Current Pain and Headache Reports (2021) 25: 44
https://doi.org/10.1007/s11916-021-00963-2

ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Interventional Therapies for Pain in Cancer Patients: a Narrative Review

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Accepted: 21 April 2021 / Published online: 7 May 2021

Abstract

Purpose of Review Pain is a prevalent symptom in the lives of patients with cancer. In light of the ongoing opioid epidemic and increasing awareness of the potential for opioid abuse and addiction, clinicians are progressively turning to interventional therapies. This article reviews the interventional techniques available to mitigate the debilitating effects that untreated or poorly treated pain have in this population.

Recent Findings A range of interventional therapies and technical approaches are available for the treatment of cancer-related pain. Many of the techniques described may offer effective analgesia with less systemic toxicity and dependency than first- and second-line oral and parenteral agents. Neuromodulatory techniques including dorsal root ganglion stimulation and peripheral nerve stimulation are increasingly finding roles in the management of oncologic pain.

Summary The goal of this pragmatic narrative review is to discuss interventional approaches to cancer-related pain and the potential of such therapies to improve the quality of life of cancer patients.

Keywords Cancer pain · Interventional pain management · Quality of life · Musculoskeletal pain · Spine-related pain · Visceral pain · Neuromodulation

Introduction

Pain is profoundly impactful and prevalent in the lives of patients with cancer [1]. Untreated or poorly treated cancer pain has the potential to have wide-ranging effects on quality of life, functional status, and psychological well-being [2–4]. Epidemiologic studies often characterize pain in patients with cancer as directly caused by the neoplastic process, occurring as a complication of therapeutics, or unrelated to the neoplastic process [5]. For a substantial portion of cancer patients, pain is pervasive in all activities of daily life [6]. Both pain and depression have extensive negative implications on health-related quality of life, disability, and healthcare usage in the cancer patient population [1]. As the number and overall

This article is part of the Topical Collection on *Alternative Treatments for Pain Medicine*

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life expectancy of cancer survivors continues to increase, persistent pain of any etiology must be targeted with a multidisciplinary approach tailored to individual patient needs.

A systematic review conducted in 2014 reported pain prevalence rates of 39.3% after curative treatment, 55.0% during anticancer treatment, and 66.4% in advanced, metastatic, or terminal disease. What is equally as concerning as the high prevalence of pain is the observation that moderate to severe pain, defined as a numerical rating score greater than 5, was reported in 38.0% of all patients [7•]. In spite of published guidelines for pain management, cancer pain clearly continues to be undertreated [8, 9]. With escalating concerns about the adverse effects of long-term use of systemic opioids, cancer patients with chronic pain are increasingly looking toward physical therapy, psychosocial intervention, complementary and alternative techniques, and interventional procedures [10]. An array of techniques are available to interventional pain physicians and such approaches have been recognized with inclusion as a fourth step in the World Health Organization analgesic ladder [11]. Interventional approaches to pain management may offer valuable benefits to cancer patients as an integral component to multidisciplinary treatment of cancer pain.

Interventional Therapies for Musculoskeletal Pain

Introduction to Musculoskeletal Cancer Pain

The most common cause of cancer-related pain is somatic pain from bony metastases. In patients with advanced cancer, 60 to 84% report experiencing bone pain described as highly debilitating and detrimental to overall quality of life [12, 13•]. The malignancies most commonly associated with bony metastases included cancers of the prostate, lung, breast, and blood. Metastases were most often located in the vertebrae (69%), pelvic bones (41%), long bones (25%), and skull (14%) [14]. Most patients describe experiencing mild to moderate dull aching base pain with intermittent and severe breakthrough pain [15].

The mechanism of musculoskeletal pain in cancer patients is complex. At a cellular level, pain is derived from a complex interplay between tumor cells, bone cells, inflammatory cells, myocytes, and sensory neurons. A reciprocal interaction exists between metastatic cancer cells and osteoblasts or osteoclasts that incites release of chemical mediators that disrupt native control of bone density [16]. Pain is generated by multiple mechanisms including stimulation of endosteal nerve endings via bony destruction, release of pro-inflammatory mediators, mechanical stretching of periosteum, fractures, and local tissue invasion by tumors [17]. Impingement and infiltration of nearby muscle and fascia may induce local hypersensitivity and myofascial pain syndromes. Pain signals from areas of bone metastasis and hypersensitive myofascial trigger points are communicated by inflammatory and neuropathic pathways and modulated at the level of the tissues, nerves, spinal cord, and brain [15, 18]. In addition to the direct effect of cancer cells on bone, musculoskeletal pain in cancer patients may also be caused or exacerbated by antineoplastic therapies. About one-third of patients who undergo radiation therapy to bony metastases will experience focal bone pain [19]. Chemotherapeutic agents, cytotoxic compounds, and hormonal modulators have all been associated with development of arthralgias [20, 21].

As methods of cancer detection improve and therapeutics become more efficacious, more patients will experience and live with cancer-related musculoskeletal pain. Palliative pain control appears to not only improve quality of life but possibly prolong survival [22]. Radiotherapy and local surgery are mainstays of antineoplastic therapy for bony metastases but also afford the added advantage of symptomatic control via reduction of tumor volume and local tissue infiltration [15]. First- and second-line analgesics include non-steroidal anti-inflammatory drugs (NSAIDs), opioids, bisphosphonates, anticonvulsants, corticosteroids, and targeted therapies such as tanezumab and denosumab. In spite of the broad array of therapies, however, patients continue to experience poorly controlled pain and the need for more effective pain management is becoming widely acknowledged [12]. Modalities such as ultrasound, acupuncture, and manual therapy including myofascial release, massage, and trigger point compression have demonstrated benefits in treatment of both metastasis- and antineoplastic-related cancer pain [23•, 24, 25]. Additional techniques available to interventional pain physicians for cancer-related musculoskeletal pain include trigger point and joint injections.

Intervention: Trigger Point Injections

A trigger point is an area of skeletal muscle with a characteristic referred pattern of pain on palpation. Such areas may exhibit spontaneous electrical activity suggestive of aberrant action potential generation [26]. Trigger point injections have demonstrated benefits in reduction of focal myofascial musculoskeletal pain in both the non-cancer population and specific subsets of cancer patients [27–29]. Benefits are thought to be mediated by relaxation of local muscle tension, which facilitates improved perfusion, replenishment of adenosine triphosphate (ATP), and removal of metabolic and nociceptive compounds [30]. The most commonly targeted muscles for cancer-related trigger points include the masseter, levator scapulae, gluteus medius, quadratus lumborum, trapezius, sternocleidomastoid, and temporalis muscles [28, 31].

The efficacy of trigger points has been explored for management of cancer-related myofascial pain. A study conducted by Lee et al. explored the efficacy of trigger point injections as an adjunct to existing analgesic therapy including opioids, benzodiazepines, steroids, and muscle relaxants. The majority of this cohort of advanced cancer patients, with primarily pulmonary and gastrointestinal neoplasms, experienced significant reductions in pain scores within 3 days of trigger point injections. No patients reported worsened pain or significant adverse effects [28]. A study of post-mastectomy patients also observed improvements in pain symptoms in 74% of patients with a single session of ultrasound-guided trigger point injections of the subscapularis and/or pectoralis muscles [29]. Factors associated with efficacy included fewer overall trigger points and location of trigger points in the neck and upper back versus lower back or hip. Injections also tended to be more effective if the trigger point was directly caused by a neoplastic process or clinically co-localized, in which both a tumor and myofascial trigger point were located at the same site [27].

The procedure is performed by identifying the target trigger point and sterilizing the overlying skin. With the trigger point stabilized between the index finger and thumb, a needle is repeatedly inserted at a 30° angle without complete withdrawal from the muscle belly. In this fashion, dry needling may be performed, or local anesthetic may be injected. Needling may continue until relaxation of the trigger point is palpated [32]. Injections are indicated in patients with identifiable and palpable bands of muscle with referred pain patterns consistent with myofascial trigger points. Absolute contraindications may include active infection at the injection site or local bony defects. Relative contraindications may include severe coagulopathy, allergy to local anesthetics, severe fibromyalgia, and history of keloid formation. Complications are largely limited to local irritation, hematoma formation, allergic reactions, or vascular injury [32].

Intervention: Joint Injections

In spite of its prevalence as a therapy in the non-cancer population, joint injections for cancer-related musculoskeletal pain have not been widely evaluated. The efficacy of the technique, however, for joint pain in the setting of arthritis and degenerative or inflammatory disease may hold promise for pain related to neoplastic processes [33]. Joint injections most commonly involve introduction of local anesthetic with or without corticosteroids into the target joint space(s). It is important to note that without more evidence to guide safe practice, joint injections should be applied cautiously to areas of active malignancy. Clinicians may consider targeting joint pain associated with antineoplastic therapies or joints in less proximity to active neoplasm.

Clinical trials have demonstrated the short-term analgesic efficacy of intra-articular injections for patients with knee osteoarthritis, shoulder impingement syndrome, lateral epicondylitis, greater trochanteric pain syndrome, de Quervain's tenosynovitis, and lumbar radiculopathy [34]. Case reports have described the use of intra-articular corticosteroid injections to the knee in the palliative setting. Fu et al. describes bilateral corticosteroid injection for palliation of osteoarthritis in a patient with end-stage progressive meningioma. In this case, pain was secondary to mechanisms likely unrelated to the primary malignancy but was nonetheless an effective analgesic method [35].

Joint injections are often performed with landmark-based technique in which the patient is positioned to facilitate access to the target joint. With fluoroscopy, the needle is advanced with intermittent fluoroscopic guidance to the relevant joint space. Entry in the joint may be confirmed with injection of 0.3 to 0.5 mL of contrast to outline the joint space. With confirmation of needle placement, the corticosteroid and/or local anesthetic injectate may be introduced to either a tactile end-point, extracapsular escape, or a maximum volume [36]. Absolute contraindications may include systemic or local infection and allergy to injectate components. Relative contraindications may include severe coagulopathy, leukopenia, osteomyelitis, or type II diabetes mellitus with poor glycemic control. Complications may include worsening pain, injury to nerves or surrounding structures, and local or systemic infection [37, 38].

Introduction to Spine-Related Pain

Back pain, especially of the lumbar spine, is a common condition in the general population with 70% of adults reporting a history of at least one episode [39]. According to the National Health and Nutrition Examination Survey conducted in 2009–2010, 13.1% of adults in the United States (US) between 20 and 69 years of age reported having chronic lower back pain [40]. Further data from a report on The State of US Health 1990–2016 observed that lower back pain was the number one contributor to years of life with disability (YLDs) in the US general population and neck pain was listed among the top 10 conditions out of 333 total causes of disability [41].

Back pain may arise from both spinal and extraspinal structures. Extraspinal structures from which pain may originate typically include paraspinal musculature, fascia, blood vessels, and referred pain from visceral organs. Spinal structures from which pain may originate typically include facet joints, intervertebral disks, vertebral bodies (e.g., compression fractures), and spinal nerve roots (i.e., radiculopathy). Pain may be elicited from the aforementioned structures through multiple mechanisms including degeneration or injury. Pathology of surrounding structures such as neoplasm, inflammation,

hematoma, and abscesses may compress nerve roots or the spinal cord itself. Systemic inflammatory disease can manifest as direct inflammation of spinal and extraspinal structures. And finally, anatomic deformities of the spine such as scoliosis and spondylolisthesis may generate pain depending on the extent of the deformity [39].

Though the majority of back pain is not associated with cancer, metastatic cancer is the most common systemic disease that affects the spine and accounts for about 0.7% of lower back pain. The spine is the most common location of osseous metastases and comprises about 68% of cases in which neoplasm metastasizes to bone [14]. Mechanisms of back pain in cancer patients parallel those in non-cancer patients but special attention should be given to conditions such as vertebral compression fractures. Cancer patients are not only at significantly higher risk than the general population for suffering a compression fracture but the fractures tend to be of increased severity [42]. Cancer patients also have an increased rate of bone loss as a consequence of tumor osteolysis, adverse effects of chemoradiation and antineoplastic therapeutics, generalized osteoporosis from chronic steroid administration, and malnutrition [43]. Of note, spinal cord compression and radiculopathy may also be present in up to 20% of patients with metastatic cancer to the spine [44]. Spinal cord compression manifests as back pain in 95% of patients but may also be associated with weakness, sensory abnormalities, or autonomic dysfunction in at least 50% [45].

The overall prevalence of spinal metastases observed by microscopic analysis of 832 spines of deceased patients with metastatic cancer was 36.1% [46]. The most common primary malignancies that led to spinal metastases were breast and lung cancer. Metastatic lesions were most common in the thoracic spine, accounting for about 70%, and followed by the lumbosacral spine (15–20%) and cervical spine (10–15%) [47]. Anatomically, lesions tended to be located in the vertebral body (80%) or paravertebral space (10–15%) and less commonly, epidural or intradural [45]. The most common primary tumor of the spine is multiple myeloma and it is one of most studied in the context of interventional pain management for spinal lesions [48].

Other etiologies of back pain, including sacroiliac (SI) joint arthropathy and facet joint arthropathy, may also be seen in cancer patients. Such conditions may exist as a comorbidity unrelated to the malignancy or arise from or be worsened by neoplastic processes or antineoplastic therapies. Facet arthropathy is a common condition in the general population with 19% of adults between 45 and 64 years exhibiting radiographic evidence of cervical facet arthropathy, a metric that increases to 57% in adults older than 65 years. Lumbar facet arthropathy is equally impressive with 67% of adults between 45 and 64 years of age and 89% of adults over 65 years of age manifesting computed tomography (CT) evidence of lumbar facet arthropathy [49]. Reports of tumors either metastasizing to or compromising the facet joint itself are uncommon in the published literature [50]. Chondrosarcoma is a primary tumor derived from cartilaginous elements that may arise in the spine in up to 10% of cases, often affecting posterior elements of the vertebrae including the facet joint [51].

Sacroiliac joint pain has been observed in up to 25% of the general population with lower back pain and is often secondary to degeneration of the joint, inflammation (i.e., sacroiliitis), or abnormal joint mechanisms and trauma [52]. Metastatic lesions may also cause sacroiliac joint-related pain and mimic sacroiliitis. Though relatively uncommon, case reports of metastatic lesions to the sacroiliac joint have been reported in patients with rectal cancer [53] and Hodgkin's lymphoma [54]. Primary malignances including epithelioid sarcoma have also been described as a potential etiology of sacroiliac joint pain that mimics sacroiliitis [55]. At least one case report has described paraneoplastic syndromes mimicking sacroiliac joint pain. In a patient who was initially misdiagnosed with ankylosing spondylitis, tumor-induced osteomalacia was identified as the cause for progressively worsening back pain and disability [56].

Intervention: Medial Branch Blocks and Radiofrequency Ablation

Medial branch blocks (MBBs) and radiofrequency ablation (RFA) are often indicated for patients with chronic back pain of suspected axial etiology. The procedures target the medial branch nerves, which convey nociceptive signals from the facet joint, at the intersection between the superior articular process and transverse process of adjacent vertebrae. In medial branch blocks, the aforementioned target is approached with a 22-G spinal needle under fluoroscopic guidance and local anesthesia and/or corticosteroid is administered. Relief may be short-lived, thus making the procedure more diagnostic than therapeutic [57]. A positive response to a MBB, often defined as more than 50% pain relief, tends to be a predictor of positive response to medial branch nerve neurolysis via RFA [58]. Despite widespread use of medial branch neurolysis with RFA for non-cancer chronic back pain, literature on the use of MBB and RFA neurolysis in cancer pain is lacking but may be of value to cancer patients with facetogenic or non-radicular back pain [57].

The use of ablation techniques, including RFA, that directly target the tumor itself is increasingly popular for cancer pain relief. Ablation may be used to decrease the inflammation associated with neoplasm to decompress adjacent structures or target structures conveying nociceptive signals for neurolysis [57]. Depending on the location of the tumor, various ablation techniques have demonstrated pain relief in primary and metastatic tumors of the peripheral skeleton [59–62], pelvis [63], and spine [64]. Though the literature on radiofrequency ablation in cancer patients has centered on the

use of direct ablation of metastatic lesions, future studies should address the potential benefit of medial branch radiofrequency ablation in patients with spine-related cancer pain.

MBBs and RFA are considered safe procedures with a low incidence of complications. The target anatomy is relatively distant from vital structures in the spine. Complications tend to be associated with inappropriate placement of the needle or sudden needle displacement and injury to neural structures [65]. In a cohort study of 7500 patients who underwent 43,000 facet joint nerve blocks, the most common complication was intravascular injection of local anesthetic, which occurred in 11.4% of patients, followed by local hematoma in 1.9%. Other complications including vasovagal symptoms, severe bleeding, or significant soreness and nerve root irritation occurred in less than 1% of patients [66]. Fortunately, severe complications are rare but complete denervation of a spinal root with radiofrequency ablation has been reported in a patient who had the procedure performed under general anesthesia [65].

Intervention: Epidural Steroid Injection

Epidural steroid injection (ESI) is the delivery of corticosteroid and/or local anesthetic into the epidural space with the goal of decreasing inflammation and to potentially minimize spinal cord or nerve root compression and irritation. The procedure has demonstrated benefits for short-term pain relief but evidence is conflicting with respect to reducing the need for surgical interventions in patients with radiculopathy or symptoms of spinal cord compression [67]. The procedure is usually performed under fluoroscopic guidance with one of two approaches: interlaminar or transforaminal. The interlaminar approach is most commonly employed and entails accessing the posterior epidural space between the lamina of adjacent vertebrae. Needle placement is confirmed by loss-of-resistance technique and injection of contrast. The transforaminal approach may be more technically challenging and consists of depositing medication at the level of the existing nerve root through the intervertebral foramen. This approach has been thought to improve spread into the ventral epidural space and possibly facilitate delivery of a higher concentration of steroid to the location of inflammation and compression. No concrete evidence exists demonstrating superiority between approaches with respect to pain relief and overall function [68].

Lumbar back pain is the most common indication for ESI. An observational study of 25,479 patients with spine pain reported that 12.6% of patients with pain in the lumbar spine were recommended ESI. Of the patients with cervical and thoracic symptoms, however, ESI was only recommended 3.7% and 1.8% of the time, respectively [69]. This is potentially explained by the challenges of diagnosing thoracic radiculopathy, as symptoms tend to be limited to the trunk and not localized to either the upper or lower extremities [70]. For cervical radiculopathy, extraspinal malignancies including tumors of the thyroid, esophagus, and pharynx should also be ruled out as a potential cause of cervical radiculopathy prior to ESI [71]. Oh et al. published a recent pragmatic review that included 10 patients with spine malignancy who underwent epidural steroid injection. Thoracic ESI appeared to be the most effective, providing at least moderate relief in 100% of the cases, followed by lumbar injections which provided at least moderate relief in 86%. Caudal injections were found to be significantly less effective [72].

Reviewing imaging studies is recommended prior to performing interventional procedures of the spine. This is of particular relevance to cancer patients who may have surrounding neoplasm or associated pathology. Cancer lesions tend to be highly vascularized and, depending the location, may be associated with an increased risk of epidural hematoma with ESI [73]. A theoretical risk also exists of potentially seeding tumor cells into the epidural space. Of the limited published literature, Demaree et al. retrospectively reviewed 80 patients with hematologic malignancies who underwent epidural blood patch for refractory post-dural puncture headache. No patients had subsequent evidence of spread to the central nervous system [74]. Literature is lacking with respect to other malignancies. Intravascular injection is the most common complication and seen in 4.3% of epidural steroid injections [75] and up to 23% of transforaminal injections [68]. Nerve root irritation is seen in about 1% of epidural steroid injections and 4.65 of transforaminal injections. Local hematoma, vasovagal reaction, dural puncture, and post-dural puncture headache are seen in less than 1% of total cases [75]. Severe complications including epidural hematoma, paraplegia, tetraplegia, and epidural abscess have all been reported in the literature but the frequency is unknown.[65(p20)]

Intervention: Sacroiliac Joint Injection and Ablation

Sacroiliac (SI) joint injections and radiofrequency ablation have demonstrated efficacy with respect to improving pain and function in patient with SI joint-related pain and sacroiliitis [52]. Intraarticular SI joint injections may be performed under fluoroscopic or ultrasonic guidance. The most common needle used to access the joint is a 22-G Quincke needle. In the fluoroscopy-guided technique, the C-arm is used to locate the posterior distal third of the SI joint with cephalo-caudal tilt and contralateral oblique angulation to optimize the view. The needle is oriented coaxial to the fluoroscopy beam and advanced into the lower pole of the joint. Correct positioning may be confirmed with contrast. With confirmation of the correct needle position, steroid and/or local anesthetic is injected into the joint. In the ultrasound-guided technique, the probe is oriented transverse to identify the posterior superior iliac spine, lateral border of sacrum, and

ilium. The probe is then advanced caudally to visualize the SI joint. A needle may then be inserted in-plane or out-of-plane into the joint. In a study comparing the fluoroscopy-guided and ultrasound-guided techniques, no significant differences in clinical outcomes were observed but the ultrasound technique was associated with a significantly longer procedure time [76]. Ablation techniques may also be used to address SI joint pain by targeting the joint itself or lateral branch nerves responsible for sensory innervation. Lateral branch nerve radiofrequency ablation appears to be more effective than direct joint ablation. A notable limitation of targeting the lateral branch nerve, however, is that it may not adequately address pain originating from the ventral aspect of the joint [52].

SI joint injections have demonstrated efficacy for both pain management in the general population and palliation of pain in cancer patients. Hutson et al. studied 19 patients with sacroiliac tumors who underwent SI intraarticular steroid injections and lateral branch RFA. The intraarticular injection group, consisting of 13 patients, reported mean post-procedural pain reduction at 1 month of 5.1 points on an NRS. The RFA group, consisting of 6 patients, reported pain reduction of 7 points on an NRS. Mean duration of pain relief was 3.7 months and 5.3 months in the intraarticular injection and lateral branch RFA groups, respectively [77]. Complications of sacroiliac joint injections appear to be relatively rare and may include intravascular injection, local pain at the injection site, bleeding, infection, or epidural spread of medications. The prevalence of specific complications has not been reported in the literature [65].

Intervention: Vertebral Augmentation

Vertebral augmentation is a group of minimally invasive techniques that aim to restore vertebral body height and function, often in the setting of vertebral compression fractures. Under CT guidance, one of two procedures may be performed depending on the degree of deformity. Vertebroplasty involves injection of polymethylmethacrylate (PMMA) cement into the vertebral body to fill in and stabilize the defect, thus possibly reducing symptoms including pain. A needle is inserted into the vertebral body using CT or fluoroscopic guidance, usually through a transpedicular approach. Kyphoplasty is a variation that aims to reduce the height and angle of vertebral kyphosis. Again, a needle is inserted into the vertebral body through a transpedicular approach. A balloon catheter is inserted first to create a cavity into which PMMA cement is subsequently injected [48]. Experts recommend treating up to 3 adjacent levels in a single session [48].

Vertebral augmentation techniques are indicated for painful vertebral body tumors, symptomatic vertebral angiomas, and painful compression fractures in patients with severe osteoporosis [78]. Multiple prospective studies and randomized controlled trials have demonstrated efficacy of vertebroplasty or kyphoplasty in controlling pain and improving quality of life in patients with metastatic spinal lesions and multiple myeloma [79–81]. Cement augmentation and kyphoplasty have also been successfully used to treat patients with vertebral metastases from renal cell carcinoma. Spinal metastases from renal cell carcinoma (RCC) occur in up to 15% of patients with this type of cancer and tend to be very aggressive and resistant to chemoradiation. These lesions may be hypervascular and are commonly associated with pathologic fractures and spinal cord compression. Langdon et al. published two cases of patients with spinal metastases from RCC who were treated with vertebroplasty and kyphoplasty and remained pain free with no signs of spinal cord compression 1 year after the procedure [82].

Direct CT-guided RFA followed by cement augmentation is a relatively novel approach for the management of pain and disability caused by vertebral body metastasis, which has been shown to be effective in improving pain and quality of life and reducing disability in this population [83]. In a cohort of 50 patients with vertebral bony metastases, a mean 4-point decrease in numerical rating pain scale 3 months was observed after the procedure. This was accompanied by a statistically significant decrease in the Oswestry Disability Index and a statistically significant increase in the Functional Assessment of Cancer Therapy-Bone Pain questionnaire [83]. Another study explored the safety and effectiveness of vertebroplasty following lumbar decompression and radiofrequency ablation in patients with spinal metastases from lung cancer, showing significant improvements in mean VAS score and quality of life [84].

Absolute contraindications include a bleeding diathesis or active infection. Neoplastic lesions with epidural extension should be managed with cautions due to the risk of spinal cord compression from tissue displacement or cement leakage. Neural foramina leakage causing radiculopathy and cement leakage into the venous system causing cement embolism are uncommon complications from vertebral augmentation procedures [78]. McDonald et al. reported some degree of cement leakage in 19% of patients with multiple myeloma undergoing vertebral augmentation, all of which were asymptomatic [85]. In a longitudinal prospective study by Markmiller et al., the incidence of radiculopathy secondary to cement leakage following kyphoplasty or vertebroplasty was 2.6%, but all patients had resolution of symptoms 6 months post-procedure [81].

Interventional Therapies for Visceral Cancer Pain

Introduction to Visceral Cancer Pain

Visceral pain is a common and debilitating condition within the cancer population that is estimated to affect approximately

70% of patients with advanced disease [86]. Neoplasms generate visceral pain through numerous mechanisms including chemical release from cancer and immune cells, distension or obstruction of luminal organs, and direct nerve compression or infiltration [86, 87]. Often characterized by ill-defined deep, squeezing, or colicky sensations, visceral pain originates from nociceptors within internal organs of the cardiovascular, respiratory, gastrointestinal, and genitourinary systems. Localization is challenging due to the low density of visceral sensory innervation and secondary hyperalgesia caused by referral to parietal somatic structures. Visceral pain is often associated with dysautonomia including pallor, sweating, nausea or vomiting, and cardiovascular perturbations [87]. Mechanisms continue to be poorly understood but are generally thought to involve sensitization of primary sensory afferent innervating visceral organs, dysregulation of descending pathways that modulate spinal nociceptive transmission, and hyperexcitability of spinal ascending neurons that receive synaptic input from the viscera [88]. Recent advances in interventional pain therapies have shown promising results in individuals suffering from visceral pain secondary to cancer pathologies.

Intervention: Stellate Ganglion Block

The sympathetic stellate ganglion, also called the cervicothoracic ganglion, is a structure formed by the fusion of the inferior cervical ganglion with the superior thoracic sympathetic ganglion. In the majority of the population, it is located anterior to the transverse process of C7 and neck of the first rib, medial to the scalene muscles, and anterolateral to the longus colli muscle. It is delineated from the cervical pleura inferiorly by the suprapleural membrane. The stellate ganglion mediates sympathetic input to the ipsilateral upper extremity, chest, face, and head and is a target for blockade in painful conditions including, most notably, complex regional pain syndrome [89].

Numerous techniques for stellate ganglion blocks (SGB) have been demonstrated and published in the literature [90–92]. Carron and Litwiller originally reported targeting the sympathetic trunk with a modified paratracheal approach using landmark-based technique. The anterior C6 transverse process was identified in a supine patient by palpation of the cricothyroid notch with an index finger and subsequent lateral translation. A 2.5-centimeter (cm) 22- or 23-gauge needle was then advanced medial to the fixed index finger to a depth of approximately 1 cm. A total of 3 milliliters (mL) of 1 to 2% lidocaine without epinephrine was injected. Contrast medium of a similar volume was introduced to confirm adequate spread to the targeted ganglion and fascial plane. Presence of Horner's syndrome, increased skin temperature, and lack of galvanic skin response were suggestive of a successful SGB [90].

In 1995, Kapral et al. investigated ultrasound-guided imaging alongside landmark-based technique for SGB [91]. Imaging modalities had been increasingly explored due to complications with landmark-based technique including pneumothorax, vertebral artery puncture, and seizures from intravascular injection of local anesthetic [93, 94]. The landmark-based technique described by Kapral et al. identified the C6 vertebral tubercle by palpation in a supine patient with slight neck extension. With the index and 3rd finger between the carotid artery and trachea, a 3.5-cm 22-gauge needle is inserted until contact with the C6 tubercle. The needle is then withdrawn approximately 1–2 millimeters (mm) before injection of 8 mL of 0.25% bupivacaine. In the same set of patients, the investigators also used ultrasound to map out a field bordered by the carotid artery, trachea, longus colli muscle, and C6 transverse process. A 22-gauge needle is advanced with direct visualization to the C6 transverse process and 5 mL of 0.25% bupivacaine is injected in the area. Ultrasound imaging is able to visualize spread of the local anesthetic depot [91]. Current ultrasound-guidance technique focuses on insertion of the needle laterally to the transverse process of C7 with final positioning above the longus colli muscle between the carotid and prevertebral fascia. Fluoroscopic guidance has also been compared with ultrasound guidance as a technique for SGB. With fluoroscopic technique, bony delineation is improved and allows for facile identification of structures for either the C6 transverse process or C7 anterior paratracheal approach. Use of contrast is an added option with fluoroscopy to confirm appropriate needle placement and to rule out intravascular injection [92].

Literature on indications for SGB in cancer patient is limited. Sharbel et al. conducted a preliminary study in 2020 evaluating preoperative SGB in lateralized head and neck cancer surgery. A study of 9 participants observed improved early postoperative pain, decreased narcotic requirements, and decreased length-of-stay [95]. Additional trials are necessary to explore the role of SGB in the perioperative setting. With respect to chronic pain, a case in 2016 described application of ultrasound-guided SGB with phenol for unilateral facial pain from orofacial cancer. The patient experienced marked pain relief and improved ability to chew and swallow [96]. SGB has also been evaluated as a promising modality in the context of post-mastectomy pain syndrome related to surgical breast cancer treatment. Of the 50 patients evaluated, 47 observed improved VAS scores, decreased daily narcotic consumption, and decreased allodynia [97]. Thermal and pulsed radiofrequency ablation have also been explored for post-mastectomy pain syndrome with promising results. In both groups, pain relief measured by VAS was improved within the first week, in addition to improved quality of life and patient functional capacity [98].

A systematic review of complications associated with SGB identified 260 cases with reported adverse events with 51.5%

of the cases using image guidance. Of the total cases, 64 (24.6%) and 70 (26.9%) reported the use of ultrasound and fluoroscopy guidance, respectively. The most common systemic adverse effects were transient voice hoarseness and light-headedness. One case reported death from massive hematoma and subsequent airway obstruction. Another reported quadriplegia from pyogenic cervical epidural abscess and discitis [99]. Severe hypertension has also been observed [100]. The most common local complications include blood aspiration and hematoma formation [101–103]. Given the proximity of the stellate ganglion to additional structures, other adverse effects including brachial plexus blockade, headache, ptosis, and seizures have also been reported [99].

Intervention: Celiac Plexus Block and Neurolysis

The celiac plexus is composed of a network of nerve fibers located within the retroperitoneal fat and anterolateral surface of the aorta, epigastrium, crus of the diaphragm, and posterior to the pancreas and stomach [104–106]. It is constructed of paired smaller ganglia most commonly located at the T12, and L1 vertebral levels [104]. The plexus is a target for celiac plexus blocks (CPB) and neurolysis as the plexus transmits afferent fibers responsible for nociception [89]. A plethora of techniques have been described for both CPBs and neurolysis including posterior para-aortic, anterior para-aortic, transintervertebral disk, and endoscopic approaches. Image guidance with ultrasound, computed tomography (CT), fluoroscopy, and magnetic resonance imaging (MRI) have been explored to improve technical success rates and minimize complications [107].

For the posterior para-aortic approach, a patient is positioned prone or supine. A 20 to 24-gauge needle is advanced anteriorly to traverse the diaphragm and enter the antecrural space. The needle is positioned 1 to 2 cm anterolateral to the aorta, between the superior mesenteric artery (SMA) and celiac trunk [106]. After confirmation of needle position, a neurolytic agent is injected on either side of the aorta. The most common agents include 20 to 30 mL of 50 to 100% ethanol or 20 to 25 mL of 3 to 20% phenol. Discomfort on neurolysis may be minimized by pre-emptive injection of local anesthetic [104].

The anterior para-aortic approach is notable for the need to cross multiple visceral organs including the stomach, liver, and pancreas [104]. Though image guidance has lower overall complication rates, the approach is generally reserved for patients with contraindications to the posterior approach like altered anatomy or invasive tumors [108, 109]. With the patient positioned supine, a 20 to 24-gauge needle is inserted through the abdominal wall and advanced posteriorly through the retro-pancreatic space. The needle is positioned 1 to 2 cm anterolateral to the aorta, again, between the SMA and celiac trunk [106]. After confirmation of needle position, 30 to 50 mL of neurolytic agent is injected adjacent to the celiac plexus bilaterally [104].

The posterior trans-aortic approach entails direct puncture and crossing of the aorta with the patient positioned prone [107]. The needle enters at the L1 vertebral level approximately 4 to 6 cm left of midline and then advanced along a left paravertebral trajectory to meet the posterior aortic wall about 2 cm distal to the L1 transverse process. With additional advancement, the needle processes through the posterior and then anterior walls of the aorta to land in the pre-aortic space. Correct needle positioning is confirmed with a few milliliters of contrast to evaluate for retro-pancreatic spread and negative aspiration. 25 to 30 mL of neurolytic agent is administered [110].

The endoscopic approach uses ultrasound guidance and takes advantage of the close proximity of the aorta and celiac plexus to the gastric wall [111]. Endoscopic ultrasound (EUS) affords direct and real-time visualization. The EUS scope is advanced to the level of the celiac artery and rotated clockwise until the celiac artery disappears from view. The celiac plexus is visualized as a small cluster of hypoechoic structures. A fine needle flushed with saline is then advanced through the biopsy channel and enters through the posterior gastric wall to position next to the anterolateral border of the aorta. With negative aspiration, the celiac ganglia are directly injected first with 3 mL of local anesthetic and then 10 ml of 98% alcohol. Neurolytic agents may also be used after a single or double injection at the celiac trunk origin [112, 113].

Finally, the intervertebral CPB approach may be considered if a patient's anatomy precludes performance of the para-aortic approach [105]. With the patient in the prone or lateral decubitus position, a needle is inserted through the T12-L1 or L1-L2 intervertebral disk space at an oblique angle. With CT or fluoroscopic guidance, the needle is advanced into the antecrural space and to the aorta at the level of the celiac axis. With confirmation of correct needle placement, approximately 25 to 30 mL of neurolytic agent is injected in a single or double-step fashion [105, 114].

CPB and celiac plexus neurolysis have demonstrated efficacy in managing pain related to multiple intra-abdominal conditions including pancreatic cancer [115] and related chronic pancreatitis [111–113]. Yondonjamts et al. described additional indications related to stomach, esophageal, colorectal, liver, gallbladder, and bile duct cancer [116]. In a meta-analysis of neurolytic celiac plexus block in 1145 cancer pain patients, partial to complete pain relief was reported in approximately 90% of patients alive at 3 months and in 70% to 90% until death beyond 3 months [115]. A 2017 study by Cao et al. also demonstrated superior pain control of percutaneous neurolytic celiac plexus blocks, as measured by Numeric Rating Score (NRS) and Karnofsky Performance Status (KPS), compared with traditional medication strategies. A health economics evaluation in the same population

demonstrated reduction in medicine-specific costs and total healthcare costs in the neurolysis treatment group [117]. In general, exclusion criteria have focused on patients with severe heart, liver, or kidney dysfunction. Additional contraindications described include severe coagulopathy, thrombocytopenia, abdominal aortic aneurysm, and active infection [118]. A unique contraindication described has been patients with bowel obstructions due to the potential for unopposed parasympathetic innervation and possible perforation [119].

The most common described adverse effects of CPB or neurolysis include transient local pain [115]. Additional side effects include diarrhea and hypotension, both attributed to unopposed parasympathetic innervation after sympathetic celiac blockade [115, 119]. Though rare, lower extremity weakness has been reported in the setting of anterior spinal artery injury or vasospasm with subsequent spinal cord ischemia [112]. Additional rare complications reported include hepatic or splenic infarctions from celiac trunk thrombosis and gastric or small bowel infarctions from celiac artery vasospasm [120, 121]. Advancements in image guidance have decreased the risk of improper needle placement and complications including hematuria from kidney puncture, peritonitis, pneumothorax, and retroperitoneal hematomas [119, 122].

Intervention: Ganglion Impar Block

The ganglion impar is a solitary retroperitoneal structure located at the level of and anterior to the sacrococcygeal junction [123]. Numerous visceral sympathetic afferent nerves that innervate deep pelvic structures including the perineum, distal rectum, anus, distal urethra, vulva, and distal 3rd of the vagina converge at the ganglion impair [124]. Multiple techniques have been described, with the trans-sacrococcygeal approach being the most common. In a 2015 case series, Ahmed et al. describe the trans-sacrococcygeal approach, originally performed in 1995, with the patient in the prone position [125]. A 22-gauge beveled needle is inserted, under fluoroscopic guidance, to pierce the dorsal sacrococcygeal ligament at the midline. The needle is advanced through the vertebral disk to place the tip anterior to the ventral sacrococcygeal ligament. Needle tip placement is confirmed with injection of contrast dye into the retroperitoneal space and 4 to 6 mL of 8% phenol in saline is subsequently injected [124].

Additional techniques have been described in a 2013 review on the ganglion impar block [126]. The anococcygeal approach uses fluoroscopy to guide a 22-gauge needle through the anococcygeal ligament to locate the tip retroperitoneally at the sacrococcygeal junction [127]. The transverse coccygeal approach uses a needle to cross the coccyx through one of the inferior joint spaces in between the coccygeal segments [128, 129]. A similar variation, the inter-coccygeal technique, was also described in which a 22-gauge 2-inch spinal needle is guided under fluoroscopy into the disk space between the first and second coccygeal joints. Other techniques that do not cross the sacrum or coccyx have also been reported. One technique involves insertion of a needle below the transverse process of the coccyx with subsequent angulation to position the needle tip anterior to the sacrococcygeal joint [130]. Another uses a 25-gauge needle with a 20 to 30° bend at the tip in a "corkscrew" fashion for a paracoccygeal approach [131]. Other imaging modalities including CT have also been explored [89].

Ganglion impar neurolysis was first described in 1990 for patients experiencing pain secondary to perineal cancer [127]. Additional indications for pain included other malignancies including cervical, colonic, bladder, rectal, and endometrial carcinomas. Ganglion impar block for perianal pain has also been described [126]. Specific contraindications to the block include sacral invasion of metastases, local pelvic infection, or recent radiation and chemotherapy [132]. A discussion of life expectancy and goals of care may be additional considerations.

Albeit being uncommon, adverse effects specific to the block have been reported including rectal perforation or sciatic nerve impingement. The potential for infection with the anococcygeal approach is a concern that warrants particularly close attention due to the proximity of the anus [133]. Trans-sacrococcygeal approaches have been implicated in disk rupture [134]. Other complications including motor, sexual, bladder, and bowel dysfunction have also been described [135, 136].

Intervention: Lumbar Sympathetic Block

The lumbar sympathetic chains are located in the retroperitoneum, posterior to the great vessels and anterior to the psoas muscles and vertebral bodies [137]. Visceral afferent pain fibers within these chains travel with sympathetic and parasympathetic nerves whose cell bodies are located in the dorsal root ganglion. The sympathetic chains are a common target for lumbar sympathetic blocks (LSBs) [138, 139]. In a 2020 study by Spiegel et al., LSBs were performed with patients in the prone position and with assistance of fluoroscopy or CT guidance. The needle insertion target is at the L2 to L3 level with fluoroscopic guidance in both anteroposterior and lateral views to confirm tip location anterior to and within the upper one-third of the vertebral body. With negative aspiration to confirm not only absence of blood or air but also cerebrospinal fluid, 1 mL of iohexol is injected to evaluated for appropriate spread on the anterior surface of the vertebral body. Subsequently, 10 mL of 0.25% bupivacaine or 9 mL of 0.25% bupivacaine with 1 mL of 40 mg/mL triamcinolone is injected [139].

A study published in 2018 compared ultrasound and fluoroscopy as imaging modalities for LSBs. For the ultrasound technique, a 5–2-MHz low frequency probe is used in a paramedian sagittal approach to locate the lumbosacral junction and to subsequently identify the L2 and L3 vertebrae.

With identification of the vertebrae, a modified transverse scan is then performed. The target of the needle tip is anterior and medial to the psoas major muscle on the anterolateral aspect of the lumbar vertebral body. Needle insertion is performed from lateral to medial using an in-plane technique. With confirmation of needle tip position and negative aspiration, 3 mL of contrast dye is administered to exclude vascular injection on both AP and lateral views. As contrast dye is visualized spreading on the specific sympathetic chain, 10 mL of 0.25% levobupivacaine is injected. For the fluoroscopic technique, the lower third of the L2 or upper third of the L3 vertebrae was targeted. The needle is advanced toward the anterolateral edge of the target vertebra with a tunnel vision technique and the C-arm is adjusted 25 to 35° laterally. The needle is subsequently advanced to the anterolateral margin of the vertebral body and with positioning confirmation and negative aspiration, 3 mL of contrast dye is injected. As sympathetic spread is confirmed, 10 mL of 0.25% levobupivacaine is injected [140].

Along with celiac and superior hypogastric plexus blocks, LSB has had demonstrated benefits for cancer patients with abdominal or pelvic pain symptoms [141]. In a 2004 study, 60 patients with abdominal or pelvic cancer were divided in three groups and observed for 8 weeks. Of the two groups who had interventional sympathetic blocks including neurolytic celiac superior hypogastric, or lumbar sympathetic ganglion chain blocks, a significant reduction of pain and opioid consumption, in addition to improved quality of life, was observed. In a recent retrospective review, the utility of LSB for cancer-related pain of the back, abdomen, pelvis, and legs was evaluated. The study observed effective pain relief, defined as ≥30% relief for at least 1 day, in at least 675, 82%, and 75% of individuals for back, abdominopelvic, and leg pain, respectively [139]. LSB is often a precursor to additional therapies including neuromodulation but is increasingly explored as a therapeutic modality in and of itself.

LSB is a well-established procedure for management of cancer-related pain but complications have been reported. As with other sympathetic blocks, hypotension and diarrhea are often seen due to unopposed parasympathetic innervation [139]. Other rare complications have included anterior thigh pain from possible genitofemoral nerve damage [142], intralymphatic injection [143], ureteral injury [144], and retroperitoneal hematoma [145]. Spiegel et al. also noted the potential for lack of efficacy from neural anatomy distortion and hindered medication spread due to abnormal space-occupying lesions [139].

Intervention: Superior Hypogastric Plexus Block

The superior hypogastric plexus (SHGP) is a retroperitoneal structure that lies anterior to the L5/S1 disk and vertebrae bilaterally [146]. It is a target for superior hypogastric plexus blocks (SHPB) as afferents from visceral organs of both the lower abdomen and pelvis are transmitted through the plexus [124]. The most common approaches for SHPBs are the transdiscal, posterior paravertebral, and anterior technique [147]. For the transdiscal approach, patients are positioned prone with a pillow under the iliac crest. A C-arm is directed cephalad for alignment of the endplates and then 15 to 25° oblique to optimize the image of the disk. With an entry point 5 to 7 cm from midline, the needle is advanced by tunnel vision lateral to the inferior aspect of the facet joint. 0.5 mL of contrast is injected into the disk to verify needle position and the needle is advanced until loss of resistance to confirm exit from the disk. Ten milliliters of phenol in saline is subsequently injected, followed by 2 to 3 mL of air to prevent dissemination of neurolytic agent within the disk [148].

For the posterior paravertebral approach, patients are again positioned prone with a pillow under the iliac crest. Fluoroscopy assists with identification of the L4-5 spinous processes. A 15-cm, 20-G needle is inserted 5 to 7 cm lateral from midline and directed approximately 45° medial and caudal to miss the transverse process of L5 and the sacral ala. As the needle tip is visualized at the anterior junction of L5-S1 in the lateral view, a loss of resistance is felt to suggest that the needle has traversed the psoas into the retroperitoneal space. Satisfactory positioning is indicated by contrast within the lateral bony edge, anterior to the psoas, and above the sacral nerve roots. 8 mL of phenol in saline 10% is injected on each side followed by 2 to 3 mL of air [148]. A modified transdiscal approach has also been described in which the entry point is 7 to 8 cm lateral to the L4-5 level, significantly more lateral than the original transdiscal approach [149]. Less common approaches including transvascular and transvaginal have been described in the management of chronic pelvic pain in the setting of endometriosis [150].

SHPBs have found an increasing role in the management of pelvic pain associated with cancer of pelvic visceral organs [147]. The presence of nociceptive afferent fibers that innervate pelvic organs alongside corresponding sympathetic nerves facilitates inhibition by neurolytic agents [127, 151]. Neurolytic SHPB has been described in patients with extensive gynecologic, colorectal, and genitourinary cancer with incapacitating pelvic pain. In a group of 26 patients, 18 reported more than 50% reductions in visual analog pain scores (VAPS) within two blocks in addition to reductions in oral opioid therapy [152]. SHPBs have also been combined with ganglion impar neurolytic blocks for management of pelvic and perineal pain related to pelvic and perineal malignancies. In a group of 15 patients who underwent combined block, pain scores were reduced from a mean of 7.87 ± 1.19 pre-procedurally to 2.40 ± 2.10 1 week post-procedurally ($P < 0.05$) without complications or serious side effects. Overall, SHGB has been reported to be a procedure with minimal adverse effects. Complications may include injury to local

structures including bowel, bladder, or vasculature like the common iliac artery. In addition, intervertebral disk puncture may cause discitis, disk rupture, or herniation [148].

Intrathecal Drug Delivery

Once viewed as a last resort or "salvage therapy" for patients who failed systemic opioid therapy, intrathecal drug delivery systems (IDDS), including implantable intrathecal pumps, have had expanding indications in the management of cancer-related pain [153]. A particular advantage of IDDS is the potential for opioid and non-opioid medications to directly enter into the intrathecal space and bypass the blood-brain barrier [154]. Currently, the Food and Drug Administration (FDA) has approved morphine, baclofen, and ziconotide for intrathecal administration [155].

The IDDS generally involves a catheter implanted in the subarachnoid space to allow opioids or adjunctive medications to infiltrate directly into the central nervous system. The catheter is connected to a continuous, external infusion pump that is surgically embedded into the abdominal wall. The mediation reservoir, located within the pump, is easily accessed percutaneously with a needle through a port for pump refills and other programming modifications [156]. In the context of neuropathic and nociceptive pain, both morphine and ziconotide have been recommended as first-line agents for continuous intrathecal delivery [157]. Recommendations suggest that morphine should not exceed 15 mg daily to minimize possible respiratory depression and granuloma formation. Ziconotide has a particularly narrow therapeutic window. Dosing starts at 0.5 μg daily and is carefully titrated with no more than an increase in 0.5 μg weekly. Other non-opioid intrathecal infusions have been trialed including clonidine, bupivacaine, ketamine, and ketorolac [158–160].

IDDS for management of chronic cancer pain syndromes has been increasingly explored for patients with intractable focal pain or intolerance to systemic opioids [161]. A large prospective study was conducted on 1403 cancer patients enrolled in an IDDS registry which included malignancies of predominantly the lung, breast, colon or rectum, pancreas, and prostate. Of the cohort of 283 patients who provided baseline pain scores, a significant improvement in pain scores was registered at 6 and 12-month time points. A statistically significant improvement was also seen for quality of life at 6-months [162]. Such findings were corroborated in a group of patients studied between 2015 and 2016 with primarily lung, colorectal, hepatic, pancreatic, prostate, laryngeal, and breast cancer. Of the patients with complete pain data sets, significant decreases in pain numeric rating scales were seen at 1 and 3 months post-procedure. Significant pain relief defined as ≥50% pain reduction in NRS was also observed in 86.4%, 79.5%, and 63.6% at discharge, 1-month, and 3-month time points, respectively [163]. Further large-scale studies may need to be conducted to explore and assess indications for IDDS with respect to specific cancer pathologies. What is increasingly clear, however, is that cancer patients with pain including neuropathic, visceral, somatic, or bone-related have derived analgesic benefits from IDDS [156]. An equally compelling population for IDDS is in patients with inadequate response to or intolerable side effects with systemic medications including opioid and non-opioid analgesics, tricyclic antidepressants, or antiepileptic agents [164–167].

Contraindications to IDDS may be related to the intrathecal medications or the implant procedure itself. For example, ziconotide is relatively contraindicated with history of psychosis, dizziness, confusion, or elevated creatinine kinase. Contraindications to IDDS implant include coagulopathy, local or systemic infection, or gross anatomic abnormalities of the spine [157].

Adverse effects are often related to the medication itself. For morphine, the most concerning reported side effects include respiratory depression, catheter-tip granuloma, and medication dependence [157, 168]. Other common adverse effects include sedation, urinary retention, pruritus, and cognitive impairement [153]. For ziconotide, adverse effects are predominantly within the CNS and include cognitive effects, psychiatric effects, nausea, nystagmus, and confusion [154, 169]. In a study of IT therapy for 55 highly opioid tolerant patients with advanced cancer, early complications included mild bleeding in 2, headache in 4, bladder catheterization in 6, reoperation for bleeding or change in catheter position in 6, unrelated death in 1, and stroke in 1. Late complications included local infection in 2 and discontinuation of therapy due to spinal compression in 1 [170].

Neuromodulation for Cancer Pain

Intervention: Dorsal Column Stimulation (Spinal Cord Stimulator)

Spinal cord stimulation (SCS) is the most common modality of neuromodulation and has been increasingly investigated as a treatment modality for chronic pain in the cancer population [171]. A test trial is often conducted to evaluate for adequate patient response prior to permanent implantation [172]. Electrodes are guided into the epidural space on the dorsal surface of the spinal cord. Implantation is often guided by fluoroscopy and may be performed with an open surgical laminotomy to expose the dura or a minimally invasive technique with epidural needles. An impulse generator connected to the electrodes is also inserted percutaneously. The impulse generator is programmed via an external device [173]. Concrete mechanisms of action continue to be elusive but

proposed mechanisms include activation of Aβ fibers with subsequent suppression of spinothalamic tracts via GABAergic and cholinergic inhibitory interneurons [172].

Though literature continues to be sparse in confirming the role of SCS in refractory cancer-related pain, numerous explored indications are worth noting [171]. The first two SCSs implanted were in patients diagnosed with bronchogenic and pelvic carcinoma [170]. Additional indications have included breast cancer with or without brachial plexus invasion, intra-abdominal cancer, and iatrogenic complications including chemotherapy or radiation-induced peripheral neuropathy [172]. In 2012, a group investigated SCS therapy for 15 cases of lower back pain related to colon cancer, anal cancer, and sacral angiosarcoma [174]. SCS has also been explored in pain related to squamous cell carcinoma of the anus with inguinal metastasis, colon cancer with epidural spread and radiation-induced neuropathic pain, and post-prostatectomy neuropathic testicular pain [175, 176]. Relative contraindications for SCS placement include existing pacemakers or defibrillators [177]. Coagulopathy and active infections are absolute contraindications [178].

Complications related to SCS therapy have included cerebrospinal fluid leak, lead fracture, electrode migration, implant infection, and post-procedural pain at the electrode sites with movement [179]. Additional complications reported include implant device failure, aseptic meningitis, and skin hematomas [180]. The overall incidence of such complications, however, is uncertain [171].

Intervention: Dorsal Root Ganglion Stimulation

Located within the dural sheath, the dorsal root ganglion (DRG) is a structure responsible for sensory transduction and modulation [181, 182]. The DRG is housed within the neural foramina and spans the spinal cord and vertebral column to the periphery bilaterally. The individual ganglion is an enlargement of the dorsal root that contains somata of primary sensory neurons. A mixture of nerve fibers pass through the ganglion including myelinated Aδ and unmyelinated C-fibers that convey nociceptive information [181]. The DRG has been implicated in the development of neuropathic pain and has been an emerging target for neuromodulation [181, 183].

Insertion of DRG leads is performed percutaneously. An introducer sheath encasing the lead is passed into the epidural space through a Tuohy needle and, with fluoroscopic guidance, placed in the intervertebral foramen. A trial stimulator tests the lead and patient feedback is elicited for analgesia, reduction in allodynia, and/or adequate coverage with paresthesia. With confirmation of lead positioning, a strain relief loop is released into the epidural space to minimize the risk of lead migration. An implantable pulse generator (IPG), which is able to accommodate up to four quadripolar leads, is then inserted subcutaneously. Post-procedural stimulation is titrated and programmed to ensure optimal coverage [184, 185]. Neuromodulation at the DRG has multiple proposed mechanisms of analgesia including upstream vasodilation, stabilization of peripheral sensitized nociceptive, downstream deactivation of sensitized neurons in the dorsal horn, and potential modulation of supraspinal pathways integral to chronic pain development [183].

DRG stimulation continues to emerge as a promising target for management of chronic pain related to cancer. Large scale-studies investigating efficacy in this population are limited. Of the available literature, a retrospective study in 2015 investigated the use of pulsed radiofrequency DRG stimulation in 15 patients with intractable pain from metastatic vertebral lesions. The study observed that almost all patients experienced significant pain relief at rest and with ambulation at 3 weeks. Notable contraindications were neurological deficits, coagulopathy, or significant cardiovascular disease [183].

Reported adverse effects have predominantly been for indications including phantom limb pain, complex regional pain syndrome, failed back surgery syndrome, and post-surgical pain [184]. Deer et al. noted post-procedural increases in pain, lead migration, and device inactivation [186]. According to the 2017 review by Harrison et al., adverse effects may be disproportionately influenced by operator or hardware considering the novel nature of this technique. Only a small percentage of neuromodulators are familiar with the technique currently and further development of both hardware and technical skills may promote safety of DRG stimulation.

Conclusion

With the growing number of cancer survivors globally, a significant fraction may experience chronic pain through the course of the disease. Whether directly caused by neoplasm, occurring as a complication of therapeutics, or wholly unrelated, chronic pain in cancer patients continues to be undertreated. Understanding the value and role of interventional pain techniques as a core component in the WHO analgesic ladder is imperative for any clinician who cares for patients with cancer. Our narrative review aims to create a detailed understanding of interventional therapies available in the treatment of cancer-related plan. A number of the techniques described in this review may offer effective analgesia with less systemic toxicity and dependency than traditional first- and second-line oral and parenteral agents. Interventions including dorsal root ganglion stimulation and peripheral nerve stimulation are emerging as exciting therapeutics with a potential role in oncologic pain [187]. Considering the extensive negative impact of pain on quality of life, functional status, and psychological well-being, interventional approaches should be evaluated as an early option

and central component of a multidisciplinary approach to treating pain in cancer patients.

Declarations

Conflict of Interest The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Kroenke K, Theobald D, Wu J, Loza JK, Carpenter JS, Tu W. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. J Pain Symptom Manag. 2010;40(3):327–41. https://doi.org/10.1016/j.jpainsymman.2009.12.023.
2. Given CW, Given B, Azzouz F, Kozachik S, Stommel M. Predictors of pain and fatigue in the year following diagnosis among elderly cancer patients. J Pain Symptom Manag. 2001;21(6):456–66. https://doi.org/10.1016/S0885-3924(01)00284-6.
3. Porter LS, Keefe FJ. Psychosocial issues in cancer pain. Curr Pain Headache Rep. 2011;15(4):263–70. https://doi.org/10.1007/s11916-011-0190-6.
4. Kurtz ME, Kurtz JC, Stommel M, Given CW, Given B. Physical functioning and depression among older persons with cancer. Cancer Pract. 2008;9(1):11–8. https://doi.org/10.1111/j.1523-5394.2001.91004.pp.x.
5. Portenoy RK. Cancer pain Epidemiology and syndromes. Cancer. 1989;63(11 Suppl):2298–307. https://doi.org/10.1002/1097-0142(19890601)63:11<2298::aid-cncr2820631140>3.0.co;2-a.
6. Breivik H, Cherny N, Collett B, de Conno F, Filbet M, Foubert AJ, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. Ann Oncol. 2009;20(8):1420–33. https://doi.org/10.1093/annonc/mdp001.
7.• vanden Beuken van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, Tjan-Heijnen VCG, Janssen DJA. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manag. 2016;51(6):1070–1090.e9. https://doi.org/10.1016/j.jpainsymman.2015.12.340 **This systematic review and meta-analysis suggests that in spite of the increased attention to assessment and management, moderate to severe pain continues to be widely prevalent in cancer patients.**
8. Cleeland CS. Undertreatment of Cancer Pain in Elderly Patients. JAMA. 1998;279(23):1914–5. https://doi.org/10.1001/jama.279.23.1914.
9. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med. 1994;330(9):592–6. https://doi.org/10.1056/NEJM199403033300902.
10. Moryl N, Coyle N, Essandoh S, Glare P. Chronic pain management in cancer survivors. J Natl Compr Cancer Netw. 2010;8(9):1104–10. https://doi.org/10.6004/jnccn.2010.0079.
11. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician Med Fam Can. 2010;56(6):514–7 e202-205.
12. Mercadante S, Arcuri E. Breakthrough pain in cancer patients: pathophysiology and treatment. Cancer Treat Rev. 1998;24(6):425–32. https://doi.org/10.1016/S0305-7372(98)90005-6.
13.• Falk S, Bannister K, Dickenson AH. Cancer pain physiology. Br J Pain. 2014;8(4):154–62. https://doi.org/10.1177/2049463714545136 **This paper describes the mechanisms of cancer pain physiology including elements of inflammatory and neuropathic pain and alterations in sensory processing.**
14. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12(20):6243s–9s. https://doi.org/10.1158/1078-0432.CCR-06-0931.
15. Zajączkowska R, Kocot-Kępska M, Leppert W, Wordliczek J. Bone pain in cancer patients: mechanisms and current treatment. Int J Mol Sci. 2019;20(23):6047. https://doi.org/10.3390/ijms20236047.
16. Milgrom DP, Lad NL, Koniaris LG, Zimmers TA. Bone pain and muscle weakness in cancer patients. Curr Osteoporos Rep. 2017;15(2):76–87. https://doi.org/10.1007/s11914-017-0354-3.
17. Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. J Clin Oncol. 1991;9(3):509–24. https://doi.org/10.1200/JCO.1991.9.3.509.
18. Suputtitada A Myofascial pain syndrome and sensitization. Phys Med Rehabil Res. 2016;1(5). doi:https://doi.org/10.15761/PMRR.1000127
19. Hird A, Chow E, Zhang L, Wong R, Wu J, Sinclair E, et al. Determining the incidence of pain flare following palliative radiotherapy for symptomatic bone metastases: results from three Canadian cancer centers. Int J Radiat Oncol. 2009;75(1):193–7. https://doi.org/10.1016/j.ijrobp.2008.10.044.
20. Fernandes R, Mazzarello S, Hutton B, Shorr R, Majeed H, Ibrahim MFK, et al. Taxane acute pain syndrome (TAPS) in patients receiving taxane-based chemotherapy for breast cancer—a systematic review. Support Care Cancer. 2016;24(8):3633–50. https://doi.org/10.1007/s00520-016-3256-5.
21. Crew KD, Greenlee H, Capodice J, Raptis G, Brafman L, Fuentes D, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol. 2007;25(25):3877–83. https://doi.org/10.1200/JCO.2007.10.7573.
22. Irwin KE, Greer JA, Khatib J, Temel JS, Pirl WF. Early palliative care and metastatic non-small cell lung cancer: potential mechanisms of prolonged survival. Chron Respir Dis. 2013;10(1):35–47. https://doi.org/10.1177/1479972312471549.
23.• Chernack B, Knowlton SE, Kohler MJ. The use of ultrasound in palliative care and hospice. Am J Hosp Palliat Med. 2017;34(4):385–91. https://doi.org/10.1177/1049909115625960 **This paper comments on the increasing popularity of ultrasound as a diagnostic and therapeutic modality in reducing symptom burden in palliative care and hospice patients.**
24. Crew KD, Capodice JL, Greenlee H, Brafman L, Fuentes D, Awad D, et al. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor–associated joint symptoms in women with early-stage breast cancer. J Clin Oncol. 2010;28(7):1154–60. https://doi.org/10.1200/JCO.2009.23.4708.
25. Pinheiro da Silva F, Moreira GM, Zomkowski K, Amaral de Noronha M, Flores Sperandio F. Manual therapy as treatment for chronic musculoskeletal pain in female breast cancer survivors: a systematic review and meta-analysis. J Manip Physiol Ther. 2019;42(7):503–13. https://doi.org/10.1016/j.jmpt.2018.12.007.
26. Jafri MS. Mechanisms of myofascial pain. Int Sch Res Not. 2014;2014:1–16. https://doi.org/10.1155/2014/523924.

27. Hasuo H, Kanbara K, Abe T, Sakuma H, Fukunaga M. Factors associated with the efficacy of trigger point injection in advanced cancer patients. J Palliat Med. 2017;20(10):1085–90. https://doi.org/10.1089/jpm.2016.0541.
28. Lee CY, Kim EJ, Hwang DG, Jung MY, Cho HG. The effect of trigger point injections on pain in patients with advanced cancer. Korean J Fam Med. 2019;40(5):344–7. https://doi.org/10.4082/kjfm.18.0065.
29. Shin HJ, Shin JC, Kim WS, Chang WH, Lee SC. Application of ultrasound-guided trigger point injection for myofascial trigger points in the subscapularis and pectoralis muscles to post-mastectomy patients: a pilot study. Yonsei Med J. 2014;55(3):792–9. https://doi.org/10.3349/ymj.2014.55.3.792.
30. Wong CSM, Wong SHS. A new look at trigger point injections. Anesthesiol Res Pract. 2012;2012:1–5. https://doi.org/10.1155/2012/492452.
31. Robbins MS, Kuruvilla D, Blumenfeld A, Charleston L IV, Sorrell M, Robertson CE, et al. Trigger point injections for headache disorders: expert consensus methodology and narrative review. Headache J Head Face Pain. 2014;54(9):1441–59. https://doi.org/10.1111/head.12442.
32. Hammi C, Schroeder JD, Yeung B. Trigger point injection. In: StatPearls. StatPearls Publishing; 2020. Accessed November 14, 2020. http://www.ncbi.nlm.nih.gov/books/NBK542196/
33. Cheng OT, Souzdalnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. Pain Med Malden Mass. 2012;13(6):740–53. https://doi.org/10.1111/j.1526-4637.2012.01394.x.
34. Cato RK. Indications and usefulness of common injections for nontraumatic orthopedic complaints. Med Clin North Am. 2016;100(5):1077–88. https://doi.org/10.1016/j.mcna.2016.04.007.
35. Fu JB, Dhah SS, Bruera E. Corticosteroid injections for knee pain at the end of life. J Palliat Med. 2015;18(7):570–1. https://doi.org/10.1089/jpm.2015.0095.
36. Rifat SF, Moeller JL. Basics of joint injection. General techniques and tips for safe, effective use. Postgrad Med. 2001;109(1):157–60, 165-166. https://doi.org/10.3810/pgm.2001.01.834.
37. Kennedy DJ, Schneider B, Casey E, Rittenberg J, Conrad B, Smuck M, et al. Vasovagal rates in flouroscopically guided interventional procedures: a study of over 8,000 injections. Pain Med. 2013;14(12):1854–9. https://doi.org/10.1111/pme.12241.
38. Plastaras CT, Joshi AB, Garvan C, Chimes GP, Smeal W, Rittenberg J, et al. Adverse events associated with fluoroscopically guided sacroiliac joint injections. PM&R. 2012;4(7):473–8. https://doi.org/10.1016/j.pmrj.2012.02.001.
39. Deyo RA, Rainville J, Kent DL. What can the history and physical examination tell us about low back pain? JAMA. 1992;268(6):760–5.
40. Shmagel A, Foley R, Ibrahim H. Epidemiology of chronic low back pain in US adults: data from the 2009–2010 national health and nutrition examination survey. Arthritis Care Res. 2016;68(11):1688–94. https://doi.org/10.1002/acr.22890.
41. US Burden of Disease Collaborators, Mokdad AH, Ballestros K, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. JAMA. 2018;319(14):1444–72. https://doi.org/10.1001/jama.2018.0158.
42. Kanis JA, McCloskey EV, Powles T, Paterson AH, Ashley S, Spector T. A high incidence of vertebral fracture in women with breast cancer. Br J Cancer. 1999;79(7-8):1179–81. https://doi.org/10.1038/sj.bjc.6690188.
43. Aghayev K, Papanastassiou ID, Vrionis F. Role of vertebral augmentation procedures in the management of vertebral compression fractures in cancer patients. Curr Opin Support Palliat Care. 2011;5(3):222–6. https://doi.org/10.1097/SPC.0b013e328349652d.
44. Klimo P, Schmidt MH. Surgical management of spinal metastases. Oncologist. 2004;9(2):188–96. https://doi.org/10.1634/theoncologist.9-2-188.
45. Byrne TN. Spinal cord compression from epidural metastases. N Engl J Med. 1992;327(9):614–9. https://doi.org/10.1056/NEJM199208273270907.
46. Wong DA, Fornasier VL, MacNab I. Spinal metastases: the obvious, the occult, and the impostors. Spine. 1990;15(1):1–4.
47. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. Ann Neurol. 1978;3(1):40–51. https://doi.org/10.1002/ana.410030107.
48. Hariri O, Takayanagi A, Miulli DE, Siddiqi J, Vrionis F. Minimally invasive surgical techniques for management of painful metastatic and primary spinal tumors. Cureus. 2017;9(3):e1114. https://doi.org/10.7759/cureus.1114.
49. Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. Nat Rev Rheumatol. 2013;9(4):216–24. https://doi.org/10.1038/nrrheum.2012.199.
50. Xu R, Sciubba DM, Gokaslan ZL, Bydon A. Metastasis to the occipitocervical junction: a case report and review of the literature. Surg Neurol Int. 2010;1:16. https://doi.org/10.4103/2152-7806.63911.
51. Strike SA, McCarthy EF. Chondrosarcoma of the spine: a series of 16 cases and a review of the literature. Iowa Orthop J. 2011;31:154–9.
52. Cohen SP. Sacroiliac joint pain: a comprehensive review of anatomy, diagnosis, and treatment. Anesth Analg. 2005;101(5):1440–53. https://doi.org/10.1213/01.ANE.0000180831.60169.EA.
53. Sagiv M, Slobodin G. Metastatic sacroiliitis. Isr Med Assoc J IMAJ. 2019;21(10):700.
54. Saviola G, Abdi Ali L, Trentanni C, Notarangelo LD, Desiati F, Lupi E, et al. Sacroiliitis as a manifestation of Hodgkin's disease in young females. Clin Exp Rheumatol. 2003;21(2):270.
55. Gómez Rodríguez N, Peteiro Cancelo A, Ibáñez Ruán J, González PM. Epithelioid sarcoma of the right ilium mimicking sacroiliitis. Reumatol Clin. 2013;9(2):120–2. https://doi.org/10.1016/j.reuma.2012.03.008.
56. Aslam F, Chivers FS, Doshi KB, Chang-Miller A. Positive HLA-B27 and sacroiliitis is not always spondyloarthritis. Int J Rheum Dis. 2019;22(12):2213–7. https://doi.org/10.1111/1756-185X.13738.
57. Santiago FR, Kelekis A, Alvarez LG, Filippiadis DK. Interventional procedures of the spine. Semin Musculoskelet Radiol. 2014;18(3):309–17. https://doi.org/10.1055/s-0034-1375572.
58. Cohen SP, Strassels SA, Kurihara C, Griffith SR, Goff B, Guthmiller K, et al. Establishing an optimal "cutoff" threshold for diagnostic lumbar facet blocks: a prospective correlational study. Clin J Pain. 2013;29(5):382–91. https://doi.org/10.1097/AJP.0b013e31825f53bf.
59. Vaswani D, Wallace AN, Eiswirth PS, Madaelil TP, Chang RO, Tomasian A, et al. Radiographic local tumor control and pain palliation of sarcoma metastases within the musculoskeletal system with percutaneous thermal ablation. Cardiovasc Intervent Radiol. 2018;41(8):1223–32. https://doi.org/10.1007/s00270-018-1932-1.
60. Deib G, Deldar B, Hui F, Barr JS, Khan MA. Percutaneous microwave ablation and cementoplasty: clinical utility in the treatment of painful extraspinal osseous metastatic disease and myeloma. AJR Am J Roentgenol Published online March. 2019;27:1–8. https://doi.org/10.2214/AJR.18.20386.
61. Pusceddu C, Sotgia B, Fele RM, Ballicu N, Melis L. Combined microwave ablation and cementoplasty in patients with painful bone metastases at high risk of fracture. Cardiovasc Intervent Radiol. 2016;39(1):74–80. https://doi.org/10.1007/s00270-015-1151-y.

62. Gallusser N, Goetti P, Becce F, Vauclair F, Rüdiger HA, Bize PE, et al. Percutaneous image-guided cryoablation of painful bone metastases: a single institution experience. Orthop Traumatol Surg Res OTSR. 2019;105(2):369–74. https://doi.org/10.1016/j.otsr.2019.01.001.
63. Coupal TM, Pennycooke K, Mallinson PI, Ouellette HA, Clarkson PW, Hawley P, et al. The hopeless case? Palliative cryoablation and cementoplasty procedures for palliation of large pelvic bone metastases. Pain Physician. 2017;20(7):E1053–61.
64. Cazzato RL, Garnon J, Caudrelier J, Rao PP, Koch G, Gangi A. Low-power bipolar radiofrequency ablation and vertebral augmentation for the palliative treatment of spinal malignancies. Int J Hyperth Off J Eur Soc Hyperthermic Oncol North Am Hyperth Group. 2018;34(8):1282–8. https://doi.org/10.1080/02656736.2017.1422557.
65. Bogduk N, Dreyfuss P, Baker R, Yin W, Landers M, Hammer M, et al. Complications of spinal diagnostic and treatment procedures. Pain Med. 2008;9(suppl 1):S11–34. https://doi.org/10.1111/j.1526-4637.2008.00437.x.
66. Manchikanti L, Malla Y, Wargo BW, Cash KA, Pampati V, Fellows B. Complications of fluoroscopically directed facet joint nerve blocks: a prospective evaluation of 7,500 episodes with 43,000 nerve blocks. Pain Physician. 2012;15(2):E143–50.
67. Abdi S, Datta S, Trescot AM, Schultz DM, Adlaka R, Atluri SL, et al. Epidural steroids in the management of chronic spinal pain: a systematic review. Pain Physician. 2007;10(1):185–212.
68. Chang-Chien GC, Knezevic NN, McCormick Z, Chu SK, Trescot AM, Candido KD. Transforaminal versus interlaminar approaches to epidural steroid injections: a systematic review of comparative studies for lumbosacral radicular pain. Pain Physician. 2014;17(4):E509–24.
69. Fanciullo GJ, Hanscom B, Seville J, Ball PA, Rose RJ. An observational study of the frequency and pattern of use of epidural steroid injection in 25,479 patients with spinal and radicular pain. Reg Anesth Pain Med. 2001;26(1):5–11. https://doi.org/10.1053/rapm.2001.20089.
70. O'Connor RC, Andary MT, Russo RB, DeLano M. Thoracic radiculopathy. Phys Med Rehabil Clin N Am. 2002;13(3):623–44, viii. https://doi.org/10.1016/s1047-9651(02)00018-9.
71. Childress MA, Becker BA. Nonoperative management of cervical radiculopathy. Am Fam Physician. 2016;93(9):746–54.
72. Oh DC-S, Rispoli L, Ghosh P, Gulati A. Epidural steroid injections for the management of spinal malignancy-related pain: a pragmatic review and retrospective study. Pain Pract Off J World Inst Pain. Published online October 6, 2020. doi:https://doi.org/10.1111/papr.12957
73. Pikis S, Cohen JE, Gomori JM, Fellig Y, Chrysostomou C, Barzilay Y, et al. Cauda equina syndrome after spinal epidural steroid injection into an unrecognized paraganglioma. Clin J Pain. 2013;29(12):e39–41. https://doi.org/10.1097/AJP.0b013e31829a4cc6.
74. Demaree CJ, Soliz JM, Gebhardt R. Cancer seeding risk from an epidural blood patch in patients with leukemia or lymphoma. Pain Med Malden Mass. 2017;18(4):786–90. https://doi.org/10.1093/pm/pnw218.
75. Manchikanti L, Malla Y, Wargo BW, Cash KA, Pampati V, Fellows B. A prospective evaluation of complications of 10,000 fluoroscopically directed epidural injections. Pain Physician. 2012;15(2):131–40.
76. Soneji N, Bhatia A, Seib R, Tumber P, Dissanayake M, Peng PWH. Comparison of fluoroscopy and ultrasound guidance for sacroiliac joint injection in patients with chronic low back pain. Pain Pract Off J World Inst Pain. 2016;16(5):537–44. https://doi.org/10.1111/papr.12304.
77. Hutson N, Hung JC, Puttanniah V, Lis E, Laufer I, Gulati A. Interventional pain management for sacroiliac tumors in the oncologic population: a case series and paradigm approach. Pain Med Malden Mass. 2017;18(5):959–68. https://doi.org/10.1093/pm/pnw211.
78. Gangi A, Guth S, Imbert JP, Marin H, Dietemann J-L. Percutaneous vertebroplasty: indications, technique, and results. Radiogr Rev Publ Radiol Soc N Am Inc. 2003;23(2):e10. https://doi.org/10.1148/rg.e10.
79. Pflugmacher R, Kandziora F, Schroeder RJ, Melcher I, Haas NP, Klostermann CK. Percutaneous balloon kyphoplasty in the treatment of pathological vertebral body fracture and deformity in multiple myeloma: a one-year follow-up. Acta Radiol Stockh Swed 1987. 2006;47(4):369–76. https://doi.org/10.1080/02841850600570425.
80. Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol. 2011;12(3):225–35. https://doi.org/10.1016/S1470-2045(11)70008-0.
81. Markmiller M. Percutaneous balloon kyphoplasty of malignant lesions of the spine: a prospective consecutive study in 115 patients. Eur Spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc. 2015;24(10):2165–72. https://doi.org/10.1007/s00586-014-3751-7.
82. Langdon J, Way A, Heaton S, Bernard J, Molloy S. The management of spinal metastases from renal cell carcinoma. Ann R Coll Surg Engl. 2009;91(8):649–52. https://doi.org/10.1308/003588409X432482.
83. Bagla S, Sayed D, Smirniotopoulos J, Brower J, Neal Rutledge J, Dick B, et al. Multicenter prospective clinical series evaluating radiofrequency ablation in the treatment of painful spine metastases. Cardiovasc Intervent Radiol. 2016;39(9):1289–97. https://doi.org/10.1007/s00270-016-1400-8.
84. Zhang C, Han X, Li L, Zhang C, Ma Y, Wang G. Posterior decompression surgery and radiofrequency ablation followed by vertebroplasty in spinal metastases from lung cancer. Med Sci Monit Int Med J Exp Clin Res. 2020;26:e925169. https://doi.org/10.12659/MSM.925169.
85. McDonald RJ, Trout AT, Gray LA, Dispenzieri A, Thielen KR, Kallmes DF. Vertebroplasty in multiple myeloma: outcomes in a large patient series. AJNR Am J Neuroradiol. 2008;29(4):642–8. https://doi.org/10.3174/ajnr.A0918.
86. Yoon SY, Oh J. Neuropathic cancer pain: prevalence, pathophysiology, and management. Korean J Intern Med. 2018;33(6):1058–69. https://doi.org/10.3904/kjim.2018.162.
87. Sikandar S, Dickenson AH. Visceral pain: the ins and outs, the ups and downs. Curr Opin Support Palliat Care. 2012;6(1):17–26. https://doi.org/10.1097/SPC.0b013e32834f6ec9.
88. Sengupta JN. Visceral Pain: The neurophysiological mechanism. In: Canning BJ, Spina D, eds. Sensory nerves. Vol 194. Handbook of experimental pharmacology. Springer Berlin Heidelberg; 2009: 31-74. doi:https://doi.org/10.1007/978-3-540-79090-7_2
89. Gunduz OH, Kenis-Coskun O. Ganglion blocks as a treatment of pain: current perspectives. J Pain Res. 2017;10:2815–26. https://doi.org/10.2147/JPR.S134775.
90. Carron H, Litwiller R. Stellate Ganglion Block. Anesth Analg. 1975;54(5):567–70. https://doi.org/10.1213/00000539-197509000-00002.
91. Kapral S, Krafft P, Gosch M, Fleischmann D, Weinstabl C. Ultrasound imaging for stellate ganglion block: direct visualization of puncture site and local anesthetic spread. A pilot study. Reg Anesth. 1995;20(4):323–8.
92. Situ S, Kumar Singh G, Singh S. Comparative study of fluoroscopy vs ultrasound guided stellate ganglion block. Int J Contemp Med Res IJCMR. 2020;7(2). https://doi.org/10.21276/ijcmr.2020.7.2.50

93. Wallace MS, Milholland AV. Contralateral spread of local anesthetic with stellate ganglion block. Reg Anesth. 1993;18(1):55–9.
94. Kozody R, Ready LB, Barsa JE, Murphy TM. Dose requirement of local anaesthetic to produce grand mal seizure during stellate ganglion block. Can Anaesth Soc J. 1982;29(5):489–91. https://doi.org/10.1007/BF03009415.
95. Sharbel D, Singh P, Blumenthal D, Sullivan J, Dua A, Albergotti WG, et al. Preoperative stellate ganglion block for perioperative pain in lateralized head and neck cancer: preliminary results. Otolaryngol Neck Surg. 2020;162(1):87–90. https://doi.org/10.1177/0194599819889688.
96. Ghai A, Kaushik T, Kumar R, Wadhera S. Chemical ablation of stellate ganglion for head and neck cancer pain. Acta Anaesthesiol Belg. 2016;67(1):6–8.
97. Nabil Abbas D, Abd El Ghafar EM, Ibrahim WA, Omran AF. Fluoroscopic stellate ganglion block for postmastectomy pain: a comparison of the classic anterior approach and the oblique approach. Clin J Pain 2011;27(3):207-213. doi:https://doi.org/10.1097/AJP.0b013e3181fb1ef1
98. Abbas DN, Reyad RM. Thermal versus super voltage pulsed radiofrequency of stellate ganglion in post-mastectomy neuropathic pain syndrome: a prospective randomized trial. Pain Physician. 2018;21(4):351–62.
99. Goel V, Patwardhan AM, Ibrahim M, Howe CL, Schultz DM, Shankar H. Complications associated with stellate ganglion nerve block: a systematic review. Reg Anesth Pain Med. 2019;44(6):669–78. https://doi.org/10.1136/rapm-2018-100127.
100. Kimura T, Nishiwaki K, Yokota S, Komatsu T, Shimada Y. Severe hypertension after stellate ganglion block. Br J Anaesth. 2005;94(6):840–2. https://doi.org/10.1093/bja/aei134.
101. Takanami I, Abiko T, Koizumi S. Life-threatening airway obstruction due to retropharyngeal and cervicomediastinal hematomas following stellate ganglion block. Thorac Cardiovasc Surg. 2009;57(5):311–2. https://doi.org/10.1055/s-2008-1038845.
102. Uchida T, Nakao S, Morimoto M, Iwamoto T. Serious cervical hematoma after stellate ganglion block. J Anesth. 2015;29(2):321. https://doi.org/10.1007/s00540-014-1914-7.
103. Kashiwagi M, Ikeda N, Tsuji A, Kudo K. Sudden unexpected death following stellate ganglion block. Leg Med Tokyo Jpn. 1999;1(4):262–5. https://doi.org/10.1016/s1344-6223(99)80048-0.
104. Rana MV, Candido KD, Raja O, Knezevic NN. Celiac plexus block in the management of chronic abdominal pain. Curr Pain Headache Rep. 2014;18(2):394. https://doi.org/10.1007/s11916-013-0394-z.
105. Cornman-Homonoff J, Holzwanger DJ, Lee KS, Madoff DC, Li D. Celiac plexus block and neurolysis in the management of chronic upper abdominal pain. Semin Interv Radiol. 2017;34(4):376–86. https://doi.org/10.1055/s-0037-1608861.
106. Kambadakone A, Thabet A, Gervais DA, Mueller PR, Arellano RS. CT-guided celiac plexus neurolysis: a review of anatomy, indications, technique, and tips for successful treatment. RadioGraphics. 2011;31(6):1599–621. https://doi.org/10.1148/rg.316115526.
107. Urits I, Jones MR, Orhurhu V, Peck J, Corrigan D, Hubble A, et al. A comprehensive review of the celiac plexus block for the management of chronic abdominal pain. Curr Pain Headache Rep. 2020;24(8):42. https://doi.org/10.1007/s11916-020-00878-4.
108. Romanelli DF, Beckmann CF, Heiss FW. Celiac plexus block: efficacy and safety of the anterior approach. AJR Am J Roentgenol. 1993;160(3):497–500. https://doi.org/10.2214/ajr.160.3.8430543.
109. Montero Matamala A, Vidal Lopez F, Inaraja ML. The percutaneous anterior approach to the celiac plexus using CT guidance. Pain. 1988;34(3):285–8. https://doi.org/10.1016/0304-3959(88)90124-8.
110. Ischia S, Luzzani A, Ischia A, Faggion S. A new approach to the neurolytic block of the coeliac plexus: the transaortic technique. Pain. 1983;16(4):333–41. https://doi.org/10.1016/0304-3959(83)90148-3.
111. Luz LP, Al-Haddad MA, DeWitt JA. EUS-guided celiac plexus interventions in pancreatic cancer pain: an update and controversies for the endosonographer. Endosc Ultrasound. 2014;3(4):213–20. https://doi.org/10.4103/2303-9027.144515.
112. Seicean A. Celiac plexus neurolysis in pancreatic cancer: the endoscopic ultrasound approach. World J Gastroenterol. 2014;20(1):110–7. https://doi.org/10.3748/wjg.v20.i1.110.
113. Sakamoto H, Kitano M, Komaki T, Imai H, Kamata K, Kudo M. Endoscopic ultrasound-guided neurolysis in pancreatic cancer. Pancreatol Off J Int Assoc Pancreatol IAP Al. 2011;11(Suppl 2):52–8. https://doi.org/10.1159/000323513.
114. Ina H, Kitoh T, Kobayashi MM, Imai S, Ofusa Y, Goto H. New technique for the neurolytic celiac plexus block. Anesthesiology. 1996;85(1):212–7. https://doi.org/10.1097/00000542-199607000-00028.
115. Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. Anesth Analg. 1995;80(2):290–5. https://doi.org/10.1097/00000539-199502000-00015.
116. Yondonjamts B, Odontuya D, Ganbold L. The neurolytic celiac plexus block efficacy in patients with severe, chronic upper-abdominal cancer pain. Cent Asian J Med Sci. 2016;2:76–82.
117. Cao J, He Y, Liu H, Wang S, Zhao B, Zheng X, et al. Effectiveness of percutaneous celiac plexus ablation in the treatment of severe cancer pain in upper abdomen and evaluation of health economics. Am J Hosp Palliat Care. 2017;34(2):142–7. https://doi.org/10.1177/1049909115625954.
118. Nitschke AM, Ray CE. Percutaneous neurolytic celiac plexus block. Semin Interv Radiol. 2013;30(3):318–21. https://doi.org/10.1055/s-0033-1353485.
119. Bahn BM, Erdek MA. Celiac plexus block and neurolysis for pancreatic cancer. Curr Pain Headache Rep. 2013;17(2):310. https://doi.org/10.1007/s11916-012-0310-y.
120. Gimeno-García AZ, Elwassief A, Paquin SC, Sahai AV. Fatal complication after endoscopic ultrasound-guided celiac plexus neurolysis. Endoscopy. 2012;44(Suppl 2 UCTN):E267. https://doi.org/10.1055/s-0032-1309709.
121. Ahmed HM, Friedman SE, Henriques HF, Berk BS. End-organ ischemia as an unforeseen complication of endoscopic-ultrasound-guided celiac plexus neurolysis. Endoscopy. 2009;41(Suppl 2):E218–9. https://doi.org/10.1055/s-0029-1214941.
122. Marcy PY, Magné N, Descamps B. Coeliac plexus block: utility of the anterior approach and the real time colour ultrasound guidance in cancer patient. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2001;27(8):746–9. https://doi.org/10.1053/ejso.2001.1202.
123. Gupta D, Jain R, Mishra S, Kumar S, Thulkar S, Bhatnagar S. Ultrasonography reinvents the originally described technique for ganglion impar neurolysis in perianal cancer pain. Anesth Analg. 2008;107(4):1390–2. https://doi.org/10.1213/ane.0b013e31817f6d2e.
124. Ahmed DG, Mohamed MF, Mohamed SA-E. Superior hypogastric plexus combined with ganglion impar neurolytic blocks for pelvic and/or perineal cancer pain relief. Pain Physician. 2015;18(1):E49–56.
125. Wemm K, Saberski L. Modified approach to block the ganglion impar (ganglion of Walther). Reg Anesth. 1995;20(6):544–5.
126. Scott-Warren JT, Hill V, Rajasekaran A. Ganglion impar blockade: a review. Curr Pain Headache Rep. 2013;17(1):306. https://doi.org/10.1007/s11916-012-0306-7.

127. Plancarte DR, Amescua C, Patt RB, Allende S. A751 presacral blockade of the ganglion of Walther (ganglion impar). Anesthesiology. 1990;73(3A):NA. https://doi.org/10.1097/00000542-199009001-00749.
128. Foye PM, Buttaci CJ, Stitik TP, Yonclas PP. Successful injection for coccyx pain. Am J Phys Med Rehabil. 2006;85(9):783–4. https://doi.org/10.1097/01.phm.0000233174.86070.63.
129. Hong JH, Jang HS. Block of the ganglion impar using a coccygeal joint approach. Reg Anesth Pain Med. 2006;31(6):583–4. https://doi.org/10.1016/j.rapm.2006.09.001.
130. Huang JJ. Another modified approach to the ganglion of Walther block (ganglion of impar). J Clin Anesth. 2003;15(4):282–3. https://doi.org/10.1016/s0952-8180(03)00066-7.
131. Foye PM, Patel SI. Paracoccygeal corkscrew approach to ganglion impar injections for tailbone pain. Pain Pract Off J World Inst Pain. 2009;9(4):317–21. https://doi.org/10.1111/j.1533-2500.2009.00291.x.
132. Sousa Correia J, Silva M, Castro C, Miranda L, Agrelo A. The efficacy of the ganglion impar block in perineal and pelvic cancer pain. Support Care Cancer. 2019;27(11):4327–30. https://doi.org/10.1007/s00520-019-04738-9.
133. Agarwal-Kozlowski K, Lorke DE, Habermann CR, Am Esch JS, Beck H. CT-guided blocks and neuroablation of the ganglion impar (Walther) in perineal pain: anatomy, technique, safety, and efficacy. Clin J Pain. 2009;25(7):570–6. https://doi.org/10.1097/AJP.0b013e3181a5f5c7.
134. Loev MA, Varklet VL, Wilsey BL, Ferrante MF. Cryoablation. Anesthesiology. 1998;88(5):1391–3. https://doi.org/10.1097/00000542-199805000-00031.
135. Reig E, Abejón D, del Pozo C, Insausti J, Contreras R. Thermocoagulation of the ganglion impar or ganglion of Walther: description of a modified approach. Preliminary results in chronic, nononcological pain. Pain Pract Off J World Inst Pain. 2005;5(2):103–10. https://doi.org/10.1111/j.1533-2500.2005.05206.x.
136. Demircay E, Kabatas S, Cansever T, Yilmaz C, Tuncay C, Altinors N. Radiofrequency thermocoagulation of ganglion impar in the management of coccydynia: preliminary results. Turk Neurosurg. 2010;20(3):328–33. https://doi.org/10.5137/1019-5149.JTN.2852-09.0.
137. Furman MB, Berkwits L. Atlas of image-guided spinal procedures.; 2018. Accessed October 15, 2020. http://www.sciencedirect.com/science/book/9780323401531
138. Spencer NJ, Zagorodnyuk V, Brookes SJ, Hibberd T. Spinal afferent nerve endings in visceral organs: recent advances. Am J Physiol Gastrointest Liver Physiol. 2016;311(6):G1056–63. https://doi.org/10.1152/ajpgi.00319.2016.
139. Spiegel MA, Hingula L, Chen GH, Legler A, Puttanniah V, Gulati A. The use of L2 and L3 lumbar sympathetic blockade for cancer-related pain, an experience and recommendation in the oncologic population. Pain Med. 2020;21(1):176–84. https://doi.org/10.1093/pm/pnz142.
140. Ryu J-H, Lee CS, Kim Y-C, Lee SC, Shankar H, Moon JY. Ultrasound-assisted versus fluoroscopic-guided lumbar sympathetic ganglion block: a prospective and randomized study. Anesth Analg. 2018;126(4):1362–8. https://doi.org/10.1213/ANE.0000000000002640.
141. de Oliveira R, dos Reis MP, Prado WA. The effects of early or late neurolytic sympathetic plexus block on the management of abdominal or pelvic cancer pain. Pain. 2004;110(1-2):400–8. https://doi.org/10.1016/j.pain.2004.04.023.
142. Rathmell JP, Nelson GJ. Atlas of image-guided intervention in regional anesthesia and pain medicine: incl. fully searchable text and image bank. 2nd ed. Wolters Kluwer, Lippincott Williams & Wilkins; 2012.
143. Haynsworth RF, Noe CE, Fassy LR. Intralymphatic injection: another complication of lumbar sympathetic block. Anesthesiology. 1994;80(2):460–2.
144. Dirim A, Kumsar S. Iatrogenic ureteral injury due to lumbar sympathetic block. Scand J Urol Nephrol. 2008;42(5):492–3. https://doi.org/10.1080/00365590802045038.
145. Samuelsson SM, Hoegstr-Om S. Retroperitoneal hematoma following lumbar sympathetic nerve block. Sven Lakartidningen. 1964;61:2894–903.
146. de Courcy JG. Interventional techniques for cancer pain management. Clin Oncol R Coll Radiol G B. 2011;23(6):407–17. https://doi.org/10.1016/j.clon.2011.04.003.
147. Rocha A, Plancarte R, Nataren RGR, Carrera IHS, Pacheco VADLR, Hernandez-Porras BC. Effectiveness of superior hypogastric plexus neurolysis for pelvic cancer pain. Pain Physician. 2020;23(2):203–8.
148. Gamal G, Helaly M, Labib YM. Superior hypogastric block: transdiscal versus classic posterior approach in pelvic cancer pain. Clin J Pain. 2006;22(6):544–7. https://doi.org/10.1097/01.ajp.0000202978.06045.24.
149. Liliang P-C, Hung C-M, Lu K, Chen H-J. Fluoroscopically-guided superior hypogastric plexus neurolysis using a single needle: a modified technique for a posterolateral transdiscal approach. Pain Physician. 2018;21(4):E341–5.
150. McDonald JS. Management of chronic pelvic pain. Obstet Gynecol Clin N Am. 1993;20(4):817–38.
151. Plancarte R, de Leon-Casasola OA, El-Helaly M, Allende S, Lema MJ. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Reg Anesth. 1997;22(6):562–8.
152. de Leon-Casasola OA, Kent E, Lema MJ. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Pain. 1993;54(2):145–51. https://doi.org/10.1016/0304-3959(93)90202-z.
153. Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S, et al. The Polyanalgesic Consensus Conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. Neuromodulation J Int Neuromodulation Soc. 2017;20(2):96–132. https://doi.org/10.1111/ner.12538.
154. Bruel BM, Burton AW. Intrathecal therapy for cancer-related pain. Pain Med. 2016;17(12):2404–21. https://doi.org/10.1093/pm/pnw060.
155. Dupoiron D. Intrathecal therapy for pain in cancer patients. Curr Opin Support Palliat Care. 2019;13(2):75–80. https://doi.org/10.1097/SPC.0000000000000427.
156. Xing F, Yong RJ, Kaye AD, Urman RD. Intrathecal drug delivery and spinal cord stimulation for the treatment of cancer pain. Curr Pain Headache Rep. 2018;22(2):11. https://doi.org/10.1007/s11916-018-0662-z.
157. Deer TR, Pope JE, Hanes MC, McDowell GC. Intrathecal therapy for chronic pain: a review of morphine and ziconotide as firstline options. Pain Med. 2019;20(4):784–98. https://doi.org/10.1093/pm/pny132.
158. Mastenbroek TC, Kramp-Hendriks BJ, Kallewaard JW, Vonk JM. Multimodal intrathecal analgesia in refractory cancer pain. Scand J Pain. 2017;14(1):39–43. https://doi.org/10.1016/j.sjpain.2016.10.002.
159. Eisenach JC, DuPen S, Dubois M, Miguel R, Allin D. Epidural clonidine analgesia for intractable cancer pain. The Epidural Clonidine Study Group Pain. 1995;61(3):391–9. https://doi.org/10.1016/0304-3959(94)00209-w.
160. Yang CY, Wong CS, Chang JY, Ho ST. Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. Can J Anaesth J Can Anesth. 1996;43(4):379–83. https://doi.org/10.1007/BF03011718.
161. Gulati A, Puttanniah V, Hung J, Malhotra V. Considerations for evaluating the use of intrathecal drug delivery in the oncologic

patient. Curr Pain Headache Rep. 2014;18(2):391. https://doi.org/10.1007/s11916-013-0391-2.
162. Stearns LM, Abd-Elsayed A, Perruchoud C, Spencer R, Hammond K, Stromberg K, et al. Intrathecal drug delivery systems for cancer pain: an analysis of a prospective, multicenter product surveillance registry. Anesth Analg. 2020;130(2):289–97. https://doi.org/10.1213/ANE.0000000000004425.
163. Zheng S, He L, Yang X, Li X, Yang Z. Evaluation of intrathecal drug delivery system for intractable pain in advanced malignancies: a prospective cohort study. Medicine (Baltimore). 2017;96(11):e6354. https://doi.org/10.1097/MD.0000000000006354.
164. Penn RD, Paice JA. Chronic intrathecal morphine for intractable pain. J Neurosurg. 1987;67(2):182–6. https://doi.org/10.3171/jns.1987.67.2.0182.
165. Onofrio BM, Yaksh TL. Long-term pain relief produced by intrathecal morphine infusion in 53 patients. J Neurosurg. 1990;72(2):200–9. https://doi.org/10.3171/jns.1990.72.2.0200.
166. Follett KA, Hitchon PW, Piper J, Kumar V, Clamon G, Jones MP. Response of intractable pain to continuous intrathecal morphine: a retrospective study. Pain. 1992;49(1):21–5. https://doi.org/10.1016/0304-3959(92)90183-c.
167. Tutak U, Doleys DM. Intrathecal infusion systems for treatment of chronic low back and leg pain of noncancer origin. South Med J. 1996;89(3):295–300. https://doi.org/10.1097/00007611-199603000-00007.
168. Webster LR. The relationship between the mechanisms of action and safety profiles of intrathecal morphine and ziconotide: a review of the literature. Pain Med Malden Mass. 2015;16(7):1265–77. https://doi.org/10.1111/pme.12666.
169. Saulino M, Kim PS, Shaw E. Practical considerations and patient selection for intrathecal drug delivery in the management of chronic pain. J Pain Res. 2014;7:627–38. https://doi.org/10.2147/JPR.S65441.
170. Mercadante S, Intravaia G, Villari P, Ferrera P, Riina S, David F, et al. Intrathecal treatment in cancer patients unresponsive to multiple trials of systemic opioids. Clin J Pain. 2007;23(9):793–8. https://doi.org/10.1097/AJP.0b013e3181565d17.
171. Lihua P, Su M, Zejun Z, Ke W, Bennett MI. Spinal cord stimulation for cancer-related pain in adults. Cochrane Database Syst Rev. 2013;2:CD009389. https://doi.org/10.1002/14651858.CD009389.pub2.
172. Flagg A, McGreevy K, Williams K. Spinal cord stimulation in the treatment of cancer-related pain: "back to the origins.". Curr Pain Headache Rep. 2012;16(4):343–9. https://doi.org/10.1007/s11916-012-0276-9.
173. Costantini A. Spinal cord stimulation. Minerva Anestesiol. 2005;71(7-8):471–4.
174. Yakovlev AE, Resch BE. Spinal cord stimulation for cancer-related low back pain. Am J Hosp Palliat Care. 2012;29(2):93–7. https://doi.org/10.1177/1049909111410414.
175. Nouri KH, Brish EL. Spinal cord stimulation for testicular pain. Pain Med Malden Mass. 2011;12(9):1435–8. https://doi.org/10.1111/j.1526-4637.2011.01210.x.
176. Yakovlev AE, Ellias Y. Spinal cord stimulation as a treatment option for intractable neuropathic cancer pain. Clin Med Res. 2008;6(3-4):103–6. https://doi.org/10.3121/cmr.2008.813.
177. Deer TR, Mekhail N, Provenzano D, Pope J, Krames E, Thomson S, et al. The appropriate use of neurostimulation: avoidance and treatment of complications of neurostimulation therapies for the treatment of chronic pain. Neuromodulation Appropriateness Consensus Committee. Neuromodulation J Int Neuromodulation Soc. 2014;17(6):571–97; discussion 597-598. https://doi.org/10.1111/ner.12206.
178. Kloss BT, Sullivan AM, Rodriguez E. Epidural hematoma following spinal cord stimulator implant. Int J Emerg Med. 2010;3(4):483–4. https://doi.org/10.1007/s12245-010-0174-z.
179. Shimoji K, Hokari T, Kano T, Tomita M, Kimura R, Watanabe S, et al. Management of intractable pain with percutaneous epidural spinal cord stimulation: differences in pain-relieving effects among diseases and sites of pain. Anesth Analg. 1993;77(1):110–6. https://doi.org/10.1213/00000539-199307000-00022.
180. Meglio M, Cioni B, Rossi GF. Spinal cord stimulation in management of chronic pain. A 9-year experience. J Neurosurg. 1989;70(4):519–24. https://doi.org/10.3171/jns.1989.70.4.0519.
181. Esposito MF, Malayil R, Hanes M, Deer T. Unique characteristics of the dorsal root ganglion as a target for neuromodulation. Pain Med Malden Mass. 2019;20(Suppl 1):S23–30. https://doi.org/10.1093/pm/pnz012.
182. Hogan QH. Labat lecture: the primary sensory neuron: where it is, what it does, and why it matters. Reg Anesth Pain Med. 2010;35(3):306–11. https://doi.org/10.1097/AAP.0b013e3181d2375e.
183. Krames ES. The dorsal root ganglion in chronic pain and as a target for neuromodulation: a review: DRG-A robust target for neuromodulation. Neuromodulation Technol Neural Interface. 2015;18(1):24–32. https://doi.org/10.1111/ner.12247.
184. Harrison C, Epton S, Bojanic S, Green AL, FitzGerald JJ. The efficacy and safety of dorsal root ganglion stimulation as a treatment for neuropathic pain: a literature review. Neuromodulation J Int Neuromodulation Soc. 2018;21(3):225–33. https://doi.org/10.1111/ner.12685.
185. Liem L, Russo M, Huygen FJPM, van Buyten JP, Smet I, Verrills P, et al. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation J Int Neuromodulation Soc. 2013;16(5):471–82; discussion 482. https://doi.org/10.1111/ner.12072.
186. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. Neuromodulation J Int Neuromodulation Soc. 2013;16(1):67–71; discussion 71-72. https://doi.org/10.1111/ner.12013.
187. Mainkar O, Solla CA, Chen G, Legler A, Gulati A. Pilot study in temporary peripheral nerve stimulation in oncologic pain. Neuromodulation Technol Neural Interface. 2020;23(6):819–26. https://doi.org/10.1111/ner.13139.