and neuropathic consequences of tumor invasion, cancer treatment can also contribute to cancer pain. Several chemotherapeutic regimens, most notably vincristine, can cause painful polyneuropathies. While most patients with these conditions have their symptoms subside with termination of the chemotherapy, some patients experience a progression to chronic neuropathic disease.

When standard medical treatment options for neuropathic pain have failed, peripheral nerve blocks and indwelling epidural catheters can be viable options. Epidural catheters are typically used for labor and delivery, and for perioperative pain control for abdominal and thoracic surgeries. In the perioperative setting, they are placed for 3–4 days after surgery to aid with pain control. It is typically removed after this time to reduce infection risk. In patients suffering with intractable pain, epidural catheters can be placed for longer durations of time. The advantage of an epidural catheter is that it provides direct local anesthetic to the spinal roots, which can effectively reduce both nociceptive and neuropathic pain. This can help reduce the doses of opioids and other medications that can have systemic, neurocognitive effects on the patient. The risks and benefits of epidural catheter placement must be weighed in each patient, as epidural abscess and meningitis are known complications of catheter placement, and both of these complications can have significant morbidity and mortality for the patient [10].

2.6 Opioid-Induced Neurotoxicity

Opioid-induced neurotoxicity is a phenomenon that occurs due to the accumulation of certain opioid metabolites. It is distinct from opioid side effects that result in sedation or drowsiness and clinically presents with neuroexcitation as the hallmark factor. Cancer patients are at higher risk for developing opioid-induced neurotoxicity due to the high doses of opioids that these patients may require [11]. Morphine and hydromorphone have morphine-3-glucuronide and hydromorphone-3-glucuronide metabolites, respectively. These 3-glucuronide metabolites have no analgesic effects, but they do have neuroexcitatory effects when accumulated in large doses, resulting in neurotoxicity [12]. Patients typically present with myoclonus as the presenting symptom. With progression of the disease, patients may present with hyperalgesia, delirium, and tonic–clonic seizures. Hyperalgesia refers to an increased sensitivity to pain that occurs over time with chronic opioid administration [13]. Due to the worsening pain that occurs with progression of cancer disease, many patients with hyperalgesia may mistakenly have their opioids increased in order to better treat the patient's pain. Clinicians should carefully monitor for other excitatory signs/symptoms when escalating the doses of morphine and dilaudid in the patients. The treatment of opioid-induced neurotoxicity involves

opioid rotation, decreasing the total morphine equivalent dosage. Opioid rotation works by means of switching to an alternative class of opioids which decreases the overall toxic metabolite accumulation in the individual [14]. Intrathecal delivery of the opioid by means of an intrathecal pump can also decrease the likelihood of opioid-induced neurotoxicity because the dose of the opioid delivered to the patient is significantly lower, resulting in less accumulation of toxic metabolites. Benzodiazepines can be used to help decrease the symptoms of opioid neurotoxicity. Naloxone, however, is ineffective in reversing this toxicity.

2.7 Renal Failure

Cancer, especially in advanced disease, is associated with end organ dysfunction or failure. Renal failure in particular has important implications for opioid management as many opioids are dependent on the kidneys for metabolism and/or excretion [15]. Inability to excrete metabolites due to renal dysfunction or failure can result in accumulation of these metabolites and subsequent morbidity for the patient. For example, morphine has the active metabolite morphine-6-glucuronide. Patients with renal failure have accumulation of morphine-6-glucuronide due to an inability to excrete it. As such, the effects of morphine administration in these patients are prolonged and unpredictable. It is for these reasons that morphine is not recommended for patients with renal failure. Codeine, a prodrug of morphine, is also contraindicated in renal failure. Similar to morphine, meperidine has the active metabolite normeperidine. Normeperidine decreases the seizure threshold in patients and predisposes them to seizures. This can occur in patients that have no previous history of seizures. Thus, meperidine is contraindicated in renal failure.

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Cancer Treatment Related Pain

3

Purvi Patel

When discussing cancer treatment, it is important to be aware of the potential toxicities and side effects associated with these treatments. Pain and side effects related to treatment are a common cause of non-compliance or even discontinuation of potentially beneficial treatments. This chapter will review the pain and side effects that different cancer treatments can cause. Treatment of this pain will be discussed in a separate chapter.

3.1 Chemotherapy-Related Pain

3.1.1 Infusion Pain

As the chemotherapy agent is injected into the veins, it can cause venous spasms (sudden and transitory tightening of the vein with associated inflammation). The effect can be lessened by slowing down the rate of infusion or applying a warm compress to the affected area.

Chemical phlebitis is inflammation of the intima caused by the medication. It is most commonly seen with peripheral IVs. Because it is due to the chemical being infused, it is not improved by slowing down the rate of infusion. Common chemotherapies that can cause phlebitis are vinorelbine and 5-FU. Chemotherapy regimens lasting more than 24 h can also cause phlebitis [1].

Urticaria (avascular reaction resulting in elevated papules or plaques, which are often erythematous and extremely pruritic) can occur as a direct result of the chemotherapeutic agent being infused. Anthracyclins are common agents that cause urticaria.

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Vesicant extravasation is when the chemotherapeutic agent leaks out of the vein into the surrounding tissue. It can lead to blistering and tissue injury that can cause tissue death and resulting pain [1].

3.1.2 Hepatic Artery Infusion Pain

Hepatic arterial infusion is the process of administering chemotherapy directly to the liver by an implanted pump. This is most commonly done for liver cancer, liver metastases and melanomas. This can cause severe abdominal pain that coincides with the infusion and can often be lessened by slowing down the rate of infusion.

3.1.3 Intraperitoneal/intravesical Therapy Pain

Intraperitoneal chemotherapy refers to the administration of chemotherapy directly into the peritoneum between the abdominal cavity and abdominal organs. This is commonly used to treat cancers of the abdominal region (i.e. gastric, appendiceal) or gynecological cancers (i.e. ovarian) [1]. The pain is a result of serositis, inflammation of serous tissue, of the peritoneum. It is important to distinguish pain as a result of serositis versus pain secondary to infection [1].

Intravesical therapy is the administration of chemotherapy directly into the bladder. This can cause cystitis, abdominal pain and bladder erosion [1].

3.1.4 Chemotherapy Toxicity

- *CIPN:* One of the most common side effects and causes of pain related to systemic chemotherapy is chemotherapy induced peripheral neuropathy (CIPN). A meta-analysis on over 4,000 patients found the prevalence of CIPN to be 68.1% in the first month, 60.0% at 3 months and 30.0% at 6 months [2]. Neuropathic pain is a major dose-limiting side effect of potentially curative treatment. CIPN can be acute or chronic, can resolve with reduction or discontinuation of treatment, or remain as a permanent side effect with long term abnormalities on neurologic examination. It commonly occurs after the first dose and increases in severity with continued treatment. It is described as constant burning, tingling, shooting or numbness in the hands and feet and is located along the distribution of the injured nerve. In the affected areas, there can be increased sensitivity to temperature or pressure/touch. Presentation of symptoms can be large fiber signs such as ataxia and motor weakness, or be purely sensory [3]. However, pure motor weakness without sensory findings is not typically seen [3]. Activities of daily living are impacted by the effect on fine motor skills (i.e., buttoning clothes, picking things up, grasping, writing), difficulty with ambulation and balance, fatigue and even sleep/mood disturbances. The were

agents most commonly shown to cause CIPN include taxanes, platinum agents and vinca alkaloids [3].

- *Mucositis* (inflammation of the mucosal membrane) can occur anywhere from the oral cavity to the anus and is caused by direct toxicity and/or bone marrow suppression [1]. It can present as soreness in the mouth or gums or cause ulcerations. Mucositis can affect the patient's ability to swallow and speak, and if ulcers are present they can increase the chance of infection, lead to poor nutrition and delay drug administration [3]. It is most commonly seen with drugs that affect DNA synthesis such as fluorouracil and methotrexate, with radiation to the head and neck, and in patients who receive high doses of chemotherapy for bone marrow transplantation [3].

The World Health Organization (WHO) has developed a grading system for mucositis severity:

Grade 0: no symptoms, grade 1: soreness with or without erythema, grade 2: ulceration and erythema, grade 3: ulceration and erythema affecting oral intake, grade 4: ulceration and formation of exudate not allowing for oral intake.

Similarly, the National Cancer Institute (NCI) developed a functional grading system for mucositis:

Grade 0: normal, grade 1: able to tolerate solid food, grade 2: able to tolerate liquids only, grade 3: oral intake not tolerated, grade 4: life threatening consequences.

- *Headaches* are a common side effect of intrathecal chemotherapy and are thought to result from cerebrospinal fluid leakage from the dural puncture [1]. These headaches can be associated with nausea, vomiting, ocular or auditory symptoms and are often exacerbated when upright and alleviated with supine [3]. Chemotherapy associated headaches can last for several days or longer.
- *Arthralgias and myalgias* are commonly seen with cancer treatment, and because patients with cancer are already often debilitated, they are more susceptible to this pain. Cancer causes weight loss and muscle wasting, which can lead to decreased mobility and increased risk of fracture [3]. Common agents causing myalgias and arthralgias include paclitaxel and aromatase inhibitors. Symptoms that are persistent and severe often require a change or reduction of treatment.
- *Cutaneous toxicities* include palmar-plantar erythrodysesthesia, commonly referred to as hand-foot syndrome, dermatitis and herpetic neuralgia. Hand-foot syndrome is classified by painful and erythematous rashes on the palms and soles, which can sometimes progress to bulla formation or peeling skin. This can be extremely painful, and can affect quality of life, but is usually self-limited and treated symptomatically. EGFR inhibitors affect the basal keratinocytes and can therefore cause painful dermatitis [4]. Patients receiving immunosuppressive therapies, or those with hematological malignancies, are at increased risk for herpetic neuralgia (a painful condition causing blister formation, affecting the

skin as well as nerve fibers), and if persistent will lead to postherpetic neuralgia (continued pain after blisters have resolved).
- *Limb ischemia*, including Raynaud's phenomenon (temporary overreaction of the blood vessels in fingers or toes in response to cold or stress), or transient ischemia of the digits or toes, are associated with therapies such as bleomycin, vinca alkaloids, gemcitabine and cisplatin. Ischemia occurs from direct effects on endothelial cells or from a more complex response including vasospasm, thrombus formation and vasculitis. Ischemia can persist even when the therapy is stopped.

Most chemotherapy protocols call for concurrent steroid administration. Steroids have been shown to cause osteonecrosis, or avascular necrosis, (loss of blood supply to bone which ultimately leads to bone death) with both intermittent and continuous use [3]. It is commonly seen in the jaw or weight-bearing joints. When occurring near a joint, it can cause collapse of the joint resulting in arthritis, decreased range of motion and increased pain with movement. Steroids can also cause diffuse myalgias, hyperglycemia and psychosis [3].

3.2 Radiotherapy Related Pain

Radiation therapy uses high energy waves to destroy or damage tumor cells and side effects are more common in rapidly dividing cells such as those of the skin or gastrointestinal tract [3]. Effects can be seen during treatment (acute effects) or anywhere from weeks to years after treatment (late effects). Pain early on during treatment is due to inflammation, flare or procedural pain, whereas is pain seen after the completion of treatment (up to months or years later) is often due to fibrotic tissue [4].

3.2.1 Acute Effects

In the acute phase of radiation induced pain, mucosal inflammation and tumor flare are two of the most common causes [4].

Acute mucosal inflammation includes stomatitis, mucositis, pharyngitis, esophagitis, gastritis, enteritis and proctocolitis [4]. Atrophy of the squamous epithelium can occur anywhere from the oral cavity to the anus, and not only causes pain but can also lead to vascular damage.

Tumor flare is a temporary increase of pain in areas that have been radiated seen commonly in patients being treated for bone metastases. Pain is caused directly from the tumor, inflammation of the tumor, or electrolyte disturbances such as hypercalcemia [5].

Direct effects on the skin cause changes in pigmentation (temporary or permanent) and burns.

3.2.2 Late Effects

Late effects of radiation therapy can occur up to years after treatment. While acute effects are typically seen in cells that divide rapidly, late effects are usually seen in cells with slower turnover (fat cells, subcutaneous tissue, brain, muscle and organs) [3]. Symptoms include sclerosis, osteonecrosis of bone (i.e., mandible, femoral head), muscle contractures or plexopathies. Fibrosis of the skin and soft tissues and myofascial pain syndromes can also occur [3].

Long-term damage to bone (i.e., decreased bone density) can also result in fractures [3].

3.2.3 Procedural Pain

Brachytherapy is the process of inserting temporary or permanent radioactive implants into a tissue or body cavity. It is typically used to treat genitourinary malignancies (i.e., prostate cancer, gynecologic malignancies) but can also be used to treat cancers of the head and neck and breast. The process itself can result in pain from implantation or the patient positioning necessary to accurately target the affected area. Once implanted no pain is typically felt.

3.2.4 General Side Effects

Pain associated with radiation therapy is vast and affects multiple organ systems including the skin, gastrointestinal tract, lungs, musculoskeletal system and nervous system. Common symptoms include abdominal pain/cramping, arthralgias, myalgias, arthritis, noncardiac and non-pleuritic chest pain, dysmenorrhea, dyspareunia, dysuria, otalgia, headache, hepatic pain, pelvic pain and rectal or perirectal pain [6].

3.2.5 Radiopharmaceutical Related Pain

The American Cancer Society describes radiopharmaceutical medications as liquid drugs comprised of radioactive substances, often bound to monoclonal antibodies. These medications are taken orally or intravenously and bind to cancer cells with the help of an antibody. Once bound, they emit radiation and destroy the cancer cell. This treatment is commonly used for prostate and thyroid cancer although radionuclide therapy has been indicated for patients with painful bone metastasis as well.

Radioactive iodine therapy used for the treatment of differentiated thyroid cancer has been shown to cause pain and/or swelling in the neck or parotid region. Gastrointestinal effects include xerostomia, altered taste, difficulty swallowing, nausea/vomiting or diarrhea [7]. Other generalized symptoms such as headaches, insomnia, fatigue and body numbness, while not common, have also been seen [7].

Radioactive isotopes can be used to treat pain related to bone metastases because of their ability to be rapidly absorbed in areas of increased osteoblastic activity [8]. Flare response has been shown to occur in 10% of patients within the first few days of treatment, regardless of the agent used [8]. Flare is an initial aggravation of pain thought to be related to the release of cytokines and has been thought to be an indicator of a good response to the therapy [8]. Onset of pain relief can take days or weeks and therefore is generally not recommended in patients with limited life expectancy [8].

3.3 Hormone Therapy Related Pain

3.3.1 Flare Syndrome

Tumor flare reaction is an increase of a lesion related to stimulation from treatment [5]. Locally, advanced and metastatic prostate cancers are often treated with androgen deprivation therapy. The goal of treatment is to reduce male hormones that have the potential to positively affect cancer cells [1, 3]. This therapy can cause flare, and the rise in prostate-specific antigen (PSA) can lead to new lesions [9, 10]. The flare reaction, as well as the new lesions that may develop, can cause increased pain at sites of metastasis, as well as other problems such as with urination, urethral obstruction and even neurological complications (including spinal compression and paraplegia) [11]. Five to ten percent of postmenopausal women with breast cancer treated with anti-estrogen therapy experience a similar type of flare reaction [12]. The pain is often described as musculoskeletal pain and is typically seen at the start of therapy [13].

It is important to be aware of the potential for flare with hormonal therapy, in order to distinguish it from disease progression. Early recognition and management are also important since flare reaction is associated with increased morbidity.

3.3.2 Aromatase Inhibitor Arthralgia

Aromatase inhibitors (AIs) suppress plasma estrogen levels by inhibiting or inactivating aromatase, which is used to convert androgens to estrogens. Aromatase inhibitors are commonly used as an adjuvant treatment for postmenopausal women with hormone receptor positive breast cancer. Decreased estrogen can cause menopausal symptoms and increased bone demineralization, which can in turn increase the chance of fractures [14]. While the etiology is not fully known, estrogen is thought to play an important role in skeletal maturation and accrual of bone mass [14], and it is thought that this loss of bone is what causes the bone pain. It is important to measure bone mineral density at baseline for patients receiving AIs.

One of the most prevalent AI associated symptoms is myalgia/arthralgia (diffuse muscle aching, joint pain/stiffness). Since this therapy is often carried out for 5 or more years, it poses a significant impact on quality of life and daily functioning and is a major reason for discontinuation of treatment.

3.4 Immunotherapy Related Pain

3.4.1 CAR-T Cell Therapy

Chimeric antigen receptor (CAR-T cell therapy uses T cells to directly attack cancer cells. As CAR-T cells multiply, they release large amounts of cytokines (known as cytokine release syndrome), which can cause inflammatory pain and resulting fever and body aches. More severe cases of cytokine release syndrome can cause tachycardia and hypotension. Some studies have found CAR-T cells in cerebrospinal fluid, indicating the ability to cross the blood brain barrier and therefore have the potential to cause neurologic toxicity (including paralysis, speech and movement disorders and seizures) [15].

3.4.2 Interferon Therapy

Interferons are proteins naturally produced by our immune system to help stimulate immune cells to fight disease. They can be manufactured and given to patients to produce similar effects. They are commonly used to treat hepatitis C and chronic myeloid leukemia (for their ability to reduce the growth and division of leukemic cells). Because interferon therapy is often given for extended periods of time (6–12 months), there is a greater chance for side effects to develop, although conversely, they can also improve with time. Common side effects of interferon treatment include edema at the injection site, myalgias, arthralgias, headaches, fever and fatigue [1]. One case study found that a 19-year-old male with Philadelphia positive chronic myelogenous leukemia treated with interferon alpha therapy for 45 months developed systemic lupus erythematosus disease features, including malar rash and migratory arthralgias [16]. Interferon alpha used for chronic hepatitis C treatment has also been shown to cause neuropathy, acute confusional states and manic conditions [17, 18].

3.4.3 Growth Factor Associated Pain

Growth factors, such as granulocyte CSF and interleukin-3, stimulate the bone marrow to produce granulocytes and stem cells and can therefore lead to bone pain, fever, headaches, myalgias and arthralgias [1]. Nerve growth factor (NGF) helps to grow, reproduce and maintain neurons. It is elevated in inflamed tissues and may

lead to terminal sprouting, in turn causing an increased perception of pain. This is further supported by the evidence that neutralizing the action of increased NGF decreases inflammatory hypersensitivity [19]. NGF expression in the dorsal root ganglion during inflammation is thought to play a role in persistent pain [19]. Epidermal growth factor receptor (EGFR) inhibitors activate nociceptive fibers in basal keratinocytes and cause pain as a result of skin changes, such as erythema and papulopustular eruption [4]. Tyrosine-kinase inhibitors can cause palmar-plantar erythrodysesthesia, also known as hand-foot syndrome, which causes burning, numbness, edema, hypersensitivity and desquamation of the palms and soles [4].

3.5 Procedural Pain

Procedures important to the diagnosis and treatment of cancer can themselves cause pain.

3.5.1 Diagnostic Testing

Bone marrow biopsies cause pain in a majority of patients who get them, with the sternum being the most painful site [4]. Lumbar punctures, used for both diagnostic and therapeutic purposes, can cause cerebrospinal fluid leakage and subsequent post dural puncture headache [4]. Transrectal ultrasound-guided prostatic biopsy is a common cause of pain in the workup for prostate cancer. Pain is due to the needle penetration of the prostatic capsule [4].

3.5.2 Post-operative

- *Post-amputation* pain can be phantom pain (painful sensations in the missing limb) or stump pain (painful sensations in the residual limb). The theory of this pain has shifted over time from psychogenic to neuropathic. This pain can be classified as supraspinal, spinal and peripheral. Supraspinal somatosensory reorganization in the area of the amputated limb is responsible for phantom pain and phantom sensations [20]. Spinal reorganization causes persistent signaling in the stump, which leads to aching and burning pain [3]. Peripherally, axonal nerve damage causes inflammation, regenerative sprouting and increased input, which also amplifies stump pain [20]. Having pain prior to amputation increases the risk of developing phantom pain later.
- *Post-mastectomy, post-thoracotomy and post-radical neck dissection* carry similar components of pain. Pain occurs after partial or complete nerve severance. Damage to nerve membranes causes hypersensitivity to abnormal sensory input in the central nervous system [3]. This pain is described as a continuous burning or dull, aching pain that is exacerbated by touch, movement or stress [3].

Post-mastectomy pain occurs from the surgery itself (cut nerves and tissues) or from surgical sequelae such as lymphedema or scar tissue. Pain following thoracotomy can be neuropathic from the direct nerve damage, or musculoskeletal involving the muscles of the shoulder girdle [3]. Nahum et al. describe *shoulder syndrome* as being the pain that results from limited shoulder movement [21]. Pain from neck dissections is related to injury of the cervical plexus and typically occurs weeks to months after surgery [3].

3.5.3 Tumor Embolization

Tumor embolization is the process of placing embolic agents through a catheter into a blood vessel to block blood flow to an area of the body. Because this causes death of cells and tissues, it naturally leads to pain. One of the main side effects is soft tissue necrosis, particularly when one or more vessels are occluded or when liquid agents are used. Head and neck embolizations can cause headaches or temporo facial pain, pulmonary and bronchial artery embolization can cause pleuritic chest pain, liver embolizations can cause pain in the right hypochondrium and vascular necrosis from splenic embolizations can cause fever and abdominal pain [22].

3.5.4 Chemical Pleurodesis

Chemical pleurodesis is the process used to eliminate the pleural space. First, the effusion, if present is drained, or the intrapleural air is removed. Inflammation and fibrosis are then induced with chemical irritants or by performing mechanical abrasion. The purpose of chemical pleurodesis is to try and prevent recurrent pleural effusions or recurrent pneumothorax. One of the most common complications includes pain related to the sclerosing process or directly from the sclerosing agents [23]. There is also the possibility of acute pain from the chest tube that typically needs to stay in place for 24–48 h following the procedure, or until the lung has adhered to the chest cavity.

3.5.5 Percutaneous Drain Insertions

Percutaneous drains (inserting a tube through the skin for the purpose of draining fluid) are typically inserted for abscesses, leaks, infected hematomas, urinary obstructions or biliary obstructions. They carry less morbidity and mortality compared to open surgical drainage and can therefore play an important role in the management of critically ill patients. The most common complications include bleeding, sepsis, cellulitis and injury to nerves or vital organs. The process itself can cause pain from the insertion of the tube, or from complications of the procedure. The procedural pain in these instances is typically acute and resolves within days.

3.6 Supportive Therapy Related Pain

3.6.1 Bisphosphonates

Patients with painful bone metastases are often treated with intravenous bisphosphonates, which can cause systemic inflammatory reactions and resulting pain [4]. In some patients, pain can be so severe that it limits activities of daily living and can last up to several days. Osteonecrosis of the jaw is when the upper or lower jaw bone becomes exposed and begins to die from a lack of blood supply. This is a common side effect of patients receiving bisphosphonates and RANKI inhibitors.

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Cancer Pain Management—A European Perspective

4

Denis Dupoiron

4.1 Introduction

Cancer pain management is a major challenge in both Europe and the United States. Recent studies show that the incidence of cancer pain remains high and even increases at an advanced stage of the disease. In a recent literature review, but Van Beuken found a prevalence of pain significantly higher in Europe compared to North America [1]. Pain remains the most common symptom at an advanced stage of cancer [2].

Many characteristics of cancer are similar on both sides of the Atlantic. First, the incidence of cancer is increasing steadily while mortality is stabilizing (North America 101/100,000 vs Western Europe 104/100,000) leading, de facto, to a greater number of patients who suffer [3]. The main reasons for these findings are, on the one hand, the aging of the population and, on the other hand, the effectiveness of anticancer therapies, such as targeted therapies, which considerably improve overall patient survival [4]. For example, from both sides of the Atlantic ocean, incidence of uterine cancer has decreased dramatically from the beginning of this century while melanoma of the skin incidence increased [5]. As an example of mortality improvements, the metastatic ten year survival rate of kidney cancer increased from 10% in 2000 to 67.5% in 2018.

However, these treatment advances are not found in the control of cancer pain. Indeed, in a recent review of the literature, Van Beuken [1] showed that compared to a previous study [6] there has been no improvement in the management of cancer pain and that at an advanced stage of the disease, the percentage of patients suf-

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fering has increased from 64 to 66%. In addition, in the same study, there was an increase in the prevalence of pain in cancer survivors (39%).

However, unlike the USA, Europe is a patchwork, and the management of cancer pain varies widely depending on the organization of care and access to pain treatment. Great differences are found between, on one hand Western and Northern Europe and, on the other hand, Eastern and Southern Europe. Most of these differences are explained by the contrast in health systems, health care policies and level of expenditure for diagnosis and treatment. Similar differences are observed between the United States and different European countries.

4.2 Epidemiology of Cancer in Europe

Cancer is the second leading cause of mortality noted by the Organization for Economic Co-operation and Development (O.E.C.D.) countries after circulatory diseases, accounting for 25% of all deaths in 2015, up from 15% in 1960 [5].

Epidemiology of cancer is nearly the same between Northern Europe and the USA with more than 300 new cases for 100,000/year [5, 7]. The lowest rates of cancer were reported in some Latin American and Mediterranean countries such as Greece and Turkey and Eastern Europe with around 200 new cases or less per 100,000 population. Mortality has decreased in most countries except in Eastern and Southern Europe. In a 2015 study, Stevens et al. [7] found that mortality rates from cancer in the U.S.A. were lower and had declined faster between 1995 and 2007 than in most Western European industrialized countries [6]. This fact needs to be addressed by healthcare systems in Europe, as a strong relationship between gross domestic product (GDP), expressed as parity purchasing power, and the 5-year age-and cancer site-adjusted relative survival is observed [8].

4.3 Epidemiology of Cancer Pain in Europe

Pain is the main criteria leading patients (30% of patients) to seek out health care on which a diagnosis of cancer was made [9].

4.3.1 Prevalence of Cancer Pain in Europe

In a large Europe-wide survey [10], European Pain In Cancer (E.P.I.C.), in 2007, of 5084 adult patients contacted, 56% suffered moderate to severe pain at least monthly and 69% reported pain-related difficulties with everyday activities. The cancers most responsible for pain are pancreatic cancers, head and neck cancers and lung cancers. In the same study, pain has the highest prevalence in Italy and the lowest in Sweden. It also appears that an Iron Curtain still divides Eastern and Western Europe when it comes to access to adequate pain management. South-eastern European countries have limited resources and manpower to allocate for

delivery of effective care for cancer-related pain [11]. In a recent literature review, pain prevalence rates were 39.3% after curative treatment; 55.0% during anticancer treatment and 66.4% in advanced, metastatic, or terminal disease. 63% of patients experienced breakthrough pain [1]. In a meta-regression analysis, the authors of this publication found higher rates of cancer pain in Asia than in Europe, but no difference between Europe and North America.

4.3.2 Cancer Pain is an Unsolved Problem in Europe

4.3.2.1 No Improvement During the Last Decades

One of the major characteristics of cancer pain in Europe is the lack of improvement in the management of pain over the last 20 years. For example, in France, two studies [12, 13] with strictly similar methods in both surveys have been conducted on the incidence of pain in cancer 15 years apart. They showed no real improvement (56% versus 57%) in the percentage of cancer patients suffering.

4.3.2.2 Undertreatment

It is estimated that undertreatment of cancer pain affects up to 51% of patients. [14]. Deandrea showed that undertreatment of cancer pain is more frequent in patients from Europe (51%) than those from United States (33%) and that undertreatment is more frequent in cancer patients from countries with a gross national income per capita less than $40,000 per year [15]. Undertreatment of pain is particularly prominent in countries formerly cut off by the Iron Curtain and in Balkan countries. Eastern European countries lack national policies to support pain treatment, and pain clinics that offer multidisciplinary pain strategies are few [11].

In Western Europe, Van Beuken found 42% of patients with inadequate pain treatment in the Netherlands, and in France the rate was 57% in the 2010 survey [12]. The WHO (World Health Organization) ladder doesn't seem efficient to improve cancer pain treatment, especially at an advanced stage of the disease [16]. For Gouda in 2005 [17], female gender, minority status, and advanced age were risk factors for undertreatment.

4.3.2.3 High Levels of Pain

Another important characteristic of cancer pain is the high level of pain. In the EPIC study [10], 94% of patients reported that they experience moderate to severe pain (rated 5–10 on the pain scale). 21% of patients suffering from moderate to severe pain experience it daily, and 4% regarded their pain as 'the worst pain imaginable'. In another study conducted in the Netherlands [18], 44% of patients suffered from moderate to severe pain. In the French 2010 study, 55% of patients report having at least one high intensity crisis daily.

4.3.2.4 Pain in Cancer Survivors

In Europe, as in the United States, cancer survival rates have improved considerably since the beginning of this century. In the United States, the cancer-related death

rate dropped by 1.1% per year from 1993–2002, while overall cancer mortality decreased from 251/100,000 inhabitants in 1991 to 171.8 per 100,000 in 2010 [4]. Similarly, in Europe there is a comparable trend, with a stabilization of mortality despite an increase in incidence. The standardized mortality rate is lowest in Northern Europe (168/100,000) and highest (200/100,000) in Eastern Europe, but there are also large variations in each of the regions [7]. The reasons for this are essentially improved screening and prevention, but also the improvement of cancer treatments, be it surgery, chemotherapy or radiation [19]. In France, between 2006 and 2011, cancer incidence increased by 14% and mortality by only 1% [20]. In this context, the challenge of pain in cancer survivors has become one of the most important concerns.

In a literature review, van Beuken found that 33% of patients had pain after cancer treatment in 2004 and in a 2014 update, this rate increased to 39% [1]. The most common problem encountered is pain after breast cancer surgery. A remarkable Danish study indicated that the incidence rate was 47% in that country [21].

Reported Chemotherapy Induced Peripheral Neuropathy (CIPN) incidence rates range from 4% to more than 76% [19]. No specific studies showed any difference between the USA and Europe. There is also no differential incidence data for pain sequelae after radiotherapy (10%) in an international survey [22].

4.3.3 Prevalence of Neuropathic Pain

Neuropathic pain (NP) is an important component or cancer pain, often under diagnosed and undertreated. In a recent literature review, Mulvey [23] found a global rate of 28% of patients suffering neuropathic pain. However, there is variability in data and most of the available data are from Western and Northern Europe. Irving had indirectly estimated the prevalence of cancer NP among American patients suffering from any pathological NP type, and this was found to be 5.6% [24]. Rayment [25] reports a rate of 17 % of neuropathic pain, and Garzon Rodriguez [26] 32% of pure neuropathic pain with 47% of Mixed pain. In a recent Spanish study, Perez found a rate of 20.4% of patients suffering neuropathic pain [27]. Despite its widely recognized importance, in the USA, there is a lack of specific studies on neuropathic pain incidence in cancer patients. However, Lema asserts that the cost of chemotherapy-induced neuropathic pain in the USA is approximately $2.3 billion per year [28].

4.4 Costs of Cancer Pain Treatments

4.4.1 Reimbursement Models

The greatest difference in the management of cancer pain between Europe and the USA is predominantly due to the differences in insurance and reimbursement models. In fact, there are five major types of health insurance models in the world.

4.4.1.1 The Tax-Funded Model

This system is funded by taxes and compulsory contributions and therefore this system is provided by governments. The first system started in Great Britain after the Second World War, and it is called NHS (National Health Service). Spain, New Zealand, and some Scandinavian countries have the same model in which everybody is covered.

4.4.1.2 The Employment-Based Insurance Model

The system is, in this model, funded by employers and workers through pay deduction. Countries with this model include Germany, France, and Japan. Unemployed people are also covered in this system. Moreover, for cancer patients, all treatments are fully free of charge in France.

4.4.1.3 The National Health Insurance Model

This system combines a combination of private sector and government insurance funding. This kind of reimbursement system is found in Canada, where everybody is covered with a high level of quality of care, but may experience long wait times.

4.4.1.4 The Private Insurance Model

Funding in this system is based on premiums, and insurance coverage is provided by private insurance companies. The main country where this system exists in pure form is the USA. It only covers those who are insured but Medicare Hospitalization Insurance and Medicaid help others. The "Obamacare" program tried to amend this problem, as 11% of Americans did not have health insurance before this law. The affordable Care Act provides 3 different models: health maintenance organizations (HMO), preferred provider organizations (PPO), and indemnity insurances.

4.4.1.5 The Out-Of-Pocket Model

The patient, in this model, pays at point of use. This model offers medical services with no centralized funding system and many people don't have enough resources to pay for healthcare.

Overall, through Europe, nearly 100% of patients are covered by medical insurance, except in Eastern and Southern countries like Poland, Hungary, the Slovak republic, and Greece where free public health care systems do not include complete treatment charges (Fig. 4.1), while 9% are currently not covered in the USA [5].

4.4.2 Costs of Cancer Pain

Healthcare spending per person is quite different between the USA and Europe. The USA spends about twice as much per capita as most European countries. (Fig. 4.2). There is limited data on cancer pain costs in the literature. However, more data is available on cancer costs. For example, US spending on cancer care, in

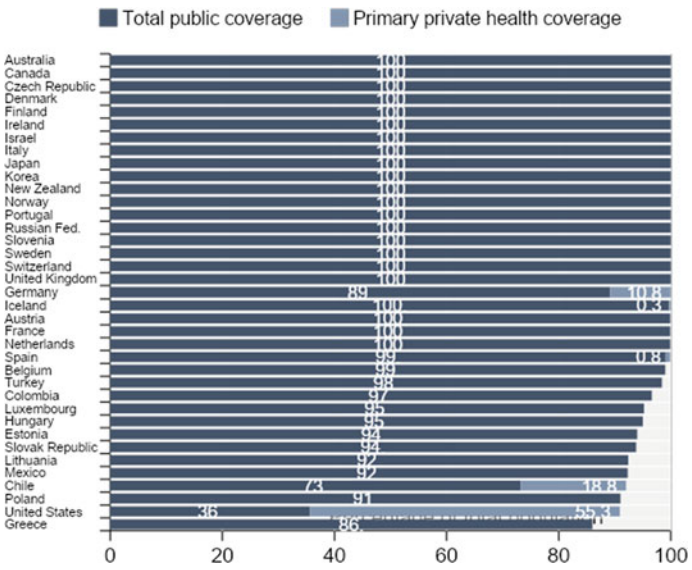

Fig. 4.1 Health at a Glance 2017: OECD indicators. Reproduced from OECD © 2017 [5]

2010 US dollars, increased from $47,000 per cancer case to $70,000 per case from 1983 through 1999—a 49% increase. During the same time, in ten European countries, spending on cancer care in 2010 US dollars increased from $38,000 per cancer case to $44,000—a mere 16% increase [29]. Cost differences between European countries can be partly explained by differences in gross domestic product and health system configuration [30].

Spending in excess of European costs by US patients with the cancer types included in the analysis thus totaled $158 billion over the period 1983–99. Differences in US costs reflect more rapid uptake of new technologies that may lead to differences in survival. For pain, one study estimates for 2008 that the national cost of pain (cancer and non-cancer pain) ranges from $560 to $635 billion [29].

Only one study on cancer pain cost is available, from Sweden [30]. 10% of pain treatment costs are for cancer pain. For the USA, only data for inpatients treated for cancer pain are available from 2011 to 2015. The median total hospital charge is $48,156 [31]. Another important finding is that most of the differences among European nations are a consequence of the differences in availability more than reimbursement rates for painkillers [32]. A recent systematic investigation of legal and regulatory barriers to opioid access in 11 countries from Southern and Eastern Europe highlighted the existence of excessively strict rules and regulations especially in Bulgaria, Estonia, Hungary, Latvia, and Lithuania [33]. That led to Pauline Anderson [34] affirming in 2011 that another Iron Curtain still divides Eastern and Western Europe when it comes to access to adequate pain management.

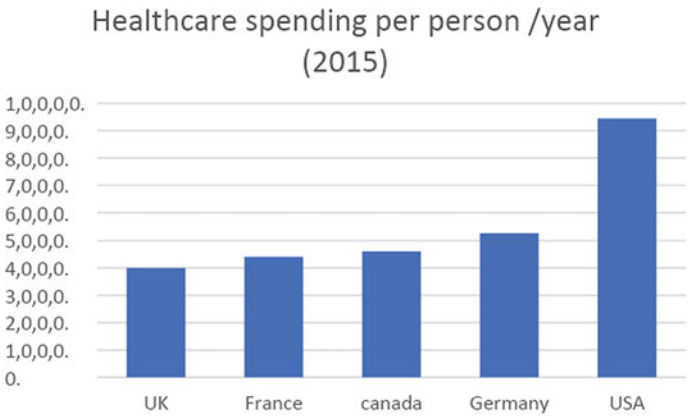

Fig. 4.2 Healthcare spending rates

4.5 Assessment of Cancer Pain

For Judith Paice from the Special Interest Group of IASP [35], assessment of cancer pain begins with a patient rating of pain intensity, but also often involves very complex emotions, fears, family distress, misconceptions related to pain treatment, and expression of suffering. So, she recommends a comprehensive assessment to identify physical, psychological, social, and spiritual aspects as well as pain intensity evaluation.

4.5.1 European Findings (Overall)

Most (72%) patients reported that their clinician asked them about their pain at most consultations [10]. Only 15% of patients reported that their clinician measured their pain using a pain scale. Italy, Israel, France, and Switzerland are the countries where most respondents acknowledged the use of a pain scale unprompted, with 44%, 28%, and 20%, respectively. Overall, 50% of patients believed that their healthcare professional did not consider their quality of life as an important aspect of the overall care plan and a smaller overall percentage believed their healthcare professional did not understand that pain was a problem (12%).

4.5.2 Neuropathic Pain

One of the most important issues is the underassessment and undertreatment of neuropathic pain. One of the main factors causing this is that too many scales for Neuropathic pain assessment are available and used in Europe. A standardized

approach or taxonomy used for assessing neuropathic pain in patients with cancer is needed to improve treatment outcomes [36]. The DN4 (Douleur Neuropathique 4) scale turned out to be the most sensitive for cancer neuropathic pain (confirming neuropathic pain in 78.5% of all the study patients), while the LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) scale turned out to be the least sensitive (confirming neuropathic pain in 48.49% of all the study patients). In contrast, specificity values were high for all tools (range 77–100%) [37].

4.5.3 Guidelines

National clinical practice guidelines have been developed in most Western European countries to assist practitioners in managing cancer paint. The efficiency of these guidelines on pain treatment has not often been evaluated, except in the Netherlands, where a 2011 study indicated that, despite the national guidelines published in 2008, documentation of pain intensity in patients' hospital records remain low, and differed significantly between the academic hospital (50%), the large teaching hospital (28%), and the peripheral hospitals (21%) [38]. On the other hand, a recently published evaluation of 9 clinical practice guidelines for neuropathic cancer pain management showed that the quality of these guidelines varied widely, and that the governmental guidelines had higher quality scores than professional society guidelines [39]. A standardized European guideline of high quality would likely improve physicians' ability to detect and manage cancer pain.

4.5.4 Breakthrough Pain

In a larger study in Europe, the prevalence of breakthrough pain was 63% of patients using analgesics [10]. In another literature review, the prevalence rate is 57% in Europe versus 30% in 10 studies from America [40]. The difference in opioid consumption probably explains that huge difference. A comparative study between European and Canadian surveys showed no large difference in characteristics of breakthrough pain between Canada and Europe, and 40% of patients presented more than 3 episodes/day [41].

4.5.5 Who Manages Cancer Pain in Europe

The European survey in 2007 [10], showed that only 24 % of cancer patients had ever been referred to see a pain management specialist or to a pain clinic. The highest rates are in Italy (50%) and Israel (40%), and the lowest in Romania (6%). This study demonstrated that a number of different physicians are involved in cancer pain treatments. Medical oncologists (42%) and General Practitioners (19%) are most often cited by patients to have the main responsibility, and pain specialists are only cited by 3% of patients.

4.6 Cancer Pain Treatments

Deandrea in a literature review affirms that Europe faced an undertreatment of cancer pain versus America [15]. Opioid consumption is probably one of the key factors in this statement. It is probably the biggest difference in the treatment of cancer pain between the USA and Europe.

4.6.1 Opioids

4.6.1.1 Consumption

Europe faces under-consumption of opioids, unlike the United States, which faces overconsumption, and during the last years has had to fight against the "Opioid epidemic." In 2016, over 42,000 Americans died from opioid overdoses, 21 % more than in 2015 [42]. Achieving the right balance in the appropriate use of opioids for the treatment of cancer pain is complex. Almost a quarter of patients who experience moderate to severe pain (rated 5 or more) are not receiving treatment for their pain. The United States morphine consumption was in 2016, 50.6 % of the world global consumption for 5.1% of the world population while European consumption was 25.4% for 11.7% of the population. Globally, more than 75% of the world consumption was from USA and Europe , while developing countries accounted only for 6% of global consumption[43]. In 2015, the amount of opioids prescribed was 700 MME (Morphine Milligrams Equivalent) per capita, in the USA, 213mg in France and 47 mg in Poland [38] (Fig. 4.3).

In many European countries, excessively zealous or poorly considered laws and regulations to restrict the diversion of medicinal opioids into illicit markets profoundly interfere with the medical availability of opioids for the relief of pain [44]. Fear of addiction by patients, family members, and oncology professionals also presents a serious obstacle to the provision of adequate pain control.

Global opioid consumption increased from 28 mg to 42 mg morphine equivalents per capita in the period from 2005 till 2012. Only 46% of cancer patients using analgesic medication are on strong opioids (Morphine, Oxycodone, Fentanyl, Hydromorphone, Methadone, Buprenorphine). European country of origin and low gross national income per capita were predictive of a higher proportion of patients having uncontrolled pain [44]. While there has been a significant increase in opioid consumption in Western Europe, there has been little change in the last 20 years in Eastern Europe. In the majority of Western European countries, most opioids are available at no cost to patients with cancer pain. In general, the opioid formularies of many East-European countries are substantially more limited. Limitations affect availability of some analgesics like fentanyl or hydromorphone, but also some formulations, like sustained released formulation and transmucosal formulation for breakthrough pain. For example, in the Ukraine, only codeine, oral immediate release and injectable morphine are available. [45]

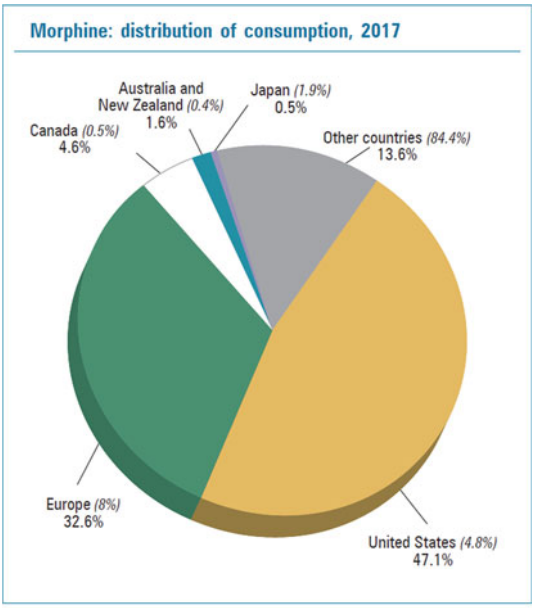

Fig. 4.3 Data on morphine consumption. Reproduced from International Narcotics Control Board, 2017 [43]

4.6.1.2 Restrictions on Prescriptions

Furthermore, regulatory restrictions make it nearly impossible for many Europeans to access relief of cancer pain. That undermines their quality of life. In some countries, the degree of legal intimidation is such that fear of criminal prosecution contributes to deliberate undertreatment by clinicians to avoid risk of persecution or prosecution. Issues are reflected in substantial differences in opioid consumption between European countries and in profound differences in morphine consumption between Western and Eastern European countries.

Most of the East-European and a minority of the West-European countries require that patients, particularly outpatients, receive a permit or be registered to be eligible to receive opioid prescriptions for the management of cancer pain. Some countries restrict the authority to prescribe opioids to physicians with special permits or to practitioners of certain subspecialties and time prescription limits (28 days in France). Moreover, opioid prescription requires duplicate prescriptions and a special prescription form. In addition, the distribution by pharmacists is limited (only 7 days of treatment at the same time in France) and the patient has to bring back the packaging of the pills to the pharmacist.

Finally, several countries use pejorative or stigmatizing terms (dangerous drug, poisons) for opioid analgesics in the regulation controlling their prescription. For example, in France, driving is prohibited while taking opioid analgesics and the patient is liable to prosecution [46].

4.6.2 Cannabis

For the cancer patient, cannabis has a number of potential benefits, especially in the management of symptoms [47]. Cannabis is useful in the treatment of anorexia, chemotherapy-induced nausea and vomiting, pain, insomnia, and depression.

Cannabis has been authorized since 2013 in most Western European countries. Some countries that have passed laws supposedly allowing for the provision of medicinal cannabis do not actually permit anyone to use it. Unlike in the USA, only 6 countries authorize medical cannabis; recently Greece followed Czech Republic, Finland, the Netherlands, Spain, and Portugal, which was the first European country to legalize the drug in 2001. Sativex, a whole plant medicinal cannabis extract, is indicated for the relief of multiple sclerosis symptoms and the treatment of severe neuropathic-related cancer pain. The use of Sativex® has been approved in 17 European countries, but only 9 have already made it available. In most Eastern European countries, medical cannabis remains prohibited [48].

4.6.3 Neuropathic Pain Treatments

Two topical treatments are currently licensed by the European Medicines Agency (EMA) for peripheral neuropathic pain: lidocaine 5% medicated plaster (post-herpetic neuralgia) and the capsaicin 8% patch (peripheral neuropathic pain). When compared head-to-head with the oral standard of care, both treatments demonstrated effective pain relief without the systemic adverse events associated with oral therapies [49].

However, in Europe, great differences in reimbursement and availability of these topical treatments for neuropathic pain explain disparity in use from country to country, with a larger use in Germany where Capsaicin is available for GPs, vs in France where the patch is available only in a hospital setting.

4.6.4 Interventional Therapies

Limited data is available on the use of interventional therapies for cancer pain in Europe. Only one study by interview was realized in 2012 [50]. Despite its limitations, this study shows that anesthesiologists are the most represented specialty in the interventional treatment of pain. There are few programs for specialized pain training for physicians, and no specific programs for the learning of interventional techniques. In addition, only 3 countries have reached consensus for the use of interventional treatments in the treatment of cancer pain (GB, Netherlands, and France) [51–53].

Reimbursement is also an important limitation for the use of interventional therapies in Europe. For example, setting up an intrathecal pump is only allowed in Netherlands for patients with a life expectancy of more than one year, and some treatments like Ziconotide are not available in countries such as Belgium, or are

hard to get as in the UK, where the physician has to ask the national health service for the authorization to use it.

4.7 Palliative Care in Europe

4.7.1 Development

The United States now has 1800 hospitals with palliative care programs. US hospitals with more than 50 beds experienced a threefold increase in palliative care programs from 2000 to 2015 [54]. In 2000, 25% of these institutions had a palliative care program and, by 2015, the number had risen to 75%. Moreover, 90% of hospitals with more than 300 beds and 100% of the National Cancer Institute's Comprehensive Cancer Centers now have palliative care services.

In Europe, the development of palliative care is less homogeneous (Fig. 4.4). Here too, we find the same differences in spending between the countries of Northern and Western Europe on the one hand and the countries of Southern and Eastern Europe on the other [55]. However, the UK has long been a pioneer in the management of palliative care. In a recent study, the U.K. achieved the highest level of development (86% of the maximum possible score) [56], followed by Belgium and the Netherlands (81%), and Sweden (80%) [55]. In a 2007 article, Jan Stjernsward proposed a Public Health Strategy to improve palliative care throughout European countries: first, develop a specific appropriate policy; second, ensure adequate drug availability; third, provide palliative care education for policy makers, health care workers and the public; fourth, implement palliative care services at all levels throughout the society. This approach has demonstrated that it provides an effective strategy for integrating/establishing palliative care within a country [57].

4.7.2 New Ethical Considerations for End of Life

4.7.2.1 Evolution in Ethical Considerations for End of Life

Traditional ethical ideas for end-of-life care are under fire in Europe. End-of-life patient care, especially for those with cancer, has long been guided solely by the Hippocratic oath, which refused active participation at the end of life. However, for two decades, ideas have evolved regarding the end of life. In this context, the laws on the end of life evolved during the second half of the 20th century, including decriminalization of euthanasia in Switzerland in 1942. The Netherlands became, in 2002, the first country to authorize euthanasia and assisted suicide. Belgium followed a few months later which since 2013 has allowed it for minors.

In the USA, active euthanasia is still prohibited, but five states allow Physician Assisted Suicide (P.A.S.), since 2016. Oregon was the first to legalize PAS in 1997. This state requires that the patient make two successive oral requests and one

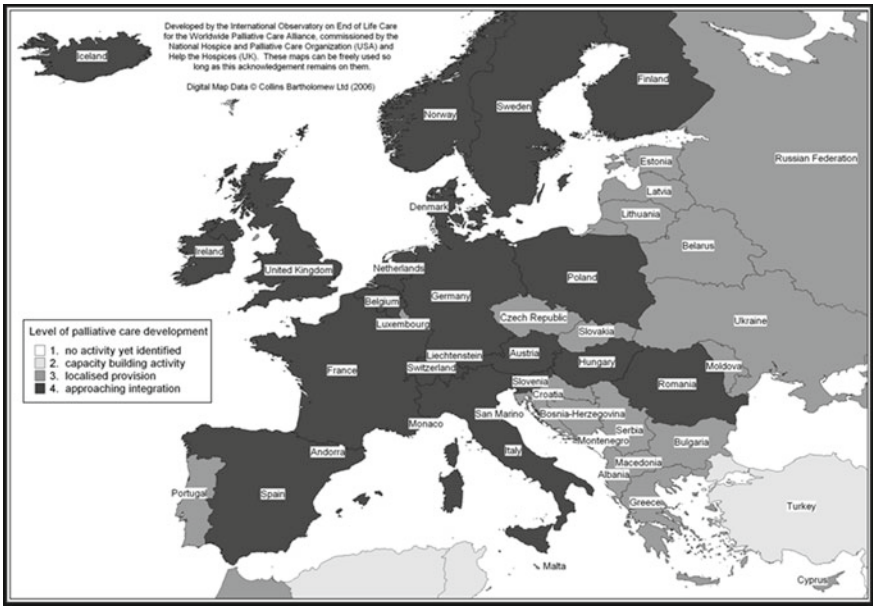

Fig. 4.4 Hospice-palliative care service development in Europe. Reproduced from Wright et al. 2008 [58]

written request, before proceeding to PAS. Two doctors must validate this request and the patient must self-administer the lethal drugs.

Cancer is the main motivation for a demand to abbreviate the end of life in 70 to 80% of cases, regardless of country, and pain is the cause of this request in 25% of cases in Oregon, 35% of cases in the state of Washington and 50% in the Netherlands [59].

In other countries like France, PAS, and euthanasia are banned, but a new law allows a terminal continuous sedation for patients at the end of life, if the patient asks for it or has requested it through anticipated end-of-life directives, and also if that request comes from a trusted person designated by the patient. Sedation is implemented only after a multidisciplinary meeting of care givers and only if the physician agrees. Finally, in most countries of Eastern Europe, these practices are prohibited.

In the United States, a plateau in public support for these changes has been observed over the last 10 years (60%). In Europe, between 1999 and 2008, support for euthanasia in Western European countries continues to increase. However, at the same time, there has been no increase or even a decrease in the acceptance of euthanasia and PAS in most Central and Eastern European countries. These changes appear to correlate with a strong decline in religiosity in Western Europe and an increase in religiosity in Eastern Europe

4.8 Conclusion—Future Directions

Compared to the USA, there is less focus in the EU on cancer pain and fewer patients referred for treatment. There is a need within the EU to develop specialized cancer pain consultations not only to treat pain during active cancer treatment but also into survivorship. To achieve these goals, better training for caregivers must be implemented. Modern communication techniques available online now allow a much wider access to such training. This is the goal of the European Federation of ISAP Chapters (EFIC) Education Platform (https://www.europeanpainfederation.eu/new-efic-education-platform/). Moreover, the same techniques should allow secure remote consultations, to improve access to cancer pain treatment in underserved areas.

In addition, we must also have a comprehensive policy for the management of cancer pain in Europe. It's clear that the differences are striking between the different countries of our community. The publication of common guidelines would be a first step toward such harmonization. Another step is to devote more resources to more equitable distribution of analgesics. Finally, an important point for Europe, unlike the United States, would be to promote a coherent and reasonable policy on the prescription of analgesics so that the current disparities are reduced while at the same time, avoiding an overconsumption crisis.

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Pain in the Cancer Survivor

5

Matthew R. D. Brown, Paul Farquhar-Smith, and David J. Magee

Recent decades have demonstrated significant strides in cancer screening, diagnostics and therapeutics. As such there have been dramatic changes in survival following a diagnosis of cancer. Data from the American Cancer Society reports that 5-year survival rates for all cancers have increased from 49% in 1975 to 69% in 2015 [1], a trend which has been observed globally [2, 3]. Impressive advances have been accompanied by novel clinical phenomena and challenges [4]. We are currently witnessing marked growth of a population of cancer survivors, many of whom have unique pathological, social and psychological sequelae. Notably, this cohort is encountering a number of pain states with varied pain phenotypes [5].

Accurately depicting the number of cancer survivors worldwide is challenging. Currently, there are an estimated 15.5 million cancer survivors living in the USA [6], which represents nearly 5% of the population. This figure is projected to reach nearly 7% (26.1 million) by 2040 [6]. Cancer survivorship is a relatively novel concept, lacking consensus regarding its precise definition [7]. In the USA, the National Coalition for Cancer Survivorship (NCCS) regards a patient 'from the time of diagnosis and for the balance of life' as a cancer survivor [8], whilst the National Cancer Survivor Initiative, in the UK, defines a cancer survivor as someone 'living with and beyond cancer' [9]. However, the European Organisation of Research and Treatment of Cancer (EORTC) Survivorship Task Force defines a cancer survivor as 'any person who has been diagnosed with cancer, has completed his or her primary treatment (with the exception of maintenance therapy), and has no evidence of active disease' [10]. The nuances within these definitions may reflect varied clinical pathologies and challenges reported within this cohort. Clearly, the incidence of pain in cancer survivors will depend upon the definition utilized.

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Many studies have considered the unmet clinical care needs of cancer survivors, identifying common themes [11–15]. Survivors report experiencing an average of 11.5 symptoms, although only approximately 25% of these are felt to result in needs that are unmet [15]. Breast cancer survival and younger age have both been linked to greater unmet needs [14] and pain represents a common theme occurring amongst these symptoms and needs. This rapidly evolving landscape of cancer survivors encompasses a broad range of pain phenotypes [5]. In this chapter, we focus on pain in cancer survivors not covered elsewhere within this book.

5.1 Pain Assessment in Cancer Survivors

Assessment is an integral element of pain management independent of pain phenotype. Undoubtedly a thorough history taking, examination and consideration of relevant investigations are of paramount importance and enable the clinician to determine a putative aetiology and formulate a pain management plan in conjunction with their patient.

Many assessment tools have been validated across a variety of populations and in different pain states. Unidimensional tools, which predominantly focus upon pain intensity, fail to address parameters that are frequently reported as most important to patients. In 1964, Dame Cicely Saunders, coined the term 'total pain', reflecting the multidimensional nature of cancer pain which often encompasses physical, psychological, social and spiritual domains. This consideration of the multifactorial and complex nature of pain can equally be applied in cancer survivors; therefore, these elements should ideally be incorporated within the assessment. The authors are unaware of any specific assessment tools that have been validated for use in cancer survivors. This raises a question: to what extent should pain in cancer survivors be considered similar to either cancer-related pain or to other non-cancer pain conditions?

What is evident is that a diagnosis of cancer impacts the way patients both experience and communicate pain [16]. Not only do those with ongoing disease describe a lower health-related quality of life [17] but survivors also report greater issues with psychological morbidity when compared to a reference population [18]. Pain assessment tools validated only in non-cancer-based populations, therefore, may not be directly transferable to cancer survivors. In the absence of specifically validated tools for use in cancer survivors, one must acknowledge and incorporate the multidimensional aspects of the pain which are commonly encountered in this cohort.

Other considerations include what pain may represent to the patient and attention to specific anti-cancer treatments. It is important to appreciate that approximately 50% of cancer survivors report a moderate to severe fear of cancer progression or recurrence [19] and pain itself is associated with both a fear of progression and recurrence [20]. Although pain can be a sign of either, relationships between pain intensity and variability of disease are not well established [21]. Secondly, consideration of the anti-cancer therapies is fundamental to the assessment of pain of

cancer survivors. Not only do many pain phenotypes relate to oncological treatment received, but maintenance therapy and subsequent treatments may well have an impact on the pain experienced.

5.2 Causes of Pain in Cancer Survivors

Figure 5.1 provides an overview of the pain states that are relevant specifically to cancer survivors.

5.2.1 Pain from Tumours

Although varying definitions of 'cancer survivors' exist, many begin at the time of initial diagnosis, continue through treatment and beyond. As such, tumour-related pain is a relevant topic that is covered in greater depth elsewhere within this book. Pain directly resulting from an expanding tumour, growing into healthy host tissue is the archetype of cancer pain. A complex bidirectional association exists between a tumour and its microenvironment [22], such that a malignant lesion does not exist in isolation but rather has a dynamic relationship with host cells [23]. Current concepts regarding tumour-related pain suggest that nociception is initiated by mediators secreted within the tumour microenvironment [24]. With growing evidence that underlying common biological principles underpin all the 'hallmarks of cancer' [25], interest is growing linking disorders of metabolism and potential

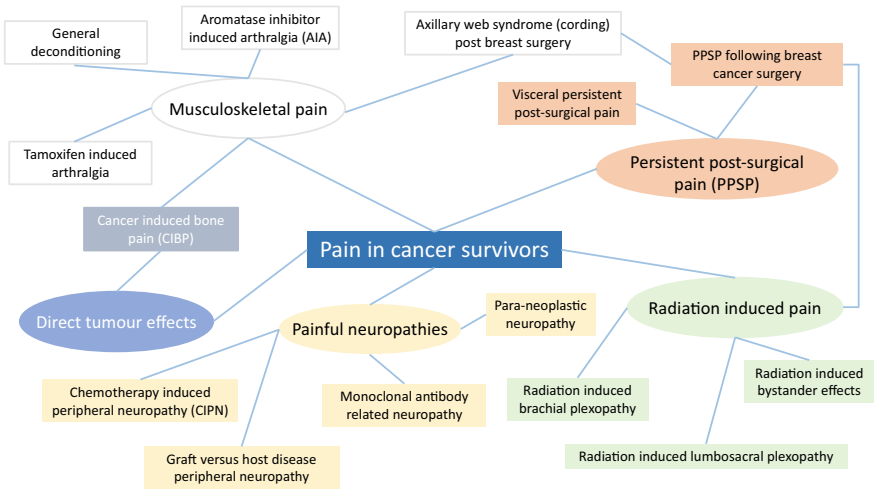

Fig. 5.1 Pain states of cancer survivors

nociceptive metabolites. For instance, dysregulation of lipid metabolism is a major feature of cancer pathogenesis [26] and lipid metabolites have been implicated in numerous pain states [27]. Work continues to explore this link in an attempt to fully characterize these metabolites and their contribution to tumour-related pain.

5.2.2 Cancer-Induced Bone Pain

Cancer-induced bone pain (CIBP) is typified by a triad of dull background pain, movement-induced (incident) pain and spontaneous pain flares [28]. CIBP is a multifaceted entity, whose pathophysiology comprises multiple mechanisms, namely: local tissue destruction, periosteal anatomical disruption, release of proinflammatory mediators and changes in sensory innervation [28]. These mechanisms are often intertwined. Tumour cells 'corrupt' normal bone homeostasis by releasing a number of inflammatory mediators, such as interleukin (IL)-1, IL-6, transforming growth factor (TGF)-ß and receptor activator of nuclear factor-κB ligand (RANKL) [29]. In response to these factors, osteoclasts are recruited and activated, resulting in atypical bone destruction and subsequent remodelling. The resulting net bone resorption facilitates space for continued tumour expansion [30].

Developing bone lesions cause disruption and inflammation to surrounding periosteum [31]. The periosteum, marrow and cortex are all densely innervated by sensory fibres [32, 33]. Nerve growth factor (NGF), released from tumour stroma [34], results in atypical sprouting of sensory fibres and microneuroma formation [35]. These neuronal tissues are sensitized by mediators produced by the tumour and its surrounding stroma, consequently reducing excitatory thresholds [36]. Moreover, the excitatory neurotransmitter glutamate is secreted by certain tumour types [37].

Dorsal root ganglion (DRG) and dorsal horn reorganization occurs in the presence of bone metastases [38]. Changes observed include neuroplastic remodelling of excitatory fibres within the substantia gelatinosa of the dorsal horn of the spinal cord, raised levels of calcitonin gene-related peptide (CGRP) [39] and the expression of $Na_v1.8$ sodium channels [40], all contributing to changes in central sensory modulation and transmission [41]. Figure 5.2 provides an overview of many mechanisms integral to CIBP.

5.3 Treatment-Related Causes of Pain

5.3.1 Persistent Post-surgical Pain (PPSP)

5.3.1.1 Features of General PPSP

Surgery is an integral component in the management pathway of many malignancies. Persistent pain resulting from surgical procedures is of great relevance to cancer survivors, not only because of its incidence, but also due to the impact it has upon quality of life and poor recovery of function outcomes [42].

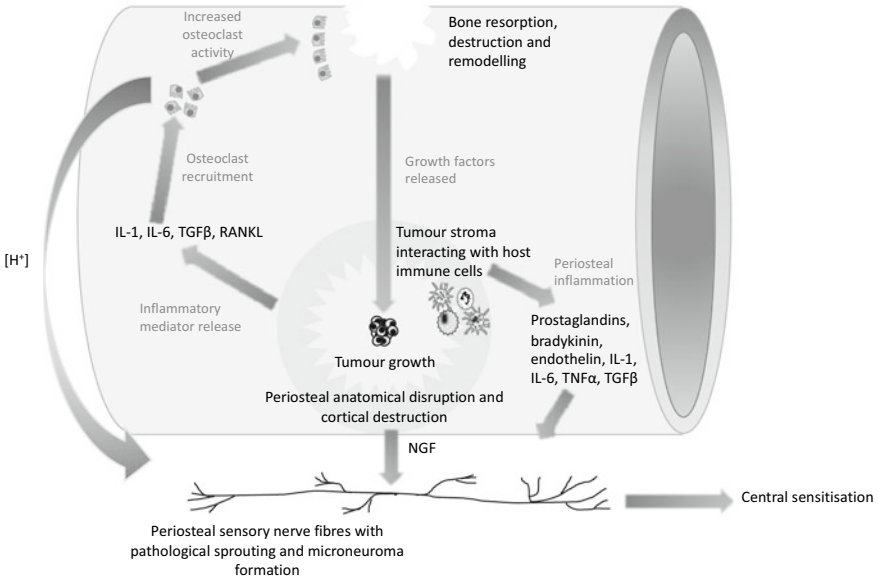

Fig. 5.2 Mechanisms of cancer-induced bone pain

To date, no formalized definition of PPSP exists but consensus states that it is pain which:

1) Develops, or increases in intensity, subsequent to a surgical procedure
2) Is either a continuation of acute postoperative pain, or develops after an asymptomatic period
3) Has a duration of at least three to six months and significantly impacts quality of life
4) Is localized to the surgical field, the territory of a nerve or dermatome associated with the surgical field
5) Other causes (e.g. recurrence of malignancy or infection) have been excluded[43].

PPSP develops more frequently following certain procedures, including thoracotomy (30–50%), limb amputation (30–85%), herniorrhaphy (20–60%) and breast surgery (15–55%) [44, 45], although it can occur after any surgery, even if relatively limited [46]. A large Norwegian study showed that close to 20% of subjects experience moderate to severe pain beyond three months after surgical procedures [47].

Up to 68% of patients with PPSP report neuropathic features, such as hyperesthesia, hyperalgesia, hypoesthesia and allodynia [48, 49]. The presence of these features is associated with a greater impact upon quality of life [50]. A proportion of individuals with PPSP will have no sensory changes even when quantitative sensory testing (QST) is performed [51]. Interestingly, despite peripheral nerve injury

being a risk factor for PPSP, the relationship is not straightforward. One study has identified that 100% of participants undergoing rib retraction demonstrated intercostal nerve trauma in the immediate postoperative period [52]. Unfortunately, this cohort was not followed up to determine the incidence of persistent pain but PPSP following rib retraction is not consistently observed [53] suggesting that not all experiencing intraoperative nerve trauma proceed to develop persistent pain. Furthermore, attempts to delineate the relationship between intercostal nerve damage and PPSP have failed to establish a direct link [54].

5.3.1.2 PPSP Following Breast Cancer Surgery

Persistent post-breast surgery pain represents a considerable burden to the population of breast cancer survivors [55]. Although variable, it is reported to occur in approximately 15–55% of patients following breast surgery [45, 56]. Given that breast cancer accounts for over 25% of all new cancer cases in women globally [57], absolute numbers requiring treatment are large. This coupled with the fact that breast cancer survival rates are high [58], which result in a substantial population of survivors. As surgery remains the mainstay of treatment for breast cancer patients [59], most of this cohort will have undergone a surgical procedure. Persistent post-breast surgery pain manifests with variable characteristics. Neuropathic pain is common (68%) in those with persistent pain following breast cancer surgery [48], with features localized to the scar, breast/thoracic wall, the axilla, and the medial aspect of the upper ipsilateral limb [60]. Of note, attempts to preserve the intercostobrachial nerve have not demonstrated a significant reduction in its incidence [56], mirroring the relationship observed between intercostal nerve trauma and subsequent pain post-thoracotomy.

5.3.1.3 Risk Factors for PPSP

The mechanisms underpinning PPSP remain poorly understood; however, the period of transition from acute to persistent pain is critical [61]. There are a number of identified risk factors for the development of PPSP and these are detailed in Table 5.1 [62–69]. Risk factors have been utilized to develop risk-stratification tools, allowing individualized risk prediction, potentially permitting early intervention and targeted resource use [70].

5.3.1.4 Mechanism-Based Treatments

The transition from acute to persistent pain represents a key target point for the prevention or mitigation of PPSP. Many studies have attempted to ameliorate the perioperative nociceptive barrage, including the use of various pharmacological agents or regional anaesthesia; however, data remains somewhat inconclusive. Small size of studies, and heterogeneity in study designs, outcome data and analgesic regimes, limits the clinical utility of their findings. A Cochrane review investigating the use of regional anaesthesia for thoracotomy and breast surgery, reports a moderate reduction in PPSP rates, although the strength of these findings are limited by the relative low quality of the studies included in the review [71, 72].

Table 5.1 Risk factors for the development of persistent post-surgical pain

Patient factors	Surgical factors	Other factors
Anxiety	Longer duration of procedure	Chemotherapy
Depression	Nerve retraction or destruction	Postoperative pain
Genetic factors	Open surgical procedure	Radiotherapy
Pain catastrophizing	Drain use	Surgery in low volume centres
Pre-existing pain		
Raised BMI		
Young age*		

* Older age risk for phantom limb pain

The multiple risk factors and the processes leading to PPSP make the identification of a 'silver bullet' intervention, that will completely prevent its development, highly improbable. Complex approaches, comprising a number of concurrent interventions (such as 'transitional pain services' and focused psychological interventions), may provide a more productive approach [73].

5.3.2 Visceral Persistent Post-surgical Pain

The body of literature pertaining to PPSP is growing, predominantly exploring prevalence and risk factors. To date, this has mainly focused on the somatic domain with relatively little research considering visceral persistent post-surgical pain. The body of work that has been conducted has largely concentrated on prevalence and risk factors with limited information regarding the course, history or the contributory mechanisms. As such, visceral persistent post-surgical pain is not well-defined.

5.3.2.1 Epidemiology

In keeping with somatic PPSP, the incidence appears to be high [74]. After radical prostatectomy, the incidence of PPSP is reported as 14.3% at three months and 1.2% at six months and is associated with greater disability, lower physical, and mental function at three months [75]. Post-nephrectomy, the incidence is reported as 28.6% at three months and 8.6% at six months [76]. PPSP rates following abdominal hysterectomy have been observed as 25.1%, 9.9% and 6.7% at four months, one year and two years, respectively [77]. The same publication reports lower incidence following vaginal hysterectomy with incidences of 11.8%, 4.1% and 2.2% at the same time points. Of note, all these studies are associated with a high attrition rate from three to six months, potentially impacting the latter figures reported. Laparoscopic visceral surgery is also associated with a high incidence of PPSP, although arguably less than when compared to open surgery. One retrospective study reports an incidence of 17%, at a median time point of over three years, again associated with a negative impact upon quality of life [78].

5.3.2.2 Risk Factors

From the limited studies conducted, the following appear to be risk factors:

- Younger age [77]
- Pre-existing pain within the surgical field [75, 77–79]
- Pre-existing pain, remote to the surgical field [75, 77, 80, 81]
- Acute postoperative pain [80]
- Preoperative anxiety [76, 77]
- Comorbidity and disability [76]

5.3.2.3 Prevalence of Neuropathic Pain in Visceral PPSP

Data pertaining to the prevalence of neuropathic pain in visceral PPSP is limited. Visceral PPSP following abdominal hysterectomy has been reported as predominantly neuropathic, with an incidence of 51.9% using the Douleur Neuropathique 4 (DN4) questionnaire, and sensory changes around the scar site in 19.4% of patients [82]. The GENDOLCAT study reports pain to be neuropathic in 44% following abdominal hysterectomy (and 24.5% following vaginal hysterectomy) [77]. In another study of patients with PPSP following hysterectomy (reporting NRS of greater than 4), 48% and 41% had neuropathic pain (DN4) at three and 12 months, respectively [83]. Visceral PPSP appears to be neuropathic in approximately half of patients.

5.3.2.4 Potential Mechanisms and Treatments

Mechanisms underpinning visceral hyperalgesia may provide guidance on potential therapeutic options [84]. Such examples include $Na_v1.9$ voltage-gated sodium channels, which are vital in inflammatory activating mechanisms in visceral pain states [85] and the protective nature of the presence of A118A (SNP of OPRM1) [86].

Given the hypothesized mechanisms and risk factors identified, minimizing acute postoperative pain could potentially reduce or mitigate the development of visceral PPSP. Retrospective data has linked the use of epidural and intrathecal anaesthesia in combination with general anaesthesia (GA) to reduced persistent pain and early changes of wound hyperalgesia following major abdominal surgery [87]. These findings have since been reported by case controlled [88] and prospective cohort studies [77]. Neuraxial blockade, therefore, may be considered as a potential strategy to reduce visceral PPSP presumably by reducing acute postoperative pain. However, these studies failed to report consistent reductions in acute pain. It remains to be determined whether the use of regional anaesthesia ultimately exerts any potential effect on PPSP through reductions in acute postoperative pain or by some other undetermined mechanism. With this consideration in mind, alternative strategies for reducing acute postoperative pain exist. One such example is the use of patient-controlled analgesia (PCA). This has been linked to reductions in both moderate to severe acute pain and visceral PPSP following major abdominal

surgery [89]. In this large study, enrolling a total of 12,015 patients, incidence of PPSP was 34.2% in those with non-PCA, compared to 27% in those in the PCA group.

Recently, gut microbiota has been both implicated in the development of, and proposed as a potential therapeutic modality for, visceral pain [90]. Preclinical studies have demonstrated antibiotic and probiotic therapies can influence visceral pain, with their effect on gut microbiota implicated. This process has been indicated as the mechanism behind the observations that antibiotics have been shown to both enhance and reduce visceral pain [91, 92], whilst probiotics reduce visceral hypersensitivity and up-regulate analgesic receptors [93, 94]. Furthermore, visceral hypersensitivity observed in germ-free mice is abolished by colonization with conventional microbiota [95]. The evidence that many chemotherapeutic agents dysregulate gut flora, [96] and findings that the gut microbiota is altered following surgical procedures [97, 98], would implicate that those undergoing surgical procedures with neoadjuvant chemotherapy are at a higher risk for the development of visceral PPSP.

5.3.3 Chemotherapy-Induced Peripheral Neuropathy (CIPN) and Other Treatment-Related Causes of Sensory Neuropathies

CIPN continues to be relatively well represented within the literature, as such the following will focus on elements that have not yet been widely explored.

5.3.3.1 Neuropathy Associated with Newer Myeloma Treatments

Bortezomib, a proteasome inhibitor, is used in the management of refractory or relapsed myeloma and is associated with a high incidence of peripheral neuropathy [99]. Its route of administration has changed from intravenous (i.v.) to subcutaneous (s.c.), and despite anecdotal reports of reduced incidence of neuropathy associated with this change, a trial of 446 patients failed to demonstrate this [100]. For rates of neuropathy, this publication reports, 48% vs. 41% for any grade of neuropathy, 20% vs. 18% for greater than grade 2 neuropathy and 6% vs. 4% for greater than grade 3 neuropathy in the IV vs. SQ arms, respectively. None of these differences were statistically significant.

Lenalidomide and pomalidomide (thalidomide analogues, which act by reducing both tumour angiogenesis and immunomodulators) are two newer agents used in myeloma management. Both of these agents appear to be associated with lower incidences of neuropathy. No grade 3 or 4 neuropathy was observed during a trial of 221 patients receiving pomalidomide, with or without low-dose dexamethasone [101]. Furthermore, any grade neuropathy associated with pomalidomide and low-dose dexamethasone has been demonstrated to be as low as 12.3% [102]. A direct comparison of patients receiving either thalidomide or lenalidomide reported incidences of peripheral neuropathy at 35% with thalidomide, compared to

29% with lenalidomide [103]. Treatment with lenalidomide alone in refractory myeloma is reported to have an incidence of 23% for all grade neuropathy and 3% for grade 3–4 neuropathy [104]. However, the use of lenalidomide and bortezomib in combination with dexamethasone demonstrated a high incidence of sensory neuropathy (80%) and neuropathic pain (32%), suggesting combination therapies may have additive or synergistic effects on peripheral neuropathies [105].

Preclinical data for carfilozamib, another proteasome inhibitor used for refractory myeloma, suggests it is potentially less neurotoxic. In a safety and tolerability study of 526 patients who received carfilozamib alone, the incidence of peripheral neuropathy was 13.9%, with only 1.3% experiencing grade 3 or 4 neuropathy [106].

5.3.3.2 Specific Neuropathies in Patients with Haematological Malignancies

Graft versus host disease (GVHD), subsequent to allogeneic stem cell transplant, may result in neuropathic pain by several mechanisms [107]. Many neuropathies have been described, and despite becoming more frequent, to date have received little attention. Haematological malignancies have been identified as antecedent illnesses associated with Guillain–Barre [108], and although in this demyelinating neuropathy, it is more common for motor and autonomic nerves to be affected, some variants involve sensory nerves and may lead to neuropathic pain symptoms [109]. Chronic inflammatory demyelinating polyradiculoneuropathies and axonal polyneuropathies have all been described and could be associated with a higher magnitude of sensory symptoms [110]. There is limited evidence to suggest the use of specific therapies but treatment of the underlying GVHD is imperative. The clinical course and manifestations are potentially complicated by other administered agents, such as chemotherapy or other immunomodulatory agents [111].

Myeloma itself may directly influence the potential for developing peripheral neuropathies. This is evidenced by both high incidences of pretreatment neuropathy, as well as increased incidences when comparing myeloma patients to other cancer patients treated with the same chemotherapeutic agents [112]. Other haematological malignancies have also been associated with peripheral neuropathies, for example, Waldenstrom macroglobulinemia, where the incidence is up to 47% [113].

5.3.3.3 Monoclonal Antibodies

Monoclonal antibodies (mAbs) represent novel therapeutic modalities for oncogenic therapy. They ultimately induce cellular death by either direct or indirect action. Indirect mechanisms may involve interference with supporting stromal cells or vascular neogenesis. The success of these agents in multiple cancer types has resulted in increasing numbers of patients receiving mAbs. An indication that mAbs could result in neuropathies should have been apparent from the observation that monoclonal gammopathy of undetermined significance (MGUS), a premalignant disorder associated with high concentrations of monoclonal paraproteins, can result in the development of neuropathies [113].

Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, is used in combination with paclitaxel in the treatment of breast cancer. The combination of bevacizumab and paclitaxel has been demonstrated to be associated with higher incidence of neuropathy when compared to paclitaxel alone. In a study of 722 patients, grade 3 or 4 neuropathy was higher in the combination group (23.6% vs. 17.6%) [114]. Nearly a decade later, a smaller-scale study demonstrated similar findings for grade 2 or higher neuropathy, after both 6 cycles (19% compared to 8%) and after 12 cycles (74% vs. 40%) [115]. Despite these findings, a study investigating the use of capecitabine alone, or combined with bevacizumab, reported no neuropathy in the 462 patients enrolled [116]. This observation implies that bevacizumab alone does not have significant neurotoxic action but requires other neurotoxic therapeutic agents to cause neuropathy.

Brentuximab vedotin, a mAb specific for human CD30 conjugated with a microtubule disrupting agent, is used for treatment of Hodgkin lymphoma and has a sensory neuropathy incidence of 48%, with over half demonstrating some improvement one year later [117]. Another study reported the overall incidence of peripheral neuropathy as 69% (half with grade 2 or higher severity), occurring at a median of 15 weeks following therapy commencement [118]. This study similarly reported some recovery over time with 74% exhibiting some recovery at two years. Other mAbs (such as ipilimumab, used in melanoma therapy) have also been reported as potentially neurotoxic [119]. Despite these observations, rates of neuropathy appear lower than that observed with other chemotherapeutic and biological agents.

A rare but relevant condition requiring consideration is POEMS syndrome. POEMS is a multisystem disorder, which may include polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. The dominant feature is commonly sensorimotor polyneuropathy [120].

5.3.4 Radiation-Induced Pain

Application of ionizing radiation causes changes in cellular DNA, ultimately resulting in cell death, and is a key component of cancer treatment. The consequences of radiotherapy depend upon numerous factors, but ultimately non-malignant tissues are also vulnerable to the effects of ionizing radiation. Nervous tissue is particularly susceptible to radiotherapy damage both through direct effects and the ensuing fibrosis that may result. Nervous tissue is sensitive to direct effects of ionizing radiation through acute electrophysiological changes and subsequent effects that are in part mediated by vascular changes [121]. Some of the longer-term effects are mediated by fibrosis and may contribute to neuropathy, and indeed neuropathic pain, with both reactive oxygen species and cytokines implicated [122]. Multiple radiation-induced neuropathic pain states have been observed [123].

5.3.4.1 Radiation-Induced Brachial Plexopathy (RIBP) and Other Plexopathies

Radiation-induced brachial plexopathy presents with variable onset and timing. Reductions in both total radiation dose and dose per fraction for breast cancer treatment have lowered the incidence of RIBP. Prevalence is under 2% when less than 55 Gy total dose is utilized [124]. RIBP may present as a temporary pathology, thought to be secondary to reversible oedema and is termed early transient RIBP. In such instances, the onset is typically rapid and resolution of symptoms usually occurs within a year [125]. Otherwise, classical presentation is with initial paraesthesia, followed by numbness and subsequent delayed progressive motor weakness, that occurs over a variable time frame and may take years to develop. The coexistence of lymphoedema subsequent to axillary dissection may exacerbate symptoms of limb dysfunction and pain [126]. An important differential diagnosis is paraneoplastic brachial plexopathy or plexopathy secondary to direct tumour involvement. In both cases, pain with progressive sensory and motor dysfunction (as opposed to progressive motor dysfunction in RIBP) are typically observed. However, in the context of cancer survivors, timely imaging such as an MRI scan is prudent to aid in distinguishing between pathologies.

Lumbosacral plexus neuropathy is reported with less frequency. It may occur after radiotherapy for pelvic or testicular disease. Despite being less well characterized, signs and symptoms may be more insidious, develop later and be associated with fewer sensory symptoms [127].

Potential therapeutic strategies include analgesic approaches as well as preventing or limiting the radiation-induced processes. Rationalization and reduction of radiotherapy have already resulted in significant reductions in the incidence of RIBP. Hyperbaric oxygen has little evidence to support its use in reduction of fibrosis and symptoms associated with it [128]. Pentoxifylline and tocopherol may have a role in reducing fibrosis after radiotherapy, with mixed but potentially promising results [129], including in combination with clodronate for lumbosacral radiculopathy [130].

5.3.4.2 Other Causes of Pain Associated with Radiotherapy

Other modalities through which radiation may lead to pain include mucositis, osteonecrosis [131] and myelopathy [132]. Radiation-induced oral mucositis is an expected tissue insult that results in acute inflammation of the oral mucosa, tongue and pharynx. The rapid cellular turnover expected of these tissues underpins their vulnerability to radiotherapy. The typical course comprises of four phases [133]; the initial inflammatory phase results from release of free radicals, proinflammatory cytokines, prostaglandins and TNF, a subsequent epithelial phase accounts for the reduction in epithelial cell turnover and ensuing breakdown and is followed by an ulcerative phase and subsequent healing phase [133]. The duration of this process is variable but can take longer than three months [134]. Radiation-induced oral mucositis can be a significant barrier to adequate nutrition and as such may impede desired cancer therapy, proving a major challenge in the treatment of head and neck cancers and often necessitating aggressive therapeutic interventions.

More difficult to delineate is a subset of neuropathic pains that are observed following either radiotherapy in isolation or after radiotherapy in combination with other anti-cancer therapies. Anecdotally, some neuropathic pains of undetermined aetiology are often attributed to radiotherapy despite the fact that doses may have been subthreshold for anticipated neurotoxicity and pain is not clearly within the field treated. To what extent these neuropathic pains can be ascribed to radiation-related exacerbation of direct tumour effects, paraneoplastic-induced pain or related to systemic, atypical manifestations of anti-cancer therapies remains unclear.

5.3.5 Haematopoietic Stem Cell Transplants

Haematopoietic stem cell transplantation (HSCT) is the transplantation of multipotent haematopoietic stem cells, peripheral blood or umbilical cord blood. Autologous denotes the process where stem cells are collected from the patient and returned to the same individual, whereas allogeneic refers to the transfer of healthy donor stem cells into a recipient. The aetiology of pain encountered following HSCT may be categorized by time course during transplantation, namely during stem cell mobilization, the conditioning phase, haematological recovery or the late post-transplant period.

In allogeneic HSCT, a significantly lower incidence of and duration of pain is reported with blood cell donors compared to marrow donors (85% vs. 68% and 14 days vs. 3 days, respectively) [135]. Persistent pain at a mean time of 19 months following iliac crest marrow harvest is reported at 34%, and more common following use of the anterior rather than posterior iliac crest for harvest [136]. A rare but painful acute complication of filgrastim stimulation is splenic rupture, that has been observed in both healthy donors and patients [137, 138].

Oral mucositis occurs more frequently in those with haematological malignancies undergoing autologous HSCT when compared with solid tumours undergoing the same procedure [139]. The incidence in some haematological malignancies treated with HSCT is reported to be nearing 80% [140, 141]. Mucosal damage secondary to GVHD following allogeneic HSCT may mimic mucosal damage observed in response to cytotoxic drugs [142].

Conditioning regimes that utilize either ifosfamide or cytarabine may result in urinary bladder irritation with severe haemorrhagic cystitis representing a particularly problematic complication of allogenic HSCT. It typically manifests within 30 days following HSCT and its occurrence is associated with moderate-to-severe GVHD or hepatic GVHD [143], and with the coexistence of adenovirus or polyomavirus infection [144]. Hepatic veno-occlusive disease (VOD), a condition characterized by painful hepatomegaly, ascites and jaundice, is reported to occur in up to 60% of those undergoing allogenic HSCT [145].

Pathologies associated with late post-transplant complications that may result in pain include chronic GVHD and opportunistic infections. Pain remains a major feature of chronic GVHD, typically arising from mucosal sites [146, 147]. Other painful manifestations of chronic GVHD reported include polymyositis and fasciitis

[144, 148]. Despite significant research and attention in recent decades, advances in the management of GVHD have been limited and the focus continues to be predominantly supportive [149]. Opportunistic infections remain a concern for immunocompromised patients. Reactivation of varicella zoster virus is reported in 15% following autologous HSCT, with post-herpetic neuralgia occurring in one-third of this cohort [150]. A higher incidence of reactivation is reported following allogenic HSCT (over 40%), with 40% of these developing post-herpetic neuralgia [151]. Notably, one study following a cohort of 100 patients undergoing either autologous or allogenic HSCT [152], demonstrated that pain, of unclassified aetiology (reported using Brief Pain Inventory) was greater at 3 months in those who underwent allogeneic HSCT, which was independent of conditioning regimen, disease or GVHD. However, this difference was less apparent after 9 months with both groups showing equal incidences of pain.

5.3.6 Aromatase Inhibitors and Pain

Lower oestrogen levels observed following menopause has long been associated with joint pain. Hormonal therapy of oestrogen dependent breast tumours comprises of either direct blockade of the oestrogen receptor (tamoxifen) or inhibiting oestrogen biosynthesis (Aromatase inhibitors (AI)), either irreversibly ('steroidal'—exemestane) or reversibly ('non-steroidal'—anastrozole or letrozole). Many side-effects have been attributed to AIs, the most frequently occurring of which is aromatase inhibitor-induced arthralgia (AIA) [153], these side effects have a marked impact on quality of life [154].

5.3.6.1 Aetiology of AIA

Several theories exist linking oestrogen and pain, including a direct effect of oestradiol on pain pathways [155]. This particular theory, however, contradicts the observation that pain tolerance is highest during the menstrual cycle when oestradiol levels are at their lowest [156]. An alternative notion relates to the observation that oestrogen receptors found in synovia are expressed with increased frequency in osteoarthritic joints [155]. Other proposed mechanisms include (auto)-immune modulation and cytokine activity [155]. Vitamin D may play an integral role. In a study of 60 women taking letrozole, only 48% with concentrations over 66 ng/mL had debilitating pain compared with 81% whose vitamin D levels were below this threshold [157]. However, no significant difference in AIA was observed in a randomized controlled trial (RCT) comparing high- and low-dose vitamin D supplementation [158].

Imaging modalities may provide insight into aetiology. Tenosynovial changes, including fluid and thickening of tendon sheaths, especially of the digital flexor tendons appear to be a consistent finding [159]. BMI has been linked to a nonlinear correlation with AIA, with greater reductions of grip strength in both high and low BMI patients [160]. This observation lead to the suggestion that lower oestrogen levels may reduce insulin-like growth factor-1 (IGF-1) and cause joint pain [161].

5.3.6.2 Prevalence, Risk Factors and Compliance

Lack of differentiation between joint arthralgia and joint 'stiffness' clouds some of the data indicating prevalence. Crew et al. [162] reported joint pain in 47% and joint stiffness in 44%, whereas others indicated prevalence may be as high as 74% [4]. AIA is reported as more likely with a higher BMI (over 30 compared with 25–30) and in patients who have received taxane chemotherapy [162]. In a study investigating 300 patients, 47% developed arthralgia, the majority of which occurred within three months and two thirds reported their pain to be moderate or severe [163]. In this study, commonest joints affected were wrists and hands (60%), knees (60%), back (54%), foot and ankle (52%). Comparative data shows little variance between AIs. Arthralgia has been reported in 48.2% of those taking letrozole and 47.9% on anastrozole, with grade 3 or 4 toxicity in 3.9% and 3.3%, respectively [164].

Side-effect-related non-compliance with AIs appears to be common in clinical settings and perhaps supersedes values reported by clinical trials. One study reported that out of 100 patients, 23 discontinued AIs, 13 of which were secondary to arthralgia [165]. Another indicated that approximately 20% of patients stopped AIs due to arthralgia [166]. AIs appear to be associated with more arthralgia than tamoxifen. One study reported joint problems in 34% taking anastrozole compared with 29% taking tamoxifen [167]. A higher BMI was again associated with more arthralgia (37% in BMI over 30, compared to 31% in BMI 25–30). Intriguingly, the cohort who developed joint problems within three months, were less likely to develop recurrent breast cancer. An additional study suggests non-compliance rates of 31% with anastrozole and 20% with tamoxifen [168].

5.3.6.3 Management of AIA

There is limited data regarding prevention or treatment of AIA pain. Switching AIs may prove helpful [155] and a single study has indicated some improvement in pain with duloxetine [169]. Many individuals report rapid improvement of symptoms upon discontinuation of AI but the incidence of persistent pain following cessation remains unestablished. Persistence of AIA with exemestane [170] is attributed to activation of autoimmune processes that persist beyond termination of treatment [171], reinforced by the potentially analgesic effects of a short course of low-dose prednisolone (5 mg) [172].

5.3.7 Chimeric Antigen Receptor (CAR) T Cell Therapy

CAR *T* cell therapy is a novel treatment that can produce lasting remissions in haematological malignancies that have failed to respond to other available therapies. Human *T* cells are modified to express CARs, proteins containing both *T*-cell activation domains and antigen recognition moieties. Their success in haematological malignancies has led to the exploration of their use in solid tumours [173]. The most frequently occurring acute toxicity related to this therapy is cytokine release syndrome (CRS). Cytokines may be produced directly by the administered CAR *T* cells or indirectly by host immune cells. Ultimately, CRS manifests with a

magnitude of symptoms, usually preceded by pyrexia, that can include headaches, arthralgias and myalgias amongst other less frequently occurring pain-related manifestations [174]. Management is once again predominantly supportive.

5.4 Specific Considerations for Treatment Options

5.4.1 Opioids

Pain directly attributable to tumours has traditionally been responsive to and treated with opioid analgesics, often requiring escalating doses in an approach embodied in the World Health Organization's cancer pain ladder for adults [175]. This strategy is often suitable for the successful control of pain in patients with advanced or terminal disease, however it fails to fully appreciate the rehabilitative aspirations for pain management in a population who have either completed treatment or have disease in remission. The detrimental effects of opioids, including potential immunomodulation and endocrine dysfunction may hinder rehabilitation. Therefore, a therapeutic predicament exists: is there a specific transition point along the journey of cancer treatment, at which the risk: benefit balance of using opioids switches? And if so, at what point does this occur?

Concerns surrounding the impact opioids may have on immune function and potential cancer recurrence are frequently expressed. Although scientific rationale for this hypothesis exist, to date no high-quality study has demonstrated this finding. In fact, a prospective cohort study of 34,188 patients failed to demonstrate any clinically relevant association between breast cancer recurrence and opioids [176].

Specifically, the use of opioids in cancer survivors who have concluded treatment remains a significant topic of debate and in the wake of the recent opioid crisis, apprehensions surrounding the subject are heightened. The precise point at which a cancer patient becomes a cancer survivor depends upon the definitions used and without unanimous agreement surrounding these definitions, subcategorizations of patients to facilitate guidance remains problematic. In the absence of any evidence pertaining to the benefit of opioids in those who have completed treatment, managing persistent pain with the same principles as those applied to persistent pain states in the absence of cancer would comprise a cautious yet wholly pragmatic approach. Any use of opioids should be stewarded by a multi-disciplinary team with prior discussions regarding both the risks and benefits. Regular patient review, which explores the efficacy, presence of detrimental effects and the potential for dose reduction/cessation is imperative. Resources are available, providing guidance on best practice with respect to opioid prescribing [177].

5.4.2 Neuropathic Pain: Topical and Systemic Treatments

As detailed previously, many of the pain states encountered in cancer survivors have neuropathic features. As with many of the pain phenotypes in cancer, evidence is sparse and as such, a multimodal, pragmatic approach is advised.

For patients with localized neuropathic pain (LNP), topical agents may provide an appropriate strategy [178]. Topical therapies typically have a more favourable side-effect profile and are generally well tolerated, improving compliance compared to systemic therapies. Potential topical agents include 5% lidocaine patches, 2% aqueous menthol cream, tricyclic antidepressants, clonidine and ketamine [179]. Efficacy is empirical and therefore requires regular review.

Although large well-designed RCTs favouring the use of lidocaine patches are lacking [180], in some circumstances, this therapeutic agent demonstrates equivalent efficacy to systemic anti-neuropathic agents with superior tolerability [181]. Its use should therefore be considered in frail patients, a state regularly encountered in cancer survivors [182, 183]. Cochrane reviews assessing capsaicin, both low-concentration cream and high-concentration patches have failed to demonstrate evidence of significant benefit, albeit with limitations impeding the ability to draw resounding conclusions [184, 185]. The use of topical menthol [186], tricyclic antidepressants [187], clonidine [188] and ketamine [189] has only been investigated in small-scale studies, frequently in the non-cancer population, with contradictory results. Further well conducted studies in cancer-related LNP are certainly required. However, trial of these agents in cancer survivors should be considered by clinicians, with informed patient consent, and regular review for efficacy and potential adverse effects.

Systemic anti-neuropathic agents require risk–benefit considerations and patient discussions. Appropriate agent selection may be directed by available guidelines [182, 183, 190]. The research agenda for newer anti-neuropathic agents continues. Such agents include novel voltage-gated sodium channel blockers, a selective angiotensin II receptor antagonist, acetyl-L-carnitine and alpha-lipoic-acid [191, 192]. There is burgeoning interest in novel biological agents for analgesic purposes in cancer-induced bone pain (CIBP). Denosumab (a human monoclonal antibody that inhibits RANKL) and tanezumab (a NGF sequestering agent) have both demonstrated efficacy [193, 194], although this appears to be due to influences on aberrant bone homeostasis rather than direct analgesic effects [195]. Their utility and long-term safety profile continue to be studied [196]. Saracatinib, an orally active Src inhibitor, has demonstrated promising results in rodent models for inflammatory pain, neuropathic pain and cancer-induced bone pain [197, 198]. Although in a recent small randomized controlled phase II trial, saracatinib was associated with significant reduction in bone resorption, it failed to demonstrate analgesic efficacy [199].

5.4.3 Interventional Approaches

Patient and institutional factors will determine the potential interventional options that may be appropriate. Indeed, certain evidence-based interventions may require referral to other specialties, for example vertebroplasty and kyphoplasty [200, 201]. These are covered in separate sections of this book.

5.4.4 Implantable Devices: Spinal Cord Stimulators and Intrathecal Drug Delivery Systems

Spinal cord stimulators (SCS) are an established therapy for the management of chronic pain [202]. Symptoms of painful diabetic peripheral neuropathy are comparable with CIPN. Significant reductions in pain scores and improvements in quality of life have been demonstrated with SCS in painful diabetic neuropathy [203], however evidence for CIPN is limited to a single case report [204]. A Cochrane review considering the use of SCS in adults with cancer-related pain concluded that there was insufficient evidence to fully define its role and that more well-designed studies are required [205]. Intrathecal drug delivery systems (IDDS) have a growing body of evidence supporting their utility in cancer survivors [206]. By facilitating targeted delivery of drugs, many of the systemic side-effects associated with opioids can be avoided. A variety of agents can be utilized intrathecally to reduce systemic analgesic requirements, as well as pain scores, whilst also potentially prolonging survival [207]. Currently, agents available to clinicians vary internationally. However, with growing use of these devices, the longer-term safety and efficacy profiles of these medications are becoming increasingly apparent and may soon lead to broader availability. Neuromodulation, intrathecal analgesia, and interventional modalities for cancer pain management more generally are covered in other chapters herein.

5.5 Conclusion

Cancer survivorship represents an expanding population with unmet needs and presents a number of challenges for clinicians, patients, carers and society. This chapter has focused predominantly on areas not routinely considered in other published texts. It is evident that cancer treatments, both novel and established, are leading to numerous persistent pain states in those living with and beyond cancer. Although our understanding is growing, we must invest time and resources into this emergent clinical challenge.

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Part II
Pharmacologic Therapies

Opioid Therapy in Cancer Pain

6

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6.1 General Introduction with WHO Guidelines

Cancer is a leading cause of morbidity and mortality, with up to 9.6 million cancer-related deaths worldwide in 2018 [1]. Pain is common in this patient population, with 55% of patients undergoing cancer treatment and 65% of patients with advanced stage cancer experiencing pain [1]. The World Health Organization (WHO) has developed guidelines to help healthcare providers in their treatment of cancer-associated pain, thus allowing for acceptable quality of life [1].

Prior to 2019, the most recent cancer pain management guidelines were issued in 1996 [1]. The WHO had developed a three-step "ladder" for cancer pain relief in adults, to guide the sequential approach to treat cancer pain with oral analgesic medications [2]. They recommended administration of medications with non-opioids first (such as aspirin and paracetamol), then mild opioids (such as

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codeine), and lastly strong opioids (such as morphine) until freedom from pain was achieved [2]. In this WHO recommendation, the use of adjuvant medications to treat anxiety was also recommended [2]. In order to maintain pain control, drugs were recommended to be given "by the clock" instead of as the situation demands [2].

In 2019, the WHO updated their guidelines to recognize that pain relief must be balanced with risks of medication treatment [3]. This was in the setting of concerns for harm due to pain medication misuse, including opioids, and scientific evidence indicating risks associated with opioid medications [3]. In January 2019, the WHO published "WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents" [3, 4]. These guidelines focus on three sections to guide the treatment of adults and adolescents with cancer pain: analgesia medications, adjuvant medications, and pain related to bone metastases [4].

The recommendations for "analgesia for cancer pain" include guidance on initiation of pain relief, maintenance of pain relief with opioids, and cessation of opioids [4]. For initiation of pain relief, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and opioids can be used "alone or in combination, depending on clinical assessment and pain severity in order to achieve rapid, effective and safe pain control" [4]. For maintenance, any opioid may be considered, but recommendations specifically include "regularly dosed immediate-release oral morphine, or regularly dosed slow-release morphine, [which] should be used to maintain effective and safe pain relief whenever oral dosing is possible. With either formulation, immediate-release oral morphine should be used as rescue medicine" [4]. Also for pain maintenance, if oral or transdermal routes are not possible, the subcutaneous route is preferred over intramuscular route to administer opioids [4]. Regarding cessation of opioids, if physical dependence for opioids develops, it is recommended that opioid dosages should be decreased gradually to avoid withdrawal symptoms [4].

The recommendations for "adjuvant medications for cancer pain" include that if indicated, steroids may be used for pain control, however for as short of a course as possible [4]. Clinical factors that affect steroid dosing include, but are not limited to, pain pattern, infection risk, state of illness, diabetes mellitus, and goals of care [4].

The recommendations for "management of pain related to bone metastases" include initiating bisphosphonate to prevent and treat bone pain [4]. Also if bone metastases are painful, "single-dose radiotherapy should be used when radiotherapy is indicated and available [4]." Radiotherapy should not be used if bone metastases are not painful [4].

The Guideline Development Group who helped create the "WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents" acknowledges other treatments for cancer pain exist, but those therapy options have limited efficacy evidence [4]. Some of these therapies include antidepressants, anticonvulsants, and opioid rotation [4]. The 2019 guidelines also refer the "three-step analgesic ladder"; however, it should only be used as a teaching tool and general guide to pain management [4]. Following the ladder steps

is not a clinical recommendation, and the WHO emphasizes it cannot replace individualized therapy for managing a patient's cancer pain [4].

6.2 Cancer Breakthrough Pain and TIRF Medications

The clinical term "breakthrough pain" is not conclusively defined or described, and in the literature investigating the topic, there is variation in the working definition of breakthrough pain and its subsets [5]. Cancer breakthrough pain has been described as "a transitory flare of pain in the setting of chronic pain managed with opioid drugs" [6]. The WHO defines breakthrough cancer pain as "a transitory flare of pain in the setting of chronic pain managed with pain medicines around the clock" [4]. It is important to recognize that breakthrough pain is different from other pain patterns such as poorly controlled baseline pain, pain emergency, and "crescendo pain" [5]. In breakthrough pain, the patient's baseline pain is relatively stable and controlled [5]. Temporally, breakthrough pain can be described by rapidity of onset (sometimes classified as sudden, paroxysmal, or gradual onset), duration (brief or sustained), and frequency [5]. Breakthrough pain is a common and heterogeneous phenomenon in patients with chronic cancer-related pain, and treatment recommendations for breakthrough pain are variable [5]. The WHO recommends that breakthrough pain should be treated with a rescue opioid, such as morphine in its immediate-release formulation [4].

Historically long-acting and short-acting opioids have commonly been used in treating baseline and breakthrough cancer pain. Please reference the various texts that have extensively covered opioid pharmacology, pharmacodynamics, metabolism, and dosing for further details, as these topics will not be addressed in this chapter. However, as transmucosal immediate-release fentanyl (TIRF) medications are specifically limited to use for cancer pain, we will review various TIRF medication options.

TIRF medications are indicated for the management of breakthrough cancer pain in adults who are on a baseline opioid regimen and are tolerant to opioid medications [7]. Opioid tolerance is specifically defined in the setting of TIRF medications; a patient must be taking at least 60 mg oral morphine per day for at least one week before qualifying for TIRF medication therapy [8]. TIRF medications are contraindicated in opioid non-tolerant patients, patients with intolerance or hypersensitivity to fentanyl, or in the management of acute or postoperative pain [8]. These medications are beneficial due to their ability to deliver potent and rapid onset analgesia through non-invasive routes [5]. Examples of TIRF medications include Actiq (oral transmucosal lozenge), Fentora (buccal tablet), Lazanda (nasal spray), Subsys (sublingual spray), and Abstral (sublingual tablet). It is important to note that TIRF medicines have different pharmacokinetics and are therefore not equivalent or interchangeable with each other [7]. These differences lead to risk of fatal overdose if one TIRF medicine is converted to another TIRF medicine (Actiq is an exception, and Actiq has specific conversion information in the medication's

Prescribing Information) [7]. If a patient changes to a new TIRF medication, the new medication must be started at the initial dose specified in the label instructions [7].

TIRF medications are used in association with the TIRF Risk Evaluation and Mitigation Strategy (REMS) access program, which has been in place since 2011. TIRF REMS is an FDA program whose function is to ensure appropriate initiation and continued use of TIRF medication, with the goal of reducing the risk of misuse, abuse, addiction, and overdose with these medications [9]. The program requires pharmacies, prescribers, patients, and wholesalers to enroll before a patient is able to utilize TIRF medications [10].

In March 2019, in the setting of the US opioid crisis, the FDA commissioner added new steps to strengthen safety requirements for TIRF medications [11]. These new steps were implemented due to review of utilization of TIRF prescription. In 2012, 14,400 patients received TIRF prescriptions, and by 2017, 4,700 patients received TIRF prescriptions [11]. Although there was a decline in utilization, the data indicated that historical prescribing patterns were not reflective of the strict labeling guidelines for TIRF medications. In 2019, the new steps implemented to strengthen TIRF REMS required that (1) prescribers document a patient's opioid tolerance concurrently with each TIRF prescription, (2) inpatient pharmacies develop internal policies to verify opioid tolerance, (3) TIRF medicine be dispensed after there is documentation of safe use conditions, and (4) a new patient registry be created to monitor for serious adverse events [11]. The goal of these new steps was to restrict use to opioid-tolerant patients, avoid inappropriate conversion between TIRF medicines, reduce accidental exposure, and provide education for the potential for misuse, abuse, addiction, and overdose [11]. This is balanced with also ensuring that adults with cancer pain, who are suffering from significant pain, meet the indications for treatment with TIRF medication, and have access to appropriate medications [11].

6.2.1 Actiq

Actiq is a lozenge that allows for rapid absorption of Fentanyl through the oral transmucosal [12]. As Actiq is in lozenge form, it is initially rapidly absorbed through the buccal mucosa; however, a fraction of the medication has a prolonged absorption through the gastrointestinal tract due to some of the medication being swallowed [12]. Overall bioavailability of this medication depends on the amount absorbed through the buccal mucosa and the amount swallowed [12]. It is estimated that this medication has 50% bioavailability [12]. This is determined by an average of 25% of the medication is absorbed through the oral mucosa, and 75% of the medication in saliva and then swallowed [12]. Of this swallowed medication, one-third does not undergo first-pass elimination and is thus systematically available [12].

Actiq comes in a variety of strengths (200, 400, 800, and 1600 mcg) [12]. It is recommended that providers start with an initial dose of 200 mcg, which is to be

consumed over 15 min [12]. After 30 min of the initial start of Actiq consumption and if pain is still unrelieved, the patient is to take an additional dose of the same strength of medication [12]. However, patients must wait 4 h before treating another breakthrough pain event when using this medication [12]. If it is proven that a dose is ineffective for treating pain after several consecutive trials, the provider can increase the dose until a single unit of Actiq provides adequate pain relief [12]. The goal of Actiq titration is to find a maintenance dose that requires one Actiq per breakthrough pain episode, to be used up to four times in a day [12].

6.2.2 Fentora

Fentora is a buccal tablet initially dosed at 100 mcg, with the only exception being patients who have used Actiq in the past [13]. Patients are instructed to place the entire tablet in the buccal cavity (between the upper cheek and gum) or under the tongue for up to 30 min and the remaining tablet to be swallowed after 30 min [13]. When tablets are crushed, sucked, chewed, or swallowed this results in less effective drug delivery and lower plasma concentrations [13]. The medication is absorbed with a 65% bioavailability, with an average amount of 50% of the medication absorbed through the oral mucosa, and 15% swallowed and absorbed through the GI tract [13]. The peak plasma concentration is approximately 1 h after administration [13]. Overall studies have suggested that Fentora has increased absorption at equivalent doses compared to Actiq, thought to be due to the drug delivery system [13].

6.2.3 Lazanda

Lazanda nasal spray is an aqueous solution formulation of fentanyl citrate used for intranasal transmucosal administration [14]. The medication is attached to a metered-dose nasal spray pump, with a visual and audible spray counter [14]. The medication is such a fine mist that patients rely on the audible and visual cues to confirm medication has been given [14]. Due to its intranasal transmucosal administration, there have been studies evaluating its efficacy in patients with allergic rhinitis [14]. The pharmacokinetic and safety profiles showed no clinically meaningful differences in exposure to fentanyl in allergic rhinitis patients [14]. However in patients with allergic rhinitis, co-administering a vasoconstrictive nasal decongestant (such as oxymetazoline), there is lower peak plasma concentrations and delayed median time of maximum plasma concentration (Tmax) of fentanyl, which could impair the analgesic effect of Lazanda [14]. It is recommended that vasoconstrictive nasal decongestants should not be used while titrating Lazanda [14].

The initial dose of Lazanda for all patients is 100 mcg [14]. Initially, it is given as a single spray into one nostril, and the spray base is 100 mcg [14]. The Tmax values range from 15 to 21 min after administration of a single dose [14]. Thus

when titrating, patients are asked to assess their pain relief 30 min after the initial spray [14]. The medication can be uptitrated by increasing the number of sprays given, the next uptitration is a single spray into each nostril (2 sprays), followed by two sprays into each nostril (4 sprays) [14]. As the medication is titrated to effect, the medication can be offered as a 400 mcg fentanyl base, in which case 1 spray will deliver 400 mcg [14]. Once a patient is on a stable dose of Lazanda, the goal is to limit Lazanda use to four or fewer doses per day, and to dose no more than every 2 h [14]. There are studies comparing the effectiveness of Lazanda versus an oral transmucosal fentanyl citrate product, and it was shown that Lazanda had approximately 20% higher bioavailability [14].

6.2.4 Subsys

Subsys is a fentanyl sublingual spray, with the initial treatment dose of one 100 mcg spray sublingually, with an exception for patients already using Actiq [15]. Once Subsys is titrated to the dose resulting in analgesia, patients should limit use to four or fewer doses per day, no closer than 4 h between uses [15]. Subsys is available in 100, 200, 400, 600, 800, 1200, and 1600 mcg strengths [15]. In a study that compared the bioavailability of Subsys versus oral transmucosal fentanyl citrate, Subsys had 34% greater maximum plasma concentration and 38% greater systemic exposure [15]. The Tmax varied depending on the dose, averaging 0.67–1.25 h from the start of administration [15].

One of the major considerations for use of Subsys is in cancer patients with mucositis, as this leads to increased Subsys exposure [15]. In a small study, cancer patients with Grade 1 mucositis had 73% greater maximum serum concentration (Cmax) in comparison with patients without mucositis [15]. Those with Grade 2 mucositis had fourfold and sevenfold higher Cmax values compared to patients without mucositis [15]. As such the recommendations are to monitor patients with Grade 1 mucositis closely for respiratory and central nervous system depression, especially when initiating therapy [15]. And furthermore, Subsys should be avoided in patients with Grade 2 or more severe mucositis (unless the benefits outweigh the potential risk) [15].

6.2.5 Abstral

Abstral is a sublingual tablet, mainly absorbed through the oral mucosa (patients are instructed to place it on the floor of their mouth, under the tongue as far back as possible) [16]. Abstral's bioavailability has been calculated to be 54% [16]. The initial treatment dose is 100 mcg, and the starting treatment dose can be adjusted only if patients have been on Actiq [16]. Abstral is available in six tablet strengths (100, 200, 300, 400, 600, and 800 mcg) [16]. Abstral is increased if adequate analgesia is not obtained with the initial dose [16]. Once adequate analgesia has been achieved, use should be limited to four or fewer times per day [16]. When

comparing 100, 200, 400, and 800 mcg tablets, the Tmax ranged 30–60 min, indicating the dose effect on Tmax [16].

6.3 Outpatient Continuous Opioid Infusion with Patient-Controlled Analgesia (PCA) for Chronic Cancer Pain

The use of patient-controlled analgesia (PCA) has been well-established for acute postoperative pain management and other indications in the inpatient settings for children and adults. Studies have also shown that in pediatric and young adult patients with cancer, PCA with or without proxy appears to be safe in the outpatient setting [17, 18].

A patient-controlled analgesia (PCA) pump can be used to administer continuous opioid infusion via the intravenous or subcutaneous route and can be considered in situations when rapid-onset analgesia is needed or oral medications are not tolerated [18]. PCA allows a continuous infusion to provide constant plasma level as well as allow patients to control their pain with supplemental boluses. This prevents delay in the administration of the medication and is adaptable to the patient's pain needs [18]. Cancer patients with a prior opioid regimen will need to be converted to an appropriate dose of continuous opioid infusion and the lockout period during chronic infusion may be longer compared to acute pain treatment [19].

Continuous opioid infusions using a programmable portable pump with bolus capabilities is a safe and reliable method of delivering analgesia in the outpatient setting, with appropriate patient selection [18]. PCA uses in the setting of palliative care at home did not have different safety and efficacy than inpatients with cancer pain undergoing cancer therapy, and no major neurological or respiratory complications were reported in the outpatient setting [18]. Two studies suggest children with cancer dying at home can have better pain control and less opioid requirement with opioids delivered by PCA [20, 21].

PCA in an outpatient setting may have a place more in the last phase of life as it allows patients to have an active role in their pain management [22]. This active participation has been reported to reduce physical and psychological suffering for all involved in their care [22]. More research is needed to determine the cost-effectiveness of outpatient PCA for cancer pain.

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Opioid-Related Side Effects and Management

7

Andrea Poon, Jakun Ing, and Eric Hsu

7.1 Introduction

The following areas will be discussed in relation to opioid-related side effects and approaches to their management in the cancer patient:

1. Nausea and vomiting
2. Opioid induced constipation
3. Peripheral opioid antagonists (PAMORAs)
4. Cancer-relevant adverse effects of opioids
5. Opioid antagonist: Naloxone

7.2 Nausea and Vomiting

Nausea and vomiting is a common side effect with opioid use and can be exacerbated in cancer patients receiving chemotherapy and other medications. For patients, it can be one of the most distressing side effects they experience [1]. Tolerance with chronic opioid use and increased dose requirement can lead to worsening symptoms. The mechanism of nausea and vomiting involves several stimuli that act at the medulla oblongata in the brain. The various major areas that trigger the vomiting center include the GI tract, the vestibular area in the temporal lobe, the cerebral cortex, and the chemoreceptor trigger zone (CTZ) [2]. Opioids

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mainly have emetogenic effects via direct stimulation of the CTZ and vestibular apparatus, as well as through inhibitory effects on gut motility. Opioids induce nausea and vomiting through stimulation of the CTZ via activation of mu and delta opioid receptors, as well as signaling through dopamine D2 and serotonin 5-HT3 receptors in the CTZ [2]. Opioid inhibition of gut motility can cause gut distention, constipation, and increased emptying time, which leads to nausea and vomiting.

The relationship between opioid use and nausea and vomiting is complex and based on several factors including the dose and type of opioid used [3]. The side effect of nausea and vomiting with opioid treatment forms a barrier to effective pain control in many patients. Common antiemetics target several receptors including dopamine, serotonin, histamine, and GABA. The majority of these receptors are located in the CTZ and the gut. It is important for clinicians to also determine the cause in order to choose an appropriate antiemetic for the patient, as shown in Table 7.1. Dopamine receptor antagonists, phenothiazines and butyrophenones can treat nausea and vomiting secondary to stimulation at the CTZ. Nausea and vomiting secondary to delayed gastric emptying can be treated with prokinetic agents and serotonin antagonists. One of the first-line treatments for opioid induced nausea is metoclopramide [2]. Histamine antagonists are effective at the vestibular apparatus and treat nausea associated with movement. Anticholinergic antiemetics target the vomiting center directly. Often, a single class may not be sufficient and combined therapy is likely beneficial for treatment. Alternatives include low-dose naltrexone and nonpharmacologic therapies including relaxation techniques and limiting dietary intake [4].

Review of recent literature shows minimal high-quality studies evaluating the management of opioid-induced nausea and vomiting in cancer patients. Sande et al. performed a systematic review and searched for randomized controlled trials from 1980 to 2017 through the MEDLINE and EMBASE databases [5]. The pertinent studies corresponded to categories including opioid rotation, the use of antiemetics,

Table 7.1 Common antiemetic medication classes and mechanisms of action

Class	Mechanism	Examples
Serotonin antagonists	5-HT3 blockade	Ondansetron, granisetron
Prokinetic agents	D2 blockade, 5 HT4 stimulation, 5 HT3 blockade	Metoclopramide
Anticholinergic agents	Muscarinic blockade	Scopolamine
Antihistamines	H1 blockade	Promethazine, hydrozyxine, cyclizine
Phenothiazines	D2 receptor blockade	Prochlorperazine, chlorpromazine,
Butyrophenones	D2 receptor in CTZ	Droperidol, haloperidol
Benzodiazepines	GABA agonist	Lorazepam

Reproduced from Porreca et al. 2009 [3].

and changes in route of administration of opioids. A few challenges of obtaining these studies include recruitment of patients in a palliative care setting, the multifactorial causes of nausea and vomiting in cancer patients, as well as defining the appropriate endpoint for nausea and vomiting. One recent study examined whether preoperative administration of dexamethasone improved postoperative nausea and vomiting (PONV) in cancer patients undergoing breast surgery. It found that dexamethasone as compared to placebo significantly reduced the incidence of PONV, as well as the need for additional postoperative antiemetic drugs [6]. Another study examined the efficacy of prophylactic treatment for oxycodone-induced nausea and vomiting via a randomized, placebo-controlled, double-blind trial [7]. The study found that prophylactic use of prochlorperazine was ineffective and not recommended for nausea and vomiting as it could also cause increased somnolence. Further research is needed to assess other antiemetic medications in patients with cancer pain.

7.3 Opioid-Induced Bowel Dysfunction

Opioid-induced bowel dysfunction (OIBD) includes a multitude of symptoms, including opioid induced constipation (OIC), dry mouth, heartburn symptoms, nausea, vomiting, and abdominal pain [8]. Unfortunately, little to no tolerance develops to the gastrointestinal side effects of opioids [8]. Peripheral opioid receptors are located in the gastrointestinal tract, and activation of peripheral mu-opioid receptors, in combination with spinal and supraspinal mu-opioid receptor agonism, leads to activation of excitatory and inhibitory pathways that induces inhibition of GI transit and inhibition of colonic expulsion [9].

7.4 Constipation

Constipation is the most common opioid induced bowel dysfunction symptom in patients secondary to opioid use. It may occur up to 47% in patients using opioids [10] and often continues throughout usage [11]. The mechanism behind constipation is multifactorial and includes inhibitory effects on gastrointestinal chloride channels, decreased relaxation of pyloric and internal anal sphincters and transit [12]. Risk factors include increasing age, female sex, and duration of opioid therapy [10]. The symptoms of opioid induced constipation include changes in stool consistency, difficulty in passing stool, incomplete rectal evacuation, and decreased frequency [13]. It is important to consider the risks and benefits of each opioid medication as there are varying degrees of constipation, as well as the amount and type of constipation therapy.

The management and treatment of constipation may be difficult due to several factors including communication among patients and physicians, consensus guidelines for diagnosis and treatment, and physician acknowledgment of the impairment of constipation on the patients' quality of life [12]. It is not surprising that there is currently underestimation of palliative care patients suffering from opioid induced constipation [14]. Constipation is often exacerbated by overall weakness and fatigue in the setting of disease progression. Morbidity and mortality can occur with OIC, and adverse outcomes include but are not limited to urinary infection and obstruction, pain, hospitalizations, fecal impaction, bloating, cramping, and reflux [15].

Treatment options include not only pharmacological, but also routine lifestyle recommendations including increased fluid uptake, activity, dietary fiber, and exercise [13]. Pharmacologic agents include laxatives, stool softeners, peripherally acting mu-opioid receptor antagonists, locally acting chloride channel activators, and serotonin 5HT agonists [13]. Prophylactic laxatives for OIC in cancer patients have been recommended [16]. This class of medication includes osmotic agents that work to retain water and stimulant agents that increase intestinal motility. Laxative therapy is the first-line treatment for OIC; however, it does not directly target the mechanism of OIC [17]. Peripherally acting mu-opioid receptor antagonists (PAMORAs) target this mechanism, with the goal of blocking peripheral opioid agonism, while minimally affecting the central nervous system (CNS) action to maintain analgesia [17] (Table 7.2).

Table 7.2 Common medication classes and mechanisms of action for opioid induced constipation

Class	Mechanism	Examples
Laxatives		
Stimulant	Stimulates enteric nerves to increase peristalsis, increases fluid and salt secretion	Senna, bisacodyl
Lubricant	Maintains water and softens stool	Mineral oil, fleet, and zymenol
Osmotic	Increases water retention of stool	Polyethylene glycol, magnesium hydroxide, magnesium citrate
Stool softeners	Increases amount of water the stool absorbs in the gut	Docusate
PAMORAs (Peripherally acting mu-opioid receptor antagonist)	Antagonist at mu-opioid receptor	Methylnaltrexone Naloxegol
Intestinal Secretagogues	Locally acting type-2 chloride channel activator that increases secretion of fluid in GI tract	Lubiprostone
Selective 5HT Agonists	High affinity serotonin agonist	Prucalopride

Reproduced from Leppert et al. 2015 [32].

7.5 Peripheral Opioid Antagonists for Opioid Induced Constipation

Opioid induced constipation is the most common side effect seen with opioid use. Although there are several pharmacological classes in the treatment of OIC, some of these alone do not target the mu-opioid receptors in the GI tract. Peripherally acting mu-opioid receptor antagonists (PAMORAs) block peripheral mu-opioid receptors. Two common medications within this class are methylnaltrexone and naloxegol.

7.6 Methylnaltrexone

Subcutaneous methylnaltrexone was the first PAMORA approved by the US Food and Drug administration. Relistor (methylnaltrexone bromide) is a quaternary amine; therefore, the medication has restricted ability to cross the blood–brain barrier [18]. It is localized in the periphery and selective for the mu-opioid receptor [19]. It is indicated in palliative care patients and chronic non-cancer pain with opioid-induced constipation (OIC) who have not sufficiently responded to laxatives [18]. The subcutaneous form was the first formulation approved for the treatment of OIC. This medication is usually given subcutaneously every other day, or at the most frequent dosing it can be given daily [18]. The recommended dosing for cancer patients based on their weight are as follows: 38–62 kg: 8 mg/dose SC every other day, 62–114 kg: 12 mg/dose SC every other day, <38 or >114 kg: 0.15 mg/kg/dose SC every other day. Furthermore, patients should not take more than 1 dose within 24 h. Doses should also be reduced in patients with severe renal dysfunction and used with caution in patients with gastrointestinal (GI) tract lesions as rare cases of GI perforation have occurred in patients with preexisting conditions that decrease GI wall structural integrity [18]. The oral form is administered as a once-daily tablet in the morning. A recent meta-analysis examining rescue-free bowel movement within four hours of methylnaltrexone administration showed significant difference among treatment groups supporting the use of the medication to induce laxation [20]. A study examining methylnaltrexone in OIC in a palliative/hospice setting with incurable cancer or other end-stage diseases showed approximately half of patients experience laxation within 4 h of receiving the drug, with a median time to laxation of less than 1 h [21]. Furthermore, 55% patients noted a decrease in constipation distress. Commonly reported adverse effects were abdominal pain, nausea and vomiting [21]. Methylnaltrexone has a favorable tolerability profile in patients [22].

7.7 Movantik

Movantik (naloxegol oxalate) is indicated in patients with OIC with chronic non-cancer pain, including those with prior cancer and who do not require weekly opioid escalation [23]. This medication is a PEGylated derivative of naloxone and is a P-glycoprotein transporter substrate. The PEG moiety reduces passive permeability through the blood–brain barrier, and the P-glycoprotein transporter substrate increases efflux of naloxegol across the blood–brain barrier. Therefore, at the recommended dose, it has limited interference with opioid analgesia and functions peripherally, targeting sites such as the GI tract [23]. Prior to starting this medication, all laxatives should be discontinued and may be restarted after 3 days if response to this medication is suboptimal [23]. Movantik is generally started at 25 mg PO daily; however, dose is decreased in renal failure or if not tolerated [23]. The half-life of the medication is between 6 and 11 h [24]. The medication is contraindicated in patients taking strong CYP3A4 inhibitors as these can increase plasma naloxegol levels and possibly precipitate withdrawal [23]. A high-fat meal can also increase naloxegol absorption by 30–45%; therefore, the medication should be taken on an empty stomach, at least 1 h prior to the first meal of the day or 2 h after the meal (PI). Other adverse effects of the medication beside withdrawal precipitation include abdominal pain, diarrhea, and GI perforation [23]. Webster et al. showed that through their questionnaires, patients taking 25 mg daily reported lower rectal and physical symptoms, as well as improved mental health, physical, and social functioning.

7.8 Cancer-Relevant Adverse Effects of Opioids

Opioids are commonly used in cancer patients with chronic and acute post-surgical pain. While systemic and long-term adverse effects of opioids include cognitive dysfunction, mood disorders, addiction, hypogonadism or other endocrine dysfunction, respiratory depression and sleep apnea or sleep-disordered breathing, the effects of opioids on an immunocompromised cancer patient is especially important [25]. There are several direct and indirect effects of opioids on the immune system and cancer cells. Opioids affect both the adaptive and innate immune systems. Immune cells such as T cells, mast cells, macrophages, dendritic cells, cytokines, and chemokines have a role in antitumor immunity. Different opioid receptors have been found on immune cells including CD4 + T helper cells, B cells, and macrophages [26, 27]. There are concerns that opioids raise the risk of infection in cancer patients. One retrospective study showed that morphine use was related to greater infection rates in comparison with oxycodone [28]. Another study showed that regardless of type of opioid, opioids can increase the risk of infection by 20% [29]. Overexpression of the mu receptor has also been associated with metastatic development in cancer patients. Opioids play a role in both peripheral and central mechanisms in immune suppression. Opioids can also directly affect immune cells via mu and toll-like

receptors as many cancer tissues overexpress mu receptors [30]. Results from studies on the effects of opioid use in cancer patient survival have been conflicting. For example, some studies have shown that opioid use has been related to increased survival at higher dosages or at the end of life. Other studies showed that there were no differences. A few studies showed that opioid use and its effects on the immune system have led to decreased survival with tumor progression.

7.9 Opioid Antagonist: Naloxone

Indications for Use of Naloxone Injection in Cancer Patients

Pain is one of the most common symptoms that cancer patients experience. Pain occurs in 20 to 50% of cancer patients, with 80% of patients with advanced-stage cancer reporting pain [31]. Cancer patients often require high-dose opioids and thus are at a high-risk group for opioid overdose. The current CDC guideline for opioid prescription provides information on improving the care of chronic pain patients while reducing risks. Naloxone is a risk mitigating medication that reverses respiratory and central nervous system depression symptoms with opioid overdose. Formulations of the medication include intravenous, intramuscular, and intranasal [38]. Currently, the intranasal form is commonly prescribed. The intramuscular or subcutaneous naloxone dose is 0.4 mg and 2 mg, respectively, while the intranasal dose is administered as 2 or 4 mg.

Naloxone has been recommended in patients with increased opioid overdose risk factors, including history of overdose, concurrent use of benzodiazepines, substance use disorder, and higher opioid dosages ($\geq$ 50 MME/day). The role of naloxone in treating cancer patients has been controversial as this patient population is often faced with life-limiting illnesses, poor functional status, and high-symptom burden [37]. Another concern regarding the use of naloxone in cancer patients is that there is often overlap of symptoms associated with imminent death and opioid overdose. With the use of naloxone, patients are at risk for worsened pain, along with physical and emotional suffering at the end of life. The benefit of prescribing naloxone in the setting of cancer patients is to mitigate the risk and reverse the symptoms of opioid overdose. Naloxone has also been found to be beneficial in reversing opioid-induced central toxicity during opioid medication titration. It is also beneficial in the setting of history or increased risk of substance abuse in the patient's family, since family members may have increased access to opioids.

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Clinical Implications of Opioid Therapy

8

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8.1 Introduction

The following clinical topics regarding opioid therapy in the cancer patient will be covered:

1. Clinical implications of chronic opioid therapy
2. Opioid tolerance
3. Opioid rotation
4. Opioid-induced hyperalgesia
5. Opioid misuse or abuse
6. Abuse deterrent opioid medications
7. Urine drug testing
8. Naltrexone as adjuvant analgesia
9. Opioid partial agonists

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10. Weaning opioids in the cancer patient
11. Summary and future directions

8.2 Clinical Implications of Chronic Opioid Therapy

Although opioids are potent central acting broad-spectrum analgesics, their effectiveness is diminished by various factors pertaining to their metabolism, drug interactions, genetic issues, adverse/side effects, and potential for abuse. All these factors present potential barriers to effective analgesia requiring specific considerations in clinical practice, which include monitoring and case-based intervention.

Adverse/side effects of chronic opioid therapy of relevance that limit analgesia include constipation, respiratory depression, nausea, endocrine effects, and immunomodulation. Constipation is the most prevalent adverse effect of chronic opioid therapy as it affects 40–95% patients on chronic opioids. Guidelines recommend monitoring for constipation and instituting a bowel regimen with a combination of stool softening agents and non-medical therapies as soon as indicated. However, considering the pervasive and progressive nature of opioid-induced constipation, clinicians should consider prophylactic therapy for constipation at the onset of opioid therapy [1]. Nausea is also relatively prevalent during opioid therapy and can be managed with various anti-emetics; however, it does not usually require prophylactic treatment at the onset of opioid therapy unless there has been a previous history of opioid-induced nausea [2]. More details on the management of these opioid related side effects can be found in the previous chapter.

Tolerance and opioid-induced hyperalgesia (OIH) are other very important adverse effects of opioid therapy that affect a subset of patients and require awareness and in-depth understanding of the mechanisms to provide effective management. Both tolerance and OIH manifest as increased pain despite opioid therapy. Tolerance results from decreased drug effectiveness, while OIH results from an augmentation of nociceptive pathways implicating NMDA and glutamate receptors. The management for one exacerbates the other; tolerance requires a dose increase, which would exacerbate OIH. Management of OIH can be complicated and protracted and generally requires a combination of weaning the opioid, switching drugs, and incorporating non-opioid analgesic or specific nociceptive receptor antagonists (e.g., methadone). Additionally, it is important to consider a progressive underlying pain disorder in the differential [3].

Another serious concern of opioid therapy is the risk of dependence, addiction, and abuse. Opioids and other drugs of abuse affect the reward center in the limbic circuit (comprising the brainstem ventral tegmental area, basal ganglia nucleus accumbens, and the orbitofrontal cortex) and can stimulate euphoria or dysphoria. Some individuals may be particularly susceptible to this effect, predisposing them to the risk of addiction and abuse [4]. For this reason, guidelines recommend a comprehensive assessment of the patient's substance use history and documentation

of their substance abuse risk stratification prior to initiating opioid therapy. Some observational studies suggest that substance abuse of other substances predisposes to opioid abuse in chronic pain patients [5].

The increased risk of overdose, addiction, abuse, and misuse warrants application of risk mitigation strategies as recommended by current practice guidelines. Potential strategies include patient education, urine drug testing, prescription drug monitoring program data, pill count, and abuse deterrent formulations. Screening strategies are employed to identify aberrant behavior, though there is limited evidence of their accuracy [6]. However, informed and sensible application of multiple screening strategies may be an effective approach to identifying aberrant behavior.

8.3 Tolerance

Opioid analgesia remains the most effective and widely accepted treatment modality for moderate to severe cancer pain. However, its efficacy and clinical use has been limited by the occurrence of tolerance and hyperalgesia, as well as dependence, abuse, and misuse [7, 8].

Repetitive use of opioids and/or escalating doses can lead to tolerance of medication. However, tolerance forms not only to the analgesic effects of the medication, but also to some unwanted side effects, including but not limited to respiratory depression, sedation, and occasionally nausea [9]. Tolerance to constipation and meiosis does not build, which can pose a significant problem when escalated doses of opioids may be indicated for adequate pain relief [7]. Interestingly, opioid tolerance does not develop as often in patients with cancer who are being treated for pain; the need for increasing doses in those patients typically is due to an increasing level of pain secondary to cancer progression. No consistent relationship between intrinsic efficacy and tolerance exists [7].

As tolerance builds, 10–30% percent of patients will begin to demonstrate poor responsiveness to opioid therapy, which could be secondary to pain profiles with less of an analgesic response [10]. Additionally, poor responsiveness may refer to intolerance of the side effects that overwhelm the benefits, which could be from comorbid medical disorders that predispose to toxicity and pharmacologic effects such as the accumulation of active metabolites (i.e., hepatic or renal failure) [10]. Tolerance is multifactorial and cannot be fully explained in terms of molecular events; however, it is believed that NMDA receptor upregulation or glutamate receptor downregulation can play a role in both long term tolerance to opioids and hyperalgesia [11].

There should be high clinical suspicion for the development of tolerance and prompt assessment for potential contributors [12]. Potential strategies for addressing poor opioid responsiveness include the following: use of a more aggressive or innovative therapy for side effects, such as coadministration of a psychostimulant for opioid-related somnolence, maximizing nonopioid or adjuvant analgesic, intrathecal therapy, nonpharmacologic intervention (transcutaneous nerve stimulation, cognitive

approach, neural blockade), or switching to another opioid (also known as opioid rotation) [10].

8.4 Rotation

Opioid rotation refers to switching from one opioid to another secondary to treatment-limiting toxic side effects or significant tolerance [12]. Based on clinical and pharmacological studies, by switching to a new drug, one may achieve a greater balance between pain relief and intolerable side effects [12]. Guidelines for opioid rotation have been developed to help prevent relative overdosing or underdosing when stopping one opioid and starting another. Equianalgesic tables have been made to help compare relative potencies and it is essential to know the approximate dose between drugs; however, application must be done carefully [12]. Variation of drug metabolism and pharmacodynamics between patients, variability in drug absorption between different administered modalities, and "incomplete cross tolerance" (inability to tolerate side effects from the newly administered drug) are some reasons why there should be a dose reduction by 25% to 50% from the calculated equivalent analgesic dose [10]. Two exceptions to the dose reduction rule exist: when switching to methadone (dose reduction should be closer to 75–90%) and switching to transdermal fentanyl (dose reduction does not apply) (Table 8.1).

Table 8.1 Equivalent analgesic dosing. Adapted from Portenoy, 2000 [61]

Drug	Equivalent dose	Sample dose	Half-life (h)
Morphine	1	15–30 mg every 4–8 h	2–3
Oxycodone	1.5	5–15 mg every 4–6 h	2–3
Oxymorphone	3	5–10 mg every 4–6 h	7–10
Hydromorphone	4	2–3 mg every 3 to 4 h	2–3
Methadone	1–20 mg/day 4 21–40 mg/day 8 41–60 mg/day 10 61–80 mg/day 12	2.5–10 mg every 4–8 h	12–150
Fentanyl patch	2.4	25 mcg If daily PO morphine is 60–134 mg	16–24 h
		50 mcg if daily PO morphine is 135–224 mg	
		75 mcg if daily PO morphine is 225–314 mg	
		100 mcg if daily PO morphine is 315–404 mg	

8.5 Opioid-Induced Hyperalgesia

8.5.1 Definition

Opioid-induced hyperalgesia (OIH) is defined as a "state of nociceptive sensitization caused by continued or escalating exposure to opioids" [14]. Patients receiving opioids for pain control could paradoxically become more sensitive to certain painful stimuli, whether due to exacerbation of the previous painful stimulus, a new source of pain, or a non-painful origin (allodynia) [14]. This phenomenon could explain the loss of opioid efficacy in some patients. Many studies have investigated the factors that can contribute to OIH as well as the cellular and molecular mechanisms [15]. Observational, cross-sectional, and prospective controlled trials have examined the expression of OIH in humans [14]. Studies presenting solid evidence for OIH in cancer-related pain are lacking, however clinical observations suggest it may be important [16].

The current theory is that neuroplastic changes result in sensitization of the nociceptive pathways of both the central and peripheral nervous system [14]. The proposed five main mechanisms include: the central glutaminergic system, spinal dynorphins, descending facilitation, genetic mechanisms, and decreased reuptake and enhanced nociceptive response.

8.5.2 Ways to Mitigate

OIH should be suspected when a patient demonstrates a loss of opioid effect in the absence of progressive illness, if escalating doses result in increased pain and sensitivity, and if an improvement in pain follows opioid dose reduction [17]. OIH can produce more diffuse pain that is less defined, which could extend to areas outside of the pre-existing pain [14]. Clinicians should have a high suspicion of OIH; however, diagnosis may be clouded in patients with delirium, where the patient is observed to become more distressed as more pain medications are administered [17]. Also, the physician could face a dilemma when trying to differentiate tolerance from OIH, since the treatment of each is quite different [14]. Currently, there is no standard means of differentiating between tolerance and OIH, which creates some ambiguity in clinical interpretation. Some authors can form a diagnosis of OIH in all patients with worsening pain during aggressive opioid escalation therapy. The key difference is that OIH can be improved by tapering the opioid whereas tolerance can be improved by increasing the dosage [18]. There is no definitive treatment for OIH. Common traditional treatment involves reducing the opioid dosage, tapering them off, or modulation of OIH with medications that antagonize NMDA receptors [14].

Ketamine, a non-competitive NMDA antagonist, has an expanding role in neuropathic pain, and there is some evidence that shows low-dose ketamine can

modulate the expression of OIH; however, larger studies need to be undertaken to determine the clinical significance [19].

Dextromethorphan, a non-competitive NMDA antagonist and a weak mu receptor agonist, has been used clinically for OIH. There have been numerous studies in chronic non-cancer pain which failed to demonstrate any clinically significant difference in attenuation of OIH [20]. However, a recent 2016 meta-analysis did demonstrate a reduction in opioid consumption and lower pain scores in post-operative pain [21].

Cox-2 inhibitors (i.e., celecoxib) have been shown to antagonize NMDA receptors in the central nervous system, thus it has been suggested that inhibition of prostaglandin synthesis could attenuate OIH by modulating the NMDA system. There is evidence that suggests a role for Cox-2 inhibitors in the modulation of OIH (36, 37).

Clonidine, an Alpha-2 receptor agonist has been used for pain control because of its ability to decrease circulating catecholamines; however, studies also demonstrate a possible role in OIH modulation [14]. Animal studies have been contradictory; however, human studies have provided direct evidence to support its role in attenuation of OIH [14].

8.6 Opioid Misuse or Abuse

The use of opioids to treat patients with cancer pain is the mainstay of treatment. Pain is the most frequent symptom in patients with cancer and is prevalent in half of all patients who receive cancer therapy and more than 70 percent of patients with advanced cancer [22]. Opioids offer a rapid onset of action, a lack of ceiling effect, relatively easy titration, no significant effect on end organ function, and straightforward dosing and prescription. That being said, the use of opioids for cancer pain has become increasingly challenging in light of the opioid epidemic and new evidence that even patients with cancer pain are at risk of misuse [23]. Misuse is defined as "any use of a prescription medication that is outside of the manner and intent for which it was prescribed" [24]. According to the FDA, opioid abuse is defined as the "intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect" [25].

A recent report from the Centers for Disease Control and Prevention (CDC) reported a 45 percent increase in opioid related overdose deaths from 2016 to 2017 [26]. As a result, the CDC has released new restrictive opioid guidelines, requirements to review the prescription drug monitoring program (PDMP) for newly prescribed patients, and a letter from the Surgeon General emphasizing a collective effort in opioid prescription reduction. Patients with cancer pain have typically been exempt from such rules and regulations as the CDC has recommended against misapplication of recommendations outside of the scope of the guidelines [27]. However, limited access to opioids secondary to nation-wide shortages, the necessity for insurance preauthorization for medications, and a 69%

decrease in prescription for cancer pain have ultimately impacted patient care [22]. Nevertheless, there is still a heavy body of evidence that demonstrates patients with cancer pain are at a higher risk of non-medical opioid abuse, with a recent study that demonstrates that 1 in 5 or up to 20 percent may be at risk [23]. It is therefore prudent to have a high clinical suspicion for opioid misuse despite tighter regulations and pain management for cancer-related pain.

It is certainly difficult to predict which cancer patients are at an inherently higher risk for misuse. Some examples of misuse behavior include but are not limited to early refill requests, resistance to change, polypharmacy, opioid sharing between family and friends, using opioids off label (i.e., insomnia and anxiety), and lost prescriptions [22]. Risk factors for opioid misuse have been identified as age less than 40, personal or family history of mental health disease, or a history of alcohol or tobacco abuse [28]. Of those listed, alcohol abuse is the most common risk factor for opioid misuse and occurs in up to 27 percent of patients with cancer and is often missed by clinicians [28]. There are three categories of assessment tools designed as universal screening for patients at a higher risk of developing opioid misuse prior to initiating therapy, as well as monitoring for misuse throughout therapy [22]. Patients that are at a higher risk of developing misuse should be referred for pain management consultation and counseling for a multimodal approach [22]. Besides identifying patients at risk, those receiving opioids should be educated on the risks, proper storage, disposal, and drug take-back programs, all of which have demonstrated reduction in opioid misuse [29].

Clinicians also play an important role in limiting the potential for abuse. Before prescribing opioids, physicians should check the PDMP and consider performing urine drug toxicology. Checking the PDMP could identify patients at risk of polypharmacy abuse, as well as identifying patients at a higher risk of respiratory overdose (i.e., co-prescribed benzodiazepines). Patients should be prescribed the lowest dose of immediate release (IR), and if long-term therapy is anticipated, the patient should be transitioned to extended release (ER) formulation [22]. IR formulations have an overall higher risk of abuse and overdose-related deaths secondary to a quicker onset of action and more rapid reward [30]. However, ER formulations have a higher rate of fatal overdose within the first 2 weeks of initiating therapy [22].

If a patient is identified as misusing opioids, a non-judgmental and non-confrontation approach should be implemented. The psychological impact of terminal illness confounded with other mental health comorbidities can create a fragile state of mind, vulnerable to stigmatism and judgment. The safety of the patient should be the cornerstone of conversation, maximizing empathy while offering an interdisciplinary approach [22].

8.7 Abuse Deterrent Opioid Medications

Patients receiving opioids greater than 100 morphine milligram equivalent (MME) doses have an increased risk of death, and the CDC currently recommends avoiding increasing dosage to ≥ 90 MME/day or carefully justify a decision to

titrate dosage to $\geq$90 MME/day [27, 31]. The opioid with the highest abuse potential is oxycodone. On the other hand, buprenorphine (a partial opioid agonist) has the lowest abuse potential. Most of the abuse occurs by oral administration (i.e., chewing then swallowing which disrupts the extended release formulation) [32]. A subset of patients then progresses to snorting and intravenous injection. Only a reported 2.3% of users will progress to smoke prescription opioids (however, among fentanyl abusers this reaches almost 50%) [33].

Abuse deterrent opioid medications have been formulated to help minimize abuse to enhance outcomes and reduce healthcare costs, which reached 8.6 billion in 2001 [32]. Manufacturers are now implementing formulations with abuse deterrent properties. Three main categories or approaches of abuse deterrent medications exist: fortress approach (ability of the medication to maintain its extended release characteristics despite attempts to crush it), neutralizing approach (attempts to crush medication will result in release of a neutralizing antagonist), and aversive approach (large quantities ingested will result in release of unpleasant side effects) [32].

Examples of fortress approach type medications include Morphabond (morphine sulfate), OxyContin (approved April 2010) and Xtampza ER, the latter two which contain extended release oxycodone coated with a plastic sheath, effectively preventing the user from crushing it. Examples of neutralizing approach deterrent medications include Suboxone (buprenorphine/naloxone approved in 2002) and Embeda (morphine/naltrexone approved in 2009). If the medication is swallowed, the antagonist effects of naloxone and naltrexone are negated. However, if the medication is tampered with, then the antagonist is released. Studies demonstrate lower abuse potential with suboxone therapy as compared to buprenorphine alone [34]. Aversive approach medications included Acurox (oxycodone/niacin previously under FDA review), which cause symptoms such as warmth, flushing, itching, and sweating if larger than intended doses are ingested [35].

8.8 Urine Drug Testing

The role of urine drug testing (UDT) in opioid therapy in the clinical setting is mainly an objective measure of compliance and drug efficacy. The objective is to determine the presence of prescribed opioids and screen for the presence of non-prescribed substances. Clinical practice guidelines recommend testing prior to initiating opioid therapy, periodically during opioid therapy, and whenever there is concern of substance use, misuse/abuse, or diversion [13, 36]. There is some evidence, based on observational studies, that urine drug testing can improve compliance [37] and decrease concomitant substance abuse [38]. Additionally, data obtained from UDT can identify aberrancies in drug metabolism, facilitating the assessment, diagnosis, and management of drug metabolism interactions, resulting in more effective therapy.

Though specific federally regulated UDT protocols have been established, these are often not indicated in clinical practice, in part because the mandated concentration cutoffs are too high to be of clinical relevance. Federally regulated testing typically evaluates for marijuana/tetrahydrocannabinol (THC), cocaine (benzoylecgonine), opiates, phencyclidine (PCP), and amphetamine/methamphetamine (the "Federal Five").

There are three types of urine drug tests commercially available that are used in clinical practice: Immunoassays, liquid chromatography (LC), and gas chromatography (GC). Immunoassays are qualitative tests that can determine the presence or absence of a substance, or multiple substances, in solution. Immunoassays are relatively inexpensive and rapid, providing results within minutes to hours, compared to the quantitative tests, LC and GC, which take 1–5 days for results. Due to their convenience and availability, immunoassays are widely used in clinical practice and function best for screening purposes. Because of cross-reactions and relatively low sensitivity, immunoassays are far less accurate than quantitative tests, due to the increased risk of false positive and false negative results. For example, structurally similar compounds such as over-the-counter decongestants cross-react with immunoassays resulting in a false positive for amphetamines; similarly, the decreased specificity for synthetic opioids or benzodiazepine can result in false negatives [39]. It is therefore recommended to confirm questionable or suspicious immunoassay results with confirmatory quantitative testing using LC or GC.

LC and GC are highly sensitive and specific, and they can detect trace drug amounts below the standard cut off. Both LC and GC can analyze metabolites and assess for drug interactions. Though this requires high-level analysis laboratory testing, it enables the detection of sample adulteration such as "pill scraping," dilution attempts, and samples not originating from the patient. Quantitative drug testing is, however, significantly more expensive and time consuming than the immunoassay-based point of care testing.

There are particular issues to address when integrating UDT to clinical practice that are of notable mention; these include identifying the appropriate testing frequency or interval, planning how to address UDT results, and the implications of UDT to the physician–patient relationship.

Though UDT is necessary for monitoring during chronic opioid therapy and should be administered at the initiation of therapy, the frequency of testing during therapy is debatable. On the one hand, routine testing has been advocated as a clinically practical approach that provides consistency in monitoring and serves to "normalize" the request for sample when aberrancy is suspected. On the other hand, others argue that routine testing may stigmatize patients [40] and increase cost to the patient without evidence of efficacy. Another concern is that physicians may be inappropriately incentivized to perform routine testing for monetary gain. Current guidelines do not recommend routine testing; rather, and it is recommended to test when indicated—at initiation of therapy, when unexpected issues arise, during dose escalation or switching drugs, with deviant behavior (e.g., early refill requests,

pill count aberrancies, PDMP discrepancies), and periodically about every 3 months [13, 41] to assess for adverse effects and compliance issues, [13, 36].

Experts recommend establishing a protocol to address confirmed aberrant UDT results, as inappropriate handling of these results may have major repercussions for the patient such as loss of access to opioid based therapy, risk of withdrawal, and damaged physician–patient relationship that may impair potential future physician–patient encounters. This requires consideration of whether to continue opioid therapy with restrictive conditions or terminate therapy in the setting of non-compliance, diversion, or misuse [42]. Notable options worth considering if attempting to continue therapy can include close observation, negotiated behavior modification, treatment restrictions or contract revision, addiction medicine consultation, and/or referral to drug rehabilitation center. The attitude toward UDT should be to optimize and facilitate patient care [43]. Current guidelines and expert opinion strongly recommend contextual medical decision making regarding UDT results, as opposed to a clinical decision based solely on UDT results. The protocol should also have provisions for aberrant results due to metabolism, drug interactions, or genetic variance. This often involves reviewing the patient's medication list and trialing a different drug that is more compatible with the patient's medication list.

8.9 Clinical Use of Opioid Antagonist Naltrexone as Adjuvant Analgesia

Naltrexone is a non-selective antagonist of the mu, kappa, and delta opioid receptors and has been FDA approved for the rehabilitation of opioid and alcohol abuse to prevent relapse in those with addiction. Dosages for substance abuse purposes usually begin at 25 mg orally daily with the typical daily dose around 50–100 mg [44]. However, at low doses (4.5 mg or less), naltrexone can act as an immunomodulator in autoimmune diseases as well as in malignancies [45]. It has been suggested that naltrexone binds to opioid receptors on various immune or cancer cells and inhibits the proliferation of T and B cells [46]. Although the exact mechanism is unknown, research indicates that with the inhibition of opioid receptors, upregulation of opioid receptors occurs on the cell membrane level, in addition to a resultant increase in the amount of endogenous endorphins that are secreted by the hypothalamus [47]. The increasing number and density of opioid receptors on tumor cell membranes make them more responsive to endorphins which ultimately result in apoptosis of malignant cells [48]. Numerous case reports suggest that the addition of Naltrexone 4.5 mg to an active cancer treatment regimen, whether as a sole agent or in conjunction to chemotherapy, has shown a decrease in tumor size and even partial or complete remission in patients with active disease.[1]

[1] *LDN and Cancer*.https://www.lowdosenaltrexone.org/ldn_and_cancer.htm.

The resulting anti-inflammatory and analgesic effects of this opioid antagonist have also been suggested to improve symptoms of numerous disease states including fibromyalgia, multiple sclerosis, Crohn's disease, among other chronic pain disease states [49, 50]. Most of the literature has been implicated in the improvement of patients with fibromyalgia when compared to placebo; it has been observed that patients with more pronounced elevations in inflammatory markers, such as an elevated erythrocyte sedimentation rate, show the greatest benefit in their symptoms with the addition of naltrexone to their maintenance therapy [51].

Hence, fibromyalgia patients with newly diagnosed malignancies may potentially be maintained on naltrexone therapy for management of cancer-related pain. In the event that the naltrexone is suboptimal in managing the increasing cancer pain, patients who are believed to be better candidates for opioid management must be transitioned off the naltrexone treatment prior to initiating any opioids, given its antagonist effects.

8.10 Clinical Use of Opioid Partial Agonists

Before discussing the impact of partial agonists and their role in the management of cancer pain, we will briefly review the various subtypes of opioids and their effects on the different opioid receptors in the body (μ-, κ-, δ-). In general, opioids can be categorized as full agonists, partial agonists, mixed agonists, and antagonists [52]. Full agonists bind to and activate the receptors; they have both the affinity for the receptor subtype, as well as efficacy in activating the receptor and its downstream effects. Pure antagonists bind to the receptor with adequate affinity but block the action of the effects of the receptor. Partial agonists bind the receptor with adequate affinity, but the efficacy of the ligand-receptor activity is relatively decreased. Mixed agonist–antagonist agents produce an agonist effect at one receptor subtype, while causing an antagonist effect at another [52]. Table 8.2 alphabetically lists the various opioids based on these four categories, while Fig. 8.1 provides a graphical illustration of the pharmacologic effects of these various agents.

Buprenorphine is the only opioid partial agonist approved for the management of moderate to severe chronic pain and can be used in the management of cancer pain.

Buprenorphine is a semisynthetic mixed partial u-opioid agonist, with antagonistic properties at the kappa and delta receptors. Its high affinity to the u-opioid receptor and slow dissociation contribute to the relatively long duration of action of the drug. It is primarily metabolized by the liver and excreted in bile.

It is known for its high analgesic potency (roughly 75–100 times more potent than morphine), pronounced anti-hyperalgesic effects, and favorable tolerability [49, 53]. Buprenorphine is considered to have a safer profile in respect to respiratory depression, cardiac QT prolongations, renal impairment, and immunologic effects, making it highly suitable when considering long-term opioid management for cancer patients, especially when compared to other standard WHO Step III opioids [53–55]. Because of its ceiling effect and restricted euphoria, it is

Table 8.2 Classification of agents with varying opioid receptor effects

Full agonist	Partial agonist	Mixed agonist–antagonist	Antagonist
Codeine Fentanyl Heroin Hydrocodone Hydromorphone Levorphanol Meperidine Methadone Morphine Oxycodone Oxymorphone	Buprenorphine Butorphanol Pentazocine Tramadol	Buprenorphine Butorphanol Nalbuphine Pentazocine	Naloxone Naltrexone

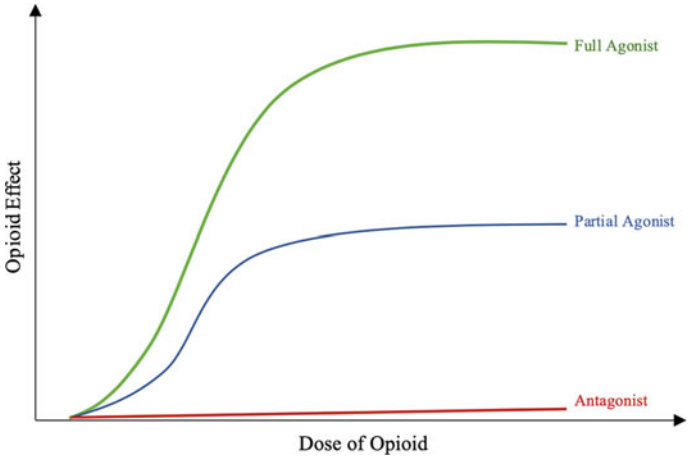

Fig. 8.1 Schematic illustration of the relative effect of the various opioids based on classification

considered to have low abuse potential. The anti-hyperalgesic properties decrease the incidence of developing tolerance in patients on buprenorphine for maintenance treatment and are believed to play a role in the drug's efficacy in managing neuropathic pain as well [53]. The most common side effects include nausea and erythema or pruritis at the site of patch application [54].

A Cochrane systematic review published in 2016 attempted to provide a comparison on the efficacy of the various forms of buprenorphine to other traditional oral and transdermal opioids. And although data is limited due to the nature of the studies reviewed, these studies have shown at least an equivalent analgesic effect in patients receiving buprenorphine, if not superior compared to placebo and other Step III opioids, including morphine and transdermal fentanyl [56].

Buprenorphine is available in various forms including parenteral injections, sublingual tablets, mucosal buccal films (Belbuca), and transdermal preparations (BuTrans and Transtec). Due to extensive first pass metabolism, however, the oral bioavailability is low at only 15% [56]. Although literature reviews have suggested an inconclusive role in the management of cancer pain, some studies have suggested that the transdermal formulation has been associated with greater analgesic efficacy in the treatment of moderate to severe cancer pain [56]. The transdermal route allows for maintenance of therapeutic serum drug concentrations via controlled release of drug over a more prolonged period of time [53]. The most common transdermal formulation available delivers 5, 10, 15, or 20 μg/hour for 7 days (BuTrans). This is equivalent to about 48 mg morphine/24 h. However, there are higher dosages available outside the USA that release 35, 52.5, or 70 μg/h for 4 days (Transtec) [54]. For those who have sensitivity to the patch or prefer other formulations, Belbuca buccal strips are available for daily or twice daily administration in the following dosages: 75, 150, 300, 450, 600, 750, and 900 [51].

8.11 Weaning Opioids in the Cancer Patient

Because there is limited literature on the down-titration of opioids in the cancer population, no guidelines exist to assist physicians in the weaning of chronic opioid use in individuals who have received cancer diagnoses and completed treatments. However, those who undergo oncologic treatment and are concomitantly on opioids for their cancer-related pain also suffer from the aforementioned adverse effects of chronic use of such agents. Thus, avoiding extended and unwarranted opioid use should be persistently revisited, especially in patients who are in remission or those who are believed to have a prolonged life expectancy.

The 2016 CDC Guidelines for prescribing opioids for chronic pain, as well as the FDA's "Risk Evaluation and Mitigation Strategies" both suggest methods in which to assess the risk versus benefits of continued opioid therapy in chronic pain patients. This can likely be safely extrapolated to the care and management of cancer patients in remission, as well. One technique is the Pain Assessment and Documentation Tool (PADT), which includes four main domains: pain relief, patient functionality, reported adverse events, and drug-related behaviors. Many physicians also refer to this as the 4As: analgesia, activity level, adverse events, and aberrant behaviors.[2]

Another useful tool can be attributed to Dr. Lembke and Stanford Continuing Medical Education, who together developed an online CME course for physicians, solely dedicated to tapering down opioids. They incorporate her BRAVO practice which helps physicians learn techniques to how to *b*roach the patient, utilize a *r*isk–benefit calculator, navigate *a*ddiction, and determine an appropriate *v*elocity to weaning

[2]Newmark [57]

while also *v*alidating the patient's concerns and role in the process and educating them on *o*ther strategies and coping mechanisms for managing their pain [58].

Once a provider feels that a weaning protocol is warranted, the first, most important step is to have a compassionate and empathic conversation with the patient, discussing concerns and rationale for beginning an opioid taper. Although there are no specific evidence-based protocols to initiate an opioid taper, it should be done methodically and carefully, balancing an effective down-titration while mitigating symptoms of withdrawal [52].

Signs and symptoms of withdrawal can include, but are not limited to, increased sympathetic tone which can result in increased resting heart rate, hypertension, anxiety, irritability, and restlessness, as well as hand tremors and increased pupillary size [59, 60]. Patients can also complain of flu-like symptoms such as diaphoresis, shivering, lacrimation, rhinorrhea, piloerection. Most commonly, patients endorse GI upset, including nausea, vomiting, diarrhea, and abdominal cramping [52]. Quantitative scales such as the Clinical Opiate Withdrawal Scale (COWS) can help modify the velocity at which titration should occur, although most literature recommends a 20–50% decrease weekly [52]. Providers also have the option of addressing mild withdrawal symptoms with agents such as NSAIDs for arthralgias, antiemetics for nausea, antidiarrheals for diarrhea, antidepressants for anxiety and irritability, and clonidine for symptoms associated with autonomic hyperactivity.

Physicians are also encouraged to discuss proper disposal techniques for unused opioids. The FDA provides several strategies including dropping off medications to local "take-back" locations or programs, flushing the medication down the toilet if appropriate, or using other disposal techniques provided on the FDA website.[3]

8.12 Summary and Future Directions

Opioid pharmacology is an evolving field in which new drugs are specifically synthesized with varying pharmacokinetic and pharmacodynamic properties. This variety provides a useful resource to pain physicians tackling complex pain syndromes further complicated by varying genetic polymorphisms and metabolic variability inherent in each patient population, in addition to pharmacologic alterations introduced by drug interactions. Though opioid therapy is among the most effective analgesic therapies with the most threatening risks, its effectiveness and safety can be optimized by systematic application of guidelines and judicious tactful use of risk mitigating and patient monitoring strategies. The administration and management of opioid therapy requires an awareness and appreciation of its

[3]US Food and Drug Administration. Disposal of Unused Medicines: What You Should Know. https://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know. 26 Sept 2019.

complexity and inherent risk. It also requires that clinicians constantly and tactfully reassess treatment plans, apply effective communication and documentation skills, and function as the patient's fiduciary who first does no harm.

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Non-opioid Analgesics and Emerging Therapies

9

Marga Glasser, Jeffrey Chen, Mohammed Alzarah, and Mark Wallace

9.1 Introduction

Pain is a common and debilitating symptom of cancer. Cancer-related pain can occur at any point along the continuum from diagnosis to treatment to survivorship [1]. A systematic review published in 2016 estimated the prevalence of cancer pain to be 55% in those undergoing anti-neoplastic treatment, 66.4% in advanced cancer, and 39.3% in the post-treatment population. Thirty-eight percent of cancer patients in this pooled analysis experienced moderate to severe pain [2].

It has long been recognized that pain is more than a physical phenomenon. Cicely Saunders, founder of the modern hospice movement, wrote of "total pain," encompassing not only physical symptoms but also psychological, social, and spiritual suffering [3]. The International Association for the Study of Pain (IASP) recognizes pain as both "a sensory and emotional experience" [4]. Thus, a focus on pharmacologic therapy is inherently narrow in scope, and a well-designed treatment plan for cancer pain management should include such multimodal approaches as psychological-based treatments, physical and occupational therapy, exercise, integrative treatments like acupuncture and massage, and procedural interventions [5].

Mechanistically, cancer pain may be broadly classified as nociceptive pain, neuropathic pain, or bone pain. Nociceptive pain implies ongoing injury to non-neural tissue, whether to somatic structures such as bones, joints of muscles, or to the viscera [6]. Neuropathic pain, in contrast, occurs when there is injury to the somatosensory nervous system [6].

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Etiologically speaking, pain may originate from the tumor invading or compressing bone, neural tissues, or hollow organs [7]. Furthermore, cancer treatments themselves can result in pain, as in perioperative or chronic post-surgical pain, chemotherapy-associated neuropathy, radiation-associated plexopathy or myelopathy, radiotherapy-induced nerve tumors, or paraneoplastic syndromes [7]. Chronic graft versus host disease (after hematopoietic stem cell transplant for hematologic malignancies) can lead to pain symptoms of the skin, mucous membranes and eyes [8, 9]. Pain may be a direct effect of antineoplastic treatments, such as chemotherapy infusion-related pain, bisphosphonate-related myalgia, or taxane and aromatase inhibitor-related arthralgia [8, 10]. Patients may also experience chronic pain due to a variety of etiologies that predated their cancer.

Historically, the approach to treating cancer pain has been dictated by the WHO guidelines, first published in 1986 [11]. The WHO approach is a step-wise ladder of drug classes progressing from nonsteroidal anti-inflammatories to "weak opioids" such as tramadol and codeine to "strong opioids," namely morphine, with each "rung" being climbed as symptoms increase in severity. Although this algorithm has been referenced for cancer pain treatment for nearly 30 years, it is not based on level-one evidence [12]. In addition, it may be an unnecessarily narrow approach, as it does not distinguish by mechanism of pain, does not include procedural or other modalities for pain, and recommends morphine as the opioid of choice in the absence of compelling data to support its use over other opioids [12–14]. Indeed, much of the historical value of the WHO guidelines was that they provided a simple, standardized approach that could be used by practitioners in geographic areas where pain specialists were rare [12].

9.2 Mechanisms of Cancer Pain

Cancer cells and the body's immune response to them cause the release of algogenic (pain-provoking) mediators such as bradykinin, proteases, tumor necrosis factors, and others, which interact with peripheral nociceptors (pain receptors) to activate or sensitize them [15]. (Fig. 9.1) Afferent impulses from the periphery are transmitted by A-delta and C type neural fibers. A-delta fibers are myelinated, transmitting afferent impulses rapidly, while C fibers are unmyelinated and have slower transmission. These first order-neurons synapse in the dorsal horn of the spinal cord, where they release a variety of neurotransmitters, including substance P, calcitonin gene-related peptide (CGRP), and glutamate. From the dorsal horn, impulses travel to higher centers in the thalamus, hypothalamus, and brainstem via spinothalamic, spinoreticular, spinomesencephalic, and spinohypothalamic tracts, and terminate in the primary somatosensory cortex [7]. There is also a descending inhibitory system involving noradrenergic and serotonergic pathways [16]. Each waypoint along this continuum can be conceived as a target for analgesia.

Cancer pain may be continuous ("background pain") or episodic, whether spontaneous or evoked ("breakthrough pain"). The latter tends to be more challenging to treat given its episodic nature, rapid onset, and short duration [17].

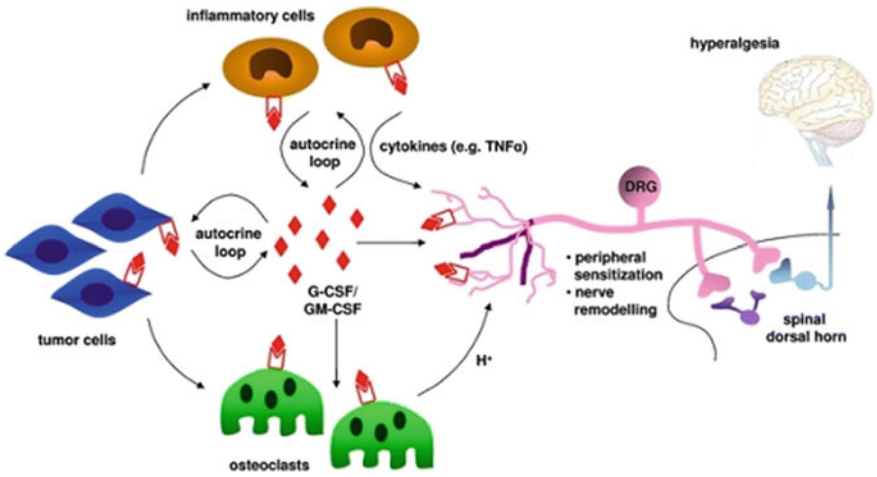

Fig. 9.1 Cancer cells, algogenic mediators, and pain pathways

Although pain is often classified mechanistically as nociceptive versus neuropathic pain, cancer pain is best understood as a mixed process involving the interaction of neuropathic and nociceptive pains, with multifocal inflammatory, ischemic, and compressive noxious stimuli all contributing to the process [16, 18].

9.2.1 Nociceptive Pain

Nociceptive somatic pain is caused by activation of peripheral nociceptors and is relayed by A delta and C fibers [7, 19]. This type of pain tends to be well-localized and sharp. Nociceptive visceral pain, in contrast, is diffuse and poorly localized and occurs when an organ is perturbed by stretching, ischemia, or tumor invasion. There may be associated autonomic symptoms of nausea and vomiting [19].

9.2.2 Neuropathic Pain

Neuropathic pain is due to damage or dysfunction of tissue in the peripheral or central nervous system [6]. Patients describe this pain as burning, shooting, electrical, tingling, itching, or as a "pins and needles" sensation. There may be associated sensory loss, paresthesia (abnormal sensation), allodynia (a painful response to a normally non-painful stimulus), or hyperalgesia (an increased response to a painful stimulus) [7, 18, 20].

Neuropathic pain in patients with cancer may be cancer-related or benign (i.e., not related to the disease, e.g., a lung cancer patient with painful diabetic peripheral neuropathy) [18].

Cancer-related neuropathic pain can occur at the level of the peripheral nerves, nerve plexuses, spinal cord, and brain. It may be caused by the neoplasm itself, by the body's immunological response to the neoplasm, or by cancer treatments [21]. Pain from the tumor itself often involves both neuropathic and nociceptive elements and can be characterized as a mixed pain [21].

Several chemotherapeutic agents, including vinca alkaloids, platinum-based drugs, taxanes, and bortezomide, are known to cause painful peripheral neuropathies, with or without motor and/or autonomic involvement [18]. The site of toxicity may be at the peripheral nerves or at the dorsal root ganglion [22]. Additionally, paraneoplastic processes associated with small cell lung, breast, and ovarian cancers, as well as sarcoma and Hodgkin lymphoma, may cause painful subacute sensory neuronopathy via auto-immune mediated damage to sensory neurons in the dorsal root ganglia [23]. Post-surgical neuroma due to direct surgical injury or post-operative edema or scarring is another cause of neuropathic pain, and post-mastectomy, post-thoracotomy, and post-neck dissection syndromes are also well-characterized common post-surgical neuropathic pain syndromes [24].

Pain in a radicular distribution can occur when there is leptomeningeal carcinomatosis (most commonly seen in lung and breast cancer, lymphoma, and leukemia), intradural tumor, or tumor in the epidural space (from adjacent vertebral body, or growth into the intervertebral foramen from a paraspinal tumor) [25, 26].

Tumors that invade a nerve plexus can cause pain in the distribution of that plexus (e.g., cervical, brachial, celiac, or lumbosacral plexus) [25]. There may be accompanying paresthesias, weakness, and sensory loss along with the same distribution. Cancer-related plexopathy is most-likely to be metastatic in origin; however, primary lesions such as schwannoma or neurofibroma may less commonly be the source. Radiation therapy to the area of a nerve plexus can also cause a painful plexopathy [25].

An additional cause of cancer-related neuropathic pain is cranial neuralgia (e.g., trigeminal, glossopharyngeal) due to primary head and neck tumors or metastases to the leptomeninges or skull base [25, 26].

Clinical guidelines regarding the treatment of neuropathic cancer pain are often based at least partially on studies in non-cancer populations, such as patients with diabetic neuropathy, postherpetic neuralgia, and trigeminal neuralgia [21, 27]. While there is a great deal of similarity between cancer-related and non-cancer-related neuropathic pain in terms of the involved pain pathways and their associated ion channels, receptors, and neurotransmitters, the molecular signature of cancer-related neuropathic pain may be distinct enough to limit the generalizability of studies in non-cancer populations [20].

9.2.3 Bone Pain

Bone marrow, mineralized bone, and periosteum are all highly innervated structures. Cancer cells inside the bone, whether there by metastasis (most often from primary lung, breast, and prostate tumors [28]) or from primary hematologic malignancies [9], can exert noxious forces via mechanical damage, distension, and

nerve entrapment [17]. Further, metastatic induced over-expression of the receptor activator of nuclear factor kappa B ligand (RANKL) causes increased osteoclast activity and subsequent bone destruction [29]. Tumor in tissues adjacent to bone can also cause pain via localized inflammatory response. Cancer-related pathologic fractures are another potential source of cancer-related bone pain. Cancer-related bone pain can be quite challenging to treat and is a major source of functional impairment due to its association with reduced weight-bearing and activity [29].

Strong opioids such as morphine, hydromorphone, oxycodone, and hydrocodone remain the bedrock of treatment for cancer-related pain [25, 30]. Their use will be addressed in another chapter. However, given the multimodal nature of cancer-related pain, knowledge of other adjunctive therapies is essential to providing comprehensive care. A fair amount of the evidence for the use of these adjunctive therapies comes from studies in non-cancer pain patients, and randomized controlled trials of these therapies in cancer patients have been mixed with regard to whether adjunctive theories offer a benefit above and beyond opioid analgesics [21, 30]. This may be a function of inherent differences in populations (cancer patients are more frail and may manifest different pharmacokinetics or side-effect profiles). There may also be differences in the pathophysiology of cancer-related and non-cancer-related pain, as well as differences in the effects of concomitant and typically high-dose opioid use in the cancer versus non-cancer population [27, 30]. Cancer pain treatment guidelines such as those from the WHO and the European Society for Medical Oncology thus largely base their recommendations for these adjunctive therapies on data from non-cancer populations and clinical experience rather than on high-level evidence in cancer populations [31].

9.3 Adjunctive Drugs for Cancer Pain

9.3.1 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs act both peripherally and centrally to produce analgesia via the inhibition of cyclooxygenase (COX), which in turn decreases prostaglandin synthesis. The COX-1 isoenzyme is constitutively expressed in most tissues, whereas the COX-2 isoenzyme is preferentially expressed in the presence of inflammation. NSAIDs also produce analgesia via COX-independent mechanisms involving the central serotonergic, opioid, NMDA, and glutamate systems [32, 33].

Oral NSAIDs may be grouped by those that are shorter-acting (i.e., half-life less than six hours, such as diclofenac, ibuprofen, indomethacin, and ketoprofen) and those that are longer acting (i.e., half-life more than six hours, such as celecoxib, meloxicam, nabumetone, naproxen, and piroxicam). They may also be grouped based on their relative degree of COX-1 versus COX-2 inhibition, ranging from nonselective (e.g., naproxen) to preferential COX-2 inhibitors (e.g., meloxicam) to selective preferential COX-2 inhibitors (e.g., celecoxib). Aspirin, which has tenfold less inhibition of COX-2 as compared to COX-1, is less commonly used for cancer

pain. Intravenous preparations of some NSAIDs (e.g., ketorolac and ibuprofen) are also available. All NSAIDs carry the risk of cardiac, gastric, and renal toxicities, and increased risk of bleeding, with some variation by drug. Because topical NSAIDs (e.g., diclofenac) have less systemic absorption, there is lessened potential for toxicity and drug–drug interaction [34].

NSAIDs are recommended to be used as monotherapy by the WHO for mild to moderate cancer pain and to be used in addition to opioid analgesics for moderate to severe pain [35]. The American Society of Clinical Oncology and European Society for Medical Oncology make similar recommendations [5, 36]. Systematic reviews demonstrate superiority of NSAIDs relative to placebo in cancer pain; however, the evidence is less robust for the efficacy of NSAIDs in reducing pain and opioid use when used in addition to opioid analgesics in cancer patients [37, 38]. The combination of NSAIDs with acetaminophen has been shown to have superior efficacy relative to each drug used on its own [39].

9.3.2 Gabapentinoids

The gabapentinoids (gabapentin, pregabalin) are commonly regarded as first-line therapies for cancer-related neuropathic pain, owing to their relatively robust evidence base and favorable side-effect profile [25, 40]. These drugs are active at the α2-δ subunit of voltage-sensitive calcium channels, decreasing calcium influx and thereby reducing the release of excitatory neurotransmitters including glutamate, substance P, and calcitonin gene-related peptide [25, 41]. The two drugs have similar effects, although gabapentin has poorer oral bioavailability and nonlinear pharmacokinetics due to the saturation of the transport mechanism with dosage escalation, whereas the bioavailability of pregabalin is better, with linear kinetics and greater potency on a milligram per milligram basis [39]. Both drugs do not undergo hepatic metabolism and are not associated with drug-drug interactions. As the gabapentinoids are cleared by the kidneys, doses must be lowered in renal failure. Side effects of both include dizziness, somnolence, and nausea [19].

Gabapentin has been shown to be effective for a variety of neuropathic pain conditions, with data from systematic reviews to support its efficacy in postherpetic neuralgia and diabetic peripheral neuropathy [42], and data from randomized clinical trials affirming efficacy in cancer-related neuropathic pain [43–46]. Pregabalin has similarly been shown to be effective in RCTs of both cancer-related and non-cancer-related neuropathic pain conditions [46–49]. There is some observational data to suggest that pregabalin may be useful even in patients who fail gabapentin [50], and the one RCT that did directly compare the two showed an advantage of pregabalin over gabapentin, though it suffered from methodological limitations including lack of intention-to-treat analysis and inappropriate dose-comparisons [49].

Gabapentin is typically dosed at 100–3600 mg per day, starting at 100–300 mg nightly, and titrating up as tolerated (three times daily dosing) [18]. Pregabalin doses usually range from 25 to 600 mg (often in divided doses three times daily), with starting doses of 25–75 mg nightly [18].

9.3.3 Other Antiepileptic Drugs

The evidence for using other antiepileptics, such as carbamazepine, oxcarbazepine, valproate, phenytoin, topiramate, lamotrigine, lacosamide, levetiracetam, zonisamide, and tiagabine, in treating neuropathic cancer-related pain is less robust [25, 40, 46, 51, 52]. Consequently, and also due to generally worsened side-effect profiles when compared to the gabapentinoids, these drugs are typically used as second-line therapies [18, 25, 39].

9.3.4 Antidepressants

The tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may also be used in treating cancer-related neuropathic pain. Their analgesic effects are independent of their antidepressant effects and relate to the descending inhibitory pain pathways in the spinal cord via the inhibited reuptake of serotonin and norepinephrine [18, 19].

TCAs are commonly considered first-line therapies for cancer-related neuropathic pain, particularly in patients with comorbid depression [18, 27, 39]. However, the best evidence for the use of TCAs in neuropathic pain is in non-cancer patients, and treatment in cancer patients may be associated with more modest effect sizes and greater likelihood of side effects [18, 27, 43, 53].

Caution should be used when treating elderly patients with TCAs has given concern for sedation, delirium, orthostatic hypotension, and falls [25, 54, 55]. The tertiary amines amitriptyline and imipramine tend to have more associated sedation and anticholinergic effects (dry mouth, constipation, urinary retention, sweating, blurred vision) than the secondary amines nortriptyline, doxepin, and desipramine [43]. TCAs are also associated with cardiac side effects, and at high doses (>100 mg), there may be an increased risk of sudden cardiac death; they are contraindicated in heart failure and cardiac conduction blocks [18, 25]. Typical doses for TCAs start at 25 mg nightly (10 mg in elderly patients), increasing up to 100–150 mg as tolerated [18].

SNRIs such as duloxetine or venlafaxine have been shown to have analgesic effects in non-cancer-related neuropathic pain, but studies in cancer patients are limited [46, 56]. Duloxetine and venlafaxine have been studied for the prevention and treatment of chemotherapy-induced peripheral neuropathy (CIPN) with data finding both to be efficacious for treatment but not prevention [24, 57]. Based on the strength of the available evidence, the American Society of Clinical Oncology made a “moderate” recommendation for the use of duloxetine for the treatment of CIPN, which was the strongest positive recommendation that could be made for any of the treatments reviewed. Other treatments reviewed included venlafaxine, amitriptyline, nortriptyline, gabapentin, topical agents, and others [58].

9.3.5 Local Anesthetics

Lidocaine is a commonly used local anesthetic for neuropathic and cancer-related pain. It is a Class Ib antiarrhythmic with mechanism of action thought to be secondary to sodium channel and N-methyl-d-aspartate (NMDA) receptor blockage [19, 59]. The use of intravenous lidocaine to treat neuropathic pain is supported by a systematic review from the Cochrane Collaborative [60]. Randomized controlled trials in cancer pain populations have shown mixed results, with some studies showing a benefit [61, 62] while others failing to find an effect [63, 64]. Intravenous lidocaine dosing is 1–2 mg/kg/h IV continuous infusion with an optional loading dose of 1.5–2 mg/kg IV given over 20 min [59]. Adverse effects are dose-dependent, with perioral numbness, metallic taste, nausea, dizziness, and sedation at usual doses, and more serious cardiac and neurologic toxicities including bradyarrhythmias and seizures with high doses [65]. The rate of adverse effects may be higher in cancer-related pain than in other pain conditions studied [60, 66]. Given concern for cardiac toxicity, lidocaine infusion protocols typically call for continuous monitoring with electrocardiography [65].

Oral mexiletine, an analogue of lidocaine, is sometimes used on patients who have had good analgesic effect with lidocaine infusion [19, 59]. Systematic review by the Cochrane collaborative found mexiletine to be effective in treating neuropathic pain [60]. Starting doses are 150–200 mg per day with titration up to 600 mg in divided doses [59]. Dizziness, visual disturbances, and gastrointestinal side effects may limit the tolerability of mexiletine [19, 59].

Topical lidocaine 5% patch has been shown in randomized trials to effectively treat postherpetic neuralgia and other focal neuropathic pain associated with allodynia. However, a systematic review by the Cochrane Collaborative found the database to be of low-quality evidence given small sample sizes and high risk of bias, thus pooling of results was not possible [67]. Systemic absorption of topical lidocaine is minimal, but the patch should not be used in patients on class I antiarrhythmics (including mexiletine) [18, 25].

9.3.6 NMDA Antagonists

The NMDA receptor has been implicated in the development of neuropathic pain and central sensitization [7, 68]. Drugs that block this receptor have been used in cancer-related pain, particularly pain refractory to opioids [7, 31]. Drugs in this class include the anesthetic ketamine, the antitussive dextromethorphan, the Alzheimer drug memantine and the antiviral treatment amantadine (the synthetic opioid agonist methadone also exerts NMDA antagonism). Of these, ketamine has the best evidence with some randomized trials supporting its use in cancer patients [69, 70]. However, systematic reviews have found the evidence to be of low quality and insufficient to draw conclusions about efficacy [21, 71, 72]. Dosages of ketamine are 0.2–0.5 mg/kg/h intravenous continuous infusion or 10–20 mg by mouth every 8 h [59].

9.3.7 Ziconotide

A non-opioid N-type selective calcium channel blocker, ziconotide is the only drug in its class approved as an analgesic administered via intrathecal infusion. It is considered a first-line drug for administration via the intrathecal route, along with morphine and hydromorphone [73]. The mechanism of action is thought to be via direct inhibition of the N-type calcium channels in the spinal dorsal horn, thus reducing excitatory or pain transmitting signals [74]. There is data from systematic review to support the use of ziconotide in neuropathic pain [75], and randomized clinical trials have shown it to be effective in treating cancer pain [76, 77]. Ziconotide's narrow therapeutic window can make it challenging to use, but slow titration allows the drug to be better tolerated by patients [78].

9.3.8 Bisphosphonates and Denosumab

Bisphosphonates and denosumab may be used in cancer-related bone pain. Bisphosphonates, such as zoledronate, pamidronate, and others, stimulate osteoblasts to produce osteoclast-inhibiting factor, leading to apoptosis of osteoclasts and thereby decreasing bone resorption and increasing mineralization [17]. The structural changes from osteoclastic activity in tumors directly impact sensory and sympathetic nerve fibers, leading to peripheral and central sensitization of neuropathic pain. By inhibiting osteoclasts, bisphosphonates improve cancer-associated bone pain and reduce pathologic fractures [28]. Numerous RCTs support their analgesic effect across multiple cancer types, and several meta-analyses from the Cochrane Collaborative corroborate their efficacy [29, 80–82]. Side effects of bisphosphonates include renal impairment, hypocalcemia, jaw osteonecrosis, and an increased risk of atypical femur fractures during prolonged therapy [83].

Denosumab is a monoclonal antibody directed against the receptor activator of nuclear factor kappa B ligand (RANKL), which is involved in osteoclast production and activation. It has similar activity compared to bisphosphonates, and clinical trials have demonstrated a modest but significant advantage in efficacy [84–86]. The side effects of denosumab are similar to those of the bisphosphonates; however, there is a greater likelihood of hypocalcemia and a lower risk of renal impairment [87].

9.3.9 Corticosteroids

Corticosteroids have long been studied for their efficacy in the treatment of various conditions. However, their role in the management of chronic cancer pain is limited. Meta-analyses by the Cochrane Collaborative and others have concluded that the evidence for corticosteroids in the treatment of cancer pain is weak. Significant pain relief was only achieved for short periods of time and the risks of long-term steroid use (including increased risk of infection, hyperglycemia, osteoporosis, sleep disturbance, and others) outweighed the benefits [5, 88, 89].

9.3.10 Alpha Adrenergic Agonists

Alpha adrenergic agonists such as clonidine, tizanidine, and dexmedetomidine are thought to exert their analgesic effect via activation of the alpha-2 receptors in the locus ceruleus, thereby decreasing the firing of nociceptor neurons stimulated by peripheral A and C fibers [90]. Side effects include somnolence, dry mouth, bradycardia, and orthostatic hypotension. Tizanidine is administered orally, clonidine via the oral, transdermal, or intraspinal routes, and dexmedetomidine via the parenteral route. There is evidence from randomized trials to support the use of these medications in cancer pain [91–93].

9.3.11 Topical Capsaicin

Capsaicin, the active ingredient of chili peppers, is a transient receptor potential vanilloid-1 (TRPV-1) agonist. Capsaicin's analgesic effects are thought to be due to the permanent degeneration of pain afferents, via its suprathreshold depolarization of nociceptive C fibers leading to depletion of the pain neurotransmitter Substance P [41]. Both commercially available preparations (including topical cream 0.075% capsaicin or 8% capsaicin patch available by prescription) have been studied in non-cancer-related neuropathic pain with modest effect [94, 95]. Side effects are minimal and include transient burning at the application site and localized skin reaction.

9.3.12 Acetaminophen

Acetaminophen is an antipyretic and analgesic agent whose mechanism of action is incompletely understood. RCTs have demonstrated efficacy for mild cancer pain, but a meta-analysis by the Cochrane Collaborative found insufficient evidence to support or refute the use of acetaminophen, either alone or in combination with opioids [87, 96]. Once cancer-related pain is severe enough to warrant opioids, any additional effect of acetaminophen is mild at best [37, 51]. Given concerns for hepatotoxicity, particularly in cancer patients on other potentially hepatotoxic medications and chemotherapeutics, the role for acetaminophen in cancer pain management is increasingly being questioned [37, 39].

9.3.13 Medical Cannabis

Cannabis and cannabis-derived products have been investigated for use in cancer-related pain. There is data to support the use of cannabinoids in randomized clinical trials, but the strength of the evidence is not sufficient to warrant a strong recommendation for their use [5, 31, 46, 97]. In the USA, the only FDA-approved cannabinoids on the market are dronabinol, which is indicated for

chemotherapy-induced nausea and vomiting, and nabilone, which is indicated for appetite stimulation in cachexia. There is limited evidence to support the use of either in cancer-related pain. Nabiximols, an oromucosal spray containing a mixture of delta-9-tetrahydrocannabinol and cannabidiol, is approved for analgesia in cancer pain in Canada but not the USA Phase II study in the USA demonstrated superior pain relief with low and medium doses but not with the high dose. However, a subsequent phase III study failed to demonstrate a difference from placebo [98, 99].

9.3.14 Novel and Emerging Therapies

Numerous novel analgesic drugs are under current development. Given the success of nonspecific sodium channel blockade in inducing analgesia, more targeted medications against specific sodium channels such as Nav 1.7, 1.8, 1.9 are under preclinical and clinical investigation [100, 101]. These voltage-dependent sodium channel subtypes may be associated with different pain syndromes as well as modality-specific pain pathways (TABLE X) [102, 103]. Table XX summarizes other Nav specific agents in development.

Nerve growth factor (NGF) is a neurotropin that is upregulated in painful conditions. NGF binds to the tropomyosin receptor kinase A (TrkA) which leads to pain. Tanezumab, a monoclonal antibody against nerve growth factor, was initially studied to treat osteoarthritis pain. Trials were suspended due to reports of rapidly progressive osteoarthritis in tanezumab-treated subjects; however, they were resumed after it was determined that the co-administration of NSAIDs increased this risk. Clinical trials of tanezumab have been positive in the treatment of osteoarthritic pain of the knee and hip as well as chronic low back pain [104−108]. Tanezumab is currently being investigated in Phase III trials for cancer-related bone pain in Europe. Fasinumab is another NGF inhibitor that is in Phase II trials for osteoarthritic knee pain which has shown good efficacy and safety [109].

Mirogabalin is an N-type calcium channel modulator that is specific to the alpha-2-delta type II subunit. Because of more specific effects, it appears to have a better tolerability profile than nonspecific N-type calcium channel modulators. A phase II trial in painful diabetic peripheral neuropathy showed that mirogabalin improved pain and sleepover placebo [110].

Angiotensin type II (AT2) receptors are expressed on small fiber dorsal root ganglion that leads to pain when activated. EMA-401 is an AT2 receptor antagonist that has been demonstrated to reduce pain intensity in postherpetic neuralgia. The drug was safe and well-tolerated and is currently in further development [111].

Neurotoxins are currently in clinical development to treat cancer pain. Resiniferatoxin activates the vanilloid receptor in the dorsal horn leading to C-fiber death. Substance P Saporin (SP-SAP) is selectively taken up by the C fibers in the dorsal horn leading to C-fiber death. Both agents are currently in phase I trials as an intrathecally administered drug.

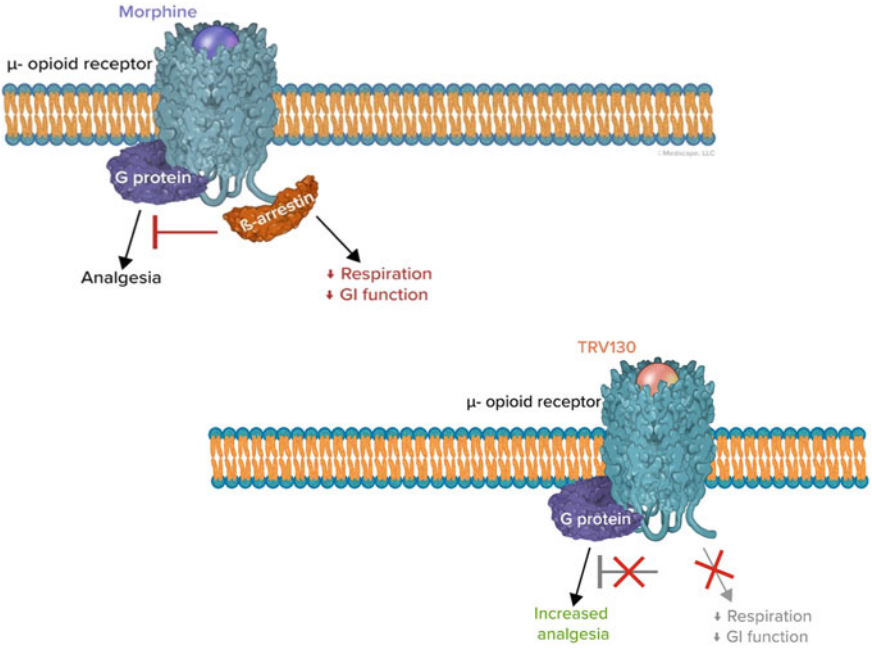

Fig. 9.2 Hypothesized preclinical mechanism of action of conventional opioids versus oliceridine (μ-GPS Modulator). Reproduced from Soergel DG, et al. *Pain*. 2014; 155:1829–1835

There are a couple of novel opioids in clinical development that may have a better safety profile and lower abuse potential. Traditional opioids activate the mu-opioid receptor through both G protein and Beta-arrestin pathways. The G protein pathway is responsible for analgesia, whereas the beta-arrestin pathway is responsible for respiratory depression, constipation and reduces analgesia [113]. Oliceridine, a mu-G protein-specific modulator, has been shown to have comparable efficacy to morphine, but a faster onset of action following bunionectomy [112] (Fig. 9.2). However, as the dose of oliceridine increases, specificity for the G protein pathway becomes less and side effects approach traditional opioids [112].

NKTR-181 is a full mu-opioid receptor agonist that has a PEG polymer attached that modulates the rate of entry across the blood–brain barrier (BBB). The PEG is strongly linked making it difficult to modify for faster BBB penetration. Miosis, which is a measure of BBB penetration and occurs within 11 min after oxycodone, is delayed to 2.8 h with NKTR-181. As presented by Ge XS, et al., at the American College of Neuropsychopharmacology 2017 Annual Meeting, abuse liability studies show that the "high" feeling is indistinguishable from placebo. Thus it may have less abuse potential compared to traditional opioids.

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Part III
Interventional and Locoregional Therapies

Palliative Radiation for Cancer Pain Management

10

Arya Amini, Ashwin Shinde, and Jeffrey Wong

10.1 Introduction

Bone is one of the most common sites of metastasis, presenting in up to 75% of patients [1]. Bone metastases can lead to a number of complications that include pain, fatigue, hypercalcemia, pathologic fractures, and cord compression [2]. Pain is the most common presenting side effect, occurring in approximately 70% of patients [3]. Radiation therapy (RT) provides effective palliation in patients presenting with painful bone metastases with few associated side effects. Historically, palliative RT offers significant pain relief in 50–80% of patients [4]. In addition, RT is useful in preventing further complications from bone metastases including fractures, cord compression, and generalized fatigue.

RT is most commonly delivered as external beam RT (EBRT), delivered from a linear accelerator which accelerates electrons to high energies which then interact with a high Z target material to produce therapeutic x-rays known as photons. Photon beams can be then targeted to a tumor target of interest. Most palliative treatment regimens are based on two- (2D) or three-dimensional (3D) planning (Fig. 10.1a). For better conformality, especially in settings of prior radiation to the same area, radiation oncologists can utilize intensity-modulated radiation therapy (IMRT) planning, also referred to as inverse planning. With IMRT, dynamic multi-leaf collimators inside the linear accelerator can modulate beam intensity and conformality during the treatment and allows for more targeted treatment. A wide range of palliative RT dose fractionation schedules exists, which will be discussed in this chapter. These include single-fraction and multiple-fraction regimens, typically including 8 Gy in a single fraction, 20 Gy in five fractions, 24 Gy in six fractions, and 30 Gy in ten fractions. All four dose regimens are part of the current

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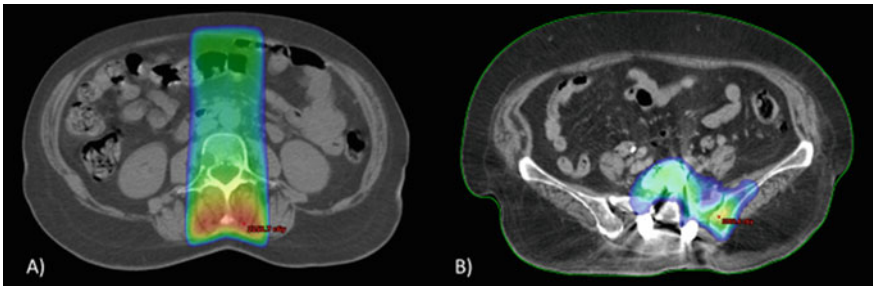

Fig. 10.1 Conventionally fractionated radiation therapy to a painful lumbar spine (L3) metastasis from non-small cell lung cancer, treated to 20 Gy in five fractions (isodose line represents 95% coverage) (**a**) and a second patient with newly diagnosed oligometastatic renal cell carcinoma following surgical debulking and stabilization of the lumbar spine (L5) followed by postoperative stereotactic body radiation therapy, 27 Gy in three fractions (isodose line represents 100% coverage) (**b**)

guideline recommendations from the American Society for Radiation Oncology (ASTRO) [5]. Furthermore, in the setting of reirradiation or radioresistant tumors, stereotactic body RT (SBRT) may be employed (Fig. 10.1b). SBRT includes higher doses in fewer treatments and has demonstrated excellent local control rates both in the definitive and metastatic setting [6–8].

10.2 Radiation Treatment Regimens

Current ASTRO guidelines support the use of several treatment regimens including 30 Gy in ten fractions, 24 Gy in six fractions, 20 Gy in five fractions, or 8 Gy in a single treatment [5]. Fractionated RT regimens are associated with an 8% need for repeat treatment due to recurrent pain versus up to 20% in patients undergoing a single treatment of 8 Gy. While the single course of RT may require a higher rate of repeat treatment, the current data demonstrate similar overall pain relief, making single-fraction palliative radiation a good option for patient and caregiver convenience. Table 10.1 demonstrates the results from current prospective randomized trials evaluating single- versus multi-fraction RT regimens.

A meta-analysis of dose fractionation RT trials for palliative bone metastases including randomized trials demonstrated no significant difference in pain relief between single- versus multi-fraction RT for bone metastases [20]. Reirradiation rates as expected were greater in lower dose, single-fraction arms. There was no dose–response relationship in patients who experienced a complete pain response when comparing 8 Gy in a single fraction to 20 Gy in five fractions or 30 Gy in ten fractions.

Table 10.1 Prospective randomized studies comparing single-fraction versus multi-fraction radiation therapy for bone metastases

Study	Number of patients	Fractionation	Overall pain relief (%)	Repeat treatment rate (%)
Hoskin et al. [9]	270	4 Gy/1 Fx 8 Gy/1 Fx	44 69	20 9
Niewald et al. [10]	100	20 Gy/5 Fx 30 Gy/15 Fx	68 83	1 1
Jeremic et al. [11]	327	4 Gy/1 Fx 6 Gy/1 Fx 8 Gy/1 Fx	59 73 78	42 44 38
Nielsen et al. [12]	241	8 Gy/1 Fx 20 Gy/4 Fx	62 71	21 12
Bone Pain Trial Working Party [13]	775	8 Gy/1 Fx 20 Gy/5 Fx or 30 Gy/10 Fx	78 78	23 10
Steenland et al. [14]	1171	8 Gy/1 Fx 24 Gy/6 Fx	72 69	25 7
Roos et al. [15]	272	8 Gy/1 Fx 20 Gy/5 Fx	53 61	29 24
Hartsell et al. [16]	898	8 Gy/1 Fx 30 Gy/10 Fx	75 86	28 2
Kaasa et al. [17]	376	8 Gy/1 Fx 30 Gy/10 Fx	Equal Equal	15 4
Foro et al. [18]	160	8 Gy/1 Fx 30 Gy/10 Fx	75 86	28 2
Sande et al. (2009) [19]	188	8 Gy/1 Fx 30 Gy/10 Fx	* *	27 5

Abbreviations: Fx = fractions (treatments), Equal = study reports equivalent outcomes between arms, * Data reported previously in earlier study by Kaasa et al. [17]

There are multiple systemic reviews published comparing outcomes between single-fraction and multi-fraction radiation regimens for bone metastases. Chow et al [4] reviewed 16 randomized trials of single- versus multi-fraction conventional RT and found no overall differences in complete response rates from pain; retreatment was 2.5 times higher in patients undergoing single-fraction RT. Acute toxicities were also not different between the treatment arms. Another comprehensive review of multi-fraction conventional RT for painful bone metastases found no differences in local control, pain control, or overall toxicity between 20 Gy in five fractions and 30 Gy in ten fractions, suggesting both regimens equally efficacious in cases where single-fraction treatment is not indicated [21].

Despite randomized data, reviews, and published meta-analyses, the use of single fractionation for palliative bone metastases overall continues to be underutilized. In a National Cancer Database study evaluating patterns of fractionation usage for bone metastases throughout the United States, authors found the use of 8 Gy in a single fraction to be extremely underutilized with only 5% of the

25,000 patients included in the study receiving single-fraction treatment [22]. Worldwide, similar trends in utilization are apparent, with usage of single fractionation varying from 3 up to 75%, with single-fraction RT being utilized the least in the United States [23].

10.3 Assessment of Bone Metastases and Multidisciplinary Care

The neurologic, oncologic, mechanical, and systemic (NOMS) decision framework is one tool used in the multidisciplinary management of spinal metastases [24]. The NOMS framework includes minimally invasive and open surgery, in addition to SBRT and conventionally fractionated EBRT. The neurologic component assesses the presence or absence of myelopathy and radiculopathy. For example, patients with cord compression should be considered for rapid decompression first followed by RT, rather than upfront RT. The Bilsky score [25] which measures the extent of epidural disease is also utilized in this assessment. The oncologic component is defined by whether the tumor is radiosensitive or radioresistant or previously radiated. In general, tumors found to be more radiosensitive include breast, prostate, lymphoma, seminoma, and myelomas. Radioresistant histologies include renal cell carcinoma, melanomas, and those of gastrointestinal origin. For those presenting with radioresistant histologies, especially in those with favorable prognosis and well-controlled systemic disease, consideration for SBRT should be given. Additionally, the oncologic category includes spinal tumors receiving prior RT given the necessity for more conformal RT with ablative dosing that can be offered from SBRT over conventional EBRT. The third component of the NOMS framework includes mechanical stability. Unstable vertebral metastases at risk for further compression fracture may benefit either from minimally invasive approaches including vertebral body augmentation with kyphoplasty, for example, placement of pedicle screws and rods or larger, open surgeries to place hardware. The last factor of the NOMS framework includes systemic disease. Patients with oligometastatic disease, for example, have far better prognosis than patients with multiple metastases who have already progressed on multiple lines of systemic therapies, suggesting SBRT for the former cohort and palliative RT for the latter group where prognosis is limited (<6 months).

The Metastatic Spine Disease Multidisciplinary Working Group which consists of medical oncologists, radiation oncologists, surgeons, and interventional radiologists from multiple comprehensive cancer centers has also published their recommendation [26]. The guidelines provided by this working group are separated into five main categories: asymptomatic spinal metastases, uncomplicated painful spinal metastases, stable pathologic vertebral compression fractures, unstable pathologic vertebral compression fractures, and metastatic epidural spinal compression. Treatment recommendation consists of single modality or combined

modality therapies which include the following: observation, EBRT, SBRT, ablation, vertebral augmentation, and surgery.

Another useful tool for clinicians who need to assess patients' life expectancy is the TEACHH model [27]. In a combined study of patients treated with palliative-intent RT at Brigham and Women's Hospital and Dana-Farber Cancer Institute, patient and disease characteristics were evaluated to develop a life expectancy prediction model. Under multivariate analysis, six factors represented by the acronym TEACHH were found to be significant predictors of overall survival in patients undergoing palliative RT. The following variables were found to be significant: type of cancer (T) including breast, prostate, lung, or other, European Cooperative Oncology Group (ECOG) performance status (E) of 0–1, 2, and 3–4, age (A) including < 60 years versus ≥ 60 years, prior palliative chemotherapy (C) (0–2 versus > 2), prior hospitalization within the last 3 months (H), and hepatic metastases (H).

10.4 Stereotactic Body Radiotherapy (SBRT) for Spinal Metastases

SBRT offers ablative doses of RT delivered over a few treatments (Fig. 10.1b). It has a steep dose gradient allowing minimal dose spill off to adjacent structures including the spinal cord. With daily image-guided RT (IGRT) using cone-beam computerized tomography (CBCT), SBRT treatment plans can be very conformal allowing for improved sparing of critical structures and allowing for ablative doses of RT leading to higher rates of local tumor control, generally above 80% at 5-year follow-up [28]. Durable local control in bone metastases especially involving the spine has become more critical as patients with metastatic disease are living longer due to improved systemic therapies.

Radiobiologically, the higher dose per fraction with SBRT-based treatments has been shown to provide improved local control over standard fractionation. As the survival and proliferation of tumor cells are directly dependent on the blood supply, SBRT has been shown to have a direct effect on tumor vasculature. Hypoxia can increase the expression of vascular endothelial growth factors which are associated with higher-grade tumors and metastatic disease [29]. High-dose RT with 10 Gy or higher in a single fraction has been shown to cause severe vascular damage in human tumor xenografts or animal tumors [30, 31]. Additionally, the vascular injury and ensuing chaotic intra-tumoral environment (hypoxic, acidic, and deprived of nutrients) caused by high-dose fraction SBRT may significantly hinder the repair of RT damage [32].

There may be several roles for SBRT in palliative bone metastases. One function is in the setting of reirradiation following progression after a prior treatment with conventionally fractionated RT. This is discussed in the next section. Outside of reirradiation, other situations that may support the role for more aggressive local palliation with SBRT include patients with spinal metastases with limited cord

compromise (Bilsky criteria grade 0-1b), those with radioresistant tumors (renal cell carcinoma, melanoma, gastrointestinal malignancies), patients with limited metastatic disease burden (oligometastatic), and those with more favorable prognosis (>6 months) [33]. The term "oligometastases" [34, 35] refers to an intermediate stage of metastases where the number and site of metastatic disease are limited, and potential local forms of treatment including surgery, radiation, and ablation could be used for curative intent. The rationale for adding local ablative therapies in certain metastatic patient who otherwise has well-controlled systemic disease is that many can progress at sites of increased tumor burden including bony sites such as the spine. There are multiple ongoing national trials evaluating the role for local ablative therapies in oligometastatic disease. The NRG-BR002 trial includes breast cancer patients with either a) four or fewer sites of metastases if in the peripheral lung, bone or spine or b) two or fewer metastases if one involves the liver, central lung, or lymph node/adrenal gland, and compares standard of care systemic therapy with or without local therapy with either SBRT or surgical ablation to oligometastatic sites of disease [36]. A similar NRG study (NRG-LU002) is being performed in non-small cell lung cancer (NSCLC) where patients who have three or less metastatic sites (excluding the primary) and have stable disease after four cycles of first-line systemic therapy get randomized to maintenance systemic therapy alone versus maintenance systemic therapy with the addition of SBRT to all sites of metastatic disease [37]. A recently published multicenter, randomized controlled phase 2 trial by Gomez et al [38] evaluating NSCLC with oligometastatic disease with three or fewer metastatic lesions after first-line systemic therapy in patients with a ECOG performance status $\leq$ 2, found consolidative SBRT to metastatic sites improved progression-free survival when compared to the maintenance alone arm. Data from Gomez et al [38] are encouraging, and results from the ongoing NRG studies will be important in guiding therapy for oligometastatic patients.

10.5 Reirradiation for Bone Metastases

While there are no defined criteria as to when to consider repeat RT treatment for peripheral bone metastases, there are multiple studies demonstrating both safety and efficacy of reirradiation, and it should be considered an option in patients with recurrent or persistent pain depending on the dose of their prior RT treatment. In the Dutch Bone Metastasis randomized controlled trial comparing single-fraction to multiple-fraction radiation in painful bone metastases, they found that 24% compared to 6% of single- versus multiple-fraction treatments required retreatment [14]. Van der Linden [39] further evaluated this same cohort of patients and demonstrated reirradiation to be safe and overall effective in 63% of retreated patients. Specifically for patients who received upfront single-fraction radiation, reirradiation improved response to pain in 75% of patients.

In regard to reirradiation for spinal metastases, ASTRO guidelines suggest that they can be successfully reirradiated, but care must be taken in accounting for total dose to organs at risk, such as the spinal cord [5]. For these cases, especially when there is concern for total spinal cord dose, estimating the biologic effective dose (BED) is recommended to reduce the risk of radiation-induced myelopathy. There are now multiple studies demonstrating both safety and efficacy of palliative reirradiation for painful spinal metastases with pain relief ranging from 50–87% [39–42]. When there is concern for potential myelopathy due to a prior RT treatment, more conformal techniques such as IMRT can be utilized to reduce dose to organs at risk including the spinal cord.

SBRT is another option allowing delivery of high dose RT to spinal metastases with a steep dose fall off sparing critical structures including the spinal cord. There are multiple retrospective single-institution studies demonstrating the safety and efficacy of SBRT in the reirradiation setting for spinal metastases [43, 44]. Sahgal et al [43] performed a retrospective review of 39 patients with 60 spinal or paraspinal metastases treated with SBRT; 37 out of the 60 tumors received prior RT. The median total dose of SBRT was 24 Gy in three fractions. One- and two-year progression-free probabilities were 85 and 69%, respectively. For the salvage group (31 of the 37 patients who were reirradiated due to image-based tumor progression), the one-year progression-free probability was 96%. There was no RT-induced myelopathy or radiculopathy reported. Mahadevan et al [44] performed a similar study of reirradiation with SBRT for 60 patients (81 spinal lesions) who had radiologic progression with epidural involvement. RT dose was 24 Gy in three fractions for tumors that did not involve the spinal cord and 25 to 30 Gy in five fractions for tumors abutting the spinal cord. They found 93% of patients had stable to improved disease with only 7% experiencing disease progression; 65% of patients experienced pain relief and no myelopathy or radiculopathy were reported. Perhaps the largest series evaluating reirradiation with SBRT to spinal metastases is from the University of Pittsburgh [45]. The study included 500 lesions followed prospectively; 69% of patients included had prior conventional EBRT and underwent retreatment with SBRT. Local control rates were as high as 88%, and long-term pain control was 86%. The only prospective study evaluating the role of SBRT in reirradiation for spinal metastases is from MD Anderson [46]. There were 61 patients included, all of whom underwent single-fraction SBRT to previously radiated spinal metastases. The 18-month local control rate was 88%, and two patients experienced adverse events (grade $\geq$ 3) including hemicord syndrome in one patient and radiculopathy in the other, resulting in right food drop with associated numbness and pain.

Spine SBRT offers tumoricidal doses of RT that is highly conformal. Due to the higher dose per fraction, radiation oncology facilities offering this treatment should have an experienced team with the appropriate technology and immobilization devices to properly deliver treatment.

10.6 Quality of Life Outcomes Following Palliative Radiation

There are multiple studies evaluating quality of life (QOL) outcomes following palliative RT for painful bone metastases, which not only account for pain relief, but additionally evaluate mechanical functionality following treatment in addition to both acute and late toxicity from RT. Perhaps one of the oldest studies evaluating QOL outcomes after RT for palliative bone metastases published in 1977 included 158 patients in which the Karnofsky performance status (KPS) was utilized to measure QOL [47]. QOL was defined as good if patients had a KPS of 70–100% (able to care for personal needs). The study demonstrated that 73% of patients experienced pain relief and of those surviving more than 3 months, 60% maintained a good quality of life and were able to maintain activities of daily living (ADLs). McDonald et al [48] conducted a review which included eighteen articles, seventeen of which included QOL data collected prospectively. The most common tool used was the Brief Pain Inventory (BPI); the six studies which used BPI showed improvement in functional interference at one month post-RT. Additional assessment tools including the Edmonton Symptom Assessment Scale (ESAS) and the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires support the role for palliative RT in stabilizing or improving pain and function post-treatment.

10.7 Utilization of Palliative Radiation in the Preventative Setting

While the primary utilization of palliative RT is to improve pain and QOL in patients with metastatic disease, RT can also be potentially beneficial in asymptomatic patients who present with metastatic disease to weight bearing bones including the femur or who have vertebral body metastases at risk for compression fractures. Fractures most commonly occur in the upper and lower extremities, in addition to the vertebrae of the spine. It can be very painful and debilitating, making patients immobile and at risk for developing life-threatening events such as deep venous thrombosis (DVT) and pulmonary embolisms (PE). Patients presenting with impending fractures of the femur or humerus should be considered for surgical stabilization if at high risk or RT alone for those at lower risk for fracture. For those undergoing surgical stabilization, RT is often given after. Mirels criteria [49] is one tool that can be utilized to assess risk of impending pathologic fractures in long bones. For patients with vertebral body metastases, a Spinal Instability Neoplastic Score (SINS) [50] was developed to assess risk for potential spinal compression fractures. These patients should also be on bisphosphonates.

10.8 Toxicity from Palliative Radiation

Overall, palliative RT can be advantageous both due to effective pain relief and limited side effects of treatment. As discussed earlier in this chapter, RT can be repeated at the same site up to the maximum RT dose tolerability of adjacent organs at risk, which typically include the spinal cord, esophagus, and bowel. It is also noninvasive and can provide effective pain relief without major breaks in systemic treatment, which can occur in invasive procedures including surgery. RT-induced side effects typically include fatigue, inflammation to the bowel causing loose stool or diarrhea, and a pain flare which is a temporary increase in bone pain occurring after RT treatment. These side effects are acute and resolve after treatment is complete. Long-term side effects are typically very rare and include wound healing complications (if after surgery), osteoradionecrosis (extremely rare with palliative doses), risk of fractures, and injury to the bone marrow which typically occurs in the setting of patients who are already at high risk for bone marrow toxicity due to prior systemic therapies or additional therapies such as beta-emitters [51].

Pain flares can be a common side effect following RT treatment. Incidence of pain flare can be as high as 40% with EBRT and 70% with SBRT [52]. In a large, double-blind randomized placebo-controlled phase 3 trial, 298 patients treated with 8 Gy in a single fraction to painful bone metastases were randomized to receive dexamethasone or placebo given before the start of RT and 4 days following the completion of RT. The results demonstrated a reduction of pain flares from 35% in the placebo group to 26% in those receiving dexamethasone.

10.9 Future Directions

With improvements in systemic therapies, local ablative therapies will become increasingly important. While some tumors may have a durable response with single-modality therapy, larger and more radioresistant tumors may benefit more from combined modality therapy. Several studies have demonstrated improved efficacy with no major differences in toxicity when combining RT with radiofrequency ablation (RFA) for example [53, 54]. From a RT standpoint, improved treatment modalities such as SBRT allow for higher ablative doses with increased conformality, reducing doses to nearby organs at risk. Combining SBRT with systemic therapy including immunotherapy is an active area of ongoing research, to assess both efficacy and safety. Early studies suggest a synergistic role between SBRT and immunotherapy, which appears promising [55].

Management of painful bone metastases as discussed can often be complex, requiring multimodality care. In general, a multidisciplinary approach is needed with input by various specialties including radiation, medical oncology, surgery, interventional radiology, and palliative care, to provide the best treatment for these patients.

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Ablation Techniques in Cancer Pain

11

Jonathan Kessler

Painful bone metastases are a frequently encountered problem in oncology practice. The skeletal system is the third most common site of metastatic disease and up to 85% of patients with breast, prostate, and lung cancer may develop bone metastases during the course of their disease [1, 2]. Unfortunately, a majority of patients with bone metastases will develop symptoms including pain, instability, and potential fracture, all of which significantly contribute to morbidity and decreased quality of life [2–4]. While new treatments for metastatic cancer have improved overall patient outcomes and increased survival, this has led to a longer duration of disease and higher prevalence of metastatic bone related symptoms [4]. Therefore, it is imperative that the oncology community develop new methods for treating these patients.

Cancer cells may spread to the bone via vascular or lymphatic pathways or directly extend into bone from adjacent sites of disease in the surrounding organs or soft tissues. Once the cells establish themselves within a bone, they may secrete a variety of factors that stimulate bone resorption and remodeling [5]. The changes may result in structural damage, periosteal irritation, or nerve compression, all of which may lead to severe pain [3, 6]. Additionally, the tumor cells may produce a variety of cytokines and tumor-derived factors that may sensitize nerves and potentiate painful stimuli [7–9]. Local tumor control of osseous metastases can arrest this process by destroying the inciting cancer cells. Furthermore, local tumor control can prevent secondary complications of bone metastases, such as nerve compression or pathologic fracture, which may also cause significant pain and disability.

Image guided tumor ablation refers to a variety of technologies that utilize medical imaging to focally target and destroy areas of tumor involvement. Tumor

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ablation has become a standard treatment for a variety of primary and metastatic tumors. It provides high rates of local tumor control and may be curative in early stage tumors arising from sites such as the lung, liver, and kidney [10–12]. Additionally, image guided tumor ablation improves patient outcomes and effectively controls several types of metastatic tumors at a variety of locations throughout the body [13–16]. However, ablation of musculoskeletal metastases offers a unique challenge. In this situation, in addition to providing local tumor control, ablation must also achieve local pain control and symptom relief. Therefore, several unique issues must be considered when performing ablation of musculoskeletal metastases.

11.1 Pre-procedure Evaluation

Focal pain from an osseous metastasis may be effectively managed with a variety of techniques including analgesics, radiation therapy, systemic chemotherapy, and surgical intervention. Therefore, it is imperative that patients are triaged effectively and appropriate patients are selected for ablation. Furthermore, some patients may benefit from combining these therapies, and methods for sequencing the various treatments must be considered. These goals are best achieved through a collaborative, multidisciplinary team approach.

When evaluating a patient for ablation, the physician must first perform a comprehensive history and physical examination. The location, duration, and character of the patient's pain are key elements to assess. Patients with multifocal bone metastases or significant organ involvement may have multiple sites of disease contributing to their symptoms. In such cases, focal treatment of a specific lesion may not significantly impact a patient's overall pain assessment [17]. Furthermore, patients with radiculopathy or signs of neuropathic pain may also have lesions already involving major nerves, which may preclude safe treatment with ablation. Additionally, some authors have recommended restricting ablation to cases where patients have moderate or severe pain only, as lower levels of pain may be difficult to completely eliminate [18–20]. However, occasionally, a patient's pain may be relatively well controlled with analgesics, but certain drug side effects, such as constipation and somnolence, may contribute to a poor quality of life. In such instances, it may still be appropriate to offer local tumor ablation.

On physical examination, the ideal candidate for tumor ablation will have pain that clearly localizes to the site of disease seen on imaging. Poor correlation between the imaging findings and the clinical exam should prompt investigation for an alternative source of the patient's symptoms. Patients should also be evaluated to determine the appropriate method of anesthesia for the procedure. Percutaneous ablation may be performed safely with either conscious sedation or general anesthesia [17, 18]. Occasionally, local anesthesia alone is appropriate in compliant patients [21, 22]. The method of anesthesia should aim to optimize both patient and physician comfort. Appropriate candidates for conscious sedation should be able to

lay still comfortably with appropriate analgesia and follow instructions should breath holding be necessary for probe placement. The physician should also take into account the patient's current opioid use when selecting a method of anesthesia. Patients using high doses of opioids have typically developed a higher level of tolerance and may be difficult to adequately sedate with standard opioid and benzodiazepine medications. There are other situations, however, when conscious sedation may be preferred over deeper levels of anesthesia. For example, when performing ablation near critical nerves, a lower level of sedation allows the patient to report new neuropathic symptoms during the ablation, potentially alerting the physician earlier to unintentional nerve ablation and preventing permanent nerve injury.

After the clinical examination has been performed, the patient's imaging must be reviewed and scrutinized for several key features. Depending on the location of the lesion, either CT or MRI may be performed to characterize the suspected lesion. CT can be extremely useful in many patients as it is readily accessible, provides excellent osseous anatomic detail, and can be performed safely in patients with metallic implants. Additionally, CT is the most common imaging modality used for intra-procedural lesion targeting, and obtaining a baseline CT can aid with pre-operative planning. On the other hand, MRI provides superior soft tissue detail compared with CT. It may better define the tumor margin and marrow extension. It also better delineates the adjacent nerves and is crucial when planning ablation near significant neural structures. Therefore, in many patients, these modalities are complementary and both may be necessary to fully evaluate the lesion [23].

Regardless of the modality chosen, several factors should be evaluated on the patient's imaging. The extent of the tumor and any adjacent critical structures must be assessed. Local cure of metastatic lesions is possible when the tumor can be completely encompassed within an ablation zone [24]. Therefore, to the extent possible, 5–10 mm of margin should be targeted for ablation to ensure adequate microscopic tumor destruction [25]. However, achieving this may be difficult if the tumor abuts critical structures such as major motor or sensory nerves and bowel. If these structures cannot be adequately displaced, then the ablation should target the bone tumor interface, as this is frequently the primary source of pain and effective palliation may be achieved even without complete tumor ablation [20, 26].

The extent of bone destruction or sclerosis should be assessed on pre-procedure imaging. Tumor ablation of lytic bone lesions may further weaken the bone and potentially increase the risk of pathologic fracture, especially when treating lesions in weight bearing areas. On the other hand, osteosclerotic lesions may be difficult to access with standard devices, and treating these lesions may require alternative means of bone access, including large gauge biopsy devices or mechanical bone drills.

The physician should also assess the lesion to ensure a safe needle trajectory is available to target the lesion. If a safe trajectory is not immediately visible, alternative patient positioning, CT gantry tilting, or advanced maneuvers such as hydrodissection may be required. Finally, the planned zone of ablation should be evaluated for any adjacent hardware, which may be present in lesions previously

stabilized by surgical intervention. Certain metallic implants may interfere with radiofrequency current, a commonly used ablation modality, and in such instances, alternative ablation modalities may be required.

11.2 Ablation Technologies

11.2.1 Radiofrequency Ablation

Radiofrequency ablation (RFA) is a method of heat-based thermal ablation. In RFA, a probe is placed within a volume of tissue and used to generate a rapid alternating electrical current. As the current travels through the tissue, local frictional agitation generates heat around the RF probe, resulting in a rise in tissue temperature. When temperatures reach a critical threshold, cells undergo coagulative necrosis and cell death [27]. This technology has been utilized successfully in a variety of tissue types and produces reliable and predictable ablation zones [28]. Two categories of RFA probes exist, monopolar, and bipolar. Monopolar RFA generates energy at the tip of the radiofrequency probe. The electrical density is highest immediately around the probe, but dissipates rapidly with increasing distance from the probe, resulting in focal temperature increases. Temperatures are therefore highest immediately surrounding the RF probe but expand from the probe by means of thermal conduction. The current is ultimately dispersed through grounding pads placed on the patient's legs, thereby completing the electrical circuit [27, 29, 30]. This method has been proven highly clinically effective and comes in a variety of commercially available platforms [28]. Bipolar radiofrequency ablation utilizes two electrodes placed within the tissue. One point generates energy, while the second electrode, which may be within the same RF probe or a second probe, completes the electrical circuit. This configuration creates a defined area of electrical density and reduces the reliance on thermal conduction. It can therefore produce faster and more focal ablation zones. However, bipolar RFA may require more precise electrode positioning to ensure uniform tissue destruction and can be more susceptible to local alterations in tissue conductivity [31–33].

Despite these limitations, RFA has demonstrated efficacy in the treatment of a variety of painful bone disorders and is a viable first line treatment option for certain primary bone lesions [37–40]. Several clinical studies have also demonstrated that it effectively reduces the pain from osseous metastatic disease, reduces opioid use, and provides durable symptom reduction. Additionally, RFA has been shown to provide pain relief in patients who have failed other focal therapies, such as external beam radiotherapy, and may be effectively repeated in cases of recurrent pain after initial successful ablation [17, 41, 42]. Additionally, in cases where the structural integrity of the bone is compromised, RFA may be effectively combined with percutaneous cement injection to stabilize the bone and help prevent future fracture [43–45].

When employing RFA in the treatment of osseous lesions, practitioners need to be aware of several technical limitations. As described above, RFA relies heavily on both electrical and thermal conduction. Therefore, variations in tissue characteristics, such as tissue water content and blood flow, can greatly impact radiofrequency ablation zones [34, 35]. This may be particularly important in bone, due to its inherently low-electrical conductivity. Additionally, vascular soft tissue lesions within bone may cause local cooling effects that can limit thermal conduction. Both of these factors may result in less predictable and effective ablation zones [36].

11.2.2 Microwave Ablation

Microwave ablation (MWA), similar to RFA, causes tissue destruction by targeted heating of tissue resulting in coagulative necrosis and cell death. However, the mechanism of tissue heating with microwave ablation is unique and offers several potential clinical benefits over other forms of heat based ablation [46]. Microwave spectrum energy causes local tissue heating by means of frictional energy generated from water molecule oscillation. Due to this, MWA does not rely on electrical conductivity and is therefore much less susceptible to local tissue characteristics. Furthermore, MWA relies primarily on active tissue heating, rather than tissue conduction, to produce cellular death. This can allow for more uniform heating, higher temperatures, and larger ablation zones [21, 47]. Additionally, unlike RFA, where multiple applicators may cause electrical interference, multiple MW probes may be combined to produce larger confluent ablation zones [48–50].

The advantages of MWA may be particularly useful in certain types of metastatic bone lesions. Given its ability to generate large ablation zones, MWA may be well suited to treat larger lesions, where multiple overlapping RF ablation zones would be needed [47, 51]. Additionally, all hyperthermic ablations may be attenuated by local tissue cooling caused by medium and large sized blood vessels within the ablation zone [35]. MWA, due both to its ability to achieve higher temperatures and its decreased reliance on thermal conduction, can often overcome these cooling zones and achieve adequate ablative temperatures surrounding larger blood vessels [47, 52]. Blastic osseous lesions also present a challenge for RFA. Sclerotic bone is a poor electrical conductor and high areas of electrical impedance within blastic bone lesions may limit the propagation of RF energy and hinder effective ablation. MW energy, on the other hand, propagates through all biologic tissues and can effectively treat both lytic and blastic lesions. Finally, MWA, due in large part to its reliance on active heating, as opposed to tissue conduction, can achieve similar sized ablations in substantially less time than required of other ablative modalities [21, 22, 47, 51].

Despite these potential advantages, careful consideration must be taken prior to MWA. To date, only limited data exists regarding MWA of bone lesions. Several retrospective series have demonstrated comparable efficacy to RFA, with symptom improvement in greater than 90% of patients [22, 51]. However, no prospective

trials have evaluated microwave ablation in comparison with radiofrequency ablation. Furthermore, due to its ability to achieve higher temperatures in shorter amounts of time, there is a greater risk of potential non-target ablation resulting in thermal injuries to surrounding tissues. Additionally, available microwave ablation devices vary greatly in their technical specifications and each device may produce different ablation sizes and shapes depending on the probe choice and generator settings. Practitioners must often rely on experience and preclinical data to decide which probe and settings are best suited to a specific ablation. Given this variability, there is typically a greater learning curve required to achieve comfort with this technology [52].

11.2.3 Cryoablation

In contradistinction to hyperthermic modalities, cryoablation causes cellular death by means of tissue freezing and the creation of intracellular and extracellular ice. In cryoablation, temperatures beyond −40 °C are created surrounding the ablation probe by pumping a gas, typically argon, through the probe to its distal end, where it is allowed to expand rapidly. This expansion causes a rapid decrease in temperature within the probe by means of the Joule–Thomson effect. The low temperature then propagates to the surrounding tissue through thermal conduction [27]. As the cells freeze, cell membranes are damaged. Additionally, the ice causes osmotic changes in the extracellular space that results in cell dehydration. Both of these ultimately contribute to a well-defined area of cell death [53, 54].

Cryoablation has demonstrated efficacy and cost-effectiveness in the treatment of a variety of primary and metastatic tumors [13, 14, 55]. In several studies of musculoskeletal metastases, cryoablation has repeatedly demonstrated the ability to provide local tumor control, durable pain relief and results in significant reduction of adjunctive narcotic use [56–59]. There are several potential advantages of cryoablation for the treatment of musculoskeletal metastases. First, unlike RF and MW ablation, the lethal zone of tissue destruction, or “lethal ice”, are readily visible with conventional imaging modalities, such as CT and ultrasound. On CT, this is seen as an ovoid hypodense zone. This visualization allows more confident prediction of ablation zones and more reliable protection of adjacent critical structures, such as bowel and nerves. Additionally, cryoablation allows the operator to employ multiple probes simultaneously. This allows for both larger ablation zones and the ability to design customized ablation zones by placing the probes in varied and unique configurations that optimize tumor coverage [19]. Furthermore, the hyperthermic methods of ablation have been shown to induce short term irritation of local sensory nerves, which may result in potentially initial, acute worsening of pain [17, 18]. However, this phenomenon appears to be much less common with cryoablation, where both acute and chronic nerve damage appears to be more rare [60, 61]. Consequently, patients undergoing cryoablation may potentially receive more immediate pain relief and require a shorter post-procedure hospitalization (Fig. 11.1). This benefit may also allow ablations to be performed under a lower

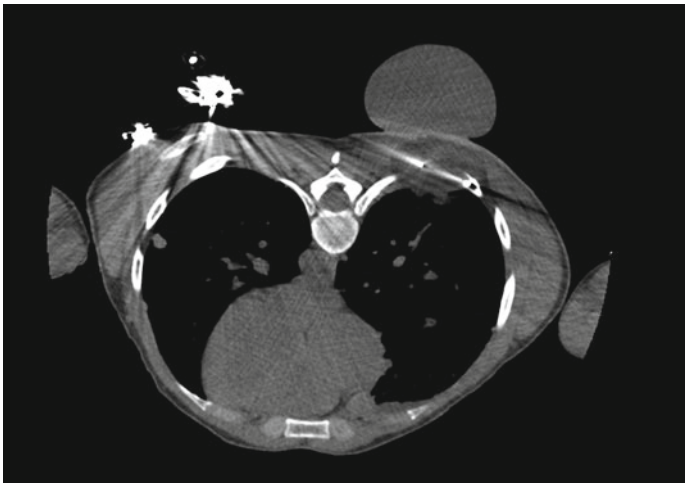

Fig. 11.1 CT-guided cryoablation of painful rib lesion

level of sedation, which can be beneficial in patients with medical comorbidities [19, 62–64].

Nonetheless, there are several limitations to cryoablation. Unlike RF or MW ablation, vessels within the ablation zone are not coagulated by the ablation itself, potentially leading to higher rates of post-procedure bleeding [59]. Additionally, bleeding risk is further complicated by the typically larger needle diameter of the cryoprobes compared to that of either RF or MW [27]. Also, unlike RF or MW ablation, cryoablation requires a two-staged ablation protocol, with two freeze cycles separated by a period of tissue thawing. As a result, ablation times for cryoablation typically exceed two times that of the hyperthermic modalities [19]. Finally, in certain situations it may be preferable to combine ablative therapy with percutaneous cement injection to strengthen the bone and prevent fracture. However, due to the long time required for full thawing of cryoablated tissue, post-ablation cementoplasty may not be feasible at the time of the ablation and a second procedure may be necessary.

11.2.4 High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is a relatively new technology being utilized for bone and soft tissue ablation. This modality has demonstrated great promise, achieving high rates of symptom palliation and local tumor control in treating both primary and metastatic bone and soft tissue tumors [65–68]. Unlike the previously described modes of ablation, HIFU is performed completely non-invasively. In this form of ablation, high-energy ultrasound waves are focused

on a target volume of tissue producing local molecular friction and acoustic cavitation. This in turn causes local heating with temperatures reaching 65–100 °C within 1 s [69–71]. There are several key advantages of HIFU compared with the other forms of ablation. Firstly, unlike the other forms of ablation, HIFU is performed completely non-invasively, thereby eliminating the procedural related risk of bleeding or unintentional organ injury that exists from percutaneous needle placement. Additionally, unlike the previously described forms of ablation, HIFU is primarily performed using MRI guidance. MRI provides superior soft tissue contrast compared to CT or US and can therefore often better delineate and quantify soft tissue tumor extension. Therefore, by utilizing MRI guidance, HIFU allows real time assessment of the lesion during ablation. Additionally, certain MRI systems allow for MR thermometry, which can be used to provide real time monitoring of the ablation zone [72]. Despite these advantages, several issues limit the widespread use of HIFU for the treatment of painful osseous lesions at this time. Since HIFU is performed noninvasively, there is no means of mechanically separating the targeted tumor area from adjacent critical structures. Therefore, if tumors closely abut critical organs or structures, safe treatment may not be possible. Furthermore, organ or bowel motion during treatment may alter the position of the targeted lesion and potentially interfere with safe delivery of the ultrasound waves [66, 72]. Moreover, each application of HIFU can only encompass a small volume of tissue. Therefore, treatment of larger lesions can be cumbersome, requiring sequential treatments of multiple small volumes of tissue, resulting in long ablation and anesthesia times [66, 68, 73].

11.3 Combination Therapy

External beam radiation therapy has traditionally been the first line treatment for most patients with symptomatic osseous metastases, with multiple randomized trials demonstrating safety and efficacy [74, 75]. Despite this, there are several limitations to radiation therapy. Not all tumor types respond equally well to radiation therapy. Certain tumor types, such as renal cell carcinoma, melanoma and sarcomas, have a propensity for radiation resistance and tend to respond poorly to traditional radiation treatment. Additionally, even for tumor types that typically respond to standard therapy, between 20 and 40% of patients may fail to achieve optimal pain relief from palliative external beam radiotherapy [75, 76]. Moreover, even for those that ultimately achieve adequate pain relief, the onset and durability of pain relief is variable. For many patients, the full benefit of radiation therapy may not be achieved for up to 6 weeks following treatment. When adequate pain relief is achieved, it typically wanes over time, with nearly half of patients who initially respond to treatment ultimately developing a painful relapse by 18 weeks [77]. While repeat treatment of sensitive tumors may be feasible in some cases, additional therapy can often be limited by the cumulative radiation toxicity to the

surrounding structures. Finally, for patients to undergo radiation therapy, they must be able to tolerate relatively long periods of immobility, while therapy is delivered. This may be particularly challenging in patients with painful osseous metastases.

Due to these limitations, there may be several instances where combination or adjunctive therapy with percutaneous ablation may offer better outcomes than radiation therapy alone. All tumor types appear equally susceptible to thermal ablative techniques. Therefore, ablation should be considered when the offending lesion histology is typically radiation resistant. Thermal ablative therapies can also be safely performed in prior radiation fields. Therefore, patients with inadequate pain relief or recurrent pain following radiation therapy should be strongly considered for palliative ablation. Finally, the analgesic effect of percutaneous ablation may be immediate or rapidly achieved after treatment. Therefore, for patients with short life expectancies who require rapid pain relief or in patients who may not be able to tolerate radiation therapy due to severe acute pain, pre-treatment ablation may provide adequate pain relief to allow subsequent radiation therapy [73, 78, 79].

There may also be situations where prospective combination therapy may be beneficial. Early data indicate that there may be a synergistic effect of combining thermal ablation with radiation therapy [78]. As previously described, thermal ablation is the most effective in destroying tumor tissue surrounding the ablation probe, where lethal temperatures are most easily achieved. However, when treating larger lesions, the tumor at the margin of the ablation may be more difficult to effectively treat. This is especially true in cases where the tumor is in close proximity to critical structures or abuts large blood vessels. Radiation therapy, on the other hand, relies on tissue oxygen content for its cytotoxic effect. This is typically highest along the perfused tumor margin but is relatively absent within the center of larger, necrotic tumor [80]. Therefore, by combining both therapies one may be able to overcome the shortcomings of both treatments and more effectively treat larger lesions. Additionally, patients treated with radiation therapy to the weight bearing bones, particularly the spine, have an increased risk of post-treatment pathologic fracture, with reported rates of between 15 and 40% [81–83]. Given this risk, there may also be a role for prophylactic ablation and cement augmentation prior to radiation therapy, which may strengthen the bone and help minimize the likelihood of this complication [84].

11.4 Spinal Metastases

The spine is the most common site of osseous metastatic disease, with up to a third of oncology patients having evidence of spinal metastases at the time of death [85, 86]. Given the inherent weight bearing load of the spinal column and adjacent neural structures, maintaining spinal stability and preventing tumor progression are of paramount importance in patients with spinal metastases. These goals may be achieved through a variety of means, but often multimodality treatment is required [85, 87]. Due to its minimally invasive nature and the ability to both treat the

offending lesion as well as stabilize the weakened bone, percutaneous ablation combined with vertebral augmentation offers an excellent treatment option for many patients.

Vertebral augmentation, with either vertebroplasty or kyphoplasty, has been performed safely and effectively for many years to treat spinal compression fractures of various etiologies. Randomized controlled trial data comparing balloon kyphoplasty versus non-surgical management of painful vertebral compression fractures in an oncologic population demonstrated significantly improved pain scores, functional outcomes, and quality of life for patients that underwent kyphoplasty [88]. However, while vertebral augmentation alone may be sufficient to control short term pain, without local tumor control, progressive symptoms are inevitable. By first treating the tumor with percutaneous ablation and then following this with cement augmentation, one may be able to provide more stable and durable symptom control [84]. Similar to lesions elsewhere, complete ablation with adequate margins should be the goal of spinal tumor ablation, and when achieved results in high local control rates [89]. However, even in instances where complete ablation is not feasible, such as cases of bulky tumor causing early neural encroachment, pre-augmentation ablation may be warranted. In such cases, ablation can create a tumor cavity, lowering the risk of exacerbating nerve compression and allowing for greater volume of cement injection and improved bone stabilization.

All thermal ablative techniques have been successfully utilized to treat spinal metastases [90–92]. Similar to ablations elsewhere, the various modalities differ in their relative advantages and disadvantages when treating spinal lesions. RFA has traditionally been utilized in the spine, and several devices have been developed specifically for this purpose. These RF probes incorporate thermocouples within the probe to allow for precise ablation zone creation, minimizing the chance of non-target ablation and nerve injury. Additionally, the probes are designed to withstand the force needed to traverse sclerotic bone and with certain designs may be able to articulate to reach lesions in challenging locations [93, 94]. MWA and cryoablation may also be effectively employed in the spine. However, with MWA, the operator should be cautious when planning the ablation zone. Microwave energy transmission through bone may be difficult to predict and ablation close to nerves can lead to unintended injury. Cryoablation, on the other hand, can be easily monitored with CT and ablation of large lesions in close proximity to adjacent nerves may be comfortably performed. However, when using cryoablation, the treated bone cannot be augmented with cement until the ice from the ablation has completely thawed. When treating large zones, this can take many hours and a separate augmenting procedure may be necessary the following day [95].

The same evaluation and precautions should be followed when treating lesions in the spine as with lesions elsewhere in the skeleton. However, due to both the structural importance of the spinal column and the adjacent neural structures, several additional issues must be addressed prior to ablation. Regardless of the modality chosen, careful neurologic assessment and imaging review must precede any spinal ablation or augmentation. The presence of neurologic abnormalities should alert the physician to carefully reanalyze the imaging, as tumor or bone

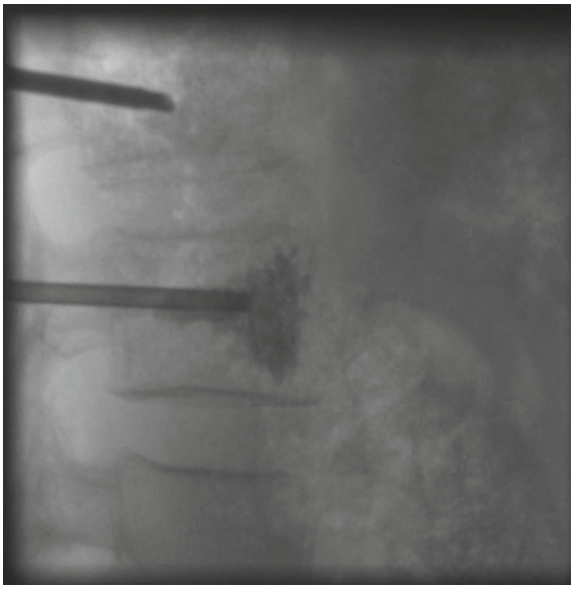

Fig. 11.2 Fluoroscopy image of lumbar 3 radiofrequency ablation (RFA) and vertebroplasty

fragments may already be compressing critical nerves. In such cases, percutaneous treatment may be inadequate and can potentially exacerbate the problem. The imaging should also be analyzed for signs of bone fracture, posterior cortex involvement, and epidural tumor extension. In such cases, augmentation with cement can be unpredictable and may lead to canal compression [96]. Many practitioners also find combination of conventional CT and fluoroscopy to be necessary for spinal augmentation and ablation [97]. High-quality cross-sectional imaging is mandatory prior to ablation to ensure adequate needle placement and a safe margin from the adjacent nerves. However, when augmenting the bone with cement, real time fluoroscopic monitoring is often the easiest method to ensure adequate and safe delivery of cement (Fig. 11.2).

11.5 Protective Techniques

Prior to performing any ablation procedure, one must carefully analyze the target lesion and the planned ablation zone to assess the potential for injury to adjacent structures. In many cases, the ablation of the surrounding tissues is of little clinical consequence and may be necessary to ensure complete tumor eradication. However, in certain situations the tumor may abut critical structures, such as nerves, bowel, or skin, and unintended ablation of these areas can result in serious complications. To help avoid such complications, several techniques have been described to add a margin of safety when performing an ablation near critical organs or tissues. Each of these techniques has its relative merits and specific techniques may be more

suited to specific ablation modalities and locations. Therefore, physicians performing ablation should become familiar with a variety of these techniques.

When utilizing heat or cold based ablative modalities, temperature monitoring of the surrounding area can help minimize the risk for non-target injury. In such cases, thermocouples may be placed between the ablation target and the critical structure to provide real time monitoring of the ablation zone [98]. When temperatures at the thermocouple approach 40 °C in hyperthermic ablation and 10 °C in cryoablation, the ablation should be terminated [99, 100]. However, in cases where no safe margin exists between the intended target and the critical structure, temperature monitoring alone may be insufficient. In such cases, it may be prudent to attempt to displace the critical structure away from the target lesion. This can be accomplished through a variety of techniques, such as injecting saline or carbon dioxide, or interposing an angioplasty balloon between the ablation zone and the critical structure [99, 101, 102]. Similarly, when lesions lie in close proximity to the skin surface, unintentional extension of the ablation into the skin can result in significant tissue damage and chronic wounds. In such cases, many practitioners opt to use cryoablation. As stated above, the superior visualization of the ice allows close monitoring of the ablation zone as it approaches the skin. Additionally, injecting saline into the subcutaneous space to displace the dermal layer or placing a warm glove on the skin surface, may be sufficient to provide adequate protection and mitigate the chance of serious injury [101].

Given the close proximity of many musculoskeletal lesions to critical nerves, a comprehensive knowledge of neuroanatomy is mandatory. However, as tumors enlarge they can distort the typical anatomy. Pre-procedure MRI may therefore be useful to better delineate the proximity and course of any nerves adjacent to the planned ablation zone [103]. When ablation is planned in close proximity to critical nerves, additional precautions may be necessary. Both heat and cold based ablations can result in permanent nerve injury. However, permanent injury is usually preceded by temporary changes in nerve function and conduction. If the patient is conscious for the procedure, the physician should be aware of any increase in patient pain or alterations in motor function that may indicate ablation of nearby nerves. However, in cases where deeper levels of sedation are required, formal nerve monitoring may also be performed. Continuous nerve monitoring with somatosensory or motor evoked potentials can be used to identify early changes in nerve conduction and indicate impending nerve injury [100, 101, 104, 105].

In situations where tumor has compromised the structural integrity of the bone, patients undergoing percutaneous ablation may be at continued high risk for pathologic fracture if nothing is done to support the weakened bone [106]. Several techniques have been developed to attempt to alleviate the risk of fracture and improve the stability of the treated bone. Many practitioners routinely combine ablative therapy with percutaneous cement injection. This is particularly important when treating weight bearing bones such as the spine, femur, and acetabulum where the risk of fracture is high and the bone is most likely to undergo compressive force [20, 107–109]. In situations where the bone is likely to undergo shearing or

torsional forces, cement fixation may be replaced by, or combined with, percutaneous screw fixation to help stabilize the bone following ablation [110].

11.6 Post-procedure Assessment and Patient Follow-up

Regardless of the ablation modality used, with appropriate planning and patient selection, significant complications from musculoskeletal ablation are uncommon [17, 56, 106]. Certain injuries, such as skin burns, may be immediately apparent following the procedure. Often these may be self-limited and safely treated with conservative measures and wound care. If more serious injury is noted, dermatologic or plastic surgery consultation may be warranted. Moreover, certain injuries, such as bowel injury, may present in a delayed manner. Therefore, routine post-operative follow-up is mandatory. New complaints of pain or fever should warrant a thorough assessment.

Immediate pre- and post-procedure neurologic assessment are also mandatory in all patients undergoing musculoskeletal ablation. Any pre-procedure deficit should be documented so that it may be compared to the post-procedure findings. New onset motor and sensory deficits should be considered highly suspicious for nerve injury. Occasionally, mild motor deficits with preserved sensation can occur secondary to local post-ablation inflammation. In such situations, a trial of steroids with close follow-up may be appropriate [18]. However, if more serious injury is suspected, referral to neurology and physical therapy may be necessary.

Patients are typically discharged from the hospital within 24 h of tumor ablation. Depending on the modality used, pain relief may occur immediately following the procedure or may be delayed for several days. Many clinicians will reevaluate patients 1–4 weeks following the procedure to assess the maximum pain relief. Patients should be instructed to continue with their pre-ablation pain regimen. P.R.N medications may be weaned as maximum pain relief is achieved. Low-grade fever, malaise, and nausea may occur following ablation, particularly if large soft tissue masses are treated. The constellation of these symptoms is referred to as "post-ablation syndrome", and are likely related to the acute inflammation following treatment. The symptoms typically resolve in 5–7 days and are usually treated with analgesics, anti-inflammatory medications, and anti-emetics.

Follow-up imaging protocols vary by institution. If one is treating oligometastatic disease, baseline imaging may be performed at one month and every 3–4 months thereafter. In the early post-ablation setting, the anatomic features of the ablation zone may be difficult to differentiate from residual or recurrent tumor. However, normal post-ablation findings will recede over time. If the diagnosis remains uncertain, PET-CT may be beneficial in differentiating post-ablation change from recurrent tumor [111]. Once maximum pain relief has been achieved, new or progressing symptoms should prompt evaluation for progressing tumor.

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Interventional Treatments for Cancer Pain

12

Manisha Trivedi and Jaisha Mathew

12.1 Introduction

Interventional pain management is a subspecialty of medicine devoted to the use of invasive techniques such as joint injections, nerve blocks/or neurolysis, neuromodulation, and epidural and selective nerve blocks to provide diagnosis and treatment of pain syndromes unresponsive to conventional medical management.

The basis of interventional pain practice lays on a profound knowledge of the anatomy and particularly the sensory innervation of different anatomical structures. When assessing patients with cancer pain, the interventionists may reflect on the anatomical structure responsible for the symptoms and the corresponding nerve supplying sensation to that structure.

Cancer and pain are closely associated with clinical entities. Recent reviews suggest a prevalence of pain in 51% of cancer patients regardless of the type and stage. This prevalence increases with the type of tumor (head and neck, lung, breast cancers have higher prevalence) and with higher staging (advanced, metastatic, or terminal) approaching 66% of cases. 20–30% of patients experiencing cancer pain are refractory to opioid therapy while 50% report inadequate pain control and 25% of cancer patients die with pain.

Cancer pain is an encompassing sequela of the cancer itself or can be a complication caused by cancer treatment. Medication management can be inadequate in the treatment of pain in some circumstances, and in others its side effect profile can limit its use [1]. The paradigm for cancer pain treatment has been evolving toward a multimodal treatment rather than a stepwise approach such as the WHO analgesic

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ladder. Chief among a multimodal treatment approach is evidence supporting the early use of interventions instead of only as a "last resort option."

This chapter aims to review available interventional pain techniques indicated in cases of poor response to conventional medical management. A brief explanation of each technique with its peculiarities and scientific evidence, when available, is presented as well as precautions. The latter part of this chapter as well as the next chapter is both dedicated to peripheral nerve blocks, while intrathecal analgesia is covered extensively in Chap. 14. Here, we cover the following topics:

Neuraxial Interventions

- Epidural Steroid Injections
- Sympathetic Blocks

Peripheral Nerve Blocks and Interventions for

- Postmastectomy Pain Syndrome
- Brachial Plexopathy and Brachial Plexus Pathology
- Post-Thoracotomy Pain Syndrome

Spinal Cord Stimulation

Precautions in Cancer Pain Patients Undergoing Interventional Procedures

12.2 Neuraxial Interventions

12.2.1 Epidural Steroid Injections

Epidural analgesia can provide pain relief from intractable cancer pain and is quite efficacious [2, 3]. In cancer pain, catheters can be inserted, tunneled subcutaneously and can be part of an infusion system to help combat intractable pain that is not addressed with oral pain medication. There are many advantages to an epidural infusion system; however, they are also associated with serious complications such as catheter dislocation/obstruction, dural fibrosis, and infection.

There are several types of specific epidural injections depending on indication and location in the spine. We will be discussing several of these techniques and procedures in the next section.

12.2.1.1 Cervical Interlaminar Epidural Steroid Injection

The cervical interlaminar technique is safest at the C7-T1 or T1-T2 as the epidural space is widest at these levels. The anatomy of each individual can vary drastically due to pathologies such as spondylosis, disc herniations and degenerative diseases. Cancer patients may have concerning bone metastasis or epidural involvement. Therefore, it is recommended that MRI be completed prior to interventions of the cervical spine.

Clinical Perspective

There are no specific indications in patient selection for this intervention. Generally, patients who experience radicular-type pain secondary to underlying disease as mentioned above may benefit from cervical epidural steroid injections for short-term analgesia. Other indications may include headache, neck pain, and cervicobrachial pain but little evidence is shown that epidurals may be of long-term benefit.

Clinically Relevant Anatomy and Imaging

Fluoroscopy is crucial in performing successful and safe interventions. A physician must be able to visualize the needle tip that has minimally entered the epidural space.

Contralateral Oblique versus Lateral views

Given the limitations of the lateral view, the contralateral oblique (CLO) view has been advocated for epidural needle placement (Fig. 12.1). It is advocated because it lends to better visualization of the needle tip and provides a reliable radiographic landmark for the location of the posterior epidural space. Gill and colleagues evaluated needle position and visualization at several angles in images obtained by fluoroscopy in patients undergoing cervical and cervico-thoracic epidural steroid injections. They determined the CLO view at 50° and at MRI-measured obliquity provides the most consistent and most posterior position of the needle tip at the point where the epidural space is accessed [4].

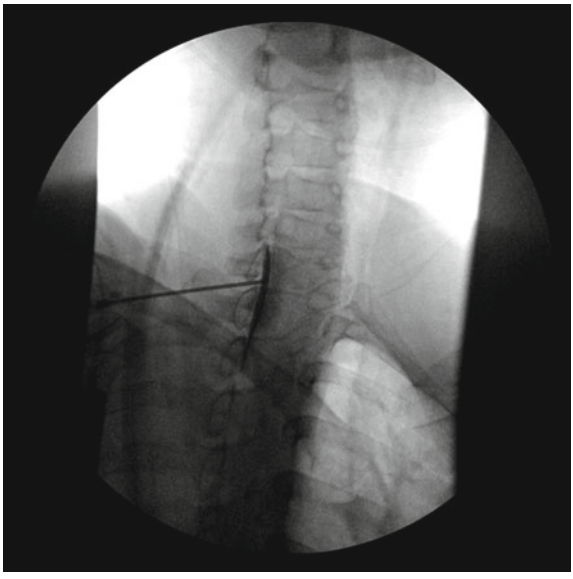

Fig. 12.1 Contralateral oblique view of needle insertion at C7-T1. Figure Courtesy of Jaisha Mathew MD

Complications

Risks of complications are elevated when performing blind technique. The most common being spinal cord injury and epidural hematoma. Other complications include subdural injection, epidural granuloma, dural puncture headache, pneumocephalus, abscess, retinal hemorrhage, and intravascular injection. Gaul and colleagues reviewed cases of meningitis admitted to inpatient units from 1992 to 2000; of the 128 cases in their review, 11 cases had an epidural abscess and 3 had an epidural abscess with meningitis after receiving a steroid spinal injection. Eight of the 14 patients were immunocompromised mainly from diabetes or metastatic cancer.

12.2.1.2 Cervical Transforaminal Epidural Steroid Injection

Cervical Transforaminal Epidural Steroid Injections should only be performed by clinicians with extensive experience and those who are able to understand and can treat rapid onset of life-threatening complications. There is poor evidence to justify proceeding with cervical transforaminal approach; oftentimes the risks do not outweigh the benefits [5].

Clinically Relevant Anatomy

A comprehensive understanding of cervical anatomy, in particular neurovascular structures, is fundamental to safely perform transforaminal epidural steroid injections in the cervical spine. The spinal, radicular medullary, and vertebral arteries are in close proximity to the neuroforamina. The vertebral arteries provide blood supply to the posterior aspect of the brain and brainstem. Additionally, the spinal and radicular medullary arteries cross the neuroforamina to supply the nerve root, and anastomose with the anterior and posterior spinal arteries after penetrating the dura [6].

Complications

Performing cervical transforaminal epidural steroid injections is not without risk. In fact, permanent neurologic complications, though rare, are a serious possibility. The cardinal complication is infarction of the CNS due to intravascular injection. This has been described through multiple case reports where particulate steroids were used. Just like cervical epidurals, inadvertent subdural or subarachnoid injections can also lead to high spinal block. Intra-arterial blocks may lead to seizures.

12.2.1.3 Lumbar Interlaminar Epidural Steroid Injection

Chronic low back pain can be a debilitating pain diagnosis and often coexists with cancer pain from other sources. It has been well-documented to have both socioeconomic impact in addition to a behavioral impact presenting in the general public. The prevalence numbers at any time for patients with low back pain 30 years ago was around 377.7 million, and this has increased in the last few years to 577.0 million people [7]. Cancer pain can exaggerate low back pain or can be the primary cause of low back pain, though the latter is less common unless pathology has directly involved the lumbar spine.

The general consensus is that epidural steroid injections provide short-term improvement of radicular pain associated with disc herniation or spinal stenosis [8].

Clinically Relevant Anatomy and Imaging

Fluoroscopic guided interlaminar access is based on blind technique, so it is imperative that physicians performing interlaminar epidurals perceives resistance of muscles as the needles pass through to ligamentum flavum or develop a "feel" for when the needle engages into the ligamentum flavum [9].

Complications

Complications from interlaminar lumbar epidurals were mostly found in case reports as large cohort studies did not reveal any major complications [10]. Clinically significant complications include chemical meningitis s/p dural puncture/intrathecal steroid administration, visual changes and transient blindness with retinal hemorrhages [11], paraplegia due to unknown mechanism, soft tissue abscess with osteomyelitis, and epidural hematoma.

12.2.1.4 Lumbar Transforaminal Epidural Steroid Injection

Lumbar Transforaminal Epidural Steroid Injections have been shown to give the most amount of pain relief when compared to both interlaminar and caudal approaches. Various techniques, such as the posterolateral approach, Kambin technique, and the safe triangle approach, have been proposed to optimize safety and avoid vital structures that, if traversed, may lead to adverse outcomes.

Clinical Perspective

The advantage of using the transforaminal technique is the ability to deliver therapeutic agents as close as possible to the nerve root impingement or cause of radicular symptoms. The main indication for lumbar transforaminal epidural steroid injections is for radicular-type pain originating in the lumbar spine.

Clinically Relevant Anatomy

Knowledge of the osseous and neurovascular anatomy of the neural foramen and block supply is essential. Each spinal nerve divides into a ventral and dorsal ramus outside the foramen. Knowledge of this dural anatomy is important because the risks of inadvertent dural puncture increase if the medial portion of the foramen is encountered [12]. The anterior spinal artery is supplied by the anterior radiculomedullary arteries, and the largest and most caudal is the artery of Adamkiewicz. The artery originates on the left side in about 85% of people and usually arises between T9-L5, most commonly at T9 and less commonly below L2 (23.5%). If injected arterially, ischemia of the spinal cord may result.

Complications

No specific technique is proven to be the safest. Levi et al. conducted a single institution retrospective review of 257 transforaminal epidurals using the Kambin technique. With this technique, it was found to have a 4.7% intradiscal injection rate, a 3.1% intrathecal injection rate, and a 6.6% intravascular injection rate [13].

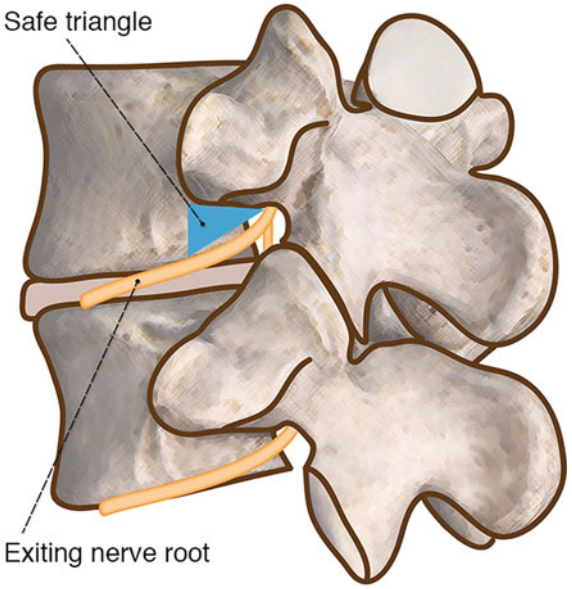

Fig. 12.2 Illustration of two lumbar vertebrae in oblique view. The safe triangle is highlighted in blue. [12] Reproduced from Mandell et al.

The safe triangle approach had a lower intradiscal injection rate; however, the incidence of intravascular injections with the safe triangle approach was 11.2% according to Furman et al. [14]. The included figure highlights the borders of the safe triangle (Fig. 12.2). Another single-institution prospective study showed that vascular injection and intervertebral injections occurred with both techniques [15]. No specific technique has been proven to be safer than the other; however, the safe triangle is a more widely accepted technique by clinicians.

12.2.1.5 Caudal Epidural Steroid Injection

The Caudal Epidural Steroid Injection was first introduced as a blind technique based on landmarks which were given mainly for surgical anesthesia in children. It has gained traction in adults for chronic pain. The inaccuracy of blind technique mainly occurs in adults and can be attributed to anatomic variance.

Clinical Perspective

Caudal Epidurals are commonly utilized to help reduce radicular-type pain. They are of benefit when patients have had previous neurosurgical or orthopedic interventions which may increase difficulty in accessing the interlaminar space.

Fluoroscopy versus Blind Technique

Fluoroscopy is often preferred due to the inaccuracy of blind technique. It has been demonstrated that blind technique is associated with a miss rate of up to 26% [16]. Fluoroscopy guidance has significantly improved the success rate of this block and is considered as the gold standard [17-19]. Ultrasound-guided technique is also an option with significant reduction in VAS scores through fluoroscopy remains gold standard [20].

Clinically Relevant Anatomy

The sacral cornua are vestigial remnants of the 5th sacral vertebra. They are 2 bony prominences at the end of the sacrum. Palpating these bony prominences are essential to locate the sacral hiatus in the blind technique. The sacral hiatus is the opening of the lower sacral vertebra and the caudal termination of the sacral canal. It is covered by skin, subcutaneous fat, and the sacrococcygeal ligament. The dural sac usually terminates at or between S1 and S2. The lower the dural sac termination, the greater risk for inadvertent dural puncture.

12.2.2 Sympathetic Blocks

Pharmacologic sympathetic blockade is used as a diagnostic tool to see whether a pain symptom is sympathetically mediated. Usually, if relief from the block lasts longer than the expected action of local anesthetic, the block may be considered therapeutic. Adding a depot corticosteroid may also prolong the action of pain relief. Once the block is considered effective, chemical neurolysis or ablative modalities may be employed for a long-lasting effect.

12.2.2.1 Sphenopalatine ganglion block

The Sphenopalatine ganglion (SPG) is the most cephalad sympathetic ganglion, and it is one of the largest groups of neurons outside of the cranial cavity. It is mainly a parasympathetic ganglion with a sympathetic and sensory component and is located in the pterygopalatine fossa. It is also known as the pterygopalatine ganglion, nasal ganglion or Meckel's ganglion. It lies posterior to the middle nasal turbinate and the maxillary sinus (Fig. 12.3). The SPG's anterior border is the posterior wall of the maxillary sinus. The superior border is the sphenoid sinus, the medial border is the perpendicular plate, and the posterior border is the medial pterygoid plate. The lateral border is the infratemporal fossa [21].

The Sphenopalatine block is indicated for a variety of facial pain syndromes and headaches. This includes Sphenopalatine neuralgia, trigeminal neuralgia mainly of the second division, cluster headaches, as well as migraine headaches. The evidence for Sphenopalatine blocks for the treatment of cancer pain is limited. There are several focused case series that show efficacy. Prasanna et al. showed efficacy with cancer in the floor of the mouth after repeated SPG blocks [22]. The largest case series was by Varghese et al., who reported 22 cases of successful treatment with 6% phenol, as a neurolytic sphenopalatine ganglion block, for pain caused by advanced head and neck cancer [23].

Technique—Intranasal versus Infrazygomatic Approach

The intranasal approach is indirect and depends on diffusion of local anesthetic across tissue layers. For this approach, the patient should be supine and a cotton tip applicator or catheter is needed. The applicator is soaked with local anesthetic and then advanced into the nostril to the nasopharynx. This is left in place for anywhere

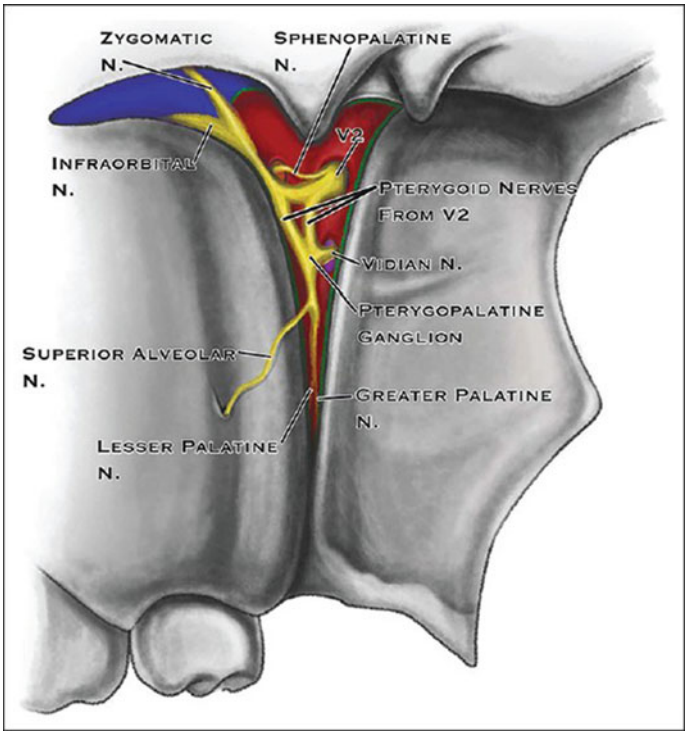

Fig. 12.3 Sphenopalatine ganglion in the pterygopalatine fossa. [24] Reproduced from Khonsary et al.

from 10 to 60 min. The swab does not come into direct contact with the ganglion; however, the local anesthetic infiltrates around it in that position [25].

For the direct infrazygomatic approach, IV access may be necessary. It is generally used as a diagnostic block prior to neurolysis [26]. Blocking the ganglion can cause ipsilateral tearing due to unopposed parasympathetic activity. Infection is possible if sterile technique is compromised or if the nasal mucosa is penetrated at the lateral aspect of the nasal wall. Bleeding and hematoma occur due to needle advancement into maxillary artery and vascular plexus near the ganglion. Damage to the globe can occur if the needle is advanced through the inferior orbital fissure [27-29].

12.2.2.2 Stellate Ganglion block

The stellate ganglion is formed by the fusion of the inferior cervical and first thoracic sympathetic ganglia. Its blockade is usually performed at the level of C6. It is mainly indicated for patients with sympathetically mediated pain of the upper extremities and upper thoracic area including CRPS types I and II or post-radiation neuritis. However, stellate ganglion blockade can also be used for vasospastic

conditions such as Raynaud syndrome and vascular insufficiency/vaso-occlusive disorders or vasculitis, arterial embolism of the face or upper extremities; pain from acute herpes zoster of the upper extremities and neck; post-traumatic stress disorder; acute treatment of electrical storm sustained ventricular tachyarrhythmias and neuropathic pain conditions in cancer pain [30].

Contraindications to the procedure include bleeding diathesis, anticoagulant therapy, patient refusal, sepsis at the site of the injection, and bilateral stellate ganglion block (or performance of stellate ganglion block in the presence of unilateral recurrent laryngeal nerve palsy or unilateral phrenic nerve palsy on the opposite side). Performing bilateral stellate ganglion blocks can cause spread and involve the phrenic nerve or the recurrent laryngeal nerve, leading to respiratory embarrassment and the possibility of obstruction of the airway.

Fluoroscopy versus US technique

Ultrasound-guided technique has gained favor among the pain physician community due to better visualization of important vascular structures during the procedure. It is preferred that IV access and monitoring are applied to the patient prior to the procedure. The final needle position should be posterior to the Carotid artery and superior to the longus colli muscle. Contrast is not necessary in this technique as vascular structures can be directly visualized [31].

Complications

Following the block, an ipsilateral Horner syndrome is anticipated and is actually an indicator of a successful block. Complications of stellate ganglion block can be divided into technical, infectious, and pharmacological. Technical complications are due to issues when performing the block. These can include injury to the brachial plexus, trauma to the trachea and esophagus, injury to the pleura and lung, and bleeding and local hematoma, especially if the patient is receiving anticoagulants. It is imperative that only an appropriately trained physician trained in this technique should complete this. Infectious complications include local abscess, cellulitis, and osteitis of the vertebral body and transverse process. Pharmacological complications are related to the dose, volume, type of local anesthetic, and site of deposition of the solution. This includes hoarseness of voice because of the involvement of recurrent laryngeal nerve or phrenic nerve paralysis, which leads to respiratory concern, especially if there is contralateral dysfunction of the phrenic nerve, or in patients with respiratory dysfunction. Intra-arterial injection into the vertebral artery or the carotid artery can produce a high concentration of local anesthetic agents in the CNS, leading to seizures. Intravenous injection can lead to seizure, but this is unlikely because of the low volume/dose of local anesthetic [32].

12.2.2.3 Celiac Plexus Block

The Celiac Plexus innervates the stomach, duodenum, pancreas, adrenals, and kidneys, biliary system and liver, small intestine, and large intestine until splenic flexure. Pain and nausea associated with malignancies of the midgut and foregut can be blocked with this procedure. Often, this will be followed by a neurolytic block for longer-lasting pain relief [33]. Plexus block is also evidenced to decrease

opioid use for pain in pancreatic cancer patients [34]. Celiac plexus blocks and/or neurolysis may be repeated if symptoms recur [35].

A common indication for this procedure is for the treatment of intra-abdominal cancer pain. It is usually used in pancreatic cancer pain treatment [36]. Phenol or alcohol neurolytic techniques are employed for longer-lasting pain relief. This is usually done under CT or fluoroscopy. In addition, endoscopic approaches can be utilized.

There are many techniques for Celiac Plexus block, including anterior (transaortic) approach, retrocrural approach and CT guided posterior approach (Fig. 12.4). The technique will vary based on physician comfort and equipment availability at their institutions.

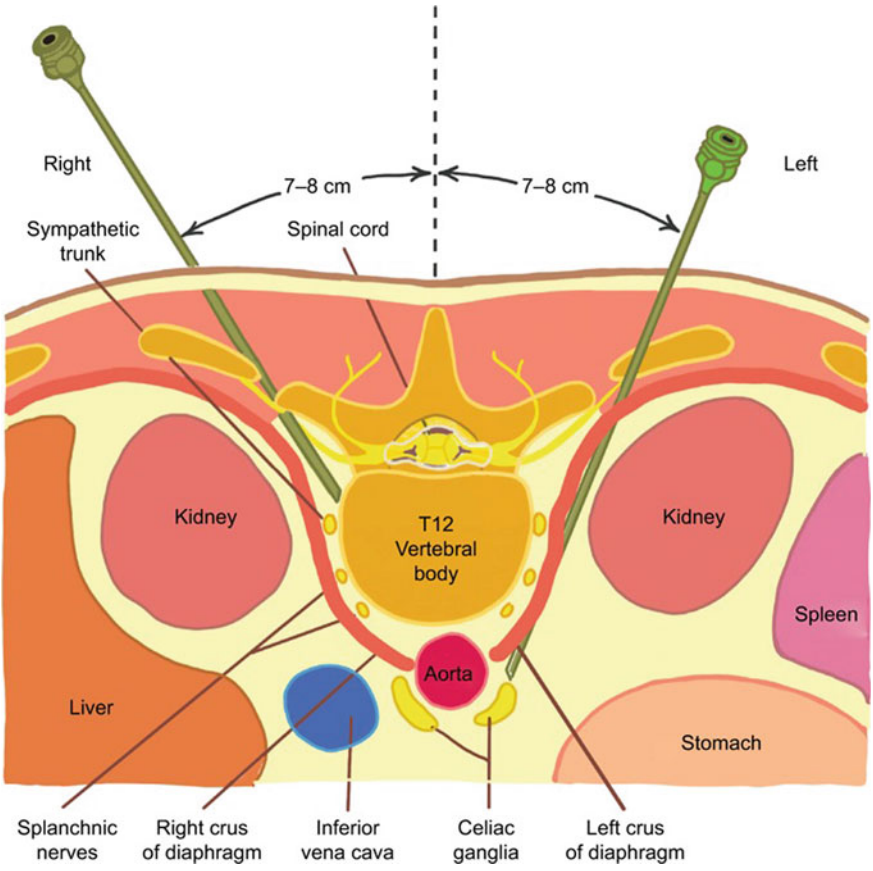

Fig. 12.4 Retrocrural approach of celiac plexus block. [38] Reproduced from Molnar et al.

For the retrocrural fluoroscopic approach, IV access should be obtained prior to performing a Celiac Plexus block. You may increase cardiac preload by infusing crystalloid [37].

Complications

Hypotension is a common complication. This occurs due to vasodilation and pooling of blood in the splanchnic vasculature. Diarrhea is also very common due to unopposed parasympathetic tone. Pneumothorax can occur and is the most common significant complication. The risk of pneumothorax increases with more cephalad needle placement. Other complications include hemorrhage or aortic puncture, or aortic wall dissection. Neurologic complications can occur including paralysis of hip flexors from unintentional lumbar plexus neurolysis in the psoas compartment [39].

12.2.2.4 Lumbar Sympathetic Block

The lumbar sympathetic chain is situated anterior to the L2-L4 vertebra. The sympathetic block is primarily indicated for control of sympathetically mediated pain of the lower extremities such as Complex Regional Pain Syndrome, Post-Herpetic Neuralgia, Phantom Limb Pain, Diabetic Neuropathy, Peripheral Vascular Disease, Groin, and Testicular pain.

Most recently Spiegel et al. found that lumbar sympathetic blockade at L2 or L3 is effective for low back, abdominopelvic, and leg pain related to cancer and cancer treatment. Lumbar sympathetic blockade was 67% effective in the back pain cohort, 82% effective in the abdominopelvic pain cohort, and 75% effective in the leg pain cohort [40].

The Lumbar Sympathetic block is usually diagnostic and can then progress to neurolysis. Neurolysis can be achieved through either radiofrequency ablation or chemical neurolysis using alcohol or phenol.

Complications

Hypotension is the most common side effect. It is recommended patients receive IV access preoperatively and cardiopulmonary monitoring intraoperatively and postoperatively. Temperature increase tends to occur due to vasodilation and increased blood flow. Temperature changes can be indicative of a successful block. Hemorrhage and hematuria can be concerning due to vasculature in the area and inadvertent puncture of the kidney [41].

12.2.2.5 Superior Hypogastric Plexus Block

Intractable pelvic and rectal pain can be addressed using a Superior Hypogastric Plexus (SHP) Block. This plexus innervates the descending, sigmoid colon and proximal rectum and pelvic organs such as the prostate, bladder, uterus, ovaries, and proximal vagina. It lies anterior to the L5 and S1 vertebral bodies. The fibers continue to the inferior hypogastric plexus. Mishra et al. conducted an RCT which reported neurolytic SHP blocks to be superior to oral morphine with respect to pain score reduction, improvement in functional capacity, and global satisfaction score [42].

Indications

Pelvic visceral pain, pelvic cancer pain, chronic non-cancer pelvic pain such as endometriosis, adhesions, interstitial cystitis and irritable bowel syndrome, and refractory penile pain are all indications for Superior Hypogastric Plexus blocks [43].

Technique

The posterior approach parallel to the vertebral bodies using otw needles is most common for SHP blocks; however, the transdiscal approach can be used and requires just one needle placement rather than two.

Complications

The complications include injury to common iliac vessels, pelvic viscera, L5 nerve root, and discitis, all of which are rare and can be avoided with proper attention to technique, preoperative antibiotics, and image guidance [44].

12.2.2.6 Ganglion Impar Bblock

The Ganglion impar is an unpaired structure located at the termination of bilateral lumbosacral sympathetic chains and supplies nociceptive and sympathetic fibers to the rectum, anus, vagina, and vulva. It is also known as the Ganglion of Walther and is the most caudal ganglion of the sympathetic chain [45].

Indication

The ganglion impar block is used to treat malignant vulvar, rectal and anal pain, intractable sacral and perineal pain, and/or coccydynia [46].

Technique

Fluoroscopic technique is preferred for the Ganglion Impar block and is completed in lateral fluoroscopic position. Neurolysis can be achieved with either Radiofrequency Ablation (usually in non-cancer pain) or Chemical Neurolysis with alcohol or phenol.

Complications

The complications include rectal injury/fistula, injury to nerves, and neuritis. However, significant complications from this procedure are rare.

12.3 Peripheral Nerve Blocks and Interventions

12.3.1 Postmastectomy Pain Syndrome

PMPS itself is not a specific diagnosis but rather describes a cluster of symptoms frequently observed in breast cancer survivors following treatment. Its name is misnomer, because symptom burden can be seen following mastectomy, lumpectomy, LN dissection, and reconstruction, as well as chemotherapy and radiation.

Generally, it is considered to be chronic breast or chest wall pain lasting at least 3 months following cancer treatment. Incidence rates are estimated at 40–50% [47].

Many patients will experience short-term nociceptive pain after breast cancer treatment. However, with PMPS, patients frequently experience persistent neuropathic type pain: burning, tingling, aching, a subjective sense of "tightness" around chest wall, or even phantom breast or nipple pain.

Neuropathic pain results from dysfunction of the peripheral nerves caused by surgery, radiation, or neurotoxic chemotherapies. Neuromas, frequently found in scar following breast or axillary incisions, are one cause of neuropathic pain and can become chronic. Although they can occur after simple lumpectomies, they are more common following more extensive surgeries such as axillary LN dissections and with the addition of radiation. Damaged nerves are easily excitatory, sending a constant barrage of painful impulses with the slightest mechanical distortion. Commonly transected nerves include intercostal, thoracodorsal, medial and lateral pectoral, and long thoracic nerves. A well-recognized cause of PMPS is intercostobrachial neuralgia. The intercostobrachial nerve is the lateral cutaneous branch of the second intercostal nerve, arising from T2. It provides sensation to the medial upper arm, axilla, and lateral chest wall. It is frequently sacrificed ALND and almost always results in numbness. However, in symptomatic patients, it can result in painful paresthesia and chronic neuropathic pain.

Musculoskeletal pain syndromes are a common cause of nociceptive-type pain and when chronic, should be included in the definition of PMPS. Chest wall pain is persistent beyond simple incisional pain can be the result of scarring of the incised tissues, leading to hypo mobile tissue adhered to the underlying chest wall.

Rotator cuff dysfunction can be a result of changes in scapulothoracic motion. Pectoralis major muscle tightness or spasms, resulting from tissue expanders or radiation, pull the acromion into the protracted and inferior position and lessen the subacromial space through which the rotator cuff tendons pass, causing rotator cuff tendinopathies.

Treatment of PMPS includes rehabilitation interventions, medications, and interventional procedures. Interventional procedures include:

1. Serratus Anterior plane Block
2. PECS 1 and PECS 2 Block
3. Intercostal nerve block
4. Neuroma injection
5. Spinal cord stimulation
6. Paravertebral Blockade
7. Suprascapular Nerve Block

12.3.1.1 Pecs 1, Pecs 2, and Serratus Anterior Plane Blocks

Over the past few years, several studies have evaluated the ability of various techniques targeting the nerves of the thoracic wall. The Pecs blocks came into the scenario to address the issues associated with Paravertebral and Epidural blocks.

The blocks are technically straightforward, in the lines of the Transverse Abdominis Plane block (TAP) which has turned out to be a very popular and successful block for dealing with postoperative pain after abdominal surgeries. The terminology of the Pecs block was coined by Rafael Blanco. It was described in 2011 after an observational study for over 2 years which included approximately 50 patients [48].

12.3.1.2 The Details of The Blocks

Pecs block or the pectoral nerve block is the name given to the Ultrasound-guided nerve block which adequately and reliably blocks the lateral and Median pectoral nerves. The technique is similar to transverse abdominis plane block, i.e., it is a facial plane block and is an extension of the infraclavicular approach to the brachial plexus block [49].

Using a curvilinear high-frequency USG probe, Pectoralis major and minor muscles are identified, and the local anesthetic is deposited in the fascial plane between the two muscles. However, analgesia provided by the Pecs block was found insufficient for mastectomies and axillary dissection as several other nerves were involved during these surgeries [48].

After further research into Sono anatomy, a modification of Pecs Block came into the picture which was called Pecs 2 block or modified Pecs block. This USG guided block covers blockade of the intercostobrachial nerve, intercostal nerves 3–6 and the long thoracic nerve which is spared with the pecs block [50]. In this modification, the fascia plane between pectoralis minor muscle and serratus anterior muscle is identified close to 3rd and 4th rib and LA is injected. Thus, unilateral Pecs 1 and 2 blocks can provide analgesia for anterior chest wall pain.

Blanco et al. continued their sono-exploration of the chest wall and identified two potential spaces in the chest wall at the axillary level, with the probe in mid axillary line. One potential space is above the Serratus anterior and the other below it. After understanding Pecs 1 and 2 blocks, it is easy to identify the serratus anterior muscle. Usually, this plane is accessed at the level of the 4th or 5th rib. While the plane is easily visible under ultrasound guidance for most patients, the actual muscles may be difficult to separate, especially after radical mastectomy.

One caveat to this approach is that the long thoracic and thoracodorsal nerves lie in this plane and thus may be blocked alongside the variable intercostal nerves that penetrate the muscular plane. Because of this concern, a deep plane has been described between the serratus anterior muscle and the tip and/or external intercostal muscle. There is evidence clinically that pain symptoms are lessened by local anesthetic injected in either of the planes.

Serratus anterior plane (SAP) blocks are used for pain in the anterior chest wall, primarily post-mastectomy pain, around the reconstructed breast. For pain in the medial arm (intercostobrachial neuralgia) or upper chest at the level of the pectoralis major insertion, pectoral nerves are targeted via Pecs 1 and Pecs 2 blocks. Most patients return every 2–3 months for repeat injections. Our usual volume is 20 ml solution of 40 mg triamcinolone with 0.25% bupivacaine.

Potential complications include long thoracic nerve block with a resultant “winged scapula” for the duration of the effect of the local anesthetic. While

performing the superficial SAP block, it may be difficult to separate the plane during the injection. This is possibly the result of scarring between the fascia of the two muscles. In these instances, recommendations include injecting deep into the Serratus anterior muscle to get to the target branches of intercostal nerves. Further research in the use of SAP blocks in chronic pain is needed through RCT for optimization of injection site and injectate.

12.3.1.3 Neuroma Injection

Cases of traumatic neuroma formation after surgery have been described in the literature. In a review by Li et al., nodular masses may be viewed by ultrasound, presumed neuromas, which could be biopsied for confirmation. Neuroma formation tends to be at the area of scars and previous incisions. Neuromas may have a similar USG structure (hyperechoic nodules) as tumors and lymphadenopathy; monitoring and further evaluation should be considered. Neuromas may be injected with local anesthetic and steroids or can be ablated or surgically resected.

12.3.2 Malignant Brachial Plexopathy

12.3.2.1 Brachial Plexus Blocks for Cancer-related Pain

Tumor infiltration of the brachial plexus is commonly seen among patients with lung cancer. It usually affects the lower elements of the nervous plexus but at times it may evolve into a pan-plexopathy. Presenting symptoms are typically pain at the shoulder and upper extremity associating with weakness, muscle atrophy, and sensory deficits. As tumor expands and invades adjacent structures, the likelihood of reaching the epidural space becomes substantial.

Pancoast tumor is defined as a malignant tumor arising from the lung apex, also referred to as superior sulcus tumor. The tumor usually affects adjacent structures such as ribs, blood vessels, and nerves (typically the lower nerve roots of the brachial plexus). As a result, patients may present with severe pain, often with neuropathic characteristics radiating toward the ipsilateral upper extremity and accompanied with sympathetic symptoms (like Horner's syndrome) caused by invasion of the cervico-thoracic sympathetic ganglion. These manifestations often appear months prior to the diagnosis of the underlying disease [51].

Radiation-induced neuropathy is another cause of brachial plexopathy. Radiation therapy is the standard of care following breast-conserving surgeries. Radiation-induced neuropathy is the result of ischemia secondary to microvascular damage, radiation-induced fibrosis, culminating in local nerve damage.

12.3.2.2 Peripheral Nerve Injections

When cancer pain is experienced in the vicinity of an identified peripheral nerve, a temporary interruption of the pain transmission can be an effective method to control neuropathic pain. The term "nerve block" describes procedures that utilize a needle to deliver a local anesthetic (LA) for analgesic purposes. A block can have both diagnostic and therapeutic values. In order to identify the anatomical area

and/or the afferent pathway involved in originating/conveying the pain sensation, a diagnostic nerve block may be effective. Prognostic blocks allow the decision to indicate more complex and permanent procedures, usually with neurolytic purposes.

Diagnostic and prognostic blocks consist of injecting a small volume of LA agent onto a nerve. The duration of the effect is usually short, depending on the potency of the LA injected. Patients are considered responders when most of their pain is significantly relieved during the following hours after the procedure.

Neurolysis indicates the focal destruction of nervous tissue by the use of chemicals or thermal methods to disrupt nerve transmission. The classical targets for nerve blocks or neurolysis are sympathetic nerves or nerves with a predominantly sensory component. It is very important to always preserve motor and sphincter functions and when possible, balance potential benefits against side effects before performing neurolysis [52].

12.3.2.3 Brachial Plexus Procedures

The involvement of the sympathetic chain and the brachial plexus may cause neuropathic symptoms radiated toward the arm and the hand. Anesthetic techniques targeting the brachial plexus may include intermittent or continuous injection of LA and steroid combined.

12.3.2.4 Ultrasound-guided Brachial Plexus Block: Supraclavicular Approach

This approach is useful as a diagnostic maneuver to help identify if the brachial plexus is subserving pain from tumor invasion. Supraclavicular brachial plexus nerve block with LA may be used to palliate acute pain emergencies, including acute herpes zoster, brachial plexopathy including cancer pain like pancoast tumor. The use of USG imaging can identify the exact location and course of the brachial plexus and is indicated for palliation of cancer pain including invasive tumors of the brachial plexus as well as tumors of the soft tissue and bone of the upper extremity.

Clinically relevant Anatomy

The fibers that comprise the brachial plexus arise primarily from the fusion of the anterior rami of the C5, C6, C7, C8, and T1 spinal nerves. In some patients, there may also be contribution of fibers from C4-T2 spinal nerves. The nerves that make up the plexus leave the lateral aspect of the cervical spine and pass downward and laterally in conjunction with subclavian artery. The nerves and artery run between the anterior scalene and middle scalene muscles, passing inferiorly behind the middle of the clavicle and above the top of the first rib to reach the axilla. The scalene muscles are enclosed in an extension of prevertebral fascia, which helps contain drugs injected into this region and provides the theoretic and anatomic basis of this technique.

Ultrasound-guided technique

The supraclavicular block is effective and useful as the brachial plexus is very compact at this level. Prior to USG the risk of pneumothorax caused practitioners to

shy away from classic supraclavicular nerve block. Ultrasound permits visualization of the pleura as well as the nerves and, if performed correctly, greatly improves the safety of this block.

To perform the ultrasound-guided injection technique, place the patient in the supine position with the head turned away from the side to be blocked. The posterior border of the sternocleidomastoid muscle is identified by having the patient raise his or her head against the resistance of the clinician's hand. The point at which the lateral border of the SCM attaches to the clavicle is then identified.

After preliminary identification of the approximate location of the brachial plexus utilizing surface landmarks, the skin is prepped with antiseptic solution. 15 ml of local anesthetic is drawn up in a 20 ml of syringe, with 40–80 mg of depot steroid added if the condition being treated is thought to have an inflammatory component.

A linear ultrasound transducer is then placed over the previously identified location in the transverse plane, and a survey scan is taken. The subclavian artery, brachial plexus, the lung and the first rib are identified. Color Doppler can be utilized to further delineate the subclavian artery and other vascular structures. The angle or the corner formed by the subclavian artery medially, the first rib inferiorly, and the brachial plexus superolaterally is then identified as the target for needle tip placement as it not only blocks the brachial plexus but also blocks fibers that form the ulnar nerve, which can often be missed when using the classic landmark approach. This ultrasound landmark has been called the "corner pocket" with the fibers of the ulnar being called the "eight ball" due to the contribution of the C8 fibers.

Complications

Phrenic nerve palsy, Horner's syndrome, hematoma, failed block, infection, and nerve injury may occur.

12.3.2.5 Interscalene Approach

Brachial plexus block within the interscalene groove involves local anesthetic blockade of the brachial plexus at the level of the roots and can produce complete anesthesia of the shoulder and clavicle. The brachial plexus is most often formed from C5-T1 nerve roots. There is a large physical distance between the C5 nerve root and T1 nerve root, resulting in ulnar sparing when LA is placed in the interscalene groove at the level of C5 or C6. With ulnar sparing, there will be intact motor function and sensation in the 4th and 5th digits. Therefore, interscalene block is less useful for pain involving areas distal to the mid humerus.

Anatomy

The interscalene block is performed at the level of the roots. At this level, the plexus lies between 2 muscles: the anterior scalene and middle scalene muscle. The most important roots to block for shoulder include C5, C6 and C7.

12.3.2.6 Suprascapular Nerve Block

It is estimated that the suprascapular nerve innervates 70% of the shoulder area, including the superior and posterior regions of the shoulder joint capsule and the Acromioclavicular joint. Suprascapular nerve blocks (SSNB) may be used for diagnostic and therapeutic pain relief of the shoulder with immediate onset and relatively good safety profile. SSNB is used to treat pain in several pathologies including adhesive capsulitis, rotator cuff tendinopathy, scapular fracture, and glenohumeral joint arthritis. When compared to intra-articular shoulder injections, SSNB has been found to provide significantly better pain relief at 12 not weeks for the treatment of adhesive capsulitis. When comparing the efficacy of physical therapy alone versus PT with SSNB, evidence suggests that there are both greater pain relief and improved function in SSNB treatment group. Based on the review of the literature, SSNB is a good short-term adjunct treatment option to facilitate painless range of motion during physical therapy.

12.3.3 Post-Thoracotomy Pain

Tumors invading the chest wall and pleura are often incurable, and treatment is targeted toward palliation of symptoms and control of pain. When patients develop tolerance or side effects to systemic opioid therapy, interventional techniques can better optimize a patient's pain [53]. Patients with thoracic chest wall pain undergo various treatment options to block pain transmission. These procedures include intercostal nerve blocks, Paravertebral nerve blocks, and intrathecal drug delivery.

12.3.3.1 Intercostal Nerve Block

Clinical Perspective: Pain of malignant origin of the chest wall, flank, and upper abdomen as well as liver and lung tumors that involve the pleura and peritoneum is amenable to treatment with local anesthetics and steroids administered into the intercostal space.

It consists of injection around the neural structure located underneath each rib. Because the main complication is the pleural puncture and subsequent pneumothorax, it is suggested to use direct needle placement with USG. The injection of the intercostal nerve provides loss of sensation distal to the point of injection following the trajectory of the nerve toward the anterior chest wall.

When a temporary intercostal nerve block provides adequate analgesia but limited to a short period of time, it may be reasonable to repeat the block adding a co-adjunct or opting for a more permanent relief by chemical neurolysis with phenol, thermal neurolysis with heat using radio-frequency or freezing the nerve with cryo-neurolysis.

Anatomy

Imaging: Ultrasound-guided Technique:

USG guided technique can be carried out while the patient is the sitting position or in prone position.

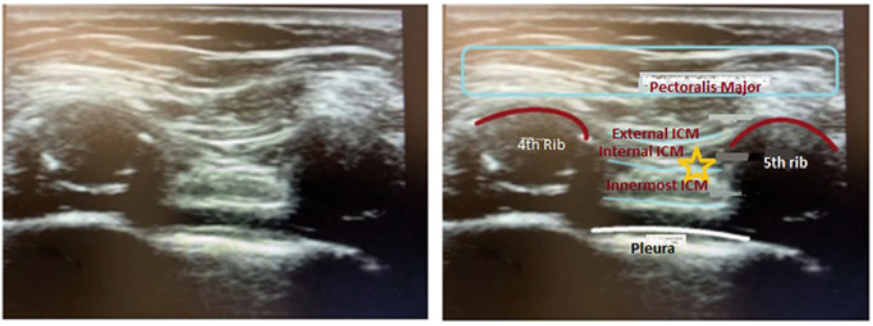

Fig. 12.5 Ultrasound anatomy of intercostal nerve block. [54] Reproduced from Lopez-Rincon et al.

The rib at the level to be blocked is then identified by palpation and traced posteriorly to the posterior angulation of the affected rib.

A linear high-frequency ultrasound transducer is then placed in the longitudinal plane with the superior aspect of the USG probe rotated about 15 degrees laterally over the affected rib and survey scan is obtained (Fig. 12.5).

The rib is identified as a hyper-echoic curvilinear line with an acoustic shadow beneath it. The three layers of intercostal muscle, the external, internal, and innermost will be identified in the intercostal space between the adjacent ribs. Color Doppler will help identify the adjacent intercostal artery and vein.

This space between the adjacent ribs provides an excellent acoustic window, which allows easy identification of the intercostal space and the pleura beneath it.

Adjacent ribs with the intercostal space in between have been described as having the appearance of a "flying bat."

The clinician advances a 25-gauge, 1.5-inch needle in plane to the inferior border of the rib between the internal and innermost intercostal muscle. After negative aspiration for heme, solution consisting of 2 ml of 0.25% or 0.5% bupivacaine with 10–20 mg of triamcinolone is injected. The needle is then flushed and withdrawn. This procedure is then repeated at the other affected levels.

12.3.4 Spinal Cord Stimulation and Oncologic Pain Management

12.3.4.1 Introduction

Spinal cord stimulation (SCS) has been used to relieve pain since 1967, when Shealy et al. pioneered the technology for a patient with metastatic cancer. Although the technique is used today mostly to relieve chronic pain associated with failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), ischemic limb pain, and angina pectoris, it also has been implemented to address

other intractable neuropathic and chronic visceral pain conditions. However, new applications for SCS are a continued area of research. Among these areas are modulation of end-organ perfusion, cancer, or tumors.

In most cases, SCS is used as a component of a multimodal therapeutic plan designed to control a patient's pain while decreasing the doses of analgesics, and in rare cases, pain medications are discontinued completely.

In its simplest form, a SCS consists of an implantable pulse generator and electrodes. Under fluoroscopy, the electrodes are usually placed in the epidural space and designed to stimulate the dorsal columns of the posterior spinal cord (Figs. 12.6 and 12.7). Newer systems have electrodes placed nearer individual dorsal roots, specifically, dorsal root ganglia, for more precision in stimulation. Once a patient confirms appropriate stimulation, the level of intensity defined as current applied to the electrodes, can be performed, with changes in amplitude, pulse width, frequency, and waveform characteristics available to modulate the signal for improved pain relief [55].

In the oncologic population, while no specific criteria exist, recommendations have been made to consider stimulation techniques for treating pain arising from stable neurologic pain syndromes. SCS in active cancer patients is not considered a contraindication but progression of disease may make them poor candidates since the pain syndrome may evolve, possibly rendering SCS insufficient to adapt to the changing pain characteristics. Treatment considerations should be discussed with the oncologist prior to the trial and implant of SCS devices. We also recommend an MRI of the total spine to evaluate the epidural space for spinal disease and lead placement.

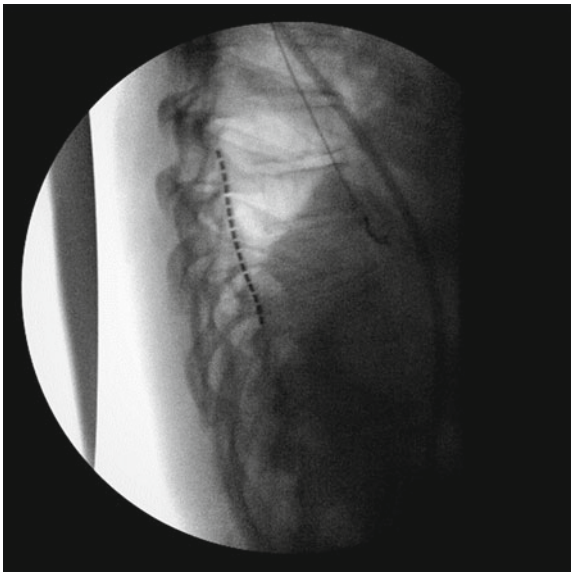

Fig. 12.6 SCS lead placement in lateral view. Photo courtesy of Manisha Trivedi MD

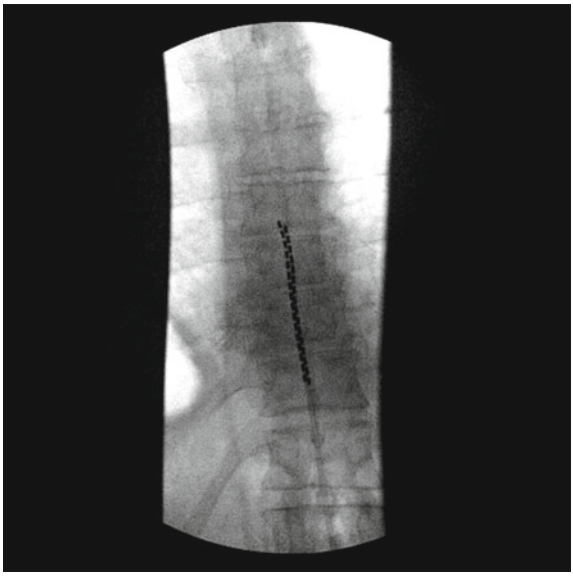

Fig. 12.7 SCS placement in AP fluoroscopic view. Photo courtesy of Manisha Trivedi MD

Specific timing for safe SCS use in the setting of ongoing cancer pain-related treatment requires study. As discussed above, these situations are complex, and many aspects of patient care are affected. Currently, it is recommended to have clear communication with the entire care team to ensure optimal patient outcomes and minimize complications. Similarly, the need for future cancer surveillance imaging requires consideration as this may influence device selection.

12.3.4.2 Future

There are multiple prospective and small randomized controlled studies that highlight a potential promising future for spinal cord stimulation for the treatment of cancer pain. Related to the challenge and urgency of cancer pain, the pain practitioner community is moving toward a multimodal approach that includes discussions regarding the role of SCS to the individualized treatment of patients.

Since 1989 when SCS obtained FDA approval, the device hardware, technology, and software contained within the impulse generators have drastically improved and along with that, patient outcomes have improved as well. The therapy appears to provide effective pain control across a variety of neuropathic pain conditions and pain-inducing mechanisms. There is an important need to study spinal cord stimulation in cancer-related pain conditions, particularly when considering the shortcomings of the current published literature in this area.

However, based upon the experience with SCS in the non-cancer pain population and on small series and case reports in cancer pain, it seems highly likely that SCS can be useful and effective therapy in many of the challenging cancer-related neuropathic pain syndrome such as post-radiation neuropathic pain, chemotherapy-induced peripheral neuropathy, and post-surgical pain syndromes. This is especially

important going forward as cancer survival rates continue to increase, patients who are afflicted with these debilitating pain conditions may endure long periods of pain and suffering if the underlined pain problem is not optimally treated.

Clinical trials comparing conventional medical therapy to SCS for the cancer pain syndromes are needed and would have the highest impact for the greatest number of patients. Additionally, assessment of pain-related characteristics that predict successful therapeutic response from SCS should also be evaluated with a focus on demographic predictor variables (i.e., age, gender), type and stage of cancer pain (somatic, visceral, neuropathic), pre-procedure opioid use, and other co-morbidities (psychiatric disorder). Until then, patients with intractable pain despite maximal medical therapy should be referred to an interventional pain specialist to assess for candidacy of advanced interventional treatment options such as a SCS.

SCS has been demonstrated to make clinically meaningful impact in the lives of patients experiencing cancer pain. There are multiple studies reporting safety, efficacy, cost-effectiveness, and opioid reduction. These therapies are increasingly utilized as tools in a multi-modal strategy for pain control and should not necessarily be reserved for patients in extremis or those who have "failed" more conservative therapy.

Although there is promising treatment potential, the overall quality of evidence for SCS has remained relatively low. Clinical practice recommendations are largely guided by expert recommendations. This issue is not unique to these modalities, as rather many widely used cancer pain treatments are not grounded in a strong evidence. For this reason, the rationale and choice of treatment must be individualized and relies upon careful weighing of risks and benefits that include shared decision-making with patients and providers [56].

12.3.5 Precautions in Cancer Pain Patients Receiving Procedures

As a principle, injections are avoided to be performed in the close vicinity of tumors for several reasons:

- Increased risk of bleeding caused by abnormal tumor vascular neo-genesis.
- A risk of seeding cancer cells along the needle track.
- There is a risk of missing the target if the tumor has distorted the local anatomy.

Given the consequences of cancer and cancer treatments on hemostasis of the body, precautions should be taken to avoid complications. Specifically, immunosuppression, coagulopathy, and the potential for poor wound healing need to be considered.

12.3.5.1 Immunosuppression

Cancer immunosuppression can occur from cancer-mediated factors or from treatment-related effects. Cancer cells create an immunosuppressive network of neurotransmitters that promote creation of immature myeloid cells and T-cells, which are attracted to the cancer site. This causes modulation causing functional inhibition of T-cells and NK-cells. Because of these changes, there is impaired phagocytosis and clearance of apoptotic cells, which induces a condition resembling auto-immune disease. Altogether, these immunosuppressive changes increase the risk of postoperative infections, in addition to tumor progression.

When considering infection risk based on cancer type, hematologic malignancies are associated with an increased risk overall. Due to functional as-Kenia, hypogammaglobulinemia and impaired B-cell immunity, these patients have an increased risk of encapsulated bacterial infections. They are also at risk of mycobacterial and vita infections from defective T-cell immunity. If myelodysplastic syndrome develops, this places the patient at increased risk of bacterial, viral, and fungal infections related to neutropenia.

Cancer treatments can also place patients at an increased risk of infection. Radiation has been shown to cause immunosuppression by increasing the production of TGF-beta. Chemotherapy causes neutropenia (ANC < 500 cells/mm^3) and decreased granulocytes may encourage bacterial and fungal infections. Close inspection of the patient's chemotherapeutic drug regimen to properly determine immunologic risks is advised.

Autologous hematopoietic stem cell transplantation causes weeks of neutropenia, which is followed by weeks or months of defective T-cell immunity. This may increase the risk of bacterial infections in the short-term and viral infections over time. Allogeneic transplantation is even more complex. Depending on a number of factors, particularly those related to the transplant match and GVHD prophylaxis, these patients are at an increased risk of infection for months afterward.

12.3.5.2 Coagulopathy

Thrombotic and bleeding complications are not uncommon in cancer, and it involves a complex interplay of underlying mechanisms. Venous thromboembolism occurs in approximately 20% of patients and is the second most common cause of death in this patient population. Due to increased clotting, there is consumptive coagulopathy involving platelets and the complement system. This is similar to DIC, but less severe, given its chronic and gradual progression.

12.3.5.3 Wound Healing

Given the wide range of treatment options, including surgery, radiation, and chemotherapeutic agents, wound healing becomes critically important in the continuum of cancer care. Nutrition plays an important role in healing process. Positive nutritional balance promotes optimal wound healing, and physicians must consider this when considering surgical intervention. Malnourished patients have an increased susceptibility to surgical site complications, including infection, and delayed wound healing.

Treatment-related effects on wound healing must also be considered. Radiotherapy causes ionization and subsequent cellular damage to vital structures. High turnover cells are more susceptible to this damage, including epithelial cells, and this may lead to delayed wound healing at sites of radiation. Similar to radiation therapy, chemotherapeutic agents preferentially target rapidly dividing cells, and this includes tissues involved with incisional healing. VEGF inhibitors are particularly detrimental to wound healing given the known effects on angiogenesis. Early administration of corticosteroids following surgery has been shown to have negative consequences on wound tensile strength [57].

12.4 Conclusion

Overall, interventional pain procedures should be offered to patients before they are too frail to undergo the procedures, and thus they should not be considered an option in isolation but rather a part of an analgesic strategy. In addition, recent therapeutic advances have allowed increased survival rates, turning cancer pain into a potentially chronic condition. Since pain is present in up to 39% of cases after curative intent, an increased survival could impact the number of patients left with persistent symptoms despite being successfully treated.

Major efforts are being conducted to demonstrate the efficacy of interventional pain management initiated at early stages of the disease, or before the pain becomes unmanageable with oral pain medications. Interventional cancer pain approaches should be regarded as a handrail accompanying all the three steps of the WHO ladder.

Oncologists must identify those patients whose pain is inadequately controlled and ask themselves if an interventional approach may be indicated. With progressive learning, the indications and contraindications become clearer, and the cases are referred in a timely and more appropriate fashion. Fluid and bidirectional communication are key to integrate successful analgesic strategies into oncologic care [58].

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Peripheral Nerve Entrapments in Cancer Pain

13

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13.1 Introduction

There has been very little recognition of the role that peripheral nerve entrapments can have on cancer pain. Recognizing this pathology can offer a treatment paradigm that can improve pain control, reduce opioid requirements and improve quality of life. In this chapter, we will review the clinical presentation of several common peripheral nerve entrapments, the diagnostic tools to help to diagnose these entrapments, and clinical outcomes of the entrapment treatment.

13.2 Definitions

Kopell and Thompson [1] stated that peripheral nerve entrapment occurs at anatomic sites where the nerve changes direction to enter a fibrous or osseofibrous tunnel, or where the nerve passes over a fibrous or muscular band. Entrapment occurs at these sites because mechanically induced irritation is most likely to occur at these locations.

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13.3 Peripheral Nerve Entrapments in Cancer

In cancer, nerve entrapment can occur by:

- physical compression by the tumor mass
- vascular compromise by the tumor, causing edema
- scarring from surgical resection
- nerve damage from radiation or chemotherapy

13.4 Pathophysiology of Entrapment

Prolonged compression causes ischemia due to compression of the vasa nervorum. There is mechanical deformation of myelin sheath, which leads to an impairment of axonal transport of nutrients.

13.5 The Scope of the Problem

Peripheral nerve entrapments are an under-recognized cause of pain in the cancer patient. The prevalence of carpal tunnel syndrome, one of the most common nerve entrapment syndromes, is 87.8 in men and 192.8 in women per 100,000 European standard population according to a recent examination of the UK General Practice Research Database (which included 253 general practices with 1.83 million patient years at risk) [2]. A systematic review of 52 studies revealed there are as many patients now suffering with pain from advanced cancers as there were 40 years ago [3], despite the rapid development of modern oncology. The reason for this phenomenon is unknown, and few people have tried to investigate this.

A couple of factors may explain this paradox. First, patients with cancer are living much longer in comparison with 40 years ago. The second factor could be that doctors tend to see all pains occurring in patients with cancer as "Cancer Pain." We can treat the tumor-related pain much better with modern oncological technologies such as chemotherapy and radiation, but there are many types of pain that are only peripherally related to the cancer, such as post-therapy consequences (from the oncologic surgery, chemotherapy, and radiation therapy), lack of movement, and cachexia. Those pains may arise as a result of nerve compression and nerve stretching, overuse of atrophic muscles, myofascial trigger points, sores, and stiffness of joints and tendons [4]. If these pains are less sensitive to opioids and other analgesics, calling them "Cancer Pain" will result in much more intensive treatment with opioids and as a result more opioid toxicities and treatment failures [5].

One of the common adverse effects of opioids, opioid induced hyperalgesia (OIH), may be much more frequent now than in the past [6]. OIH pain can be accompanied by a diffuse pain often described as "all over the body," which will only be made worse by

giving more opioids. Thus, it is critical to concentrate on the history and to make an appropriate pain diagnosis. Compressed nerves are "under the radar" of sophisticated imaging techniques and "what is not seen is not recognized."

13.6 Hallmarks of Nerve Entrapments

Patients will complain of pain that is burning, aching, or tingling in nature. There will be paresthesias with compression of the nerve, and a positive Tinel's sign (paresthesias with tapping on the nerve), which represents ectopic excitability. There is also the potential for a "double crush" syndrome, where the presence of a more proximal entrapment renders the distal nerve more vulnerable to compression.

13.7 Questions to Ask

The history of the onset of pain is a critical clue to the diagnosis. Questions to ask the patient should include:

- Where does it hurt? (Attempting to localize the initial site of the injury, as well as patterns of pain radiation)
- Where and when did it start to hurt?
- What makes it worse? What makes it better? (It is important to ask these questions in this order since patients will often respond "nothing" to "what makes it better?" if asked that question first.)
- Are there associated weaknesses or sensory disturbances?
- Are there any changes in the appearance or function of the limb?
- Is there a history of recent or old trauma?

13.8 Diagnostic Studies

There are a variety of diagnostic tools available for diagnosing peripheral nerve entrapments.

EMG/NCV—Entrapments of specific peripheral nerves can be confirmed and localized using electromyography (EMG) and nerve conduction studies (NCS), also known as nerve conduction velocities (NCV). However, these studies are not a substitute for a thorough history and clinical examination; instead, they serve as a method of clarifying and confirming suspected diagnoses [7]. These studies are generally most useful for entrapments of the extremities. EMG and NCS are typically performed at the same time, and the results must be viewed within the clinical presentation. The EMG may demonstrate some of the sequelae of nerve entrapment,

including denervation of distal muscles, which can be seen as positive sharp waves, fibrillations, and giant motor unit potentials (MUPs). For example, in an EMG study of median nerve entrapment, eleven patients with entrapment at both the wrist and elbow showed evidence of denervation on EMG; in the patients with only carpal tunnel syndrome, half showed evidence of denervation, including both fibrillations and positive sharp waves [8]. Testing adjacent muscles with different innervation within the same myotome can help rule out radiculopathy.

NCS are particularly useful for localizing and characterizing the nature of a nerve injury, by testing across segments of nerves. Evidence of demyelination, such as slowed conduction velocity or block, is sought across areas of potential entrapment. Some entrapment locations are extremely common, such as entrapment of the ulnar nerve at the elbow, the median nerve at the wrist, the radial nerve at the spiral groove, or the peroneal nerve at the fibular neck. If other specific locations are suspected due to the patient's exam, previous trauma, or surgical history, it is essential to share this information with the electromyographer in order to help guide the evaluation. Conduction studies can assess both motor and sensory function, but they only evaluate large myelinated fibers.

MRI—Magnetic Resonance Imaging (MRI) of the peripheral nerves, until recently, had limited application. MRI allows excellent differentiation of soft tissue, as well as assessment of the perineural tissue and bone, but peripheral nerves can be difficult to identify on conventional MRI, and even small amounts of patient movement can render the image difficult to interpret. MRI is particularly useful in the assessment of deeper structures that are beyond the range of high-resolution ultrasound (see below). MRI has also been helpful in distinguishing nerve entrapment from other focal nerve lesions, including invasive tumors and intrinsic nerve lesions such as schwannomas. MRI may show perineural structures impinging on the nerve, and it may also show abnormalities within the nerve itself such as focal enlargement, hyperintensity on short tau inversion recovery images, and altered fascicular patterns [9]. Denervated muscle may show a hyperintense signal that can usually be identified when entrapment is acute; on the other hand, fatty infiltration and muscle atrophy are the signs of chronic neuropathy in chronic cases [10].

Magnetic resonance neurography (MRN) is a newer technique that optimizes nerve T2 contrast; the T2 signal is known to increase after various forms of experimental nerve injury, and it has now been shown to strongly correlate with NCV findings [11]. Specific nerve entrapments that have been extensively studied using MRN include the suprascapular nerve, proximal sciatic nerve, and pudendal nerve, as well as many extremity entrapments in locations such as the popliteal fossa, tarsal tunnel, and Guyon's canal. Research into new forms of MRN is ongoing, with both new scanning protocols and new contrast media being actively studied.

Ultrasound—Peripheral nerve ultrasound (US) was first described nearly two decades ago to evaluate carpal tunnel entrapment [12]. A high frequency (>12 MHz) linear probe is commonly used for most peripheral nerves [13]. Lower frequency transducers (10–15 MHz) may be needed for nerves more than 4 cm below the skin's surface. Since most of the entrapped peripheral nerves of interest

travel with blood vessels, Doppler imaging may aid in nerve identification. Swelling of the nerve is often seen with entrapment [14], as well as increased echogenicity of muscles in CRPS [15]. Ultrasound can be used to confirm pathology and/or aid in needle localization for diagnostic injections.

Peripheral Nerve Blocks—Diagnostic peripheral nerve injections can offer both diagnosis as well as treatment of peripheral nerve entrapments, providing a unique role in the management of peripheral nerve entrapments. Injections with local anesthetic help to localize and confirm the nerve entrapment diagnosis, and the injections can treat the nerve entrapment, by a variety of potential mechanisms including hydrodissection, the anti-inflammatory effect of injected corticosteroids, and the dilution and flushing out of inflammatory mediators. Precise and atraumatic injection techniques are essential to maximize the diagnostic and treatment value of any nerve injection for peripheral nerve entrapment.

The injectate usually consists of a local anesthetic and a depo-steroid. Since the response to the local anesthetic is key to the diagnosis, it may be prudent to test the response to a variety of local anesthetics prior to the diagnostic injection. Local anesthetic resistance is an under-recognized cause of injection failure. In 2003, Trescot interviewed 1,198 consecutive patients; of those, 250 patients noted failure of relief from a prior injection or had a history of difficulty getting numb at the dentist [16]. Skin testing with lidocaine, bupivacaine, and mepivacaine was performed to identify the most effective local anesthetic. Ninety of the tested 250 patients (7.5% of the total patients, but 36% of the test group) reported numbness only to mepivacaine, and an additional 43 patients (3.8% of the total patients, but 17% of the test group) only got numb to lidocaine. Thus, 133 of 250 patients with a history of difficulty with local anesthetic analgesia (53%), and 11% of the total patients, did not get numb with bupivacaine (the most commonly used anesthetic), suggesting a significant false negative response to diagnostic injections.

Glucocorticosteroids are often used to decrease inflammation that both causes and accompanies nerve entrapment. However, these steroids need careful and judicious use. There is a risk of superficial skin injury and atrophy, and large doses of steroids can cause suppression of the hypothalamus–pituitary–adrenal axis, leading to the potential for Cushing's syndrome, which has been reported to occur with even a single dose of methylprednisolone 60 mg [17]. Care must also be used to avoid further entrapment that could occur with large volumes of injectate.

These injections can be performed using just surface landmarks, but the use of peripheral stimulation, US, fluoroscopy, or computerized tomography (CT) can improve the specificity and therefore the effectiveness of the injection. If there is only temporary relief from the diagnostic and therapeutic injection, additional therapies include neurolysis (alcohol, phenol, radiofrequency lesioning, or cryoneuroablation), and peripheral nerve stimulation. Options for surgical treatment of nerve entrapments include release or transposition of the entrapped nerve, as well as nerve transfer or grafting.

13.9 Head and Face Cancers

There are multiple nerves of the face and head that can be entrapped by tumors, or by the surgical scarring that occurs because of surgical resection. Many are branches of the trigeminal nerve. Trigeminal neuralgia is estimated to affect 4/100,000 patients per year [18] and interventional pain physicians have concentrated on injections of this nerve as it exits the foramen ovale at the base of the skull. However, those injections are quite invasive and not without significant potential complications. The peripheral branches of the trigeminal nerve can often be addressed at the bedside or in the office and can provide instant and often lasting relief of debilitating facial pain.

Supraorbital nerve

Entrapment of the supraorbital nerve can occur at any point of its path, most commonly at the supraorbital notch and corrugator muscle [19].

Diagnosis requires presence of a triad:

- pain or paresthesias in the supraorbital distribution,
- localized tenderness over the supraorbital notch,
- response to local anesthetic injection (Fig. 13.1) or ablation of the nerve.

Fig. 13.1 Supraorbital nerve injection. (Image courtesy of Andrea Trescot, MD)

Infraorbital nerve

The infraorbital nerve can become entrapped as the nerve exits the skull at the infraorbital foramen or anywhere at its path. Patients present with symptoms of the unilateral cheek, upper teeth, or nasal area pain, described as sharp, electric-like, tingling pain over the distribution of the infraorbital nerve [20]. The injections can be extraoral or intraoral (Fig. 13.2).

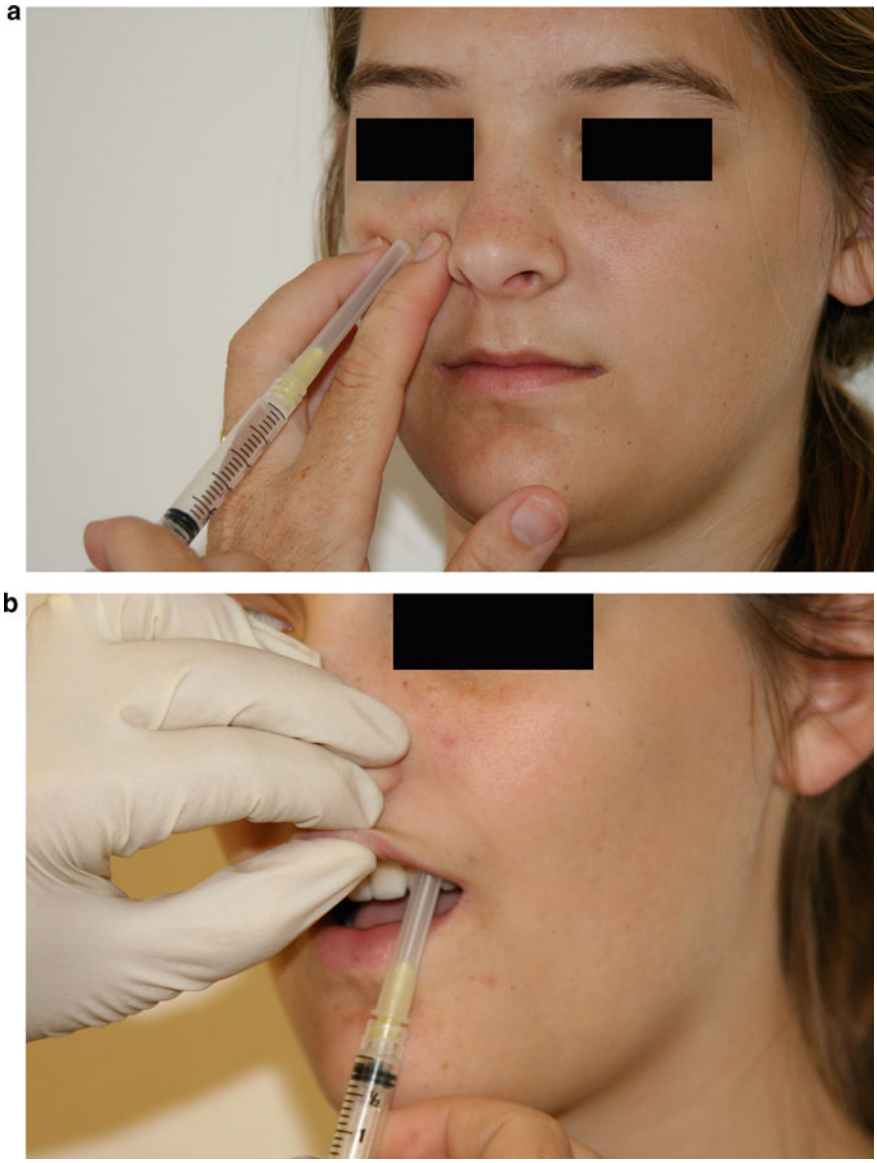

Fig. 13.2 Infraorbital nerve injection. **a** = extraoral injection; **b** = intraoral injection. (Image courtesy of Andrea Trescot, MD)

Mental nerve

The mental nerve arises from the sensory portion of the inferior alveolar nerve and is a terminal branch of the mandibular division (V3) of the trigeminal nerve (CN V). The mental nerve can become entrapped as it exits the skull at the mental foramen or anywhere at its path. The clinical picture is characterized by numbness or paresthesia in the region of the lower lip and chin, also called "numb chin syndrome" [21]. Again, injections can be extraoral or intraoral. (Fig. 13.3).

Maxillary nerves

The trigeminal (Gasserian) ganglion gives rise to three divisions: ophthalmic (CN V1), maxillary (CN V2), and mandibular (CN V3). The mandibular branch is on the lateral part of the foramen ovale, and the maxillary and ophthalmic branches are on medial. The maxillary nerve is the continuation of the V2 branch, and it is a pure sensory nerve, supplying sensation to the middle one-third of the face, from the inferior portion of the nose, the upper lip, across the cheek, and into the temple. Anterior to the trigeminal ganglion, the maxillary nerve crosses the cavernous sinus anteriorly and inferiorly and then exits the skull through the foramen rotundum.

The maxillary nerve innervates the maxillary sinus, as well as the anterior upper teeth via the anterior and middle superior alveolar nerves. It then extends through the superior aspect of the pterygopalatine fossa and enters the orbit through the inferior orbital fissure. The terminal branch of the maxillary nerve is the infraorbital nerve, which exits the skull through the infraorbital foramen to innervate the skin and the underlying mucosa from the lower eyelid to the upper lip. While the maxillary nerve is in the pterygopalatine fossa, it is connected to the pterygopalatine ganglion, through which it gives the branches to the nasal cavity, pharynx, and palate. The zygomaticotemporal branch of the maxillary nerve supplies the lateral portion of the face and temple. The maxillary nerve can be entrapped as it crosses through the foramen rotundum and as it exits the infraorbital foramen as the infraorbital nerve, resulting in sensory changes and pain in the sensory distribution of the nerve. Trigeminal neuralgia is a neuropathic pain of the face, usually in a V2 or V3 distribution, characterized by attacks or paroxysms of severe facial pain, often lasting only a few seconds or minutes [22].

Mandibular nerve

The mandibular nerve, the V3 branch of the trigeminal ganglion, innervates the motor branch of mastication and the sensory branches of the lower face. The nerve can be entrapped in the area of foramen ovale, as well as by vascular anomaly, fibrous dysplasia, scar tissue, and schwannoma, causing unilateral facial pain. The location of the pain is in the chin, inferior oral cavity, lower teeth, and buccal tissues as well as the tongue. Because the auriculotemporal nerve is a branch of the mandibular nerve, mandibular entrapment may also present as temple pain [23].

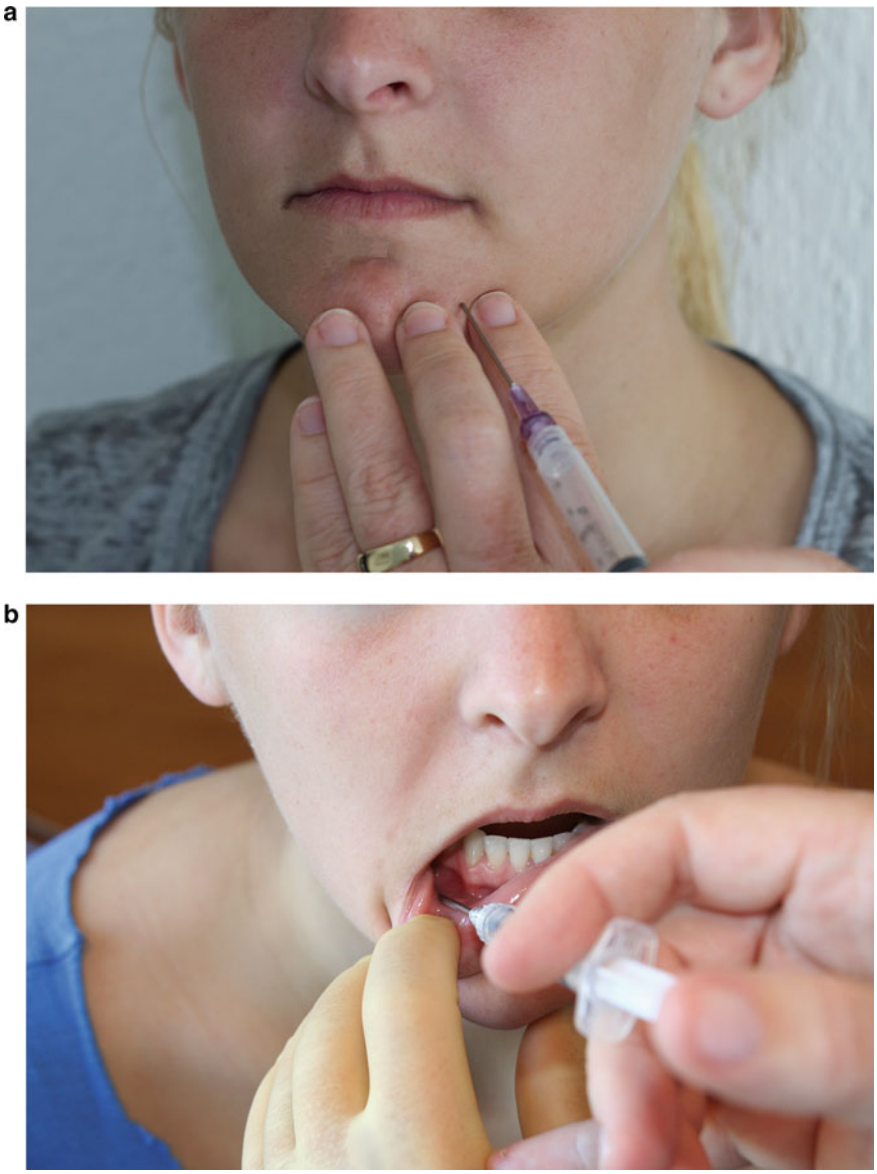

Fig. 13.3 Mental nerve injection. **a** = extraoral injection; **b** = intraoral injection. (Image courtesy of Andrea Trescot, MD)

13.10 Neck and Throat Cancers

Tumor invasion as well as the scarring from radical neck surgeries can cause a variety of very debilitating pains that can limit even the ability to swallow. Most of these injections require more sophisticated imaging such as fluoroscopy and ultrasound, though, if landmarks are palpable, there may be an indication for a bedside injection in the terminally ill patient.

Glossopharyngeal nerve

Glossopharyngeal neuralgia affects 0.7/100,000 patients per year [18].

Glossopharyngeal nerve entrapment presents as unilateral sharp, stabbing, and severe pain; precipitated by swallowing, chewing, talking, coughing, and/or yawning in distribution within the posterior part of the tongue, tonsillar fossa, and pharynx or beneath the angle of the lower jaw and/or in the ear [24]. Entrapment of the glossopharyngeal nerve could be idiopathic (not associated with any obvious entrapment) or caused by compression of the nerve by the styloid process (in this case pressure over the styloid process could replicate or exacerbate the pain). Injections can be landmark-guided, fluoroscopically guided, US-guided, or combined (Fig. 13.4).

13.11 Lung Cancer and Chest Wall Pain

The pain from lung cancers, especially with erosion into the rib, can cause pain with every breath. In addition, there can be pain from the thoracotomy or trauma to the chest wall nerves after breast surgery.

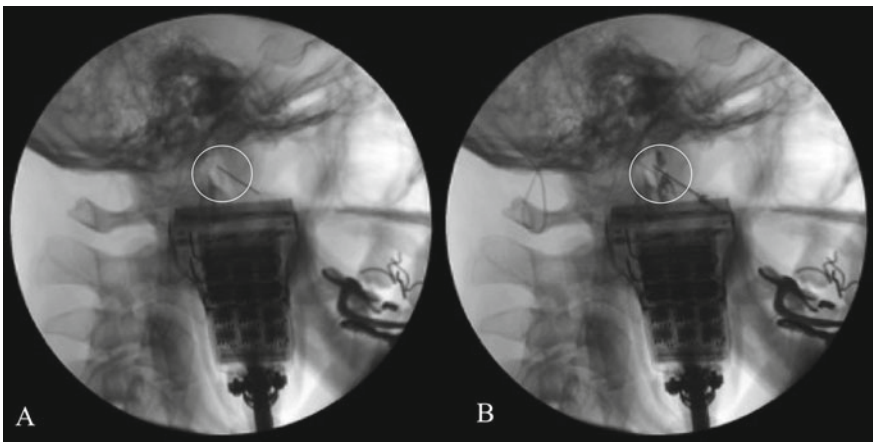

Fig. 13.4 Glossopharyngeal nerve injection using fluoroscopy and ultrasound. (Image courtesy of Andrea Trescot, MD)

Intercostal nerves

Intercostal nerves are the anterior rami of the first 11 thoracospinal nerves and the subcostal nerve as a 12th thoracic nerve. They give sensory innervation of the skin of the chest and abdominal wall; and motor innervation to intercostal muscles and abdominal wall.

Entrapment of intercostal nerves can be caused by neoplasm, sarcoidosis, pleural mesothelioma, radiotherapy, or postsurgical scarring. Pain could be described as a unilateral sharp, stabbing, and severe pain. The pain could be in the dermatomal pattern and go around the chest or abdomen, causing both chest wall and abdominal wall pain. Injections can cause pneumothorax, and so should not be performed bilaterally at the same time. Using an oblique approach may decrease the risk of pneumothorax (Fig. 13.5).

Suprascapular nerve

The suprascapular nerve (SN) is a mixed sensory and motor nerve that originates from the upper trunk of the brachial plexus and can be a cause of shoulder pain and weakness. There are two primary sites for entrapment of the SN the clinical presentation varies depending on the site of entrapment. Patients with proximal suprascapular nerve entrapment (at the suprascapular notch) primarily complain of poorly localized posterolateral shoulder pain and weakness. Diagnosis is made by injection at the suprascapular notch, using a peripheral nerve stimulator, fluoroscopy, ultrasound, or CT scan (Fig. 13.6). Entrapment of the distal suprascapular nerve at the spinoglenoid notch causes much less pain and the patient will have isolated atrophy and weakness of the infraspinatus muscle [25].

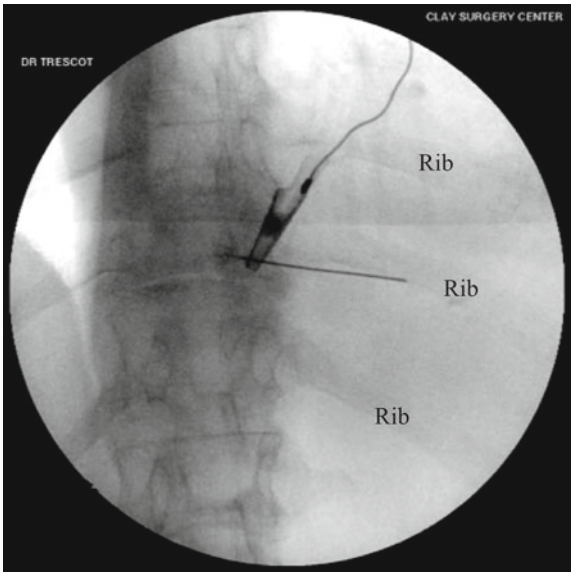

Fig. 13.5 Intercostal nerve injection using fluoroscopy and an oblique approach. (Image courtesy of Andrea Trescot, MD)

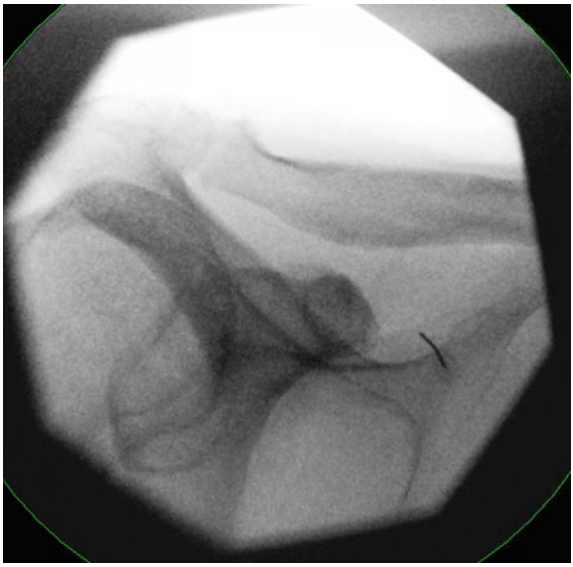

Fig. 13.6 Fluoroscopic image of suprascapular notch located just above the needle (Image courtesy of Christopher Burnett, MD)

Long thoracic nerve

The long thoracic nerve is formed of anterior branches of C5-C7 spinal nerves. The C5 and C6 spinal nerves join in or near the middle scalene muscle with C7 coming more distally. The long thoracic nerve is purely motor, meaning that it doesn't have sensory distribution. It innervates serratus anterior muscle which stabilizes the scapula on the chest wall and is essential for arm abduction and elevation. Its entrapment could be caused at any point of the course.

Medial scapular winging (prominence of the scapula) is the hallmark of long thoracic nerve injury (Fig. 13.7). Patients with long thoracic nerve dysfunction usually present with shoulder and scapula pain and weakness when lifting objects away from the body or with overhead activity.

Dorsal scapular nerve

The dorsal scapular nerve originates from cervical nerve C5 of the brachial plexus. The nerve crosses the middle scalene muscle and travels deep to the levator scapulae and the rhomboids. It is a motor nerve and provides motor innervation to the rhomboid muscles (pulls the scapula toward the spine) and levator scapulae muscle (elevates the scapula). There are two common sites of entrapment—at the interscalene muscles and at the rhomboid muscles. The most common physical exam finding is tenderness along the medial scapula when the scapula has been rotated forward (Fig. 13.8), though there may also be spasm and tenderness of the middle scalene muscle.

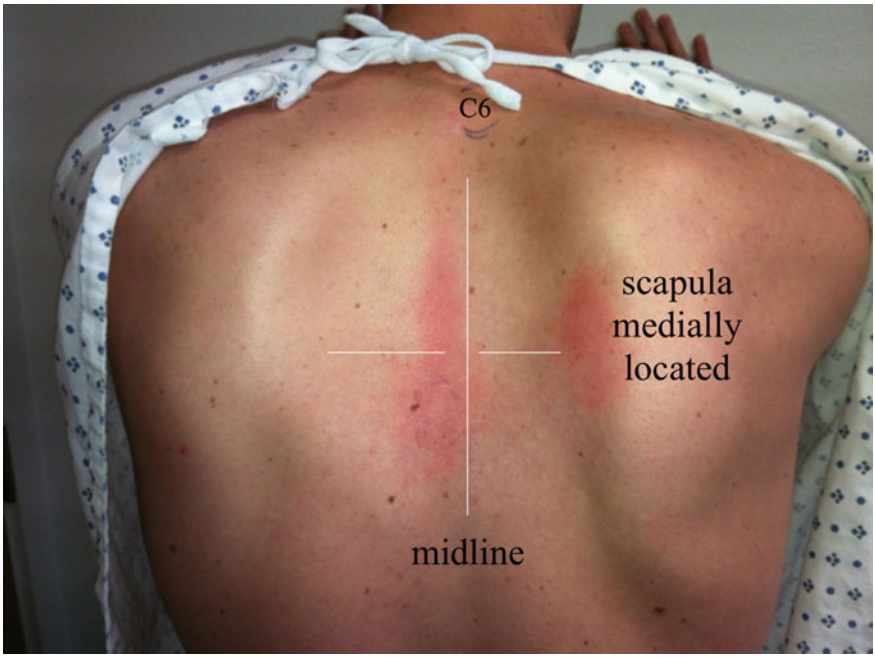

Fig. 13.7 Winged scapula from long thoracic nerve injury. Note the right scapula has prominent winging during a "wall push-up," with the medial border of the scapula more medially located than the left (Image courtesy of Heath McAnally, MD)

13.12 Abdominal Cancer/ Abdominal Wall Pain

Much of what is attributed to intra-abdominal pathology can be identified as having an abdominal wall cause or component.

ACNE

Anterior cutaneous nerve entrapment syndrome (ACNE) (also known as rectus abdominis nerve entrapment syndrome) occurs when nerve endings of the lower thoracic intercostal nerves (T7–T12) are compressed in abdominal muscles causes chronic neuropathic pain of the anterior abdominal wall. The incidence of the anterior cutaneous nerve entrapment syndrome is estimated to be 1:2000 patients [26]. The most common thoracoabdominal nerve entrapment site is near the lateral border of the rectus abdominis muscle (Fig. 13.9). The diagnosis is based on careful history and thorough physical examination, which includes Carnett's sign: the pain worsens by tensing the abdominal muscles and eases with relaxation of them (Fig. 13.10).

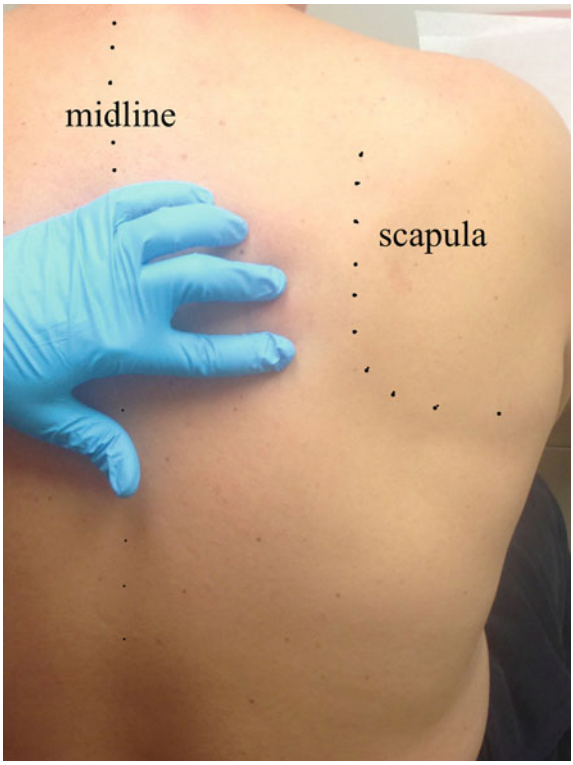

Fig. 13.8 Medial scapular examination of the dorsal scapular nerve, with the shoulder rotated anteriorly (Image courtesy of Andrea Trescot, MD)

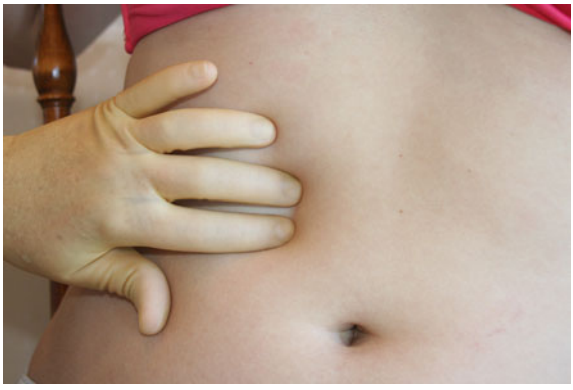

Fig. 13.9 Anterior cutaneous nerve entrapment examination (Image courtesy of Andrea Trescot, MD)

Fig. 13.10 Carnett's test (Image courtesy of Andrea Trescot, MD)

13.13 Pelvic Pain

Ilioinguinal

The ilioinguinal nerve is a branch of the first lumbar nerve. It travels from the thoracolumbar junction, through the psoas as part of the lumbar plexus, over the top of the iliac crest, along the inguinal ligament, and then anteriorly to the rectus border and inguinal canal (Fig. 13.11). It innervates the skin of the inguinal canal and the superomedial aspect of the thigh, the base of the penis, and the anterior scrotum (or labia majora). Ilioinguinal neuralgia is a common cause of chronic abdominal, suprapubic, and pelvic pain.

Genitofemoral

The genitofemoral nerve originates from the upper L1-2 segments of the lumbar plexus. It penetrates the psoas major and divides into two branches, the genital branch and the femoral branch (lumboinguinal nerve). In men, the genital branch supplies the cremaster and scrotal skin. In women, the genital branch innervates the skin of the mons pubis and labia majora. The femoral branch innervates the skin of the upper, anterior and medial side of thigh. The genitofemoral nerve could be entrapped at any point along its travel, causing symptoms based on the affected distribution branch, but the most common site of entrapment tends to be at the pubic tubercle (Fig. 13.11).

Pudendal

The pudendal nerve is a mixed sensory, motor, and autonomic nerve (parasympathetic and some sympathetic), innervating most of the pelvis. The pudendal nerve comes from the sacral nerves (S1, 2, 3, and 4), and then travels through the greater

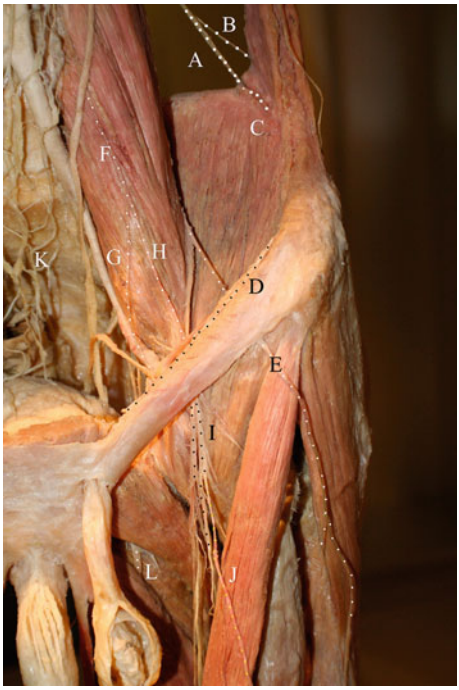

Fig. 13.11 Anatomy of some of the nerves of the pelvis, modified from an image from *Bodies, The Exhibition*, with permission. **a** = ilioinguinal nerve; **b** = iliohypogastric nerve; **c** = site of ilioinguinal nerve entrapment at the external oblique; **d** = ilioinguinal nerve over the inguinal ligament; **e** = lateral femoral cutaneous nerve; **f** = genitofemoral nerve; **g** = genital branch of the genitofemoral nerve; **h** = femoral branch of the genitofemoral nerve; **i** = femoral nerve; **j** = saphenous nerve; **k** = inferior hypogastric plexus; **l** = obturator nerve. (Image courtesy of Andrea Trescot, MD)

sciatic foramen, around the sacrospinous ligament on the ischial spine, and into the perineum through the lesser sciatic notch, underneath the sacrotuberous ligament. The nerve then passes through the ischioanal fossa into the pudendal canal (also known as Alcock's canal), and then to the rectum, peroneum, and vaginal/scrotal area (Fig. 13.12). Entrapment of the pudendal nerve can occur at multiple sites and could present as a weakness of anal and urethral sphincters or erectile dysfunction. It could also present with or without chronic pelvic pain or sensory changes in the distribution of the lower anal canal and perineal skin. The nerve can be injected landmark–guided, ultrasound-guided, or fluoroscopy-guided at the ischial spine (Fig. 13.13a), or at the ischium (Fig. 13.13b).

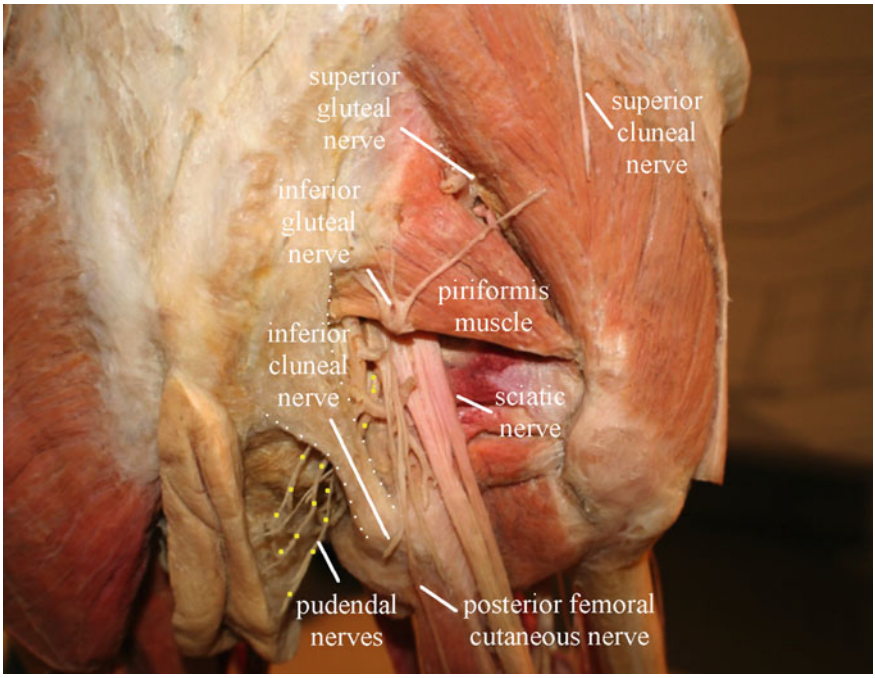

Fig. 13.12 Gluteal dissection modified from an image from *Bodies, The Exhibition,* with permission. Yellow dotted lines identify the pudendal nerve and branches. White dotted line outlines the sacrotuberous ligament. (Image courtesy of Andrea Trescot, MD)

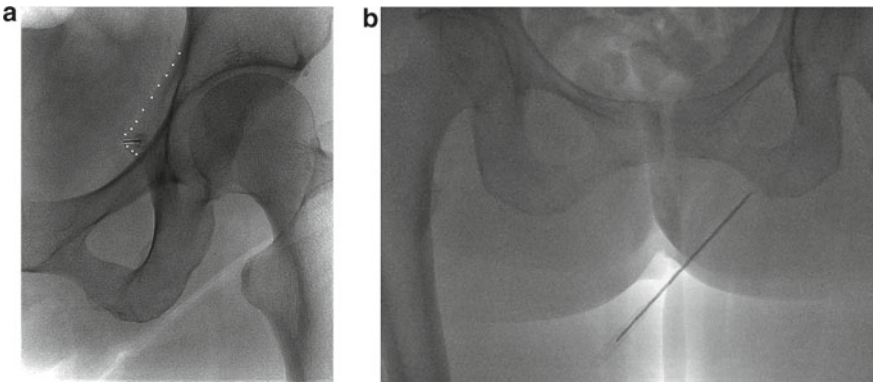

Fig. 13.13 Fluoroscopic injections of the pudendal nerve. A = injection at the ischial spine; B = injection at the ischium. (Image courtesy of Andrea Trescot, MD)

13.14 Lower Extremity Pain

Saphenous

The saphenous nerve is the largest cutaneous branch of the femoral nerve. It is a purely sensory nerve and has no autonomic or motor function. Saphenous nerve innervates the skin in the medial thigh, front/medial side of the patella (infrapatellar branch), and the anterior and medial site of the leg (medial crural cutaneous branches). Any anatomical changes caused by tumors along the saphenous nerve (Fig. 14a, b, and c) could cause saphenous nerve entrapment syndrome in which there is pain but intact motor function in the leg (distinctive from lumbar radiculopathy).

Superficial peroneal

The superficial peroneal nerve is a mixed motor-sensory nerve. It innervates the peroneus longus and peroneus brevis muscles and the skin over the antero-lateral aspect of the lower leg with the dorsum of the foot (except the first web space) (Fig. 13.15). It travels between the peroneus and the extensor digitorum longus muscles, penetrates the deep fascia at the lower third of the leg, and divides into a medial dorsal cutaneous nerve and an intermediate dorsal cutaneous nerve. In its course between the muscles, the nerve gives muscular branches to the peroneus longus and peroneus brevis muscles and cutaneous sensory branches the lower part of the leg. Entrapment of the superficial peroneal nerve is an infrequent reason (3.5–13%) of chronic leg pain [27, 28]. Superficial peroneal nerve entrapment can result in an inability to evert the foot and loss of sensation over the dorsum of the foot (with the exception of the first web space between the great toe and the second toe).

13.15 Summary and Future Directions

Peripheral nerve entrapments are a commonly overlooked cause of painful conditions, resulting in pain literally from head to toe. Even the experienced clinician may not be aware of these syndromes, and entrapment of these often small nerves can lead to debilitating pain, mimicking migraines, cardiac disease, intra-abdominal/pelvic pathology, complex regional pain syndrome (CRPS), and specific pain syndromes of upper and lower extremities. Knowledge of their entrapments can prevent expensive, ineffective diagnostic tests as well as costly and ineffective treatments such as with potent pain medications or high risk procedures.

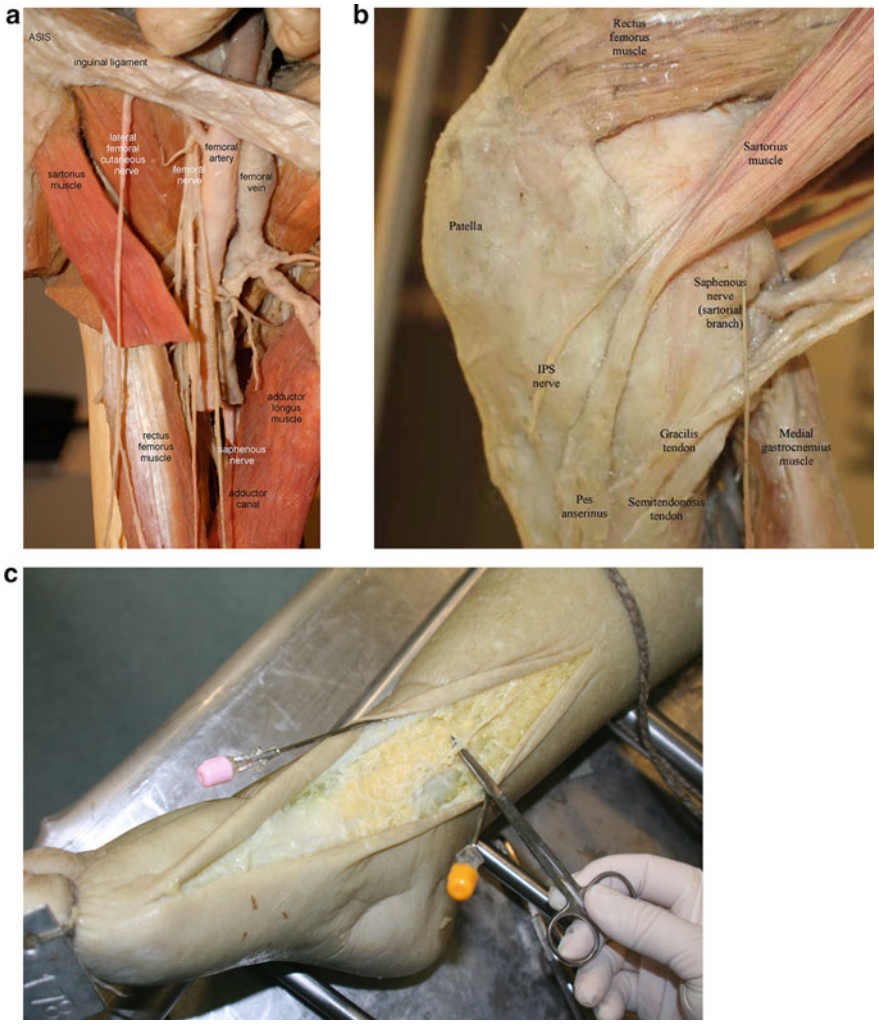

Fig. 13.14 Anatomy of the anterior leg, modified from an image from *Bodies, The Exhibition*, with permission. A = proximal leg; B = medial anterior knee; and C = distal medial leg. (Image courtesy of Andrea Trescot, MD)

Peripheral entrapments remain a treatable cause of pain; with appropriate diagnostic and treatment modalities, using physical exam, differential diagnosis, EMG/NCV, MRI/MRN, ultrasound, localized injections (landmark guided, fluoroscopic-guided, and ultrasound-guided), neurolytics, neuromodulation, and surgery, these painful conditions can be treated and managed.

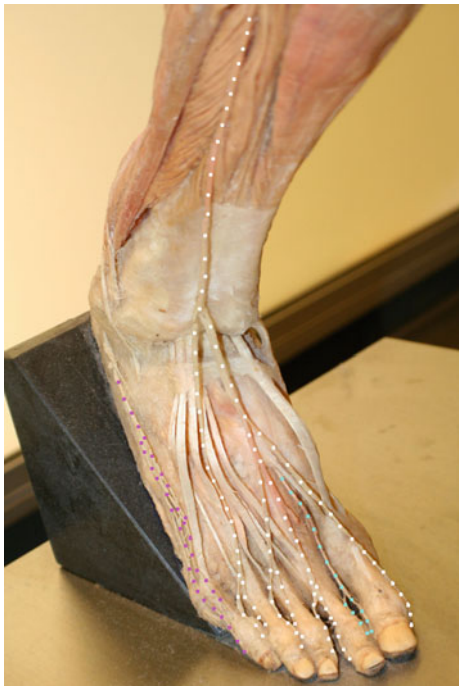

Fig. 13.15 Dorsal foot dissection, modified from an image from *Bodies, The Exhibition*, with permission. *White dots* superficial peroneal nerve, *green dots* deep peroneal nerve, *purple dots* sural nerve (Image courtesy of Andrea Trescot, MD)

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Intrathecal Analgesia in Cancer Pain

14

Denis Dupoiron

14.1 Introduction

The number of new cancer cases has been increasing globally over the last several decades. Pain is a major symptom during the evolution of the disease with approximately one-third of cancer patients with pain at an early stage of the disease, and more than two-thirds with pain in advanced stages [1]. The treatment of cancer pain remains a major challenge for both cancer patients and their providers. A recent review of the published literature by Van Beuken revealed that the number of patients suffering at an advanced stage of the disease has slightly increased since 2004, rising from 64 to 66% [1]. Within this category, many cancer patients [2] have pain resistant to high doses of opioids or unable to tolerate opioid-related side effects such as nausea or sedation. In 2000, Miguel [3] proposed a fourth level of the WHO ladder including interventional treatments for managing cancer pain. Intrathecal therapy is a major component of this fourth level of treatment.

14.2 History

Infusion of analgesics into the cerebrospinal fluid (CSF) began at the end of the nineteenth century [4], but was more widely implemented in the 1980s after the publication of the Gate Control theory [5], followed by the discovery of opiate receptors by Perth and Snider [6]. The first human experimentation in 1979 [7] demonstrated the relevance of this technique for pain treatment in eight cancer

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patients. Thereafter, the availability of fully implantable pumps spurred growth of the technique, especially over the last 20 years. Initially, only morphine was used for pain control via this technique, but, over time, combinations of analgesics have become increasingly common.

14.3 Definition

The principle of intrathecal analgesia is based on the administration of analgesics into the cerebrospinal fluid (CSF), close to the receptors present in the posterior horn of the spinal cord. The main advantage of intrathecal drug delivery systems (IDDS) is the reduction of analgesia-related side effects due to the overall smaller dosage of analgesics delivered systemically. IDDS also allows the administration of drugs to control pain that cannot be administered via any other route, such as Ziconotide. It has been proven effective in a large number of studies, including one randomized multicentric study [1]. In most of these studies, pain reduction greater than 50% has been observed, accompanied by a dramatic decrease in the rate of adverse effects [2].

14.4 Medications

14.4.1 Key Factors in Diffusion of Intrathecal Treatments

1. Spinal cord targets

   The targets for intrathecal drugs are in the spinal synapse of afferent nerve fibers Aδ and C found at Lamina I, II, and V, of the dorsal spinal horn [3]. Since the presence of opiate receptors at this level was revealed by Atweh in 1977 [4], it has become increasingly clear that a large number of receptors and mediators are involved in nociceptive signal modulation, while only a small number of them are likely to be targeted for intrathecal therapies [5,6].
2. Pharmacological Constraints: hydrophilia
   When medication is infused into the cerebrospinal fluid, it must pass through the highly vascularized and lipophilic pia mater, and then through the highly hydrophobic white matter, before it reaches the gray matter of the dorsal horn in the spinal cord. Therefore, the most lipophilic drugs will quickly pass through the pia mater and the white matter, but they will be quickly absorbed at the dorsal horn, resulting in high systemic absorption. On the other hand, the most hydrophilic drugs will tend to linger longer in the CSF (which is primarily water) and reach the spinal cord receptors later with a smaller proportion reabsorbed in the general circulation [7].

3. CSF Circulation
   In classic theory, CSF was thought to be produced by the choroid plexus and shows cranio-caudal movement thanks to hydrostatic pressure. However, we now know that CSF has a bidirectional pulsatile flow, thanks to arterial pulse and also to respiration-induced trans-thoracic pressure variations [8].
4. Level of Infusion
   This is also a major factor in the diffusion of intrathecal drugs. Bernards' work [9] has shown that diffusion of morphine and local anesthetics is much more limited than previously thought, with exponential reduction in concentrations on either side of the catheter tip. Indeed, diffusion of medication at sufficient concentrations does not go beyond a few centimeters on either side of the catheter tip [10].
5. Rate of Infusion
   This is the other key factor in the diffusion of intrathecally administered analgesics. Bernards [9] also showed an increase in diffusion, proportional to the rate of infusion, both for opiates and for local anesthetics. Moreover, local anesthetics, when administered slowly to the dorsal horn of the spinal cord, will not reach the ventral horn of the spinal cord, explaining the lack of motor effects even with high IT local anesthetic dosage.

14.4.2 Intrathecal Medications

In order to qualify for intrathecal administration, medications must share precise characteristics. First, they must not be toxic to the spinal cord and therefore must not contain preservatives. Moreover, they must be available at high concentrations. Finally, the molecule must be stable in the pump reservoir.

14.4.2.1 Opiates

Opiates are the most commonly used drugs in intrathecal administration. They act by binding to μ receptors at the level of the substantia gelatinosa of Rolando (SGR) both pre- and post-synaptically. **Morphine** is the most used molecule in intrathecal treatment. Its physical and chemical characteristics mean that it is the first-line agent par excellence. It is the most hydrophilic of the opiates, which provides it excellent bioavailability, despite a long onset period (Table 14.1) [11]. It is also available in concentrations up to 50 mg/ml, with no adjuvants. Finally, it has never been shown to be toxic for the spinal cord despite years of use. It is the only opiate approved for intrathecal use by the FDA in the USA and continues to be the first-line treatment in consensus for cancer pain [12]. **Hydromorphone** is also a hydrophilic opioid. The characteristics of this molecule are similar to those of morphine. It is three times more powerful than morphine when used in intrathecal treatment. Recommended doses range from 0.1 to 10 mg/day [12–14]. Hydromorphone is recommended in 1b Line or 2nd line by the most recent polyanalgesic consensus conference for cancer pain [12]. **Fentanyl and Sufentanil** are two very

Table 14.1 Intrathecal opiates: speed of onset and duration

	Lipophilicity:	Onset: (min)	Active for: (h)
Morphine	1	30–60	*12–24
Hydromorphone	1.4	20–30	*6–12
Fentanyl	580	5–15	*2–4
Sufentanil	1270	5–15	*2–4

hydrophobic mu agonist opioid molecules. They are fast-acting but with a high rate of absorption by the circulatory system. However, they still have a useful role to play in that they act more rapidly and may be responsible for fewer granulomas when used in long-term treatment [15]. Fentanyl is recommended in line 1b for cancer condition-related pain with localized nociceptive or neuropathic pain in association with bupivacaine. For cancer diffuse pain, fentanyl is recommended in the third line and sufentanil in the fourth line [12] under PACCS 2016 recommendations.

14.4.2.2 Local Anesthetics

Local anesthetics are voltage-dependent sodium channel blockers [16]. They are widely used in intrathecal therapy especially for cancer patients because, as sodium channel blockers, they are effective against both nociceptive and neuropathic pain. Bupivacaine and Ropivacaine are the best-suited molecules for intrathecal treatment, because of their long duration period as well as their stability in association with morphine in intrathecal admixtures. **Bupivacaine** is the most widely used local anesthetic in intrathecal pumps, due to its efficiency and its proven lack of spinal cord toxicity [17]. It is synergistic with Morphine [17] and is available in highly concentrated forms without preservatives (40 mg/ml). Finally, it has been proven stable in pumps when used in association with Morphine [18]. In the most recent consensus conference bupivacaine is recommended as first line (Ib) in association with morphine for cancer patients [12]. Its cardiac toxicity by intrathecal route is low when the common doses are considered. **Ropivacaine** is similar in profile to Bupivacaine, but it is less lipophilic and shows less cardiac toxicity [19]. However, few published studies are documenting long-term use [20,21] and there are lingering doubts concerning its spinal cord toxicity [22]. Furthermore, while high concentrated Bupivacaine is not available in some countries, Ropivacaine is the only local anesthetic available at a 10 mg/ml concentration.

14.4.2.3 Ziconotide

This is the most recent analgesic molecule for intrathecal treatment. It is a small peptide of 25 amino acids with a molecular weight of only 2500 daltons. Ziconotide is a very hydrophilic synthetic molecule isolated originally from the venom of a Pacific marine snail, the Conus Magus [23]. Ziconotide (Prialt ®) is the first Type-N voltage-dependent calcium channel blocker on the market. It has a half-life in C.S.F. of 4 to 6 h and acts by reducing the secretion of glutamate at the pre-synaptic

level. Ziconotide is a powerful medication with daily doses from 1 to 20 μg/day. It is available only for intrathecal route. Its efficacy has been proven in three randomized studies [24–26]. Ziconotide is active for both nociceptive and neuropathic pain [27]. However, it may be responsible for adverse effects, some serious in nature, e.g., neuropsychiatric, although these side effects cease when treatment is interrupted. Neither spinal cord toxicity nor tachyphylaxis has been observed during these studies. Ziconotide is approved by FDA and recommended as first-line use by the most recent Polyanalgesic Conference Consensus (PACC) for cancer patients [12].

14.4.2.4 Clonidine

Clonidine is a pre-synaptic and post-synaptic α2 adrenergic agonist. It acts both by reducing the secretion of neurotransmitters, most notably substance P, and by causing membrane hyperpolarization by increasing potassium conductance [5]. It has been shown effective in intrathecal treatment, especially on neuropathic pain, at doses from 50 to 1500 μg/day. It is used primarily in combination [28], and its use is limited by side effects such as sedation and hypertensive effects [29, 30]. Dexmedetomidine is an alternative to clonidine but only one study established a synergic effect with morphine for cancer patients [31].

14.4.2.5 Baclofen

Baclofen is a GABA B receptor agonist. This drug is hydrophilic and has difficulty crossing the blood–brain barrier. It could be active against neuropathic pain at doses from 100 to 400 μg/day [32]. Baclofen is primarily used in the treatment of spasticity, where it has proven its effectiveness.

14.4.2.6 Other Molecules

Ketamine, an NMDA receptor antagonist, is typically not recommended for intrathecal use due to a risk of spinal cord toxicity [33]. No human studies have shown evidence for the efficacy or the innocuousness of Midazolam, a GABA A receptor agonist. In a recent study, Gabapentin showed no effectiveness when used intrathecally [34].

14.4.2.7 Associations of Drugs

Due to the complexity of transmission of nociceptive messages at the spinal cord level, the involvement of a large number of chemical compounds in signal modulation, as well as symptomologies including both nociceptive and neuropathic pain, practitioners were encouraged early on to consider associations of medications that would increase pain control. Moreover, some associations have a proven synergistic effect that allows physicians to decrease doses and consequently any adverse effects. The use of intrathecal admixtures requires a prior understanding of the compatibility of various components, their stability in pumps, as well as their innocuousness for the spinal cord and medical devices used. Many associations have proven their usefulness both in vitro and in vivo. To better manage these associations, international expert consensus conferences have established guidelines

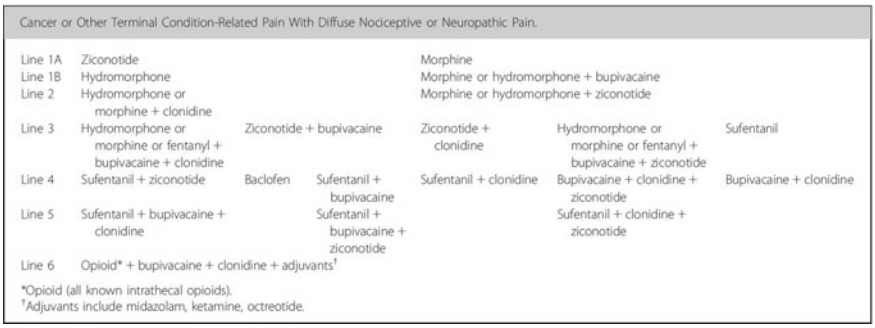

Fig. 14.1 Polyanalgesic consensus conference (PACC) 2016 recommendations for cancer patients. Reproduced from Deer et al. 2016 [14]

with lines of treatment especially for cancer pain. The latest update, done by T. Deer in 2016 [14], allows association as soon as first line b or line 2 for cancer patients (Fig. 14.1). Even if the main manufacturer does not recommend using combinations, 96% of I.T. drugs are used off-label for cancer patients [35].

14.5 Patient Selection

14.5.1 Indications

Intrathecal analgesia is an invasive technique which must be reserved for patients presenting with refractory cancer pain after a well-managed pain control program. The main indication for I.T. treatment is resistance to analgesics despite high doses of opiates, or the onset of intolerable side effects to that treatment. In oncology, intrathecal drug delivery is reserved for patients without pain relief despite well-conducted treatment following the WHO ladder. However, the technique is also proposed for patients presenting with serious adverse effects with classic treatments (opioids and adjuvants).

Initially, patients were distinguished into two groups. First, patients with a short life expectancy, for whom the implantation of an external catheter or a catheter connected to a subcutaneous port and an external pump seems the best and less expensive choice. Secondly, patients whose life expectancy appeared more than 3 months for which an internal pump seems the best initial choice [36]. Nevertheless, the last consensus conference states that intrathecal analgesia can dramatically change the life expectancy of patients, and therefore, this limit has no real significance and it seems the best choice is one with the main goal of improving quality of life. Having a multidisciplinary meeting of specialists can help in determining indication and choice of device type, considering all the parameters of the disease, and patient psychological and social contexts.

14.5.2 Contraindications

Intracranial hypertension is an absolute contraindication, as well as any obstacle to the C.S.F circulation. Other contraindications include any uncontrolled infections, serious coagulopathies, and allergies to implanted devices or to any medication involved. Patients should be without psychosis or substance dependence and must be able to agree to this course of treatment and be able to understand and follow it. Relative contraindications include, primarily, a bodyweight too low to support a pump (frequent at an advanced stage of cancer), anemia, minor coagulopathies, and limited access to medical care. Urinary and digestive stomas are not a contraindication for the implantation of an internal pump, but physicians must be aware of a higher infection risk.

14.5.3 Pre-implantation Assessment

Cancer patients who may potentially receive intrathecal analgesia are not required to undergo a psychological assessment [12]. For example, a patient with Pancoast-Tobias syndrome without pain relief despite high levels of painkillers is a good indication for IDDS, even if the patient has a coexisting mood disorder. However, patients suffering from depression, anxiety, or suicidal tendencies, must be treated for those disorders before considering implantation. It is similarly essential to be sure patients understand and accept the treatment. However, in cancer treatment, quality of life remains the key objective, and psychological assessment must not delay the implementation [37]. For some primitive tumors, with high levels of pain, like pancreatic cancer, IDDS could be considered sooner to improve quality of life [38]. It is also important to be aware of any comorbidities or any treatments that could interfere with intrathecal analgesia, such as obesity, diabetes and chronic respiratory disease.

14.6 Implantation

14.6.1 Equipment and Devices

14.6.1.1 Catheters

Generally made of silicone or polyurethane, catheters are radiopaque. Internal diameter is generally 0.5 mm. Recently, a new type of catheter has been marketed. It is a multilayer composite made of polyurethane and silicone featuring a braided body, which limits kinking and breaking, and facilitates implantation.

14.6.1.2 Pumps

Internal pumps: Current pumps are generally programmable with variable flow, unlike the first pump marketed as Infusaid 400. These continuous flow rate pumps

Table 14.2 Characteristics of different intrathecal pump models

Model	Accuracy (%)	reservoir	Flow rate	MRI	Availability
Synchromed II	87	20–40 ml	0.048–24 ml/D	3 T	Worldwide
Prometra II	97	20 ml	0–28.8 mL/day	1.5 T	
Medstream	90	20–40 ml	0.1–4 ml/d	3 T	Not available anymore
Siromedes		20–40 ml	0.25–3 ml/ d	3 T	Germany

were cheap but of limited interest for cancer patients as bolus doses were not available and because it was necessary to change the mixture to increase the drug daily dose. Electronically controlled variable flow rate pumps are now most used. They offer two access points: a central one to refill the reservoir, and a lateral one connected directly to the catheter. These pumps feature different administration modes: continuous, continuous with bolus, and programmable variable flow rate (Table 14.2).

External Pumps: Catheters may, for cancer patients with short life expectancy, be connected to a subcutaneous reservoir, and infusion is then performed by an external pump. Several systems allow practitioners to employ this technique of infusion. Pumps must offer low flow rates (0.1 ml/hour) with incrementations of 0.01 ml/hour, as well as pressure and shutdown alarms. Some systems may currently be remote-controlled through an Internet interface or the GSM network.

14.6.2 Implantation

Implantation is performed in the operating room mostly under general anesthesia. The patient lies in lateral decubitus position. Puncture is done at the lumbar level with a Tuohy needle supplied with the catheter. A paramedian approach is recommended to reduce the risk of catheter breakage. The curved end of the needle is oriented along the dura mater fibers also in order to reduce C.S.F. leakage. Once flow is observed, the curved end is oriented upwards. Next, the catheter is introduced into the needle and its progression up the C.S.F monitored under live fluoroscopy. Once the tip of the catheter is located at the right level, its position is checked laterally to verify posterior location within the canal. Next, a vertical cutaneous incision is made opposite the puncture down to the aponeuroses. A pocket is formed as layers of skin are peeled away. The catheter guide is then removed, and C.S.F must flow through the catheter end. The catheter is anchored using the device supplied with the manufacturer's kit. Secondly, the physician proceeds to an incision in the abdominal wall down to the muscle aponeurosis and a pocket is created of the same size as the diameter of the pump. An alternative place of the pocket is in the upper part of the buttock, which may be problematic for patients at the end of life who are supine most of the time. In this case, the surgery is performed in ventral decubitus position.

14.6.3 Complications

14.6.3.1 Complications Related to the Technique

Spinal Cord Injury is rare. Prevention depends on the implantation technique employed. Imaging is recommended prior to surgery to detect potential obstacles. In general, lumbar puncture and fluoroscopy during catheter movement up the spinal cord are sufficient to prevent spinal cord injuries. In addition, the catheter must encounter no resistance during this procedure. A neurological examination must be done at the end of the procedure, and MRI must be undertaken as soon as possible if any spinal cord injury is suspected. **Post-Lumbar Puncture Syndrome** is one of the most frequent complications; incidence varies in the literature from 1 to 30%. Even induced subdural hematomas and meningeal hemorrhaging have been described. Treatment consists of hydration and administration of caffeine, Sumatriptan or Theophylline. If symptoms persist, a blood patch may be considered, despite risks of infection and of catheter breakage, but only if other options fail. **Bleeding** is rare, amounting to not even 1% in Aprili's meta-analysis [39]. Preventive measures include monitoring as the patient stops taking anticoagulants prior to surgery in line with current recommendations [40]. The incidence of infection varies from 0 to 9% [41]. It is more likely to occur in cancer patients due to immunosuppression (i.e., with chemotherapy, corticosteroids). Superficial infections of the abdominal wall can cause expulsion of devices. In such cases, after surgery, drainage, and antibiotic treatment, the material may be able to be left in place. Deep infections, pump pocket infections, and meningitis almost always requires the removal of devices. Diagnosis of meningitis can be done either through catheter puncture at the specific port or by direct lumbar puncture.

Pump pocket Seroma can occur prematurely either in the pump pocket, or at the lumbar incision, or it can be a sign of C.S.F. leakage. In cancer patients, cachexia increases the likelihood of this condition. Seromas generally clear up after drainage. **Catheter Dislodgement, Breakage, and Kinking** are often diagnosed after a sudden loss of efficacy of the IT treatment. Catheter dislodgment is generally caused by inadequate anchoring. It is easily detectable by CT Scan [42]. Kinking and breakage of the catheter were frequent with silicone catheters. The multi-layer body of today's catheters considerably reduces the risk of breakage and kinking. "**Flipping" of Pumps** occurs if the pump pocket is too large, such as in cases of obesity, when a pocket seroma occurs, or when anchoring was inadequate. Diagnosis is often done during a refill when the pump refill injection point proves inaccessible and is confirmed by ultrasound, CT-scan or by X-ray, as the pump is asymmetrical. It is sometimes possible to manually flip the pump back to the correct position.

14.6.4 Complications of Intrathecal Treatment

14.6.4.1 Opiates

Respiratory Depression is rare. It can be caused by a combination of factors, including concomitant use of sedatives, chronic bronchopathy, or the use of high doses of IT opiates. It is antagonized by Naloxone [43]. **Withdrawal symptoms** may appear in the first few days following implantation and systemic opioid withdrawal. These are characterized by sweating, trembling, diffuse aches and pains, and nausea. **Urinary Retention** is a side effect of the agonist action of opiates on the sacral parasympathetic nucleus. Incidence during chronic IT administration is 3%. Men over 60 years of age are at higher risk. **Hormonal disorders** can occur, caused by inhibition of the hypothalamic-pituitary axis resulting in water and sodium retention, weight gain, sex drive decrease, and impotence in men [44]. **Itchiness and Constipation** are less common by intrathecal route than by oral route. **Spinal Mass Syndrome or Granuloma** may form at the tip of the catheter and may cause spinal cord compression. Its formation is not completely understood. Highly concentrated morphine and very low flow rates appear to be the most commonly observed risk factors [6]. The rate of incidence is estimated at between 0.1 and 0.5%. The most frequently observed signs are a return to previous levels of pain, and sensorimotor deficits. Diagnosis is confirmed by MRI; treatment is then either conservatory (ceasing infusion of medication, replacement by saline solution), or surgical resection and catheter removal. Preventive measures include the use of low concentrations of Morphine (<20 mg/ml), and the use of Ziconotide alone or in association [15].

14.6.4.2 Local Anesthetics

Local anaesthetics can be responsible for hypotension, urinary retention, and motor deficits when used at high doses. Cardiac toxicity risk is low by intrathecal route.

14.6.4.3 Clonidine

IT administration of clonidine can cause drowsiness, dizziness, and hypotension; moreover, hypertension can occur when the drug is withdrawn suddenly.

14.6.4.4 Ziconotide

Ziconotide can occasionally cause serious neurological and psychological disorders. Prevention requires slow incrementation after a low starting dose (0.5–1 μg/j) [45], as well as used in association with Morphine [46]. It is also essential to monitor creatine kinase levels, primarily at the start of treatment.

14.7 Management

14.7.1 Patient Monitoring

Following implantation, the patient should be monitored for at least 24 h if a complete withdrawal of systemic analgesics is done. The main purpose is to prevent symptoms of overdose as well as withdrawal.

14.7.1.1 Administration Modes

Continuous administration of IT medications is the only mode currently validated for use. The patient can, however, administer a bolus dose with the help of a remote control. Boluses are pre-programmed by the physician and are generally about 1/10 of the daily dose.

14.7.1.2 Refills

Refills are completed by trained practitioners. The preparation of admixtures will optimally be done in pharmaceutical conditions under laminar flow hood. A verification of concentrations of each component drug of the admixture before delivery reduces the risk of overdosage [47]. Because of the risk of infection, sterile conditions must be strictly adhered to during refills. Spillage of drug solution into the pump pocket may cause serious undesirable effects through subcutaneous diffusion. Programming must be done by the physician or trained providers.

14.8 Conclusion

Intrathecal analgesia has become over the years a credible and effective alternative to oral analgesics for refractory cancer pain. Better understanding of diffusion mechanisms and advances in technology have allowed for expanded and more efficient use of intrathecal analgesic devices. Finally, the pharmaceutical management of intrathecal mixtures has dramatically reduced errors and therefore overdoses. Gradually, this technique is becoming a better controlled and more accurate mode of drug administration, though it remains with risks. Given its effectiveness for pain and side effects of oncology treatments, it should be considered earlier in the disease trajectory to improve the quality of life of patients.

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Neurosurgical Treatments for Cancer Pain

15

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15.1 Introduction

Cancer-related pain is a uniquely challenging entity for treating practitioners for a variety of reasons, including its often severe and medically refractory nature, the emotional and social circumstances surrounding the disease process, and the frequently associated limited life expectancy. Alleviation of pain in these circumstances is of paramount importance, not only for quality of life but potentially for optimal longevity. Practitioners must have a comprehensive understanding of all the available treatment modalities. While neurosurgical management in these cases is reserved for patients experiencing intractable pain, refractory to other, less-invasive treatment modalities, refinements in techniques and technological advances have allowed for many of these options to be considered viable measures during the course of treatment, and not solely limited to treatments of last resort.

Neurosurgical management for cancer-related pain has improved dramatically over the past several decades both in its efficacy as well as in its increasingly minimally invasive nature. Many of these valuable procedures are vastly underutilized, often because of a combination of lack of knowledge of their existence by referring practitioners, as well as a lack of appropriate neurosurgical expertise, currently available only at highly specialized centers.

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When evaluating a patient for potential surgical interventions, the patient should first be assessed for a surgical debulking/resection procedure when feasible to decrease or eliminate malignant cells, relieve compression on surrounding structures, and/or maintain or restore stability of painful regions of the body. When this is not possible or practical, neurosurgical interventions aimed at modulating or ablating regions of the pain processing pathway should be considered. These interventions range from intervention at local peripheral nerves, ascending sensory spinal tracts, brainstem processing pathways, thalamic relay nuclei, and limbic circuitry pain processing nodes. Consideration is given to special circumstances such as facial pain circuitry and treatment for diffuse bony metastasis. While ablative procedures continue to be the hallmark of cancer pain treatment because of their immediate effects and often minimally invasive nature, insertion of neuromodulatory devices such as peripheral nerve stimulators and deep-brain stimulators should also be considered, particularly for those patients with longer life expectancies and those who can tolerate an implanted device. This is becoming increasingly more salient as cancer treatments become more effective and thinking shifts toward the optimization of the care of cancer survivors with potentially continued, long-standing intractable pain syndromes as a consequence of their primary disease and/or treatments.

15.2 Lesioning Procedures of the Spinal Cord, Brainstem, and Pituitary Gland

Unilateral Pain

Body Pain

Cordotomy

The surgical lesioning of the spinothalamic tracts has long been utilized as an effective remedy for intractable pain and has evolved significantly over the course of the past several decades. Whereas in the past, this procedure involved open laminectomy and direct surgical manipulation of the spinal cord (with attendant morbidity), the modern procedure is a minimally invasive percutaneous approach under CT guidance under local anesthesia with minimal sedation. This procedure is safe, effective, and particularly useful for treating unilateral, nociceptive pain at the level of the shoulders (C4 dermatome) and below. In order to perform the procedure, the patient needs to be capable of lying on the CT gantry for the duration of the procedure (30–60 min), accurately reporting sensorimotor activity to the surgeon, and free of any coagulopathy.

The goal of the procedure is to interrupt the spinothalamic tract (pain and temperature fibers) at the C1/2 level with a needle-guided percutaneous approach contralateral to the region of pain. At this level, the spinothalamic tract has a ventromedial (upper extremities) to dorsolateral (lower extremities) somatotopy. To perform a CT-guided cordotomy, the patient initially undergoes a lumbar puncture

for introduction of myelographic dye into the cerebrospinal fluid (CSF). Alternatively, a cervical myelogram can be performed as part of the procedural approach, although it may take some time for the contrast to mix evenly throughout the CSF. Once the contrast has mixed evenly, the patient is positioned supine on the CT scanner table, and a thin walled 20 gauge needle is advanced under serial imaging, eventually penetrating the dura. The area of pain will determine somatotopic targeting within the spinal cord with the more caudal regions being closer to the dentate ligament and more laterally placed. Once the needle is close to the pial surface, a thin radiofrequency probe is inserted (Fig. 15.1). Next, with the patient's cooperation, low-frequency stimulation is used to determine proximity to the corticospinal tracts (which would result in motor contractions), and higher frequency stimulation is used to elicit paresthesias in the target region of pain. Once localized, one or several lesions are made at approximately 80 °C for 60 s.

Outcomes from this procedure are generally favorable, and pain relief is usually instantaneous, although a delayed response has also been seen. In several recent series, patients experienced 83–86% reductions in pain immediately after cordotomy, and Karnofsky Performance Status (KPS) for patients with end-stage cancer with extremity pain increased by 40–83% [1, 9, 11]. Side effects are generally uncommon and can include temporary paresis, ataxia, dysesthesia, hypotension, and urinary retention in < 3% of patients. Cordotomy has been performed bilaterally, often in a staged fashion, although the use of this technique for bilateral pain in general, and bilateral upper extremity pain in particular, is limited secondary to concern for central hypoventilation syndrome (Ondine's Curse), although this has not been substantiated in recent publications. Pain relief is sustained for at least 6 months in most patients and can lose its effect over time although patients with pain relief lasting as long as 35 years have been described [1, 11, 15]. Given the

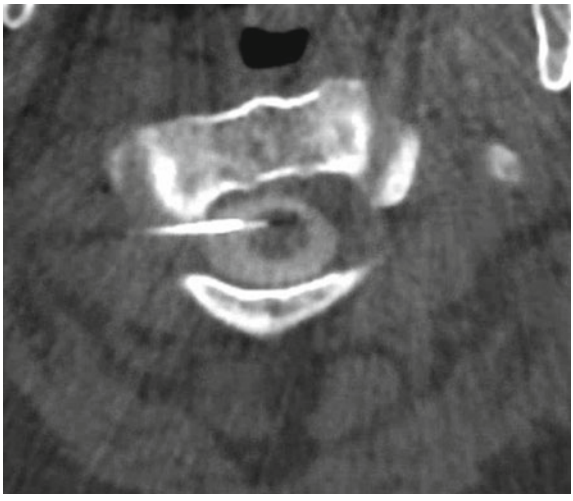

Fig. 15.1 CT-guided percutaneous cordotomy. Courtesy of William Rosenberg, MD

potential for significant benefits and a relatively minimal side effect profile, this procedure is notably underutilized by pain management specialists and oncologists.

Spinal Dorsal Root Entry Zone (DREZ) lesion

For patients who experience unilateral, primarily neuropathic pain in a topographically limited distribution, DREZ lesioning (or DREZotomy) may be an efficacious treatment option. This technique is currently most commonly utilized for patients who suffer from pain secondary to traumatic brachial plexus avulsion in an otherwise non-functional limb and has been described in various studies for the treatment of cancer-related pain [2], usually, after all medical and even first-line surgical treatments (i.e., intrathecal opioids, spinal cord stimulation) have failed or been deemed inappropriate.

This surgery is performed utilizing an open surgical technique requiring a laminectomy or hemilaminectomy to access the dorsal portion of the spinal cord. The dura is then opened, and the dorsal rootlets are identified. The procedure involves creating a lesion in the dorsolateral sulcus, where the rootlets enter the gray matter of the spinal cord with the ultimate goal of ablating the rootlets themselves, the medial portion of Lissauer's tract, and the dorsal layers of the dorsal horn of the spinal cord (Fig. 15.2). The procedure can be performed either with bipolar electrocautery, or more commonly with a radiofrequency ablation probe.

The largest series includes 367 patients who underwent DREZotomy, 81 of whom were treated for cancer-related pain. A good result (>75% pain relief) was obtained in 78 and 87% of patients who had the procedure performed at the lumbosacral level and cervicothoracic levels, respectively, [14]. In this series, the authors suggest that ideal candidates for this procedure are those with localized lesions such as Pancoast tumor, cancerous invasion of the thoracic or abdominal wall, or involvement of the lumbosacral nerves in limited distributions. There have also been limited studies investigating the use of DREZ lesioning in

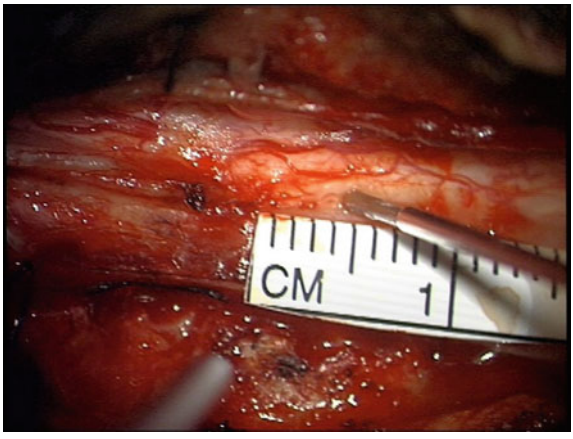

Fig. 15.2 Dorsal Root Entry Zone (DREZ) lesioning procedure. Courtesy of William Rosenberg, MD

radiation-induced deafferentation pain, with one series reporting complete resolution of pain in 5 out of 6 patients with a median follow up of 12 months [17].

Head and Neck Pain

The treatment of intractable pain of the head and neck secondary to malignancy has been a surgical challenge secondary to the unique anatomy and challenging surgical access to the trigeminal system and upper cervical nerve roots and has ultimately led to a series of distinctive surgical approaches. These approaches are reserved for when other less-invasive techniques have failed to effectively palliate symptoms.

Nucleus Caudalis Dorsal Root Entry Zone (DREZ) Lesioning

Lesioning of the dorsal root entry zone for facial pain targets the nucleus caudalis region, which is the most inferior subdivision of the spinal trigeminal nucleus extending from the spinomedullary junction down to at least the level of C2. In this region, first-order neurons transmitting pain and temperature signals from the ipsilateral face synapse onto second-order neurons residing here that then cross contralaterally to ascend in the trigeminothalamic tract. This technique is most commonly used to treat facial pain that is refractory to other procedures and has been reported variably for the treatment of malignancy-related pain of the head, and face. Similar to spinal DREZ lesioning, the technique involves an open surgical approach, and, because it is a technically involved procedure, consideration should be given to the patient's general health preoperatively. In this procedure, the patient is positioned prone on the operating room table with the head in a Mayfield clamp. A suboccipital craniectomy, as well as a C1 laminectomy, is performed. The dura is opened and the obex is identified, as well as the C2 rootlets, and lesions are made approximately 1 mm apart between these two structures with a specialized radiofrequency ablation probe (3 mm tip and 0.25 mm diameter) ipsilateral to the region of pain in the intermediolateral sulcus (Fig. 15.3) [8].

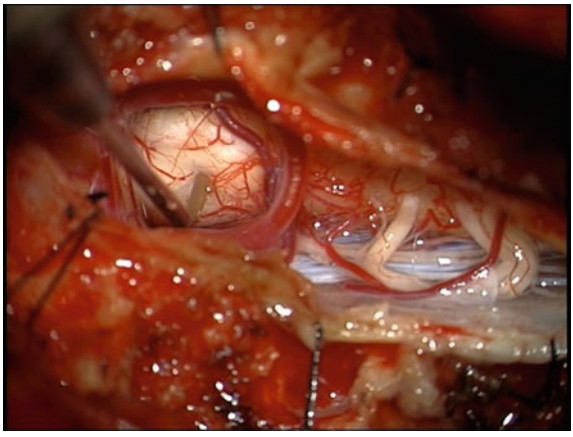

Fig. 15.3 Nucleus caudalis DREZ procedure. Courtesy of William Rosenberg, MD

This technique leads to well-described, favorable outcomes in the treatment of intractable facial pain, and has been reported specifically for malignancy-related pain in a handful of case reports and case series. In one case, series of 5 patients with unilateral, refractory cancer-related pain of the face, all patients reported good or excellent pain relief immediately after surgery [13]. On later follow up (mean 14.4 months), 3 of 5 patients reported significant improvement in pain and level of activity. Two of the 5 patients continued to sustain significant reductions in pain, however, suffered from an impaired level of activity secondary to pain. The only adverse event in the series was a patient who developed temporary postoperative cerebrospinal fluid leakage requiring placement of a lumbar drain, although it is well known that patients may also suffer from ipsilateral arm ataxia after this procedure, either temporarily or permanently, from damage to the nearby dorsal spinocerebellar tract.

Trigeminal Tractotomy

In trigeminal tractotomy (TR), the descending first-order neurons of the trigeminal nerve pain and temperature pathways are lesioned in the ipsilateral spinal tract of the trigeminal nerve (also known as the descending trigeminal tractus) en route to the nucleus caudalis. This procedure was first performed via an open technique in the 1930s, and by the late 1960s, minimally invasive percutaneous techniques using radiofrequency ablation were developed using stereotactic methods. Later versions of this procedure also involved lesioning of the second-order neurons at the nucleus caudalis at the level of the occipital cervical junction which was termed trigeminal nucleotomy (NC). Most recently, a combination procedure of trigeminal tractotomy and trigeminal nucleotomy has been proposed, guided by computed tomography (CT) to facilitate topographical localization of the electrode tip in the spinal cord (Fig. 15.4) [7].

The short time duration and minimally invasive nature of the procedure may be, especially well-suited for patients with malignancy-related pain who may be at the end of life. The procedure is performed in a comparable fashion to percutaneous cordotomy, and similarly, prior to the procedure, a lumbar puncture is performed in order to obtain a myelogram to better visualize the spinal cord during the procedure. The patient is then positioned prone on a CT scanner table, with the neck in a flexed position. This may be performed with the patient awake, or under general anesthesia. A 20-gauge needle is inserted under CT guidance at the occiput/C1 level approximately 6 to 8 mm lateral from the midline. After puncturing the dura, an RF probe is inserted into the upper spinal cord at a depth of 3 to 3.5 mm although these measurements are determined based on prior imaging in each individual and vary from 2.8–4.6 mm [7]. When the procedure is performed with the patient awake, localization of the appropriate region is then obtained via electrical stimulation and patient report of paresthesias. The final lesion is made at 70–80 °C for 60 s.

One series reported the results of 73 TR-NC procedures in 65 patients over a 20 year time period, with a mean follow up of 5.3 years (range 6 months to 16 years) [7] . Thirteen of these patients underwent the procedure for craniofacial malignancies, most of whom suffered from both nociceptive and neuropathic pain.

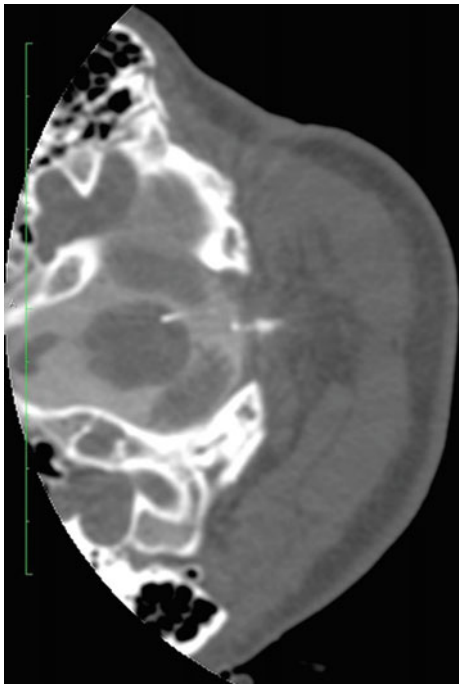

Fig. 15.4 CT-guided percutaneous trigeminal tractotomy/nucleotomy. Courtesy of William Rosenberg, MD

Of these, 11 patients achieved a grade I result (no pain) and 2 patients achieved a grade III result (partial non-satisfactory pain relief). In the latter two patients, both underwent a nucleus caudalis DREZ procedure which successfully led to pain relief in one of the two. There were no adverse events related directly to the procedure in this cohort, although the one patient who did not obtain adequate pain relief despite multiple procedures committed suicide. In the general cohort of the 65 patients undergoing this procedure for various other craniofacial pain etiologies, 4 cases of transient ataxia were observed (6%), and transient motor complications were observed in 2 cases (3%), both of which resolved within 2 weeks. Overall, trigeminal tractotomy- nucleotomy can be an effective, minimally invasive procedure that may be performed prior to considering more invasive procedures such as nucleus caudalis DREZ for the treatment of unilateral face pain secondary to malignancy.

Mesencephalotomy

Stereotactic mesencephalotomy is a procedure that targets body and facial pain pathways in the midbrain to treat refractory pain of the contralateral neck, head, and face. It is indicated for patients with intractable, unilateral nociceptive pain not amenable to cordotomy, i.e., pain distributions at or above the C4 dermatome. Similar to other neurosurgical procedures targeting intractable pain, the literature surrounding this procedure has significantly declined since the 1990s, and the procedure is at risk of being lost from the neurosurgical repertoire [6]. The

procedure is indicated for malignant pain and for patients with a limited life expectancy and aims to create a lesion in the midbrain at the target level of the inferior colliculus, 5 mm below the posterior commissure and directly lateral to the aqueduct of Sylvius, approximately 6 mm lateral to midline. The procedure creates a lesion that disrupts both the ascending spinothalamic and trigeminothalamic tracts. This procedure also targets the nearby spinoreticular pathway, which is implicated in pain arousal as well as the effective components of the pain pathways. The main adverse events associated with this procedure are severe dysesthesias following potential damage to the medial lemniscus, as well as disorders of ocular motility.

The procedure is performed using stereotactic methods via a frontal burr hole. A 1.8 mm diameter radiofrequency electrode with a 1.5 mm exposed tip is then inserted to the target level. The patient is awakened for intraoperative functional stimulation in an attempt to recreate the pain and avoid paresthesias (medial lemniscus) or eye movements (oculomotor pathways) and map the region of pain prior to lesioning. Next, a lesion is made at 60–80 °C for 60 s, with a desired endpoint of loss of pain/temperature sensation in the region of pain.

The long-term efficacy of this procedure is unknown, particularly because it is often used in patients nearing end of life but is hypothesized to be similar to cordotomy as similar tracts are ablated.

Midline visceral pain

Myelotomy

Visceral pain of the pelvic, abdominal, and retroperitoneal structures secondary to malignancy is an entity that is sometimes challenging to treat. In patients that fail conservative measures, as well as potentially first-line surgical measures (i.e., intrathecal opiates), midline myelotomy is a feasible option. Myelotomy may also be performed initially in patients who have limited life expectancies or choose not to have an implanted device. This procedure aims to segmentally interrupt commissural fibers and has been successful beyond a simplistic anatomic explanation, leading some to hypothesize that there is an extra lemniscal ascending pain pathway controlling visceral pain [20]. The procedure is most often performed using the open surgical approach, with the patient prone on the operating table and a single or multilevel laminectomy in the thoracic spine, depending on the region of pain. The dura is then opened in the midline and an incision is made in the posterior parenchyma of the spinal cord in between the dorsal columns and down to the level of the anterior commissure. The procedure has also been described using a punctate approach, where the goal is the disruption of the extralemniscal ascending pain system, usually performed at one level. This can be accomplished either via an open laminectomy approach (Fig. 15.5) or via an image-guided percutaneous RF approach (Fig. 15.6), although success with the latter technique has been less favorable.

An analysis of a series of 23 patients who underwent punctate midline myelotomy revealed that most patients were independent of opioids or had significantly reduced opioid use in a period from approximately 2 weeks to 31 months after the

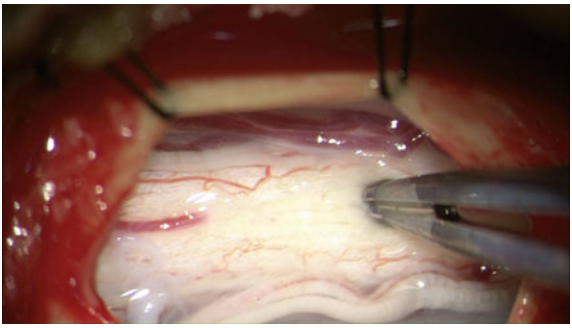

Fig. 15.5 Laminotomy with midline myelotomy using the bipolar electrocautery method Courtesy of William Rosenberg, MD

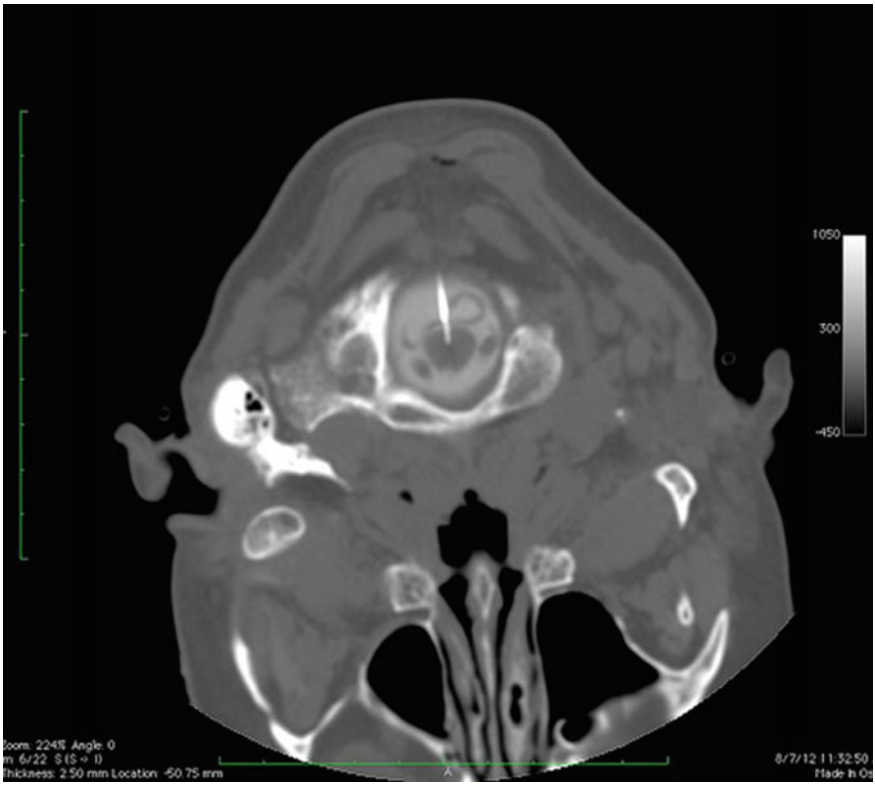

Fig. 15.6 CT-guided percutaneous midline myelotomy. Courtesy of William Rosenberg, MD

procedure [5]. In many patients, the pain recurred after a period of several weeks to several months but was significantly less intense. Some patients experienced recurrence of pain in sites adjacent to the original region of pain, and it is unclear if this represented progression of the underlying disease process. Adverse events were only sporadically reported in this series but included loss of posterior column function as well as bladder and bowel dysfunction.

In another case series, results of 11 patients undergoing commissural myelotomy at a single center were included [18]. Nine of the 11 patients underwent myelotomy for the treatment of pain associated with metastatic cancer within the pelvis or abdomen, and two patients underwent myelotomy for the treatment of pain syndromes associated with unresectable spinal tumors. Average life expectancy in this series was 43 days (range 22 days to 39 months). In their series, 8 of the 11 patients reported excellent (defined as no further pain) or good (defined as a significant reduction in pain and not requiring opiates stronger than codeine) outcomes. Adverse events included lower extremity weakness in 3 patients, one in whom the anterior spinal artery was disrupted during surgery and one who underwent intramedullary tumor resection in addition to the myelotomy. One patient reported postoperative urinary retention. Only one patient in the series did not report any benefit from the procedure, and in this patient, the myelotomy was noted not to extend to the depth of the anterior median sulcus. While side effects from this procedure may be significant, many patients in these cohorts were previously debilitated and nonetheless reported drastic improvements in quality of life secondary to pain reduction.

Diffuse Pain

Radiosurgical Hypophysectomy

Surgical and chemical hypophysectomy involving the destruction of all or part of the pituitary gland was previously a popular treatment for hormonal dependent malignancies, in particular breast and prostate cancer. Even though the procedure was initially conducted for control of the malignancy, it was widely noted that pain relief was immediate and sustained. After the advent of targeted hormonal therapies, hypophysectomy is now seldom performed for the treatment of malignancy-related pain except for in a few specialized centers. In these centers, it is performed using minimally invasive stereotactic radiosurgery (SRS) in patients with intractable, diffuse pain and particularly for those patients with diffuse, bony metastases (Fig. 15.7).

In a recent meta-analysis, 23 patients were identified who underwent pituitary SRS for malignancy-related pain, 19 of whom had bony metastases [12]. The maximum radiation dose ranges from 150 to 250 Gy, with radiation doses to the optic nerves kept below 10 Gy. Targeting strategies varied among reports, ranging from the anterior two thirds of the gland to including the whole gland and/or gland-stalk junction. There is some evidence that radiation-induced damage of the hypothalamic-pituitary axis may disproportionately involve the pituitary stalk, and

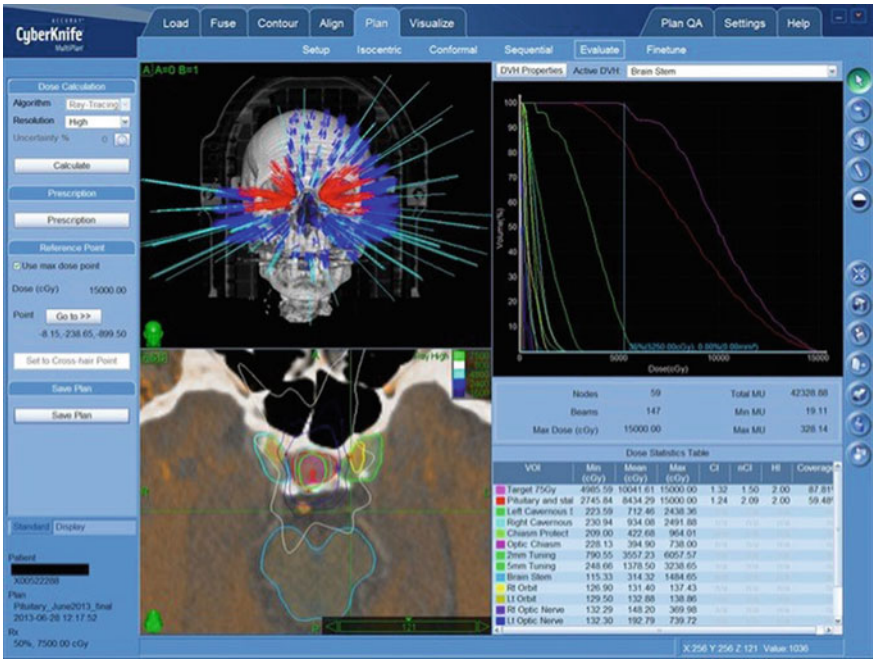

Fig. 15.7 Radiosurgical hypophysectomy pre-procedural planning. Courtesy of William Rosenberg, MD

some therefore advocate for the inclusion of the gland-stalk junction within the 50% isodose line for maximum efficacy [3].

Among these patients, 20 of 23 (87%) experienced significant pain relief, which was sustained in all patients until death or last follow up (range 1–24 months). Notably, in one series of 9 patients treated with pituitary SRS, complete relief was achieved in all patients within a few days [4]. In this cohort, 8 of 23 patients (35%) were noted to have adverse events from the procedure, mostly related to hormonal deficits including one patient with diabetes insipidus and others with decreases in luteinizing hormone, follicle stimulating hormone, total urine gonadotropin, urine osmolarity, protein-bound iodine, and triiodothyronine. These deficiencies were corrected with medical hormonal replacement.

Radiosurgical hypophysectomy is potentially a highly underutilized, non-invasive technique in the treatment of severe, intractable, malignancy-related pain, particularly in those patients with diffuse, bony metastases, likely because of lack of familiarity of the procedure. Studies are ongoing to ascertain the true efficacy of this procedure as well as to begin to elucidate its mechanism of action.

15.3 Cerebral Modulation of Pain Circuitry

When conservative and less-invasive treatments fail to adequately treat pain or are deemed inappropriate, consideration should be given to modulation of cerebral pain processing circuitry. Both lesioning techniques, as well as neuromodulatory techniques, have traditionally been employed, and targets have ranged considerably throughout the brain, with most currently targeting either the sensory-discriminative components of pain (ventral posteromedial and lateral thalamic nuclei, periaqueductal gray/periventricular gray) or emotional-affective components of pain (anterior cingulate gyrus, anterior limb of internal capsule, nucleus accumbens).

Lesioning

Lesioning of the thalamus has included medial thalamic regions such as the mediodorsal, centromedian, intralaminar, and parafascicular nuclei, although the most common current targets include the ventral posteromedial and lateral nuclei of the thalamus for face and body pain, respectively. Lesions of the thalamus have traditionally been performed through a burr hole utilizing a radiofrequency ablation probe, however, more recently this technique has been replaced by an incision-less approach utilizing stereotactic radiosurgery, as well as largely through neuromodulation utilizing deep-brain stimulation devices.

In a recent meta-analysis, 49 patients with malignancy-related intractable pain were identified who underwent stereotactic radiosurgery to create a lesion in the thalamus [12]. Of these, 24 received bilateral lesions and 25 underwent unilateral lesions with a maximum cumulative radiation dose from 140 to 250 Gy. Outcomes included 17 and 33 of 49 patients who experienced initial significant and moderate pain relief, respectively, within hours to days of the procedure. Long-term follow up in these studies was generally poor, as was consistent reporting of adverse events, which may be higher in particular with a bilateral procedure.

For lesioning procedures directed at the affective-emotional aspects of pain processing, the dorsal region of the anterior cingulate gyrus (cingulotomy) is a common target. This region is considered part of the limbic circuitry and is thought to play a role in the integration of cognitive and emotional processing. It has long been a target for the modulation of affective components of pain, and lesions have been made utilizing radiofrequency ablation techniques, stereotactic radiosurgery, and more recently, laser interstitial thermal therapy (LITT). Lesions in the cingulate gyrus are often performed bilaterally to treat patients who suffer from diffuse pain due to widespread metastases not amenable to other, more localized treatment options although it may have a role in the treatment of other refractory pain distributions.

A recent study detailed one center's experience performing bilateral cingulotomy lesions using stereotactic surgical methods in 13 patients with intractable malignancy-related pain due to widespread metastatic disease [16]. In this cohort, two frontal burr holes were made and a radiofrequency probe was used to create lesions bilaterally in the dorsal anterior cingulate gyrus. All patients reported significant pain relief immediately after the procedure. At one month follow up, 8 of

11 patients reported significant pain relief and one patient reported partial improvement. In 2 patients, the pain returned to its original severity. Upon further questioning of these patients, it was notable that they reported continuing to feel pain, but nonetheless felt a substantially reduced level of suffering. Adverse events included transient urinary incontinence, transient confusion, and mild apathy in 4 patients, which lasted for less than 1 week in 2 patients, and less than 1 month in the remaining 2 patients. A meta-analysis of stereotactic cingulotomy for cancer pain evaluating results from 8 series including 87 patients reported meaningful long-term pain relief in 32–83% of patients. While overall, cognitive changes were found to be minimal, a decline in focused attention, apathy, and decreased activity were variably found in the early postoperative period [19]. These data may point to the role of an obsessive component in suffering from refractory, long-lasting pain.

Deep-Brain Stimulation

Deep-brain stimulation is currently the most common way to modulate cerebral pain processing pathways in appropriately chosen patients with intractable, non-malignant pain, because of its reversibility and adjustability when compared to lesioning procedures. However, because the procedure involves implantation of hardware, often in stages, as well as extensive programming and cost, its use in malignancy-related pain is generally limited to those patients with a greater life expectancy. This treatment may also be essential in the care of cancer survivors who may suffer from long-standing chronic pain from their primary disease and/or sequela from treatment. There is a long history of stimulation of deep-brain targets for the modulation of pain starting in the 1950s in targets ranging from the internal capsule, ventro posterolateral nucleus and ventral posteromedial nucleus of the thalamus, the centro-median parafascicular region, the periaqueductal gray and the periventricular gray matter, the posterior hypothalamus, nucleus accumbens, and the anterior cingulate cortex [10].

Deep-brain stimulation of the thalamus and/or periaqueductal and periventricular gray is most commonly performed unilaterally to target contralateral face and body pain, and deep-brain stimulation of the emotional-affective components of pain includes most commonly bilateral targeting of the anterior cingulate gyrus, the nucleus accumbens, and the anterior limb of the internal capsule.

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Part IV
Total Pain and Rehabilitation

Physical Medicine and Rehabilitation

16

Carolina Gutierrez and Megan B. Nelson

16.1 Introduction

Cancer patients have unique symptoms from tumor burden and cancer treatments, which affect functional status and quality of life. Reports have shown approximately 65% of cancer patients have at least one functional/rehabilitation need, yet fewer than 10% of these needs get addressed during their cancer journey [1–3]. Many of these functional and rehabilitation needs are associated with pain, whether it be physical, emotional, or social pain. With the growing cancer survivor population, there is an increasing need to focus on pain, functional impairment, and quality of life. Cancer survivors are considered survivors from time of diagnosis as well as through and beyond treatment, according to the National Coalition of Cancer Survivorship. Thus, Cancer Rehabilitation Medicine assists with management of cancer-related pain from the time of a patient's diagnosis, throughout treatment, and beyond, including patients with advanced or incurable disease. Cancer Rehabilitation Medicine is a field to meet the demand of a growing cancer survivor population with physiatrists trained to address the unique rehabilitation needs of cancer survivors. This chapter will address how the field of physical medicine and rehabilitation contributes to treatment of pain in cancer patients.

Physical medicine and rehabilitation are a diverse medical field focusing on patients' daily functional status. Impairments for patients may be caused by physical or cognitive alterations, and physiatrists assist with identification and diagnosis of

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these medical impairments to then provide medical treatment to try to mitigate disability or handicaps. Physiatrists diagnose, address, and treat patient's functional impairments utilizing non-operative interventions, including but not limited to musculoskeletal injections and/or procedures, durable medical equipment prescription, pharmacologic treatments, and therapy and exercise prescription. Physiatrists prescribe and help guide therapy interventions provided by physical therapy, occupational therapy, speech therapy, pulmonary, and cardiac rehabilitation specialists.

16.2 Chemotherapy-Induced Peripheral Neuropathy

Neurotoxic chemotherapy agents can contribute to the development of chemotherapy-induced peripheral neuropathy (CIPN), including but not limited to platinum compounds, taxanes, vinca alkaloids, bortezomib, and thalidomide. Symptoms are similar to other types of neuropathy, including length-dependent numbness, tingling, burning, and/or pain. Overall incidence of CIPN is approximately 30–40% of cancer patients exposed to neurotoxic chemotherapy agents [4].

Physiatrists address neuropathic pain with the mindset of treating the pain as well as a patient's functional limitations due to the neuropathy. Neuropathy can affect fine-motor skills, such as manipulating buttons when dressing, tying shoelaces, or picking up small items. Peripheral neuropathy can also cause balance impairments that can translate into fall risk and subsequent painful injury. Physical therapy helps with strength, motor control, and visuospatial training to improve balance to prevent bodily harm.

Occupational therapy assists patients with hand exercises to improve fine-motor manipulation, increase muscle strength as well as assessing for durable medical equipment needs. Adaptive equipment is available to assist patients in functional tasks when they may not be able to fully regain their fine-motor strength. For example, a button hook with zipper pull hook and a sock aid can help with dressing, or various types of shoelaces including elastic shoelaces to ease donning shoes. These devices can reduce the emotional distress of having difficulty with typically basic daily tasks.

Desensitization is utilized by therapy professionals as well as by patients (once educated on how to perform themselves) to reduce neuropathic pain. Desensitization has been used for neuropathic pain originating from various etiologies. This encompasses touching the skin where there is hypersensitivity and allodynia present, and escalating the non-abrasive textures over time to gradually reduce the sensitivity of the skin to touch. Repetitive touch to the body areas where neuropathy is painful trains the mind and body to no longer be as sensitive to touch.

Transcutaneous nerve stimulation (TENS) has been shown to reduce pain emanating from a wide range of etiologies, including neuropathic pain, musculoskeletal pain, and arthritic pain [5]. Several studies have shown benefit with TENS units treating neuropathic pain from diabetes, [6, 7], and a presumption is that TENS could assist neuropathic pain caused by cancer treatments. TENS units

come in various forms and can be applied to skin where neuropathic pain is located. A feasibility study of a wireless, home-based device demonstrated significant improvement in CIPN related symptoms [8]. Additional research has explored the use of scrambler therapy, and a device that treats pain via noninvasive cutaneous electrostimulation, for management of CIPN. A recent randomized pilot study showed superiority of scrambler therapy compared to TENS, with significant improvement in patient reported outcomes (PROs) related to pain and neuropathic symptoms [9].

Heat, massage, neurofeedback, [10], and acupuncture [11] have shown benefit; however, caution should be taken as well with these interventions due to neuropathy causing impaired sensation and potentially impaired ability to know when harm is occurring with an intervention. Caution with more invasive interventions should also be taken in patients with impaired blood counts including neutropenia and thrombocytopenia.

Physiatrists will also address pain from CIPN with the same oral and topical medications utilized for pain emanating from any other neuropathic causes, while simultaneously addressing the functional impact from the neuropathy. Topical agents can help temporarily treat the focal pain, including anesthetic based topical agents in cream or patch form, as well as compounding agents such as baclofen/amitriptyline/ketamine gel [12–14]. Capsaicin topical cream may have benefit for neuropathic pain but has not been tested in CIPN [15]. Oral medications have shown limited efficacy in relieving CIPN compared to their ability to treat other causes of neuropathic pain such as diabetic neuropathy. Duloxetine is currently included in ASCO Clinical Practice Guidelines and NCCN Adult Cancer Pain guidelines for management of painful CIPN [16]. Additional oral medication options to trial may include but are not limited to gabapentin, pregabalin, amitriptyline, nortriptyline, venlafaxine, topiramate, and opiates [15, 17, 18]. Acetyl-L-carnitine has been used and in some cases demonstrated worsening of the CIPN [19]. Acupuncture has shown preliminary evidence in reducing incidence of high grade CIPN [20].

16.3 Neuropathic Pain

Neuropathic pain can occur in cancer patients from a wide range of etiologies. Treatment-related neuropathic pain can occur from chemotherapy agents, as mentioned in prior section on chemotherapy-induced peripheral neuropathy. Peripheral sensory neuropathy has also been reported as one of the most common neurotoxicities associated with immunotherapy drugs. Radiation can cause neural injury to the central nervous system or peripheral nervous system causing pain, for example radiation-induced myelopathy or plexopathy or mononeuropathy. Surgical treatments may require sacrifice of certain neural structures to adequately treat the cancer, creating residual neuropathic pain, or a neuroma may develop along or near

surgical incisions. Surgical reconstruction (grafts) can generate nerve damage from the procedure itself or nerve compression secondary to swelling. Phantom pain may occur in cancer patients requiring limb amputation or pelvic/shoulder girdle amputation for local control of cancer in an extremity, or from partial or complete mastectomy with phantom breast pain [21]. Tumor burden may cause neural injury and pain due to the tumor location and/or size with compression or invasion of neural structures. In addition, paraneoplastic syndromes or metastatic disease such as leptomeningeal metastases may contribute to neuropathic pain. Non-cancer-related neuropathies such as diabetic peripheral neuropathy con occur concurrently with cancer-related neuropathic pain.

Regardless of the etiology of neuropathic pain in cancer patients, physiatrists may utilize the same interventions used for CIPN as discussed previously, including medications. Some physiatrists perform injections to assist with a focal or dermatomal neuropathic pain. Anesthetic peripheral and sympathetic nerve blocks are options, as well as perineural steroid injections [22]. Examples include intercostobrachial nerve block for residual medial arm and lateral chest wall pain in breast cancer patients with post mastectomy pain [23].

Prior to proceeding with any interventions for cancer patients, one must consider potential contraindications to such medical recommendations and interventions. Potential contraindications may include avoiding use of topical/invasive interventions directly over known tumor burden, including primary and metastatic disease. Caution should be taken if a patient demonstrates hematologic laboratory abnormalities, such as cytopenias. Discussion with the oncology team should occur to ensure no contraindication of medications or interventions, while the patient is receiving specific oncology treatments, including surgery, chemotherapeutics, and/or radiation.

16.4 Musculoskeletal Pain

Cancer patients may have musculoskeletal impairments and pain related to their cancer and its treatment, as well as unrelated to the cancer and its treatment. It is important to obtain an adequate history, comprehensive physical exam, along with an appropriate medical work-up to decipher causality of the musculoskeletal complaints prior to providing treatments. It is possible pain may be multifactorial with oncology-related and non-oncology-related origin. An example is neck and shoulder pain in a patient with head and neck cancer status post radiation therapy to the neck with a pre-morbid underlying history of cervical degenerative spine disease.

The intent of this section is to focus on some of the more common musculoskeletal pain complaints from cancer patients related to cancer and its treatments, and how physical medicine and rehabilitation can assist patients.

16.5 Myalgias and Arthralgias

Myalgias and arthralgias are individual symptoms that can occur anywhere in the body, and they may occur simultaneously or separately. Myalgias and arthralgias in cancer patients can be secondary to location of tumor burden causing impact on surrounding muscles and joints, or these symptoms can be secondary to cancer treatment effects [24]. In addition, myalgias and arthralgias can be due to benign comorbid conditions; however, this chapter will focus on cancer-specific myalgias and arthralgias.

A common cause of these two symptoms occurring simultaneously in cancer patients is medication-induced myalgias and arthralgias. Aromatase inhibitors have been known to cause myalgias and arthralgias in up to half of postmenopausal women patients [25–27]. Taxanes have been shown to cause myalgias and arthralgias 10–20% of patients [28, 29]. Post-chemotherapy rheumatism has been described among patients with varying cancer diagnoses [30]. Some biologic therapies (e.g., interferon) or growth factors (e.g., filgrastim or pegfilgrastim) can cause myalgias and arthralgias.

The myalgias and arthralgias due to cancer treatments can occur throughout the body, including the back, neck, hips, shoulders, thighs, legs, feet, arms, and hands [31]. Myalgias and arthralgias will be based on the location of tumor(s) as well as based on the cancer interventions such as surgical resection, radiation therapy, chemotherapy, and/or diagnostic procedures. However, if the primary tumor metastasizes and/or additional treatment is required to other bodily areas, then additional myalgias and arthralgias may be involved. The following describes locations of potential myalgias and/or arthralgias in patients with specific types of cancer based on location of initial cancer (Table 16.1).

Pharmacologic treatments have been anecdotally trialed to reduce symptoms of chemotherapeutic-induced myalgias and arthralgias with insufficient evidence. However, some benefit may be seen with treatments such as non-steroidal anti-inflammatories (NSAIDS), atypical antiepileptics (e.g., gabapentin, pregabalin), opiates, antidepressants (e.g., duloxetine), extended use of corticosteroids, and potentially antihistamines (e.g., fexofenadine) [29, 32, 33]. Medications may come in the form of topical, oral, or injections.

The muscle pain experienced by these patients may be similar to a trigger point. Physiatrists can utilize trigger point injections with anesthetics and potentially steroids to reduce the pain as well as release the myofascial taut bands; alternatively, dry needling can be performed without any injectate. Myofascial releases with manual techniques can be performed by physiatrists and/or physical therapists, occupational therapists, speech therapists, massage therapists, and other professionals.

Proposed mechanisms through which physical therapy may contribute to pain reduction include (1) increased blood flow, (2) decreased inflammation, and (3) muscle spasm [34]. Tools utilized by physical therapists for pain reduction may include cryotherapy and sources of superficial heat (paraffin baths, heating pads) or

Table 16.1 Myalgias and Arthralgias by Cancer Type & Location

Breast	Upper/mid/lower back, shoulders, anterior chest, lateral chest, arm, hands, and abdomen
Head and Neck	Anterior, lateral, and posterior neck; upper/mid back, shoulders, and anterior chest
Lung	Upper/mid back, anterior and lateral chest, shoulders, neck
Genitourinary	Mid/low back, abdominal wall, pelvic floor, lower extremities
Gastrointestinal	Upper/mid/low back, abdominal wall, pelvic floor, anterior and lateral chest, neck, shoulders, lower extremities
Melanoma, Sarcoma, Other	Any location depending on site of tumor(s) and treatments

deep heat (laser, ultrasound, moist heat). In recent years, there has been increased interest in the use of kinesio-taping as part of a comprehensive pain control strategy.

Adaptive equipment, orthotics, and bracing can assist in treatment of myalgias and arthralgias when other conservative measures have not provided sufficient relief or as adjunctive treatment, and physiatry is well-trained in prescribing durable medical equipment (DME). For example, myalgias of the neck in combination with neck extensor weakness may benefit from intermittent use of a cervical orthotic. The Headmaster Cervical Collar ™ (Symmetric Designs in Salt Spring Island, British Columbia) is a well-tolerated option for intermittent, as-needed use for energy conservation [35]. DME including walker, cane, or scooter can be helpful on an intermittent basis for acute exacerbations of myalgias and arthralgias in the back and/or upper extremities and the lower extremities. Acute joint inflammation could benefit from bracing finger joint support rings and other orthotics for joint protection.

Exercise has shown to help reduce Aromatase Inhibitor-related arthralgia by about 30% after a yearlong exercise program including a combination of aerobic and resistance training [25]. Acupuncture, as a non-pharmacologic integrative therapy, has also shown significant benefit in reducing aromatase related joint pain among postmenopausal women with early stage breast cancer [36]. Stretching is also an important component of reducing myalgias and arthralgias. For myalgias, it is important to stretch the painful muscle as well as stretch and strengthen the muscles adjacent to the painful muscle. For arthralgias, it is important to stretch and strengthen the muscles above and below the painful joint. Strengthening muscle, improving posture and balance, and enhancing muscle endurance may contribute to pain reduction. The rehabilitation team, including physicians, are all responsible for educating patients on the significant benefit of exercise for management of cancer-related pain. It is critical that physiatrists help coordinate appropriate referrals to rehabilitation professionals with the experience needed to manage the unique needs of this patient population. There is a need to focus on the development of exercise and rehabilitation prescriptions with recommendations based on a patient's location of tumor burden, current cancer treatments, non-cancer comorbidities, medications, psychosocial structure, and baseline functional capacity.

16.6 Skeletal Pain

Skeletal pain in cancer patients may originate from primary osseous tumor burden or metastatic bony disease, as bone is the third most common site of metastatic disease after lung and liver [37]. Pain is usually the earliest and most common symptom of bone metastases [38]. About 1.5 million people worldwide are living with bone metastases, and the life expectancy is increasing in this patient population [38]. Pathologic fractures occur in 10–30% of patients with bony metastatic disease. The incidence of pathologic fracture ranges from 43% in patients with multiple myeloma to 17% in patients with metastatic lung cancer [39]. These fractures may occur in any bone with metastatic involvement, but it typically occurs in long bones with the femur accounting for about half of all cases, with risk increasing over the duration of metastatic disease [37]. Pathologic fractures may also occur in vertebral bodies or ribs, causing pain [37]. Little is known about the intensity or type of physical activity or rehabilitation required to cause a pathologic fracture, and likely multiple factors contribute to the risk, including but not limited to tumor type, location and size of tumor, body habitus, type and intensity of activity, and comorbidities such as osteopenia or osteopenia. In one prospective study of 54 patients with bone metastases receiving inpatient rehabilitation, 16 fractures occurred in 12 patients, with only 1 fracture associated with rehabilitation efforts [40].

Pain is an important sign and symptom of potential impending fracture of bone with metastasis. Metastatic bone pain requires a multi-disciplinary approach, as the patient may require radiation therapy, chemotherapy, and/or surgical techniques to stabilize the bone and reduce the pain. The primary rehabilitative aim for these patients is to identify ways for pain-limited activity to proceed. The goal is to maintain as much individual independence as possible for these patients, and minimize inactivity safely to protect patients from losing strength and endurance. If a metastasis is in a weight-bearing bone, then utilizing durable medical equipment to reduce weight-bearing and therefore subsequent pain is paramount. For example, if a cancer patient is having pain in the location of a femur metastasis when walking or bearing weight through that extremity for transfers or activities of daily living (ADLs), then prescribing a walker with weight-bearing restrictions of that extremity can help alleviate the pain and reduce the risk of a pathologic fracture, while the patient may proceed with other treatment interventions. The pain may be so severe in multiple bony sites that a manual or power wheelchair is required. If the patient has pain in the humeri from metastatic disease, then this reduces their ability to use a walker, cane, or manual wheelchair where the upper extremities are required to manage the DME or propelling the wheelchair.

A physical exam is key to identifying if the patient's pain correlates with the bony tumor burden. There may be underlying bony metastatic disease; however, a comprehensive exam may elucidate the pain generator as a tendinitis or bursitis instead. For example, a cancer patient with a humeral head metastasis complaining of shoulder pain could have a common diagnosis of rotator cuff tendinitis, and adequate treatment of the tendinitis may relieve their shoulder pain. However, when

examining a cancer patient with bony metastatic disease, the examiner must avoid portions of a manual muscle test to avoid a potential pathologic fracture. The examiner should avoid passive range of motion and resistance on strength exam in the involved extremity, and instead the examiner should evaluate active range of motion of the patient with pain-limited guidelines. Some examination maneuvers must be altered to accommodate the evaluation. Patients with spinal metastases should avoid spinal flexion/extension/rotation exams, stretches, and strengthening exercises to reduce risk of pathologic fracture.

Physical rehabilitation interventions are appropriate for patients with bony metastatic disease, while following appropriate precautions with the goal of enhancing function and quality of life. Maximizing muscle strength in a non-painful fashion can promote a patient's independence. Rehabilitation can assist with reduction of fall risk with balance training and neuromuscular reeducation, as a fall could be the impetus for a pathologic fracture. One study examined the effects of resistance training in patients with spinal bone metastases receiving radiotherapy. It found that isometric resistance exercise training of the paravertebral muscles was tolerated with no increase in fracture risk, and the exercise potentially contributed to back pain reduction [41]. Multiple exercise studies have been performed analyzing the effects of aerobic, resistance, and/or flexibility training on patients with bone metastases [38]. Appropriate precautions were taken based on the patient's bony disease, and patients did not show any increase in bone pain. There were improvements in muscle strength, muscle mass, walking speed, as well as fatigue, which helps reduce other sites of pain including myalgias, arthralgias, and even mental and emotional pain.

Physiatrists focus on rehabilitation and exercise prescription for cancer patients, including those with bone metastasis. While coordinating with the oncology team's treatment plan for bone metastases, a safe rehabilitation treatment plan focused on pain-limited activity can greatly assist patients' function, independence level, and quality of life.

16.7 Pelvic Pain

Pelvic pain may be diagnosed in female and male patients with genitourinary, gastrointestinal, sarcoma, melanoma, and other cancers. Tumor burden as well as cancer treatments can contribute to pelvic pain, including surgical resection in the abdomen and pelvis, radiation therapy to the pelvic tissues, and chemotherapy including external beam and intracavitary brachytherapy. The pelvic tissues, muscles, bones, and nerves may experience injury. Appropriately examining and diagnosing the etiology of a patient's pelvic pain is required prior to proceeding with treatment. Physiatrists may utilize topical, intravaginal, or oral medications utilized for other neuropathic and myopathic pain diagnoses, including non-steroidal anti-inflammatory agents, skeletal muscle relaxants, anticonvulsants, and serotonin-norepinephrine reuptake inhibitors or tricyclic antidepressants [42, 43].

Pelvic floor rehabilitation is tremendously beneficial for pelvic pain syndrome. There are physical therapists specially trained in pelvic floor rehabilitation, and myofascial release of the pelvic floor muscles can be performed extra-vaginally and intra-vaginally to release taut muscle bands that trigger pain. This may involve manual release of soft tissues in the abdomen, hips, low back, thighs, vagina, and in some cases, the rectum [43]. If patients have muscle weakness of the pelvic floor, then muscle strengthening is recommended, which includes Kegel exercises as well as vaginal weights allowing for resistance training of the pelvic floor. The pelvic floor may have tight muscles, or hypertonicity, contributing to pain, sitting pain, dyspareunia, and bladder/bowel dysfunction. Kegel exercises are not beneficial in patients with tight pelvic floor muscles. Hypertonicity of pelvic floor muscles can benefit from trigger point injections with anesthetics such as lidocaine, and severe pain may benefit from botulinum toxin injections [43]. Biofeedback is utilized by physical therapy along with behavior modifications to assist with pain as well. Rehabilitation exercises should be continued after physical therapy is completed with a home exercise program, empowering men and women to be able to control their pelvic pain at home.

16.8 Post Mastectomy Pain Syndrome

Post mastectomy pain syndrome is a post operative persistent pain that can occur after mastectomy and also after other breast conservative surgeries including lumpectomies, surgeries involving the chest wall, axillary area and/ or arm, radiation to the chest wall and lymph node dissection. Incidence has been reported in different studies from 11 to 44% even 3 years post surgery [44, 45]. Persistent pain has been associated with body mass index ≥ 30 kg/m^2 radiation therapy, and axillary lymph node dissection [45].

Post mastectomy pain can be described as a neuropathic pain involving the surgical site (chest) in 13–40% of the patients [45, 46]. The pain can be localized in the breast and chest wall, shoulder, axilla, and medial proximal arm. Characteristics of the pain can be described as shooting, stabbing, aching, pulling, burning sensation, and tightness. Nerve damage, mechanical imbalance, musculoskeletal problems and lymphedema may be present. Post mastectomy pain syndrome can be a limiting factor for daily activities including dressing, bathing, and work related motions and can increase with movement and overhead activities [47].

Physiatrists perform a comprehensive pain evaluation including timing and type of treatment including surgery, radiation, incitation and progression of the symptoms, type of pain, aggravating factors, impairments related to arm mobility, and interference with activities of daily living and work. A thorough physical exam provides valuable information regarding swelling, symmetry and muscle atrophy at the chest, neck and shoulder, posture, and active and passive range of motion at the shoulder evaluating for dyssynergia. Based on a comprehensive evaluation and physical examination, the physiatrist is able to educate patients and caregivers

regarding a comprehensive rehabilitation plan which may address functional impairments and include multimodal pain management.

Occupational and/or physical therapists play an important role and can assist patients by providing education regarding a home exercise program for independent practice between therapy sessions and after therapy has been completed. Stretching can be assisted by therapy in areas involved in the post mastectomy pain syndrome including shoulders, pectoralis/anterior chest and neck, and posture retraining as well as range of motion and muscle strengthening. Therapy can include other techniques such as myofascial release and taping to alleviate pain and improve function. Occupational therapy can assist patients to increase independence in these activities, decreasing disease burden and psychological pain. Caution should be taken with different modalities [including ultrasound, transcutaneous electrical neuromuscular stimulation (TENS), heat and cold] when there is the possibility of underlying active disease, lymphedema, active infection, and venous thromboembolism (VTE), among others.

A variety of non-opioid pharmacologic approaches and non-pharmacologic approaches can be used as part of a comprehensive strategy for optimizing pain control. Neuropathic pain agents can be used including gabapentin, pregabalin, and other agents including serotonin-noradrenaline reuptake inhibitors like venlafaxine and duloxetine when vasomotor symptoms such as hot flashes are present. Skeletal muscle relaxants may also be considered. Topical agents may be used, including anesthetic creams and topical capsaicin preparations, however, for safety, skin integrity must be evaluated. Trigger point injections, botulinum toxin injections, serratus plane block, intercostobrachial nerve block, and intercostal nerve blocks may be used to complement other strategies for symptomatic relief. Further discussion of these interventional approaches can be seen in Chaps. 12 and 13. Numerous studies (clinicaltrials.gov) are ongoing to assess the potential benefit of acupuncture for reduction of post mastectomy pain.

Special considerations in the management of post mastectomy pain include presence of concurrent lymphedema in the arm and/or the chest wall. Treatment of the lymphedema can have a positive effect in reduction of pain by decreasing lymphedema volume and decreasing movement restriction with an improvement in pain and range of motion. Treatment for lymphedema includes complete decongestive therapy with education, skin care, manual lymphatic drainage, compression garments as well as deep breathing exercises, stretching and range of motion exercise, and the use of pneumatic compression pumps. Exercise should be included and is safe in patients with lymphedema. Weight reduction should be considered when there is an increased body mass index (BMI). Compression garments can also be used as part of the desensitization techniques used to treat and decrease the neuropathic pain.

Psychological pain and suffering secondary to post mastectomy pain syndrome should be taken into account. A component of anxiety and or depression could be addressed with pharmacologic and non-pharmacological interventions. Selective serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine can be used for management of concurrent depression and neuropathic pain. Other medications to

consider as part of management for associated mood symptoms include selective serotonin reuptake inhibitors (SSRIs) such as escitalopram or paroxetine [47].

16.9 Post Thoracotomy Pain Syndrome (PTPS)

Thoracotomy is a common procedure used in lung cancer that includes an incision in the chest wall. Acute pain is commonly experienced secondary to retraction during surgery, resection, and irritation of the pleura, disruption of the costovertebral joints, nerve (intercostal), and muscle damage.

Acute pain can interfere with inspiration and can decrease the ability to effectively cough and clear secretions. Post thoracotomy pain syndrome, reported in 30–50% of patients, presents as a persistent pain for more than 2 months after the procedure and could be caused by intercostal nerve and muscle damage. In a study done by Hetmann et al., two thirds of patients presented with pain at baseline (before surgery), 49% at 6 months and 48% at 12 months. Sensory changes were found at 6 months including 51% of patients reporting increased sensitivity, 58% pain with normal touch, 58% pain with pressure, 39% pain with cold, 49% pain with warmth, and 45% decreased sensation [48].

PTPS most commonly presents as neuropathic pain located in the back or anterior chest wall and/or following the distribution of the intercostal nerve. It can also present as pleuritic type pain. Common physical therapy techniques for symptomatic relief may include sustained maximal inspiration, supported coughing and active cycle of breathing, deep breathing exercises, coughing, early mobilization, upper limb mobility exercises, chest wall vibrations, and trunk mobility exercises [49]. Additional interventions may include use of anti-neuropathic pain agents, injections [e.g., intercostal nerve blocks (diagnostic and therapeutic), trigger point injections], topical agents (e.g., lidocaine), TENS unit, and pulmonary rehabilitation.

16.10 Post Amputation Pain Syndrome (PAP)

PAP is a difficult to treat condition with high prevalence following limb amputation surgery [50]. Special considerations in evaluation and management include type/extent of surgery including amputation site, comorbid health conditions, and cancer history including use of neoadjuvant or adjuvant cancer therapies such as chemotherapy or radiation. Strategies which may be considered for management include: desensitization, mirror therapy, cognitive therapy, upper extremity stellate ganglion block, lower extremity lumbar sympathetic block, and phenol or alcohol block for neuromas.

16.11 Post Radiation Pain

Radiation therapy can be administered in various ways, including external beam, brachytherapy, or systemic radiation. This section will focus on external beam radiation therapy, unless otherwise stated, and how rehabilitation can assist with pain due to the radiation. Post radiation pain can be divided into acute and chronic pain. Acutely, patients may have radiation-induced dermatitis and alteration of skin and mucosa integrity for a few weeks to months during and after radiation. Patients should avoid aggressive rehabilitation interventions, such as stretching the area or massage of the skin until skin integrity is restored.

Radiation-induced fibrosis can occur in response to exposure to radiation. Radiation fibrosis syndrome is the compilation of symptoms due to progressive fibrotic tissue sclerosis [33]. Symptoms may include painful myalgias due to the muscle tightness from fibrosis, and arthralgias if joints are involved in the radiation field or secondarily due to reduced joint range of motion from fibrotic adjacent muscles. Rehabilitation treatment for pain due to radiation fibrosis includes tissue massage to stimulate blood flow and oxygen distribution to fibrotic tissues, desensitization through touch and manipulation, and regular stretching of the tissues. The recommended frequency and duration of tissue massage are unknown; however, radiation fibrosis can persist for years after radiation, thus ideally patients continue a home exercise program multiple times a week of massage, stretching, and strengthening.

Radiation-induced spasticity can cause cervical dystonia and trismus. Fibrosis and decreased muscle elasticity can result in muscle contraction and abnormal posture. This can present as cervical dystonia and/or trismus. Cervical dystonia is also called *torticollis*, presenting as an abnormal and painful posture of the neck and sometimes accompanied by spasms. The abnormal posturing can include rotation, lateral flexion, anterior flexion, and/or extension of the neck. Pain symptoms may include different areas of the neck and can increase with certain movements of the neck. Radiation-induced trismus is a decrease in mouth opening with a decreased motion of the jaw. Localization of pain may include the temporomandibular joint and mastication muscles. Rehabilitation interventions include soft tissue massage, myofascial release, passive range of motion devices for mouth opening, stretching, strengthening, engaging in stretching exercises, trigger point injections and oral medications such as NSAIDs. Botulinum toxin injections may improve head positioning and pain.

Radiation-induced myelopathy

Radiation can induce damage of the spinal cord by inhibiting myelin production causing demyelination, microvascular damage, white matter damage, and necrosis. This can present as a transient or irreversible myelopathy. Transient myelopathy presents 3–4 months after radiation and resolves spontaneously after 3–6 months. Symptoms include pain, numbness and paresthesias, with one presentation as neck pain radiating to the extremities that can be triggered by neck flexion (known as the Lhermitte's sign). Irreversible myelopathy often presents 6–12 months after

radiation and can include a wide variety of symptoms ranging from mild sensory or motor symptoms to paraplegia [51].

Localization of the pain may correlate with the area/level radiated or slightly below. Rehabilitation interventions should be targeted to the area affected including desensitization with light massage, range of motion and stretching to prevent painful contractures, orthotics and bracing to assist ambulation and/ or positioning and use of anti-neuropathic pain agents.

Other radiation-induced pain syndromes which will not be discussed in this review include radiation-induced spasticity of chest wall muscles, radiation-induced pelvic pain, radiation-induced trigeminal neuralgia, and radiation-induced brachial plexopathy.

16.12 Lymphedema

Lymphedema is traditionally thought to be non-painful; however, acute onset or exacerbation of lymphedema can be painful due to the sudden stretching of tissues accommodating the increase in fluid volume. Treating the pain associated with lymphedema includes acute and maintenance treatment.

Secondary lymphedema in cancer patients may be due to tumor burden causing compression of lymphatic flow or it may be due to cancer and or cancer treatments, including lymph node resection or damage to the lymphatic system by surgery, radiation, chemotherapy, or a combination of treatments. Lymphedema can occur in any location of the body where the lymphatic system is present. For breast cancer patients, it tends to occur in the upper extremity and/or chest wall. For genitourinary cancer, it tends to occur in the lower extremities and/or groin. For head and neck cancers, it tends to occur in the facial and neck regions. For melanoma and sarcoma patients, it may occur in any extremity distal to the tumor burden.

Exercise with aerobic activity and gradual escalation of resistance exercise has been shown to help reduce exacerbations of lymphedema, which thus translates into reducing onset of lymphedema-related pain [52]. Exercise (aerobic or resistance) and movement based mind–body approaches such as yoga are safe with appropriate modification or supervision. Exercise is considered part of lymphedema treatment, which can help decrease lymphedema volume and improve quality of life. Lymphedema treatment should be performed by a certified lymphedema therapist who may have training in occupational or physical therapy.

16.13 Psychosomatic and Psychosocial Pain

Inadequate attention to the complexity of a patient's symptom burden can contribute to suffering and worsening, uncontrolled pain. Physical medicine and rehabilitation focuses on symptom management, function, and quality of life. Care coordination with other specialty teams such as palliative care and psychiatry can

help with the development of a comprehensive, coordinated approach to pain and symptom management.

Integrative therapies can serve an important role as adjunctive approaches to help address pain and other symptoms. Integrative therapies are included in NCCN Adult Cancer Pain guidelines and include such diverse interventions as cognitive behavioral therapy, acupuncture and massage. As an example, massage therapy has been found to improve symptoms of pain, fatigue, anxiety, well-being, and sleep for the patients and caregivers [53].

16.14 Special Precautions for Rehabilitation Interventions

- Bone metastases and associated fracture risk
  - Avoid resistance with manual muscle testing of an extremity with metastatic involvement.
  - Patients with spinal metastases should avoid spinal flexion/extension/rotation exams, stretches and strengthening exercises to reduce risk of pathologic fracture.
  - Pain-limited exercise and activity are recommended.
  - Avoid interventions directly over area of known tumor burden.

- Thrombocytopenia: Benefits of physical activity and therapy could be higher compared to the risk of bleeding. Risk for bleeding during an acute inpatient rehabilitation stay related to therapy and physical activity in patients with thrombocytopenia in acute hematologic malignancy is low. In one study, the risk of bleeding with platelets < 20,000 highly related to exercise was 4% [53].
- Neutropenia—protect patients with masks and appropriate hand hygiene; patients may avoid group therapy and group exercise classes.
- Anemia due to cancer treatments—consider blood transfusion if indicated prior to physical activity, rehabilitation efforts, and exercise. Monitor cardiovascular and pulmonary status during rehabilitation.
- Caution in setting of skin and mucosa changes due to treatments such as chemotherapy or radiation.
- Precaution should be followed as per surgeon indication during and after reconstruction surgeries and/or graft placement. Examples include shoulder range of motion and lifting restrictions in breast reconstruction and appropriateness to eat by mouth after head and neck reconstruction/grafting.
- Electrical stimulation, cryotherapy, ultrasound or iontophoresis, heat therapy, and or massage and other modalities should be used with caution avoiding areas of tumor burden and areas affected by acute skin radiation changes.
- Caution should be taken with different modalities including ultrasound, transcutaneous electrical neuromuscular stimulation (TENS), heat and cold when there is a possibility of active disease, lymphedema, active infection. Their use should be evaluated case by case.

16.15 Conclusions

Cancer pain is a result of a complex interaction between physical and psychosocial factors, requiring a multi-disciplinary approach. As part of oncology care teams, physiatrists with special training in cancer rehabilitation can contribute significantly to improving patient outcomes through performing comprehensive assessments, provision of education to patients and caregivers, improving function, maximizing independence with activities, and coordination of multi-disciplinary pain management.

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Psychosocial Aspects of Cancer Pain

17

Mary Morreale

17.1 Introduction

Given the biopsychosocial model of pain, it is not surprising that a strong degree of association exists between cancer pain and psychological distress. Although there is currently no screening guideline related to psychosocial distress in cancer patients with pain, some experts recommend routine screening for psychiatric comorbidity in this patient population. Cancer patients with significant pain should be monitored for suicidal ideation and appropriately referred if need be. Several non-pharmacological interventions have been shown to reduce pain and psychiatric symptomatology including education, hypnosis, guided imagery, cognitive behavioral therapy, and collaborative care. Finally, though there is a lack of controlled studies related to the use of antidepressants for cancer-related pain, uncontrolled studies and anecdotal reports suggest that TCAs and SNRIs are efficacious for the treatment of neuropathic pain.

17.2 Cancer Pain and Psychological Distress

Current models of pain are based on a biopsychosocial paradigm, which suggests that pain exists as a result of sensory, psychological, and social factors [4]. The sensory component of the pain experience refers to nociception or the transfer of sensory information from peripheral receptors through the spinal cord to the brain. Psychological contributions are derived from the cognitive assessment of the pain

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experience, where physical discomfort is attached to unpleasant emotional states. Finally, social factors associated with pain are connected to changes in behavior in response to suffering, such as excessive medication use and avoidance of physical activity.

Given the conceptualization of pain described above, it is not surprising that pain and psychopathology, specifically depression and anxiety, have a significant degree of interdependence. Studies of patients with both chronic non-malignant pain and cancer-related pain indicate that both anxiety and depressive disorders, as defined by the Diagnostic and Statistical Manual 5 (DSM-5), are increased compared to the general population [2, 4, 30].

There are both psychological and physiological models that explain comorbidity. Psychological concepts include shared vulnerability, perhaps with genetic underpinnings; anxiety sensitivity, which posits that patients misinterpret both symptoms of anxiety and pain as catastrophic, thus increasing both; avoidance, which for patients with both anxiety and pain can lead to exacerbation of symptoms; and attentional bias, where patients display increased focus on psychiatric or physical pathology and are therefore unable to utilize additional cognitive capacity to effectively control symptoms [4, 30]. Physiological theories include changes in monoamine neurotransmitters, brain-derived neurotrophic factor (BDNF), glutamate and its corresponding receptors, as well as inflammation [31, 33].

Although there is variability in the prevalence rates reported in the literature, the evidence for an association between cancer pain and psychological distress is considered to be strong [40]. Oncology patients with pain are more apt to report depression, with greater pain symptom duration and severity increasing this risk. What is more, depression and anxiety have been shown to cause subjective amplification of pain, with greater levels of psychiatric distress associated with higher levels of pain [12, 13, 16, 18, 20, 32, 40]. Although there is a suggestion of causality in both directions, from a clinical standpoint, what is fundamental to recognize is the strong degree of association. With this awareness, appropriate screening can ensue.

17.3 Assessment

Although screening recommendations exist for psychosocial distress in oncology populations as a whole, there are currently no guidelines specifically for cancer patients with pain [3]. Given the strong association between cancer pain and psychological distress, as discussed above, some experts do recommend that comprehensive pain evaluations in the oncological setting include routine screening for psychiatric comorbidity [40]. While there are strengths and limitations to all screening measures, the American Society of Clinical Oncology (ASCO) guidelines, developed to address depression and anxiety in adults with cancer of any type, stage and treatment, suggest utilization of the Patient Health Questionnaire 9 (PHQ-9) for depressive disorders and the General Anxiety Disorder-7 for anxiety [3, 37]. Of note,

is concern in the literature regarding shared symptomatology between psychiatric disorders and medical illness, such as changes in sleep and appetite, fatigue, and diminished concentration, and how this affects screening. Some authors propose excluding or substituting those symptoms that are common to both, but there is currently no evidence to support the superiority of doing so [14].

Patients with cancer are estimated to have a significantly increased risk of suicide when compared to the general population, and pain has been shown to be a common risk factor [1]. Because of this, all patients with significant pain should be specifically asked questions regarding the risk of harm to self, and appropriately referred for emergency mental health evaluation if need be [3, 38]. There are multiple studies that support the Columbia-Suicide Severity Rating Scale (C-SSRS) as an appropriate screening tool for assessing suicidality.

Despite the lack of pertinent literature related to the incorporation of mental healthcare providers into cancer pain treatment teams and patient outcomes, this addition would be expected to be of benefit for patients with difficulty to manage pain who either have a history of psychiatric treatment or current symptoms. A consulting psychiatrist could contribute by providing a comprehensive evaluation to identify psychiatric diagnoses amenable to medication and/or psychotherapy, as well as psychosocial factors that might be impacting care and diminished response to pain treatment. A cooperative approach between pain specialists, oncology, and psychiatry would likely provide a more holistic approach to the evaluation and treatment of pain and potentially allow management to expand beyond a purely somatic focus.

17.4 Non-pharmacologic Interventions for Cancer Pain

There are multiple non-pharmacologic interventions that have been shown to be efficacious in reducing cancer pain and associated psychiatric comorbidity [21, 23]. Prior to employing any specific intervention, however, healthcare providers should educate patients and family members about the pain experience, appropriate use of medications, and expectations for treatment and symptom reduction. Simple educational techniques have been shown to decrease pain severity, and when targeted toward psychiatric disorders, have evidence of increasing remission rates [10, 24, 28]. Educational interventions that increase an individuals' sense of self-efficacy, or the belief that patient behaviors can positively impact outcomes, have been shown to decrease symptom occurrence and distress, and improve overall quality of life [39]. Programs that coach patients to engage in self-care behavior, and to monitor and report symptoms, have been shown to bolster self-efficacy [8]. Nurse, peer, and Internet-based coaching all have evidence of providing useful self-management support to patients with cancer [17].

In addition to education, social support should be strengthened if possible. Social support has been shown to increase general well-being and to diminish the impact of stressful experiences, including physical illness [6, 29]. When cancer patients

feel supported in their interpersonal relationships, reductions in the incidence of both chronic pain and depression have been noted [18]. Although there is no available data related to participation in cancer peer-support groups and effect on pain management, these programs have been shown to reduce patients' sense of isolation and improve coping skills [5].

Guided imagery and hypnosis are additional interventions that have been studied in the treatment of cancer-related pain. Although the mechanism for efficacy is uncertain, both are thought to work by focusing attention away from pain via dissociation. These interventions have shown efficacy in the reduction of acute procedural and post-surgical pain, mucositis following bone marrow transplant, and for chronic malignant pain [21]. In addition, hypnosis can lead to a significant reduction of anxiety, lower levels of depression, and more positive and less negative mood states in oncologic populations [15].

Participation in cognitive behavioral therapy (CBT) has been shown to improve pain control and overall functioning in patients with treatment-related and persistent cancer pain [9, 21]. CBT is a time-limited and structured psychotherapy designed to modify cognitive distortions and distressing thoughts associated with pain and to enhance coping skills related to pain management. The cognitive component of CBT may incorporate a variety of techniques such as the reframing of misattributions, thought refocusing, and attention diversion. Behavioral approaches include teaching patients specific relaxation techniques, for example, progressive muscle relaxation, and encouraging them to engage in distracting activities. In addition to impacting pain, CBT is well studied as an efficacious treatment for both anxiety and depressive disorders.

Finally, collaborative care, defined as a team-based approach in which a care manager supervised by a physician specialist works with a primary clinician to optimize outcomes through education, monitoring adherence and treatment response, and adjusting treatment as needed, has also been studied in cancer patients [23]. Delivered via telemedicine in the study cited, this systems-based approach led to reductions in both pain severity and symptoms of depression [23].

17.5 Psychopharmacologic Interventions for Cancer Pain

Antidepressant medications have been extensively studied for the treatment of non-malignant chronic pain, specifically diabetic peripheral neuropathy, fibromyalgia, and headache [11]. The analgesic effect of these medications is not dependent on antidepressant activity, as evidenced by the following: Pain reduction occurs in non-depressed patient populations, the dose needed to diminish pain is often lower than that necessary to treat depression, and the onset of pain relief is typically earlier than the onset of impact on mood [27]. Although antidepressant medications are thought to reduce pain via supraspinal, spinal and peripheral processes, enhancement of norepinephrine and serotonin within descending pain-mediating pathways is thought to be the primary mechanism [25]. While many

antidepressants have been studied for potential analgesic activity, only tricyclic antidepressants (TCAs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), both of which are capable of simultaneously impacting both serotonin and norepinephrine neurotransmission, consistently demonstrate this property [27, 36]. Although there is a lack of controlled studies related to the use of antidepressants for cancer-related pain, small, uncontrolled studies and anecdotal reports suggest that these medications are efficacious for the treatment of neuropathic pain, which occurs in up to 40% of cancer patients [11, 26, 27, 35]..

The majority of studies examining the analgesic effects of antidepressants have focused on TCAs. TCAs act as reuptake inhibitors of either serotonin or serotonin and norepinephrine, with most falling in the latter category [34]. TCAs are classified as tertiary amines (amitriptyline, imipramine, doxepin, clomipramine) and secondary amines (nortriptyline, desipramine). In clinical practice, amitriptyline seems to be the drug of choice. Although tertiary amines with a broad spectrum of activity are more effective as analgesics, they are less well tolerated, which can be problematic for medically frail populations [27]. The major limitation to the use of TCAs is related to antagonism of histaminic, cholinergic, and adrenergic receptors. Blockade of histaminic receptors can lead to sedation and weight gain, anticholinergic activity can cause dry mouth, confusion, urinary retention, constipation, and precipitation of acute-angle glaucoma; and anti-adrenergic activity can produce orthostatic hypotension and dizziness [34]. Finally, TCAs also block voltage-sensitive sodium channels in the heart and in overdose can lead to cardiac arrhythmia and arrest; therefore, patients with a history of significant cardiac disease should not be treated with these agents [34]. In addition to cardiac disease, TCAs are contraindicated for patients with closed-angle glaucoma, poorly controlled seizures, and severe benign prostatic hypertrophy [25].

The analgesic effects of TCAs appear to be dose-dependent [25]. Dose escalation should occur carefully, until a reduction in pain or side effects occur. Although recommendations exist for typical doses, there is large pharmacokinetic variability among TCAs. Because of this, monitoring of plasma drug concentrations can be helpful if a patient fails to respond or concerns about toxicity emerge. TCAs, like all antidepressants, are metabolized by the cytochrome p450 system and should be carefully combined with other medications, utilizing a computer-based interaction system when possible.

Similar to TCAS, the SNRIs inhibit reuptake of both serotonin and norepinephrine. Although four SNRIs currently exist, only venlafaxine and duloxetine have been studied as analgesics [25]. As duloxetine affects both serotonin and norepinephrine at lower doses, pain reduction may occur at these levels. On the other hand, venlafaxine is mostly a serotonergic agent at low doses, and therefore, more robust dosing may be required to impact pain. SNRIs are efficacious for vasomotor symptoms related to anti-estrogen therapy in breast cancer survivors and would certainly be a wise choice for women suffering from both hot flashes and neuropathic pain [19]. Unlike the TCAs, SNRIs lack significant interaction with other receptor systems and consequently have less problematic adverse effects. Side effects of SNRIs include nausea, dry mouth, insomnia or sedation, sexual

dysfunction, headache, tremor, dizziness, and constipation. In addition, SNRIs can cause excessive sweating, tachycardia, and elevations in blood pressure. Due to anti-platelet activity, risk of bleeding can be exacerbated when SNRIs are combined with other drugs that affect coagulation. SNRIs can cause a flu-like syndrome when stopped abruptly and should be tapered slowly. Of note for patients on tamoxifen, studies have suggested an increased risk for breast cancer recurrence from the use of strong inhibitors of the CYP2D6 enzyme and therefore recommend an avoidance of duloxetine [22].

17.6 Conclusion

It is clear from recent work that an association exists between malignant pain and the most common psychiatric disorders, anxiety, and depression. In order to provide comprehensive pain management in oncological settings, screening for psychosocial distress should occur utilizing validated measures. By recognizing and appropriately diagnosing comorbid disorders, pharmacological therapies, psychosocial treatments, and system-based interventions can be recommended, which are efficacious in reducing both pain and psychiatric symptomatology.

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Integrative Therapies in Cancer Pain

18

Anna Woodbury and Bati Myles

18.1 Introduction

Pain is inevitable; suffering is optional

–Haruki Murakami

The author of this quote, in 6 words, managed to encapsulate our current understanding of the complexity of pain. While pain is a universal experience, from stubbed toes to broken bones, the subjective experience and its meaning vary a great deal. Prior to advances in the field of neuroscience, pain was as mysterious and inevitable as most physical phenomena. With time, pain became less of an enigma as the structure and function of nerves, and their role in the perception of sensation became clear. Pain was one of many stories neurons shared with one another in the language of neurotransmitters and ions. Something so finite and understandable didn't have to be frightening anymore. However, we are coming to realize that even that isn't the entire story. The dance within the nervous system is not so predictable or choreographed. The brain does not passively receive information and faithfully respond in a standardized manner. Just as two individuals will respond to the same stimulus differently based on past experiences and personality, and the brain's response to pain reflects this variety. The brain is always changing, as prior experiences combine with new ones to shape and mold it into something slightly changed. The experience of pain itself changes how the brain responds to

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that pain. So, not only will two different people respond to pain differently, the same person, with time, will as well.

The response to pain and its changes over time can be seen on a molecular level, as a sustained, intense, painful stimulus leads to upregulation of pain receptors and decreased firing thresholds in the peripheral nervous system [1, 2]. This central hypersensitization can lead to allodynia (innocuous stimulation causes pain) and hyperalgesia (stimulation causes pain out of proportion to the intensity of the stimulus). In the central nervous system, gene expression changes, establishing pathways that set up new, abnormal responses to pain [1, 2]. Further, it is not only the somatosensory areas of the brain that responds to pain; affective and cognitive regions respond as well, further described in neuroimaging studies of acute and chronic pain. Physical pain is not observed dispassionately from a distance; it has a significant emotional and cognitive impact that only grows with the intensity and duration of that pain. Because of this, for some people, physical pain breeds social, psychological and spiritual pain, which then breeds more physical pain and suffering. So we are beginning to understand that while pain is universal, suffering is not. Our individual histories and neural architecture determine what pain means to each of us.

The recognition of the individual experience of pain, and the impact that the mind has on that experience, has led to a growing acceptance of mind–body therapies. These modalities, which include meditation, art therapy, yoga and hypnotherapy, are designed to use the mind/body interface as a tool to facilitate healing. This has, in turn, fostered acceptance of a broader medical approach known as integrative medicine [3]. Integrative medicine embraces all effective treatments, including conventional western medicine and complementary treatments, which fall outside of that umbrella. Within the field of integrative medicine, there is also an emphasis on the patient as a whole person, with physical complaints considered equally as important as the impact of illness on a person's functioning in various aspects of life.

Patients are enthusiastically embracing integrative medicine in large numbers. According to a 2012 National Health Interview Survey (NHIS), 33.2% of Americans have used some form of complementary medicine in the past year [4]. The NHIS conducted in 2017 was not as broad, focusing on meditation, yoga and chiropractic, but showing increases in the percentage of the population using each of these therapies both in children and adults [5]. Among oncology patients, multiple studies show that more than 50% use complementary medicine after being diagnosed with cancer and up to 91% during chemotherapy [6, 7]. Complementary therapies available for integration into conventional medicine include 5 broad categories: Mind–Body Therapies, Energy Therapies, Alternative Medical Systems, Manipulative Therapies, and Biologicals/Nutraceuticals. Some of these therapies fall within more than one category, e.g., Tai Chi/QiGong which is considered both an Energy therapy as well as a Mind–Body therapy, and could also fall within Alternative Medical Systems as part of Traditional Chinese Medicine (TCM). Table 18.1 summarizes various complementary and alternative medicine therapies available to cancer patients. Though not entirely comprehensive given the wide

Table 18.1 Complementary and alternative medicine therapies for cancer patients

Mind–body	Energy	Alternative medical systems	Manipulative	Biologicals/Nutraceuticals	Other
Meditation	Acupuncture	Homeopathy	Chiropractic	Diet	Balneotherapy
Guided imagery	Acupressure	Traditional Chinese medicine	Massage	Herbal supplements	Hydrotherapy
Hypnotherapy	Magnet therapy	Ayurvedic medicine	Osteopathy	Vitamins	Hyperbaric therapy
Tai Chi/Qigong	Reiki				Cryotherapy
Yoga	Biofields				
Music therapy					
Art therapy					
Spirituality					

range of options available outside of conventional medical care, the table provides an idea of the broad range of therapies available. Not all of the therapies have sufficient evidence to justify their use, though most of the therapies carry a low risk of harm. It is important, however, to acknowledge that the potential for harm does indeed exist, and that "natural" does not necessarily mean "safe." Research regarding these therapies for cancer is ongoing and available trials can be found on the National Cancer Institute website [8].

Given the widespread use of complementary therapies, it is important that medical providers be prepared to discuss the risks, benefits and evidence supporting these treatments. Moreover, it is important that clinicians initiate discussions about the use of complementary medicine with patients. In one study, more than two-thirds of physicians were unaware of their patients' use of complementary therapies, suggesting a significant disconnect between patients and their physicians [9]. Patients seem to be reluctant to share their use of integrative therapies, while physicians may not feel like they have adequate time or knowledge to broach this subject. By initiating discussions about all therapies being used, clinicians foster a supportive environment in which patients have permission to disclose their use of less traditional treatments. Resources from the National Institutes of Health include regularly updated summaries on complementary therapies from the National Cancer Institute (https://www.cancer.gov/about-cancer/treatment/cam/patient) as well as from the National Center for Complementary and Integrative Health (https://nccih.nih.gov/health/integrative-health).

Web References:

National Cancer Institute. *Complementary and Alternative Medicine for Patients.* 20 Sep. 2020: https://www.cancer.gov/about-cancer/treatment/cam/patient

National Center for Complementary and Integrative Health. *Complementary, Alternative, or Integrative Health: What's in a Name?* 20 Sep. 2020: https://nccih.nih.gov/health/integrative-health

In this chapter, we will discuss some of the most studied and commonly used complementary therapies available for the treatment of cancer-related pain and symptoms. Our goal is to provide a framework for discussions between medical providers and their patients to ensure safety, discussion of all available treatments, and open lines of communication. By improving our understanding of complementary and alternative treatments, we exponentially expand the arsenal of therapies that can be explored to improve a patient's ability to better manage pain and reduce suffering.

18.2 Nutritional Supplements

The term nutritional supplement, in the context of integrative medicine, is very broad. This can refer to herbs of various kinds, plant products such as aloe vera, vitamins, minerals and amino acids among others. Anything that is edible and used for medicinal purposes falls under this category. Because of the wide variety of products and traditions that inform their use, it is unsurprising that there is a great deal of anecdotal evidence supporting an array of supplements, but a relatively small amount of literature supporting their efficacy. As these are compounds being introduced into the body, they pose a particular threat, while being the complementary therapy most commonly used by patients. It is important to note both the potential side effects as well as benefits from these therapies, and evaluate the available evidence that would support or should prevent their use in specific patients.

18.2.1 Supplements for Neuroprotection

Vitamin E is a commonly used supplement that can increase the risk of bleeding, but has also been found to be neuroprotective and may have applications for the prevention of chemotherapy-induced neuropathy [9, 10]. Neuropathy is a common, dose-limiting complication of treatment with platinum-based chemotherapy (PBC). While the mechanism of action is unknown, there is evidence that mitochondrial dysfunction from oxidative stress damages peripheral nerves and causes neuropathic pain. Vitamin E is a naturally occurring antioxidant that has been shown to be significantly reduced in patients being treated with PBC [11]. Additionally, the peripheral neuropathy that develops in some patients receiving PBC is similar to symptoms experienced by people with vitamin E deficiency. These observations have led to a number of randomized trials examining the efficacy of vitamin E supplementation in the prevention of chemotherapy-induced neuropathy. One such study by Pace et al. involved 108 patients receiving at least 300 mg/m^2 cumulative dose of cisplatin. These patients had to be free of baseline neuropathy and naïve to chemotherapy. They also had to ultimately receive at least 300 mg/m^2 cumulative dose of cisplatin therapy. The subjects were randomized to receive 300 mg of vitamin E daily and for 3 months after completion of chemotherapy or placebo. Patients were then evaluated for the presence and severity of neurotoxicity using a validated neurotoxicity score (Total Neuropathy Score) as well as electrophysiologic nerve conduction and nerve potential amplitude studies. The study showed that patients who had received vitamin E had significantly lower mean neurotoxicity scores and a 0.14 relative risk of developing signs or symptoms of neurotoxicity. Additionally, the treatment group had no significant change from baseline on electrophysiological examination, while patients in the control group had significantly decreased mean sural and sensory median nerve amplitude values. This is supported by the findings of other similar studies [12–14].

Oral glutamine, both a potent antioxidant and the most abundant amino acid in the serum and skeletal muscle, has also been shown in multiple studies to prevent neurotoxicity. Glutamine is a precursor to two important neurotransmitters: glutamate and gamma-aminobutyric acid (GABA). A 2007 study by Wang et al. found that it prevented oxaliplatin-induced neuropathy in colorectal cancer patients [15]. In this study, 86 patients with metastatic colorectal cancer receiving oxaliplatin, 5-fluorouracil and folinic acid were randomized to receive glutamine or nothing as controls. The glutamine group received 15 g of glutamine twice daily for 7 consecutive days every 2 weeks starting the day of initiation of oxaliplatin infusions. Response to chemotherapy, neurologic toxicity and electrophysiological changes were all measured with the glutamine groups having significantly less neurotoxicity compared to controls without any differences in chemotherapy response and non-neurologic toxicity or survival. Since glutamine is a precursor to glutamate, a major excitatory neurotransmitter, glutamate has also been studied for neuroprotection. A 2009 study by Loven et al. showed no evidence of protection from 1.5 g daily dose of glutamate, but did provide evidence that in patients treated with glutamate who had neuropathy symptoms, and this population had significantly less painful neuropathy compared to placebo [16].

Glutathione is a molecule made in the body from cysteine, glutamate and glycine that works as an antioxidant, neutralizing free radicals. It has been shown to decrease the incidence and severity of platinum chemotherapy-induced peripheral neuropathy in multiple oncologic cancers. The 2002 paper published by Cascinu et al. demonstrated that glutathione reduced the incidence of neurotoxicity in patients with colorectal cancer being treated with oxaliplatin [17]. 52 patients receiving oxaliplatin chemotherapy for their colorectal cancer were randomized to receive 1500 mg/m^2 glutathione in a 15-min infusion prior to chemotherapy or normal saline. Electrophysiological investigations were performed at baseline and after four, eight and 12 cycles of treatment. After 8 and 12 cycles, the glutathione-treated group had statistically significant lower rates of grade 2 and higher neuropathy as graded by the National Cancer Institute's common toxicity criteria [18]. Moreover, sural nerve conduction studies showed a significant increase in latency (ms) and decrease in sensory amplitude potential (μV) and conduction velocity (m/sec) after 8 cycles of chemotherapy in the placebo group but not the treated group. In the placebo group, latency increased from 3.07 ± 0.33 to 3.19 ± 1.70 ($P = 0.03$), sensory amplitude potential decreased from 10.98 ± 6.92 to 7.20 ± 5.05 ($P = 0.05$) and conduction velocity decreased from 45.91 ± 4.59 to 39.33 ± 11.66 ($P = 0.01$) after 8 cycles. There was no significant decrease after only 4 cycles. In the treatment group latency increased from 2.98 ± 0.97 to 3.08 ± 0.99 (P = NS), sensory amplitude potential decreased from 9.09 ± 6.34 to 8.71 ± 5.50 (P = NS) and conduction velocity decreased from 39.87 ± 13.0 to 39.13 ± 11.63 (NS).

Melatonin, a neurohormone secreted by the pineal gland, plays an important role in physiologic and neuroendocrine functions such as regulating the circadian rhythm. It has also been recognized as possessing antioxidant properties, with recent animal studies supporting a role for melatonin in the prevention and

treatment of chemotherapy-induced neuropathy [19–21]. Unfortunately, there have been fewer human studies confirming these findings, particularly in patients with cancer. However, there was one large 1999 study of 250 cancer patients receiving chemotherapy that demonstrated a significant decrease in the incidence of neuropathy in patients treated with melatonin [22]. Patients with non-small cell lung cancer, breast cancer, gastrointestinal (GI) tumors and head and neck cancers receiving a standardized chemotherapy directed at their type of tumor were then randomized to either receive chemotherapy alone or with melatonin given orally at a dose of 20 mg/day every evening starting 7 days prior to chemotherapy and then continued until disease progression occurred. Along with developing significantly less neurotoxicity, patients treated with melatonin also developed significantly less thrombocytopenia, cardiotoxicity and stomatitis compared to controls.

In a systematic review of herbs used for chemotherapy induced peripheral neuropathy (CIPN), 17 trials involving 2174 patients were assessed, and it was found that herbal medicines could potentially prevent or treat CIPN with only two cases of adverse events [23]. The herbal medicines tested in these trials were primarily East Asian formulations stemming from traditional Chinese medicine (TCM), rather than the nutraceuticals and supplements described above. As such, these therapies should probably be used only under the supervision of a practitioner of TCM as an alternative medical system. A 2015 review, on the other hand, summarized research on individual herbs such as Gingko biloba 50–150 mg/kg, green tea 300 mg/kg, *Ocimum sanctum* 100–200 mg/kg, *Matricaria chamomilla* 25 mg/kg, *Butea monosperma* 400 mg/kg, Walnut 6%, *Xylopia aethiopica* 30–300 mg/kg and Curcumin 10 mg/kg, showing evidence of a positive effect in animal models of CIPN [24].

18.2.2 Supplements for Mucositis

Glutamine is an amino acid that may have beneficial effects for mucositis. Mucositis is a painful complication related to both cytotoxic chemotherapy and radiation therapy. This occurs due to damage to rapidly proliferating cells such as those in the mouth and GI system with these treatments. Multiple studies have shown that glutamine, when given in a "swish and swallow" formulation shows a consistent reduction in the frequency and severity of mucositis caused by chemotherapy and radiation therapy. One 2005 study by Aquino et al. was performed in 120 children undergoing hematopoietic stem cell transplant [25]. These children underwent a variety of treatments including whole body radiation and high-dose cytotoxic therapy. Prior to treatment, they were randomized to receive either glutamine 2 g/m^2/dose twice daily until 28 days post-transplant or a glycine placebo taken in a "swish and swallow" method started at admission for transplantation. The glutamine treatment group had a trend toward less severe mucositis, fewer days of total parenteral nutrition (TPN), and a reduction in the mean number of days of intravenous opiate use. Another 1998 study by Anderson et al. [26] studied 24 patients undergoing bone marrow transplant. In this study, patients were

administered 2 g glutamine/m^2/dose swish and swallow four times a day with glycine serving as a control. This was taken on days of chemotherapy and for 14 days following completion of treatment. Glutamine treatment was associated with a significant 4.5 day reduction in duration of mouth pain and reduction in pain severity. Similar results were seen in a 2000 study by Huang et al. in patients receiving radiation therapy for head and neck cancer [27]. A 2009 review by Noe et al. reported the reduction in the incidence and severity of mucositis using a regimen of 20–30 g of glutamine, divided BID, taken daily at the start of radiation or chemotherapy through 2 weeks after completion of chemotherapy [28]. The review also noted a lack of toxicity when glutamine was given at even higher levels.

Honey has also been found to be an effective preventative treatment for mucositis. A recent systematic review and meta-analysis revealed an 80% relative risk reduction in radiation induced oral mucositis in patients treated with honey versus controls [29]. One of the most recent studies cited involved 40 patients with oral cancer [30]. These patients were randomized to receive honey or lignocaine gel 15 min before and after radiation therapy and once before bed. A visual assessment of the oral cavity using the Radiation Therapy Oncology Group (RTOG) rating scale from 0 to 4, with 0 being normal and 4 being most severe, to rate mucositis. Strikingly, only 1/20 patients treated with honey developed grade 3 or 4 mucositis compared to 15/20 patients in the control group. This was a significant difference with a relative risk of severe mucositis in patients treated with honey of 0.067. Similar findings were seen in 2 other studies with similar treatment regimens and mucositis rating scales [21]. In all studies, patients applied honey to the inside of their mouths before, directly after, and several hours after radiation therapy. A Cochrane review draws similar conclusions [31], though clinicians are advised to be cautious when using this therapy given small study sizes and the risk of bias in all supporting studies. Because honey has such a distinct flavor and texture, recipients could not be blinded to the treatment they received.

Calendula, a type of marigold with antioxidant properties, has demonstrated utility in the prevention of dermatologic and mucosal side effects of radiation therapy [32]. In a 2013 study by Babaee et al., 40 patients were randomized to receive 2% calendula extract mouthwash or placebo given twice daily starting at the beginning of radiotherapy and continuing until its completion [33]. Oropharyngeal mucositis, as graded by the oral mucositis assessment scale, was significantly less severe in the treatment group compared to the placebo group at weeks 2, 3 and 6. It was also found to be effective in another randomized controlled trial of 254 patients scheduled to receive postoperative radiation for breast cancer [34]. The patients were randomized to have calendula or trolamine ointment applied to irradiated fields after each session, at least twice a day (more if needed), until completion of radiation therapy. The occurrence of acute dermatitis of grade 2 (moderate) or higher was significantly lower (41 vs 63%) in the patients treated with calendula.

18.2.3 Caution with Supplements

As many of these supplements are ingested, particular attention must be paid to toxicity and drug interactions. Most of the aforementioned supplements are known to be safe, with benign side effect profiles. There are known risks associated with the ingestion of glutamine and Vitamin E. Glutamine has been shown to reduce clearance and increase tissue concentrations of methotrexate in in vivo rat cancer models [35, 36]. In humans, vitamin E has been shown to reduce through levels of cyclosporine and the bioavailability of tamoxifen [37–39]. Therefore, dietary supplements should be treated similarly to prescribed medications with safety, necessity and possible drug-drug interactions being considered.

While larger controlled trials are necessary to further explore the utility of these and other supplements, the evidence supporting the use of therapies such as glutamine and vitamin E are strong. The added benefit of these products being safe and inexpensive should encourage both further investigation and use in appropriate patient populations.

18.3 Cryotherapy

Oral cryotherapy is a simple, yet effective method for preventing the painful complication of mucositis in cancer patients receiving certain types of chemotherapy. A 2015 Cochrane meta-analysis concluded confidently that cryotherapy reduces the incidence of mucositis of all severities in patients receiving 5 fluorouracil based chemotherapy for solid tumors [40]. The review included 14 RCTs involving 1280 patients, most of whom were receiving cytotoxic chemotherapy, though one study included people receiving radiation therapy to the head and neck. The overall effect was a RR of 0.61 for all severities of mucositis in the treatment group with the relative risk for moderate to severe and severe mucositis in the treatment group being 0.52 and 0.40, respectively. Generally, the cryotherapy intervention in these studies involved placing ice chips, ice cubes or ice water in the mouth 5 min prior to chemotherapy and continuing for 30 min.

The mechanism of action is unclear, but one hypothesis is that the cold decreases blood flow to the mouth and prevents exposure of the tissue to the cytotoxic effects of both radiation and chemotherapy.

18.4 Acupuncture

Acupuncture is a technique rooted in traditional Chinese medicine. The first recorded description of acupuncture comes from the *Huang Di Nei Jing*, an ancient Chinese medical text, written in 200 BC. The practice of acupuncture is based on a view of the body that differs from conventional allopathic medical understanding.

Acupuncture functions by altering the flow of qi (chee). Qi is conceptualized as an energy force present in the body that flows through channels known as meridians and regulates the body's functions. Illness is thought to occur when there is an imbalance in the flow of qi, either an excess or a blockage. Acupuncture, by acting upon particular points within meridians that lie on the surface of the body, is intended to return balance to the flow of qi. Acupuncture specifically involves the insertion of sterile needles at meridian points to influence qi, but a variety of other techniques exist to manipulate the flow of qi including laser acupuncture, cupping, tui na massage, Gua Sha, Tai Chi and acupressure [41].

In 1998, the National Institutes of Health released a consensus statement concluding that acupuncture is effective for postoperative and chemotherapy-induced nausea and vomiting as well as for postoperative dental pain [32]. This statement reflects recognition of the role that acupuncture can play in disease and symptom management, despite its philosophical differences from those of mainstream allopathic medicine. It also reflects the extensive amount of work that has been done in this field. Along with evidence for the use of acupuncture in the management of nausea, vomiting, and postoperative dental pain, there is also literature supporting the use of acupuncture in a variety of other pain complaints including: migraines, TMJ, fibromyalgia, osteoarthritis, low back pain and myofascial pain [42].

Both molecular and fMRI studies have shed light on the potential mechanism of action of acupuncture in relieving pain. In a study by Sjolund [43], the cerebrospinal fluid of humans was analyzed following electroacupuncture, revealing increased levels of endorphins. Multiple animal studies have demonstrated the release of the endogenous opiates, enkephalin, beta-endorphin, endomorphin and dynorphin during acupuncture. This suggests that the analgesic effects of acupuncture are mediated by the release of these endogenous opiates. This hypothesis is further supported by a human study demonstrating that the analgesic effects of acupuncture are reversed by the administration of naloxone [44].

Functional MRI studies have further demonstrated distinct effects of acupuncture on the brain. In a 1999 study by Wu et al. [45], acupuncture was performed on patients using both true acupuncture sites (LI.4 and ST.36, analgesic acupuncture points) and a non-acupuncture site. They found that when patients were subjected to true acupuncture, areas of the descending antinociceptive pathways in the hypothalamus and nucleus accumbens were activated, while areas important for pain association (the limbic system) were deactivated. This suggests that the mechanism of action of acupuncture, in the case of analgesia, may be a combination of the release of endogenous pain modulators and the activation of inhibitory impulses that disassociate the emotional and cognitive pain response.

When it comes specifically to treatment of cancer-related pain, there is an extensive collection of studies focusing on the use of acupuncture for this purpose. There is evidence of its effectiveness in the treatment of bone, visceral and neuropathic pain associated with a variety of cancers and their treatments.

In a 2013 RCT by Chen et al., [46] 60 patients with pancreatic cancer were randomized to acupuncture treatment or control. The acupuncture group was treated with insertion of sterile acupuncture needles on Jiaji points T8–T12 bilaterally,

which were attached to an acupoint nerve stimulator for 30 min once a day for 3 days. The control group had sham needles pushed onto the same acupuncture points without puncturing the skin. Patient pain was measured using numerical rates scales before treatment, after 3 treatments, and 2 days after treatment was completed. Patients who had undergone acupuncture treatment had significantly improved pain scores after 3 days of treatment with a 1.67 point difference from baseline in the acupuncture group, and no change in the control group; this was consistent when patients were followed 2 days later.

A 1995 case series by Guo et al. [47] found that 74.2% of 286 patients with cancer pain due to bony metastasis experienced decreased pain levels and analgesic medication use after electroacupuncture, with the analgesic effect lasting an average of 3.6 h.

A 2008 RCT of 70 patients by Pfister et al. [48] involved 58 patients with chronic pain or dysfunction related to neck dissection for head and neck cancer. These patients were randomly assigned to weekly acupuncture versus usual care including physical therapy, analgesia and/or anti-inflammatory drugs. The patients receiving acupuncture received treatment once a week for 4 weeks. During treatment, sterile acupuncture needles were inserted at points L1-4, SP-6, GV-20, luzhen and auricular shenman and allowed to remain for 30 min The Constat-Murley score, a composite of pain, function and activities of daily living was measured. This composite score decreased significantly in the group treated with acupuncture, providing evidence that acupuncture resulted in a significant reduction in pain in head and neck cancer patients after neck dissection compared with non-acupuncture controls.

A 2003 RCT by Alimi et al. [49] studied the effectiveness of auricular acupuncture in decreasing pain in 90 patients with chronic neuropathic pain occurring after treatment for cancer. A baseline visual analog score of 30 mm and on stable analgesic therapy for at least a month was required for patients to be included in the study. Most patients had neuropathic pain, though a minority were also experiencing nociceptive pain. The treatment arm received two courses of acupuncture using steel spear-headed implants (semi-permanent needles applied to the ear). There were two control arms: one group receiving acupuncture at placebo points and another with auricular seeds attached to placebo points. It was found that neuropathic pain intensity decreased significantly by 36% at 2 months compared to baseline in the auricular acupuncture group, with no decrease occurring in the placebo arms.

There have also been multiple case series (Wong 2006, Bao 2011 and Donald 2011) of patients with chemotherapy-induced peripheral neuropathy having significantly decreased or resolved pain after acupuncture therapy, though this is subject to reporting and publication bias [50–52].

An intriguing 2012 pilot study by Schroeder et al. [53] involved 11 patients with CIPN; 6 patients chose acupuncture therapy and 5 opted out. The treatment arm received acupuncture for 10 weeks at ST34, EX-LE12 and EX-LE8 points. Five of the 6 treated patients had significantly improved nerve conduction velocity and mean amplitude compared to the control group. A more recent 2019 pilot study

regarding CIPN specifically in breast cancer survivors who had been treated with taxane-containing adjuvant chemotherapy found significantly improved subjective sensory symptoms with reduced neuropathic pain and paresthesia in women randomized to immediate acupuncture (18 treatments over 8 weeks) as opposed to the waiting-list group [54].

In a 2017 meta-analysis, 5 studies involving 181 patients showed significant pain reduction after 6–8 weeks of acupuncture treatment with significant decreases in BPI (Brief pain index) score and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score [55]. One of the studies was a 2010 randomized, controlled, blinded study by Crew et al. [56] comparing sham acupuncture twice weekly for 6 weeks in postmenopausal women with breast cancer who had self-reported musculoskeletal pain related to aromatase inhibitors. Aromatase inhibitors have been shown to be more effective than tamoxifen in preventing breast cancer recurrence. As such, they are routine adjuvant therapy used in postmenopausal women with estrogen receptor positive breast cancer. Unfortunately, 50% of patients report musculoskeletal discomfort, leading to discontinuation rates as high as 13%. In the 2010 study by Crew et al. the treatment arm (TA) received full body/auricular acupuncture and joint specific point treatment. Sham acupuncture (SA) involved superficial needle insertion at non-acupoint locations. Pain was measured using the brief pain inventory short form (BPI-SF), WOMAC. The TA experienced significantly larger reductions in pain severity and pain-related interference at 6 weeks compared to the SA using BPI-SF and WOMAC at 3 and 6 weeks.

Most recently, a systematic review and meta-analysis evaluating 386 cancer patients gathered from 6 randomized control trials (high quality, by a modified Jadad scale) showed that acupuncture led to statistically significant improvements in pain scores (-1.21, $P < 0.00001$) and nervous system symptoms from "Functional Assessment of Cancer Therapy/Neurotoxicity" questionnaire scores (-2.02, $P < 0.00001$). Though the decrease in pain score may not meet criteria for a minimally clinically important difference, this review does suggest that acupuncture may be a reasonable, evidence-based treatment in cancer patients suffering from chemotherapy-induced peripheral neuropathy [57].

There are some risks associated with acupuncture. One 2010 study revealed that 6.8% of patients receiving acupuncture experienced negative short-term reactions such as pain, tiredness and dizziness [58]. In another study, in which 8.6% of patients reported an adverse effect, bleeding or hematoma were the most common [59]. In 2015, a large scale review of case reports of acupuncture related adverse events and complications in China between 1980 and 2013 was published [60]. This review identified 182 patients over 33 years who experienced adverse events with spinal cord injury being the most commonly reported complication. There were also instances of infection and hemorrhage reported. Though this doesn't capture all instances of complications experienced due to acupuncture, the fact that only 182 serious complications were reported in the literature after millions of people had been treated with acupuncture over that time frame suggests that these complications are rare.

18.5 Hypnosis

Hypnosis is the practice whereby a hypnotist moves a person to a trance-like state in which the patient is more aware, focused and open to suggestion. Multiple studies have examined the effectiveness of hypnosis on postoperative pain, mucositis, chronic pain and metastatic cancer pain.

Functional MRI studies have suggested that two structures in the brain appear to play a particularly important role in the analgesic effects of hypnosis: the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) [61]. The prefrontal cortex plays an important role in decision making and has been found to exhibit hyperactivation in patients receiving pain-directed hypnosis. Changes in the PFC were particularly noticeable when the hypnotic suggestion involved the patient remembering a pleasant autobiographical memory or invoking some other pleasant imagery. The ACC is most involved in attention and motivation, and plays an important role as it integrates sensory experience with cognitive, emotional and behavioral regions of the brain such as the PFC.

These studies focusing specifically on a population with cancer, hypnosis has been shown to be associated with a significant decrease in pain scores among patients with post-surgical, bone, and mucositis pain among others.

In a recent study in 2009 by Butler et al. [62] of 124 women with metastatic breast cancer who were followed for 12 months, patients who received hypnosis in a supportive group therapy environment were found to have significantly less increase in the intensity of pain compared to controls. Both groups had similar pain scores at the beginning of the intervention, and while the average pain scores in the control group increased over the year, those of the patient's receiving hypnosis did not significantly change.

A randomized clinical trial by Montgomery et al. in 2007 [63] examined the effectiveness of a brief, 15-min presurgery hypnosis session conducted by a psychologist compared to empathetic listening (control) in women undergoing breast cancer surgery. Patients in the hypnosis group required less intraoperative propofol and lidocaine than the control group. They also reported less pain intensity, pain unpleasantness, nausea and fatigue.

In a 2004 a prospective, randomized study by Elkins et al. [64] of 39 patients with advanced cancer (stage III or IV) and malignant bone disease were studied. These patients were randomized to receive weekly sessions of supportive attention or a hypnosis intervention. Those in the hypnotic group received at least 4 weekly sessions and demonstrated a significant decrease in pain compared to the control group.

A 1992 study of 67 patients who underwent bone marrow transplantation were randomized to hypnosis training, cognitive behavioral coping skills training, therapist contact control or usual care. The hypnosis group had significantly reduced pain from oral mucositis [65].

18.6 Guided Imagery

Guided imagery is the use of mental visualization to improve mood and physical wellbeing. During a guided imagery session, the patient is guided through an imagery technique or script designed to invoke one or more senses. This can be done one on one, in a group setting or by tape. By invoking these senses, patients can alter their perception of ongoing experiences. It is often used in conjunction with progressive muscle relaxation, a nursing intervention facilitating the tensing and releasing of successive muscle groups, while attending to the resulting difference in sensation.

There have been multiple studies detailing the effectiveness of guided imagery in improving pain in both chronic pain conditions like migraines and osteoarthritis as well as in patients with cancer pain.

A 2016 study by Charalambous et.al [66] was a randomized controlled trial of 208 cancer patients undergoing chemotherapy. Patients were randomized to an intervention group trained in guided imagery and progressive muscle relaxation and a control group that received standard care. Inclusion criteria were patients with breast or prostate cancer experiencing symptoms like pain, fatigue, depression, nausea, vomiting and anxiety. Measurements for control and intervention groups were collected at baseline and after completion of the intervention. The intervention group had significantly less pain and fatigue compared to the control group, with pain scores at the end of the intervention being an average of 2.5 and 4.8, respectively.

A 2015 study by Chen et al. [67] examined the utility of guided imagery in the management of a variety of symptoms in women with breast cancer undergoing chemotherapy. 65 women were randomly assigned to experimental or usual therapy groups. The experimental group received 1 h of relaxation with guided imagery training before chemotherapy and a CD to practice the guided imagery 20 min daily for 7 days after chemotherapy. These patients exhibited a significant decrease in insomnia, pain, restlessness, difficulty concentrating, numbness, anxiety and depression compared to usual therapy.

18.7 Music Therapy

Music therapy is the use of music to tackle various aspects of a patient's pain, including the physical, emotional, cognitive and social needs associated with serious illness. It must be administered by a qualified music therapist who assesses patients' strengths and needs and provides indicated treatment. It can be passive, such as listening, or active, e.g., playing music or composing original work.

A 2016 Cochrane meta-analysis of randomized controlled trials examined the impact of music interventions on physical and psychological outcomes in people with cancer [68]. The analysis revealed that along with significant improvements in both anxiety and depression in patients exposed to music therapy, and there was an

overall large and statistically significant pain-reducing effect among 7 studies including 528 participants.

One example of the supporting studies was one 2010 study by Huang et al. [69]. In this study, 126 patients with cancer pain were randomized to either an experimental group receiving music therapy or a control group. Music choices included folk songs, Buddhist hymns, harp and piano. The experimental group listened to music for 30 min, while the control group rested in bed. Sensation and distress of pain were rated on a 100 mm VAS before and after music. The intervention group had significantly less post-test pain compared to controls. Also, 30 min of music provided 50% relief in 42% of the music group compared to 8% of controls.

Another 2013 study by Gutsell et al. [70] was performed in 200 palliative care patients. Participants were treated with standard care or standard care with music therapy. The music therapy intervention involved music therapist guided relaxation and live music. The intervention group had significantly greater decreases in pain scores and mean changes on the functional pain scale.

18.8 Massage

Massage involves a therapist stroking, kneading, applying friction and stretching specific muscles and connective tissues with varying levels of pressure. The purpose of this can be relaxation or treatment of musculoskeletal complaints. There are many forms of massage including: Swedish, deep tissue and Shiatsu. Many studies have explored the ability of massage to promote relaxation and mental well-being, while the number of studies exploring its ability to mitigate physical pain has been smaller. There are, however, multiple studies showing massage to be effective in the treatment of lower back pain during pregnancy to labor pain, migraine headaches, premenstrual syndrome, chronic fatigue, fibromyalgia, carpal tunnel syndrome and rheumatoid arthritis [71].

There are different theories regarding the mechanism by which massage exerts its analgesic properties. One is called the Gate Control Theory (also applicable to acupuncture). This theory holds that because pressure is carried to the brain by quick firing, longer, myelinated nerves versus the shorter, less myelinated fibers used for pain sensation transmittal, the pressure sensation (in the case of massage) "closes the gate" to the pain by reaching the brain first. Another theory relates to sleep deprivation. Substance *P*, a common mediator of pain, is released at reduced levels during deeper sleep states. Massage therapy leads to lower substance *P* levels in the saliva of patients receiving massages as well as more time in deep sleep. Finally, there is a hypothesis that by increasing serotonin levels, massage therapy exerts its analgesic effect by decreasing substance *P*, cortisol or depression. Further studies need to be done to further clarify the veracity of these theories.

In regards to the effectiveness of massage in improving cancer-related pain, a 2015 meta-analysis including 12 studies and 559 participants concluded that there was strong evidence showing that massage is effective for the relief of cancer pain [72].

One 2011 study by Jane et al. [73] was a randomized controlled trial in 72 Taiwanese cancer patients with metastatic bone pain of at least an intensity of 4 on a 0–10 scale. These patients were randomized to massage therapy or social attention (a caring professional there to allow the patient to discuss their feelings and thoughts) which served as the control group. Patients in the intervention group received 3 consecutive days of a 45 min massage session with the same therapist on all 3 days. Improvement of pain over time compared to baseline was significantly improved in patients receiving massage therapy. The control group did not show a similar improvement.

A 2008 study by Currin and Meister [74] examined the impact of Swedish massage on patient reported levels of distress in four areas (pain, physical discomfort, emotional discomfort and fatigue) among 251 patients. This study was a non-randomized single group pre and post-test design with 251 participants. The study showed statistically significant reductions in distress in all areas.

A large 2004 outcome study by Cassileth an Vickers of 1290 patients over 3 years showed that massage therapy decreased symptom scores, including pain, by half [75].

18.9 Exercise

Exercise covers a wide range of activities including walking, strength training, tai chi and yoga. Multiple studies support the role of exercise, regardless of type, in the elevation of mood, reduction in stress and improved sleep. In concert with theories regarding the connection between mind and body, there have been studies further exploring if activities known to calm the mind have a demonstrable effect on the body apart from the expected improvements in strength and cardiovascular capacity. There also exists a collection of studies exploring the role of exercise in pain management and more specifically in cancer patients. A recent meta-analysis specifically analyzed the data supporting the use of tai chi in symptom management in cancer patients, and showed a trend toward decreased pain in these patients.

Two 2012 Cochrane reviews explored this question more broadly in reviews about the effectiveness of exercise of all types in the management of symptoms in both cancer survivors and patients undergoing active treatment [76, 77]. The meta-analysis involving patients undergoing active treatment included 56 trials and 4826 participants. Cancer diagnoses included breast, prostate, gynecologic, hematologic and others. The types of exercise interventions varied including cycling, yoga, Qigong, resistance training or some combination thereof. Significant improvements in fatigue, physical functioning, anxiety, depression, emotional wellbeing and physical functioning were found. Regarding pain, there was only one

RCT identified demonstrating a significant improvement in pain with exercise. The review of exercise intervention in cancer survivors included 40 trials with 3694 participants with history of breast, colorectal, head and neck, lymphoma and other cancers. They found that exercise interventions improved body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, fatigue, and pain at varying follow-up periods. The effect on pain was small and only significant at 12 weeks follow-up, but still a promising result.

One of the included papers, a 2009 study by Griffith et al. [78] studied 126 patients mostly with stage I-III prostate or breast cancer undergoing treatment including radiation and chemotherapy. These patients were divided into either a control group or a group performing a customized walking program based on baseline function and fitness. The exercise intervention was a moderate intensity walking program. This showed that along with significant improvements in cardiovascular fitness and physical function, and there was significantly less pain.

A recent meta-analysis was published detailing the effectiveness of Tai Chi and Qigong for cancer-related symptoms and quality of life [79]. This included 22 studies including 15 RCTs evaluating 1283 participants with breast, prostate, lymphoma, lung or combined cancers. Time of intervention ranged from 3–12 weeks. This intervention was associated with significantly improved decreases in sleep difficulty, depression and improved overall quality of life. There was also a statistically non-significant trend of improvement in pain with this exercise intervention. Another included study was a non-randomized trial of 67 patients with breast cancer receiving chemotherapy. The experimental group practiced a qigong regimen and had symptoms and psychological distress recorded on days 8, 15 and 22 of chemotherapy. The intervention group had significant improvements in pain, numbness, heartburn, and dizziness, compared with the control group. The authors of the meta-analysis conclude that larger, better designed studies need to occur to further solidify the role of these exercises in symptom relief for cancer patients.

18.10 Conclusion

Complementary medicine challenges us as scientists and providers to embrace the knowledge of our limitations. Acupuncture and guided imagery may not fit well in the conventional medicine paradigm, and their mechanisms of action aren't well understood, but there is a plethora of evidence to support their benefits. As clinicians, we have little choice but to inform ourselves of these therapeutic modalities, given the number of cancer patients who pursue complementary treatments. While more research is necessary to fully elucidate optimal treatment regimens, and larger, more powerful studies are needed to support preliminary results, we believe this chapter provided information regarding many safe and efficacious complementary treatments available to ease or even prevent symptom burden.

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