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R E V I E W

The American Society of Pain and Neuroscience (ASPN) Best Practices and Guidelines for the Interventional Management of Cancer-Associated Pain

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Abstract: Moderate to severe pain occurs in many cancer patients during their clinical course and may stem from the primary pathology, metastasis, or as treatment side effects. Uncontrolled pain using conservative medical therapy can often lead to patient distress, loss of productivity, shorter life expectancy, longer hospital stays, and increase in healthcare utilization. Various publications shed light on strategies for conservative medical management for cancer pain and a few international publications have reviewed limited interventional data. Our multi-institutional working group was assembled to review and highlight the body of evidence that exists for opioid utilization for cancer pain, adjunct medication such as ketamine and methadone and interventional therapies. We discuss neurolysis via injections, neuromodulation including targeted drug delivery and spinal cord stimulation, vertebral tumor ablation and augmentation, radiotherapy and surgical techniques. In the United States, there is a significant variance in the interventional treatment of cancer pain based on fellowship training. As a first of its kind, this best practices and interventional guideline will offer evidenced-based recommendations for reducing pain and suffering associated with malignancy.

Keywords: cancer pain, neurolysis, ketamine, pain pump, intrathecal drug delivery, neuromodulation, radiofrequency, spinal cord stimulation, vertebral augmentation

Introduction

There were an estimated 1.8 million new cancer diagnoses and 606,520 cancer-related deaths in the United States in 2020. Moderate to severe pain occurs in approximately 35% of all cancer patients and 80% of the patients with advanced-stage cancer.[1] While younger patients are more susceptible to acute pain exacerbations, all age groups reported pain to be the most significant impairment to their quality of life.[2] The CONCERN study evaluated cancer patients presenting to the emergency department for acute symptom management, with 62.1% of the patients reporting pain as their primary problem.[3] When presenting to palliative care, 68% of end-stage cancer patients reported pain related to their primary tumor, typically somatic in nature.[4] Nearly three-quarters of pain therapies are directed toward either the primary tumor or accompanying metastases.[4] Pain in this population is not limited to the underlying diagnosis and may stem from treatments and diagnostic procedures. Fifty-five percent of patients report significant pain from their anticancer treatment, including radiation, chemotherapy and hormone therapies.{ref 4} Common syndromes may present as mucositis,

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granulocyte colony-stimulating factors (G-CSFs) induced bone pain, radiation and chemotherapy-related dermatological pain, and diffuse musculoskeletal pain.[5] Approximately one-third of patients have significant chronic pain after curative treatment, especially chronic post-operative pain leading to severe impairment of quality of life and daily activities.[6] Cancer pain is associated with significantly increased emotional distress, with pain causing disability for active cancer patients on average of 12–20 days per month. Even after cancer survival, between 20% and 50% of the patients continue to experience pain and functional limitations years following treatment completion.[7]

A study evaluating the prevalence and characterization of pain in the oncologic patient population determined risk factors for increased pain as female gender, age over 65 years and advanced cancer stages.[8]

There are multiple studies that discuss the conservative medical management of cancer-related pain.[9] The Royal College of Physicians National Clinical Programme for Palliative Care and American Society of Clinical Oncology summarized a review for pharmacologic treatment of cancer pain.[10,11] In 2017, the World Health Organization (WHO) provided clinical guidelines for opioid administration, including when to initiate opioids, routes of administration, opioid rotation, and cessation. They also discussed adjuvant medications including antidepressant and anticonvulsants as well as bisphosphonates for bone metastasis. The European Association of Palliative Care (EAPC) published guidelines that specifically address the use of opioids including breakthrough pain for the treatment of cancer pain.[12]

There are multiple published articles that exist describing interventional pain management strategies for cancer pain; however, a formal guideline does not exist. Neurolytic blocks, intrathecal drug delivery systems (IDDS), vertebral augmentation, neuromodulation (including spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRG-S) for neuropathic pain, and radiotherapy have been described.[13–17] Gulati et al[18] and Pak et al[16] have described various interventional techniques including sympathetic blocks, neuromodulation, and intrathecal drug delivery systems for various types of cancer. In a 2019 expert consensus on the management of breakthrough cancer pain in older patients, it was noted that despite discussion between various specialties and available literature, there was no agreement on how interventional techniques should be integrated

into the therapeutic strategy.[19] However, interventional treatments are effective in providing pain relief, reducing the burden of symptoms, minimizing opioid intake, and have a low complication rate.[20] Best practice guidelines would be instrumental to bridge the gap between evidence and clinical practice. To our knowledge, there are no large studies planned or currently ongoing to define best practice guidelines for conservative and interventional management of cancer-related pain.

Currently, a significant variance in the interventional treatment of cancer pain exists due to patient volumes, potential affiliations with cancer institutions, and faculty expertise and training on cancer pain. A best practice guideline will offer evidence-based recommendations for utilizing advanced interventional therapies for cancer-related pain.

Methods
Development Process
The American Society of Pain and Neuroscience (ASPN) performed a needs-based assessment of the therapeutic efficacy and patient safety with interventional pain techniques for cancer-related pain, and determined an evidence-based best practice review was needed. A multidisciplinary panel of pain medicine specialists was selected to create a best practices guideline for conservative and interventional management of cancer-related pain. Selection was based on expertise, publications, research, clinical experience, practice setting, and diversity. Previous reviews have published guidelines on the management of cancer-associated pain; however, these were primarily focused on non-interventional therapies.[21,22] Due to the recent expansion of interventional techniques in the management of cancer-associated pain, the panel reviewed the literature to create guidelines to help structure the management of cancer-associated pain through both interventional and non-interventional adjunct therapies. We aimed to provide an overview of commonly used opioids, adjuvant medications, radiotherapy and to conduct a systematic review of the interventions offered by pain physicians for cancer pain. A meta analysis was not conducted due to the heterogeneity in study types and clinical variances in the interventions performed. Best practice summary statements and evidence grading are provided for each section. Prior to development of the manuscript, authors' financial relationships were disclosed and

recusal was required for any relevant section. Final editing for bias was conducted by an author without any conflicts of interest (AM).

Literature Search Method

A librarian-assisted literature search was performed identifying publications relevant to the management of cancer-associated pain in all types of cancer. Searches were completed using, Ovid MEDLINE (1946–2021), EMBASE (1974–2021), and Cochrane Database of Systematic Reviews (2005–2020) in addition to reference section review of all literature search identified manuscripts. Formatting of identified manuscripts included meta-analyses, randomized controlled trials, prospective studies, retrospective studies, case series, reports of expert committee, and existing international guidelines, limited to the English language.

The following search terms were used: "cancer", ''metastasis'', "cancer pain", "opioids", "ketamine", "methadone", "radiotherapy", "plexus blocks", "neurolysis", "epidural analgesia", "celiac plexus", "splanchnic plexus", "superior hypogastric plexus", "ganglion impar", "external beam radiation", "intrathecal analgesia", "spinal cord stimulation", "vertebral radiofrequency", "vertebral augmentation", "vertebroplasty", "kyphoplasty", "cingulotomy", "myelotomy", "DREZ-otomy", "radiofrequency cordotomy", and "resiniferotoxin". The authors also conducted independent literature searches which were cross-referenced and compiled for analysis and consensus review.

Evaluation and Analysis of Evidence

A total of 1,032,581 individual manuscripts were identified in the initial search. There was a total of 1638 duplicates and these were removed. The records were then filtered for "cancer pain" + "pain management" plus each key word resulting in 7308 articles. Two authors read the titles and abstracts and selected articles with a focus on interventional therapies for cancer pain. Criteria for exclusion at this stage were as follows: opioids only, acute postoperative pain in cancer patients and single patient case reports. A total of 7219 abstracts were excluded for these reasons. Eighty nine relevant abstracts were identified for review (Figure 1). Quality of evidence for each treatment class was graded from I–III as detailed in (Table 1) and a degree of recommendation was provided on a scale from A to D, or as insufficient (I), according to the United States Preventive Services Task Force (USPSTF) criteria (Table 2).[23–25]

Data Evaluation and Discussion
Opioids for Cancer Pain

Prior to evaluating best practices for interventional methods of pain relief in the cancer patient it is valuable to review the current evidence for commonly used non-invasive options.

As pain can be moderate to severe in up to 50% of all individuals with cancer,[9] opioids are commonly used in this patient population. The WHO developed a three step "Ladder" for treatment of cancer pain that recommends non-opioid medications first, followed by mild opioids, and lastly by strong opioids until the patient has achieved pain control.[26] Adjuvant medications may be initiated at any step in the treatment process. Methadone has numerous clinical and pharmacological considerations differentiating it from other opioids and is addressed separately below.

Opioid agent selection should be individualized to account for the variance in pain presentations and co-existing medical comorbidities. Morphine and codeine should be avoided in advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD); hydromorphone or oxycodone can be used with caution, while methadone and fentanyl appear to be safe to use.[27] Similarly, liver function plays a key role in the activation, transformation, and metabolism of opioid medications. Opioid selection and dosing schedule should be carefully reviewed in patients with liver dysfunction. Methadone, meperidine, and codeine should be avoided in patients with liver dysfunction, while dose adjustments might be required with morphine, hydromorphone, oxycodone, and tramadol.[28] Certain long-acting opioids with known immunosuppressive properties (ie, morphine, fentanyl, methadone) have been found to have increased incidence of infections compared to those without immunosuppressive properties (ie, oxycodone, oxymorphone, tramadol), and this must be carefully considered given the cancer-induced immunocompromised state in this patient population.[29] Ultimately, the choice of opioid might be limited by the insurance coverage. Codeine, morphine, fentanyl, and methadone are the opioids listed on the WHO essential drug list and might be more accessible compared to some of the newer opioids, such as buprenorphine.[30]

A recent overview of Cochrane reviews concluded that while the quality of evidence on the use of opioids for cancer pain was low, data show that 19 of 20 patients who engage in
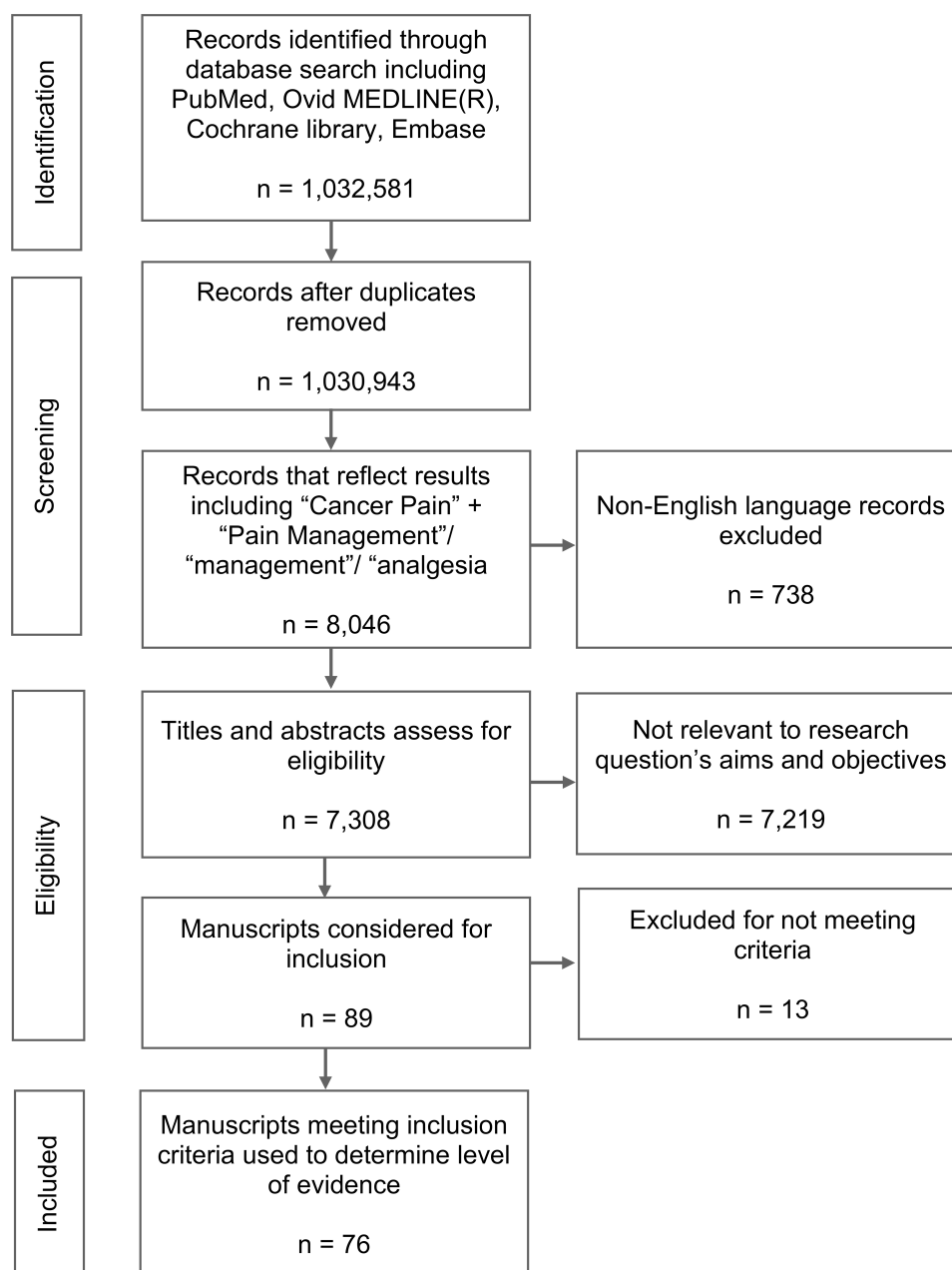
Figure 1 PRISMA diagram.

opioid therapy for moderate to severe pain will have meaningful pain reduction within 14 days.[9,31,32] In addition, they found that most patients will have adverse events, and 10–20% of cancer patients receiving opioid therapy may need to change treatment due to the severity of these side effects.[9] While the most common side effects of opioids include constipation, nausea, and vomiting, other adverse effects include sedation, respiratory depression (which can be life threatening), urinary retention, pruritus, tolerance leading to loss of efficacy. In addition, dependence (mental and/or physical) leading to risk of withdrawal, hyperalgesia, and hypogonadism leading to decreased testosterone and osteopenia are reported.[22] Given the potential for opioid use disorder, physicians must remain vigilant and perform careful evaluations and regular follow-up to address key safety concerns when maintaining patients on long-term

Table 1 Evidence Levels

Evidence Level	Study Type
I	At least one controlled and randomized clinical trial, properly designed
II-1	Well-designed, controlled, nonrandomized clinical trials
II-2	Cohort or case studies and well-designed controls, preferably multicenter
II-3	Multiple series compared over time, with or without intervention, and surprising results in noncontrolled experiences
III	Clinical experiences-based opinions, descriptive studies, clinical observations, or reports of expert committees

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Table 2 United States Preventive Services Task Force Grading

Degree of Recommendation	Meaning
A	Extremely recommendable (good evidence that the measure is effective, and benefits outweigh the harms)
B	Recommendable (at least, moderate evidence that the measure is effective, and benefits exceed harms)
C	Neither recommendable nor inadvisable (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified)
D	Inadvisable (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits)
I	Insufficient, low quality or contradictory evidence; the balance between benefit and harms cannot be determined

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opioid therapy, particularly given increased survival rates with certain types of cancer. Universal precautions can decrease the incidence of opioid misuse, and these include patient education, informed consent, a formal opioid agreement, utilization of prescription monitoring program, urine drug toxicology screening, utilizing screening tools such as the Opioid Risk Tool (ORT) and the Current Opioid Misuse Measure (COMM).[33]

Evidence Evaluation and Best Practice Statement
- Opioids should be considered for moderate to severe cancer-related pain. I-A
- Opioid agent selection should be individualized to account for the variance in pain presentations and co-existing medical comorbidities. III- B

Adjunct Medications
Methadone
Methadone is a racemic mixture of two enantiomers with applications to treat pain with nociceptive and neuropathic components. The L isomer (R-methadone) is a Mu/Delta

receptor agonist while the D isomer (S-methadone) is a NMDA receptor antagonist and serotonin/norepinephrine reuptake inhibitor. Methadone has higher intrinsic activity but lower Mu receptor affinity than morphine allowing for pain relief while minimizing related side effects.[34,35] The NMDA antagonism decreases excitatory neurotransmitter glutamate binding at the NMDA receptor site, leading to reduction of hyperalgesia, neuropathic pain, and depressed opioid receptor functionality.

According to the WHO analgesic ladder, strong opioids are considered the third step in treating adult cancer pain. Methadone is utilized when patients develop opioid tolerance, intolerance to side effects, or allergic reaction to other strong opioids such as morphine. Methadone is excreted through the feces showing benefit in patients with advanced CKD and ESRD. Patients having developed neuropathic pain from cancer treatment or compressive/radiation plexopathy may benefit from the dual nociceptive and neuropathic properties.

Methadone initiation dosing should be 2.5 mg TID in opioid naive patients with dose adjustments of 5 mg/day or

less every 5–7 days. Opioid tolerant patients should be converted to an equianalgesic dose (1:2 to 1:20 conversion factor) with maximum starting dose of 30 mg/day and dose adjustment of 10 mg/day or less every 5–7 days.[36] The analgesic half-life is 6–8 hours, so dosing every 6–8 hours is recommended.[35,37,38] Common side effects include somnolence, nausea, constipation, and xerostomia, however rarer side effects have been described and include fatal arrhythmia, serotonin syndrome, respiratory depression, pruritus, diaphoresis, and neurotoxicity. Prior to initiation, cardiac arrhythmia risk should be assessed, and a baseline EKG obtained to evaluate for QT prolongation. A QTc between 450 and 500 ms puts the patient at a higher risk for development of torsades de pointes. When QTc >500 ms, alternative therapy should be considered. Follow-up EKG is recommended 2–4 weeks after methadone initiation.[36] High gastric pH or proton pump inhibitor (PPI) use increases methadone absorption, while high urinary pH reduces methadone clearance leading to accumulation despite primarily fecal clearance.

According to a Cochrane review and secondary literature search, there is no evidence comparing methadone to placebo in the cancer population and there is weak evidence (small sample size, limited scope) with comparison to morphine. Studies demonstrate equipotent efficacy in treating mild pain when comparing methadone to morphine or transdermal fentanyl with comparable associated side effects.[32,39]

Evidence Evaluation and Best Practice Statement

- Methadone should be considered when other opioids are ineffective, or additional NMDA or serotonin receptor modulation is desired. II-3 C
- Dosing initiation is dependent on opioid tolerance with low introductory doses for naive patients. II-3 B
- For opioid tolerant patients a conservative approach is recommended starting at 75–90% less than the calculated equianalgesic dose using 1:15 to 1:20 conversion factor. II-3 A

Ketamine

Ketamine exerts its effects on multiple receptors and pain pathways. The primary mechanism of action is through non-competitive NMDA receptor antagonism.[40] The NMDA receptor has been demonstrated to be involved in the development of opioid tolerance. Ketamine has been shown in animal models to prevent fentanyl-induced hyperalgesia and subsequent acute morphine tolerance.[40,41] Ketamine has been shown to activate the mu, delta and kappa opioid receptors and is not reliably reversed with naloxone.[42] Ketamine activates descending inhibitory pathways and inhibits presynaptic neurons in the dorsal horn, thereby enhancing endogenous pain inhibition.[42,43] Ketamine can be administered via multiple routes including intravenous (IV), intranasal, intramuscularly and oral. Oral bioavailability is 10–20% given first-pass metabolism.[41]

Ketamine related side effects are primarily dissociative in origin, including dysphoria, hallucinations, evoked nystagmus and altered perception. Other side effects include nausea, vomiting, elevated liver enzymes, hematuria, dysuria, hypertension and tachycardia.[44] These side effects were rarely reported in the studies utilizing sub-anesthetic doses of ketamine for pain management. Utilizing lower doses of ketamine, careful titration, and concomitant benzodiazepines or alpha-2 agonists are helpful in mitigating these side effects should they occur.[41,44] Prior to initiation, patients should be carefully evaluated for elevated cardiovascular and cerebrovascular risk factors. For patients undergoing an IV protocol, continuous hemodynamic monitoring is required. Patients should be counselled regarding residual psychotropic effects which may occur following infusions.

The use of ketamine in cancer pain remains limited to a few RCTs with varying results in the literature.[45–48] The National Comprehensive Cancer Network and European Society for Medical Oncology guidelines on adult cancer pain management recommend considering oral or IV ketamine for refractory pain not responding to other analgesics, or adjuvants. It may also be considered in patients with central sensitization and for palliative treatment of neuropathic pain.[49,50] A Cochrane review in 2017 found insufficient evidence to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of refractory cancer pain, which was a similar finding from the systematic review by Jonkman et al.[51,52]

There is currently an absence of conclusive evidence for ketamine as an adjuvant analgesic in cancer pain as the data remains mixed.

Evidence Evaluation and Best Practice Statement

- Ketamine therapy for cancer pain should be considered on a case-by-case basis for refractory neuropathic, bone, and mucositis-related pain. II-1 B

Radiotherapy, Radioisotopes, and Bone-Modifying Agents for Metastasis

Metastatic bone disease is a significant source of morbidity and is a common manifestation of advanced cancer, particularly primary malignancies of the prostate, lung, and breast. The most common sites of metastases include the spine and sacrum, with patients often presenting with pain, pathologic fractures, and spinal cord compression.

External beam radiation therapy (EBRT) is perhaps the most common treatment modality for painful metastatic disease, with short fractionated regimens now being favored over more protracted schedules. A single treatment fraction of 8 Gray (Gy) has been demonstrated to provide equivalent pain relief as conventional 30 Gy treatments delivered in 10 treatment fractions.[53] Stereotactic body radiation therapy (SBRT), which employs multiple beams of radiation to provide highly conformal treatment, may be preferred for patients with radio-resistant cancers (ie, melanoma) or those with oligometastatic disease.[54]

Radiopharmaceutical therapy is reserved for patients who have failed traditional radiotherapy or those with polymetastatic disease who are not candidates for palliative radiation. These agents are administered IV and selectively irradiate sites of metastatic bone involvement. The most commonly used radioisotopes include samarium-153 (153Sm), strontium-89 (89Sr), and radium-223 (223-Ra). Radium-223 is generally reserved for patients with multifocal disease from castration-resistant prostate cancer, while samarium-153 and strontium-89 may be used for other cancers. Most of the treatment efficacy data for radioisotope therapy is found in patients with metastatic prostate and breast cancer; therefore, its true clinical utility for other malignancies is unknown.[55]

Bisphosphonates and denosumab may also be used for painful metastatic disease. These agents inhibit osteoclast-mediated bone resorption, potentially reducing the risk of bone fracture and related bone pain. In a Cochrane review of patients with metastatic breast cancer, bisphosphonates were demonstrated to significantly improve pain scores.[56] The analgesic potential of osteoclast inhibitors has been questioned for other cancers, particularly in patients with non-small cell lung cancer where a systematic review showed no high-level evidence that these agents reduce pain or improve quality of life metrics.[57] The use of calcitonin to reduce metastatic bone pain is also controversial, with limited evidence supporting its use.[58]

Evidence Evaluation and Best Practice Statement

- External beam radiation therapy with short, fractionated regimens are favored over conventional protracted schedules for painful metastatic bone disease. Stereotactic body radiation therapy may be preferred for radio-resistant cancers or oligometastatic disease. I-A
- There is evidence for the use of osteoclast inhibitors, though it has not been found to be effective for some cancers, such as metastatic non-small cell lung cancer. Therefore, these agents should be used as an adjuvant treatment and considered on a case-by-case basis. II-1 B

Blocks and Neurolysis

Sympathetic blocks and neurolysis are often utilized for intractable visceral cancer-related pain. A variety of neural structures may be targeted based on the location of the primary malignancy or distant metastasis responsible for the pain presentation. Fluoroscopy, ultrasound, and computed tomography are commonly used to aid with procedural guidance and to ensure accurate needle placement near the target location. Diagnostic blockade helps identify likely pain generators and differentiate between visceral versus somatic origins of pain. The upper abdominal structures (including the gastrointestinal tract from the esophagus to transverse colon, pancreas, liver, spleen adrenals, ureters, and abdominal vessels) are supplied by the celiac plexus, while the lower abdominal and pelvic structures (including the bladder, prostate, testes, seminal vesicles, descending and sigmoid colon, uterus, ovaries, vaginal

fundus, and rectum) are supplied by the superior hypogastric plexus.[59] The ganglion impar supplies the perineum, distal rectum and anus, distal urethra, vulva, and distal third of the vagina.[59]

Celiac Plexus

The greater, lesser, and the least splanchnic nerves form the celiac plexus.[60] The celiac plexus is located around the celiac artery and the superior mesenteric artery root. It is retroperitoneally located posterior to the stomach and pancreas, and anterior to the diaphragm. It is most commonly located and targeted at the level of the L1 vertebral body. However, its location may vary between the inferior aspect of the T12 vertebral body to the superior aspect of the L1 vertebral body.[60] Various posterior percutaneous approaches for celiac plexus neurolysis have been described, including transaortic, antecrural, retrocrural, and splanchnic, based on the vertebral body level and final location of the needle tip.[61,62] An anterior endoscopic transgastric approach can be performed by gastroenterologists,[63–65] as well as percutaneously via ultrasound.[66] Intraoperative approaches have been described during diagnostic laparoscopic staging[67] or exploratory surgical resection/palliation.[68] The celiac ganglion supplies efferent sympathetic tone to the gastrointestinal tract; thus, celiac plexus blockade may result in temporary orthostatic hypotension and diarrhea due to unopposed parasympathetic action. Other potential complications include retroperitoneal hematoma, local anesthetic toxicity, renal injury, and pneumothorax.[69] The risk of potentially serious neurological complications is less than 1%, as reported in a survey of 2730 celiac neurolysis procedures in England and Wales; however, none were reported in the RCTs.[70,71] Paraplegia can potentially result from direct trauma to the spinal cord or the artery of Adamkiewicz by the needle or the neurolytic agent.[69] A case of irreversible paraplegia after endoscopic ultrasound-guided celiac plexus neurolysis has been reported due to concomitant embolic occlusion of the artery of Adamkiewicz leading to spinal cord ischemia.[72] Fluoroscopic guided procedures offer the advantage of using live contrast flow and digital subtraction angiography, which can help identify vascular uptake.[73]

A systematic review conducted by Nagels et al concluded that percutaneous celiac plexus neurolysis

significantly improves pain in patients with upper abdominal cancer with a concomitant decrease in opioid consumption and side effects.[69] There are several studies evaluating the efficacy of celiac plexus neurolysis for abdominal cancer-related pain, which show better analgesia and reduced opioid consumption with the neurolysis compared to conventional medical management.[70,74–76] Although an RCT by Wong et al[70] did not find any difference in the quality of life (QOL), an RCT done by Kawamata found that celiac neurolysis prevented deterioration in QOL by the long-lasting analgesic effects.[77] Furthermore, an RCT comparing celiac neurolysis combined with local tumor ablation versus celiac neurolysis alone demonstrated superior pain relief and better survival.[78]

An RCT done by Amr et al found that patients randomized to celiac neurolysis before Step 2 on the WHO analgesic ladder had better pain control and quality of life compared to those who were randomized to receive celiac neurolysis after they failed to achieve analgesia with Step 3 on WHO analgesic ladder.[79] De Olivera et al studied the effects of neurolysis in patients taking less than 90 morphine milligram equivalents versus patients on greater than 90 morphine milligram equivalents) and found no difference in analgesic efficacy or QOL between the two groups.[80] Intra-operative celiac plexus neurolysis (in patients with suspected pancreatic cancer who underwent exploratory laparotomy and found to have histologically proven, unresectable pancreatic cancer) was associated with better analgesia, elevated mood, reduced pain interference, as well as increased life expectancy, compared to saline placebo in an RCT by Staats et al.[68,71] However, no difference in QOL or survival was shown in an RCT comparing the effects of early endoscopic celiac neurolysis done during diagnostic endoscopic ultrasound versus conventional medical management.[81]

Although several studies looking at different approaches to celiac neurolysis found no difference in results,[61,82–84] an RCT done by Ozyalcin et al suggests that splanchnic neurolysis has superior results compared to celiac plexus neurolysis for pancreatic body and tail cancer.[62] Dehydrated alcohol is the most commonly used agent and has been theorized to perform better for neurolytic procedures that must disrupt diffuse neuronal networks.[85] Various volumes of neurolytic medications

have been used for chemical celiac neurolysis ranging from 15 to 50 mL of 50–100% alcohol.[75] An RCT done by Dolly et al to evaluate the efficacy of different volumes (20, 30, and 40 mL) of 70% alcohol found that pain relief, QOL, and reduction in opioids increased with increasing volume, with 40 mL being most effective of the three volumes studied. Recently, a few studies comparing endoscopic ultrasound guided celiac plexus radiofrequency ablation to alcohol neurolysis have demonstrated better outcomes with radiofrequency ablation.[86,87]

Superior Hypogastric Plexus

Plancarte et al first described the classical technique of superior hypogastric plexus (SHP) neurolysis with fluoroscopically guided bilateral needle insertion at the levels of L5 and S1. In 227 patients with pelvic pain from an oncologic source, 70–90% of the patients achieved significant pain relief.[59] Most recently in 2019, Hou et al conducted a retrospective study on 46 patients who underwent an SHP block for pelvic pain related to malignancy, and they found a significant reduction in pain score, anxiety, and an increase in appetite.[88] The largest retrospective study done to date was recently published. One hundred and eighty patients with malignant pelvic pain underwent SPH neurolysis via fluoroscopic technique and obtained a 48% VAS score decrease and 55% decrease in opioid consumption that persisted at 3 months.[89] Mishra et al conducted the only randomized, controlled trial to date in 2013 in 50 patients with severe malignant pelvic pain randomized into either the interventional group (ultrasound-guided SPH neurolysis) or an opioid-only group. They found a greater than 50% reduction in VAS scores and opioid consumption that persisted at 2 and 3 months respectively in the interventional group compared to the opioid-only group.[90] In 2020, a study combining SPH neurolysis with a pulsed radiofrequency ablation of the S2 and S3 nerve roots demonstrated moderately better pain control than SHP alone early in treatment but had equivalent results at 6 months.[91]

Two recent review articles stated that while there are many safe and efficient ways to block the superior hypogastric plexus with varying results, there have been minimal large, prospective, randomized studies proving efficacy.[92] Mercadante et al in a 2015 systematic review and EAPC recommendations stated that given the current data, there is weak recommendation for using superior hypogastric plexus neurolysis for malignant pelvic pain.[92] The newest data, as presented above, continue to highlight the potential benefits of superior hypogastric plexus neurolysis for malignant pelvic pain, yet the area still lacks large, prospective, randomized controlled trials.

Ganglion Impar Block

The ganglion impar or the ganglion of Walther is a solitary ganglion located on the anterior surface of the sacrum. It provides the nociceptive and sympathetic supply to the perineum, distal rectum, perianal region, distal urethra, vulva/scrotum, and the distal third of the vagina.[93] The ganglion impar nerve block was first described by Plancarte et al in 1990, initially to treat sympathetic pain of malignant origin utilizing an anococcygeal approach under fluoroscopy.[59] Since then, it has been largely used to treat many non-malignant forms of pain, especially intractable perineal pain and coccygodynia, but is also utilized in the management of intractable pain resulting from rectal, anal, vulvar or other perineal cancers.[94]

Ganglion impar block or neurolysis is most commonly performed using a percutaneous transcoccygeal approach with fluoroscopic guidance as it provides a shorter needle path and a more direct approach.[95] Other anatomical approaches have also been described such as intercoccygeal joint approaches and paracoccygeal approaches if the sacrococcygeal joint or intercoccygeal joints are fused or there is an impediment to a direct approach.[95] It is most commonly performed with fluoroscopic guidance but has been described with CT, and ultrasound guidance.[96,97]

Data regarding the efficacy of neurolytic ganglion impar block in a purely oncologic population is limited to case reports and case series; however, these have consistently shown improved pain with no significant adverse effects. Plancarte et al reported on 16 patients with advanced malignancies and significant pelvic pain, and found a 60% improvement in pain symptoms following neurolytic ganglion impar block.[59] In 2008, Eker et al described a pain improvement of greater than 60% after completion of ganglion impar block in three patients diagnosed with malignant rectal neoplasia and perineal pain.[98] Another study published in 2012 described six patients with pelvic or gastrointestinal carcinomas of advanced stages, whom obtained significant pain relief following ganglion impar block, which was sustained at 2 months.[99]

In addition, studies with mixed non-oncologic and oncologic populations undergoing ganglion impar neurolysis or block have reported good outcomes. Toshniwal et al conducted a prospective observational study, which included 16 patients with mixed chronic perineal pain of both malignant and benign origin. Patients underwent the trans-sacrococcygeal approach under fluoroscopic guidance, and achieved pain reductions of greater than 50% at the two-month follow-up period.[100] In 2009, Agarwal-Kozlowski et al demonstrated a statistically significant reduction of pelvic pain in a retrospective review of 43 patients with mixed malignant and non-malignant refractory pelvic and perineal pain who underwent CT guided ganglion impar neurolysis. The authors reported a 75% decrease in VAS at 4-month follow-up.[97]

The complications of ganglion impar nerve block or neurolysis are infrequent, and include motor, sexual, bladder, bowel dysfunction, and perforation of the rectum.[101] Ganglion impar nerve blocks and neurolysis, while lacking RCTs in perineal oncologic pain, has been shown to be effective and safe in helping with these pain conditions.

Evidence Evaluation and Best Practice Statement

- Celiac plexus neurolysis should be performed for pancreatic cancer-related moderate-to-severe abdominal pain that is refractory to analgesics. I-A
- Splanchnic neurolysis should be considered in patients with intractable abdominal cancer-related pain due to advanced body and tail located pancreatic cancer. I-B
- Early neurolysis is associated with better outcomes. II3-B
- Superior hypogastric plexus neurolysis should be considered in patients with intractable pelvic cancer-related pain. II-B
- Ganglion impar neurolysis should be considered in patients with intractable perineal cancer-related pain. III-B

Epidural and Intrathecal Analgesia

Intrathecal analgesia via an implanted pump is indicated when cancer pain is severe despite adequate trials of conventional medication or when dose-limiting side effects are present. Randomized controlled trials,[102,103] prospective studies[15,104–106] and systematic reviews[107] have demonstrated analgesic efficacy and side effect reduction.

Cost-effectiveness has also been established in a large US payer database.[13]

Pharmacokinetics of Intrathecal Opioids

An important advantage of delivering opioids intrathecally is a reduction in opioid-related side effects.[102] Targeted drug delivery allows the elimination or reduction of oral opioids in addition to dramatic reductions in serum opioid levels.[104] In the swine model, intrathecal morphine and hydromorphone tend to enter the spinal cord rather than entering the systemic circulation because of their relative hydrophilic properties (with respect to fentanyl and other lipophilic opioids).[108] This is further supported in the swine model which showed a relatively focal intrathecal spread of morphine restricted to 5–10 cm caudad and cephalad.[109] Thus, in the clinical model, we expect morphine and hydromorphone infusions to act on the spinal cord near the location of the catheter tip. However, based on computer modelling data, dispersion of the opioid may be influenced by the flow rate and injectate velocity of the solution from the intrathecal pump.[110] More importantly, dispersion of the opioid in cerebrospinal fluid (CSF) seems to be more related to the cardiac cycle rather than other physiologic systems (ie, respiration).[111] Thus, catheter location, injectate velocity, cardiac cycle variables, and properties of the opioid are the most important variables in determining the kinetics and dispersion of an opioid within the CSF and intrathecal space.

Trial Procedure in Cancer Pain

Trialing practices are controversial and have questionable utility in the cancer pain setting with recent guidelines stating that trialing should be optional.[112] There have been no prospective studies to support trialing in cancer pain and recent studies of IDD in cancer pain typically did

Table 3 Advantages and Disadvantages of Intrathecal Trialing in Cancer Pain

Disadvantages of Intrathecal Trialing	Advantages of Intrathecal Trialing
• Delays definitive therapy in a population with limited life expectancy • Many cancer patients are on anticoagulation; trialing requires an additional discontinuation of anticoagulation therapy and increased risk of thromboembolic events. • Additional risk of trial • Additional cost • Inpatient trials are laborious	• Payor authorization • Assessment of efficacy in the reluctant patient • Assess for tolerability

not trial.[104,105] A pump manufacturer database demonstrates that only 21.6% of cancer pain patients received a trial before implant.[113]

With level I evidence supporting the efficacy of IDDS, as well as compelling cost-effectiveness data, trialing should be considered discretionary based upon factors such clinician preference, patient population, referral patterns, and the payor environment. Selected payors still require a trial before approving coverage for an IDDS, but many will waive this in the setting of cancer pain (Table 3).

In certain scenarios, trialing may have utility to help assess the individual patient's response to the therapy, including analgesia, side effects, functional improvement, and appropriate starting doses after implantation.

Trials can be performed via single bolus injections, intermittent boluses with an indwelling catheter, and continuous infusions. No trialing methodology has been found to be superior for predicting long-term success.[112,114] Therefore, the decision of which modality to utilize is often dependent on the provider's practice setting and preferences. Single intrathecal bolus trials are usually done in an outpatient setting and are perhaps the most cost-effective method. Limitations include short duration of action and an inability to target particular dermatomes. Catheter trials, with placement in the intrathecal or epidural space, typically require an inpatient admission and allow for dose titration at a targeted dermatome. Multiple medications can also be trialed during the same hospitalization. This may be preferred for patients where opioid tolerability is a concern. It is important to point out that intrathecal trials have not been proven to better simulate a permanent system, though epidural infusions may overestimate starting intrathecal dosages.[112,115] Additionally, patients undergoing indwelling catheter trials receive high flow and bolus drug delivery, which will result in more widespread dissemination of the injectate and will not effectively predict the very low flow therapy provided by an implantable system. Trialing practices for cancer pain syndromes remain diverse, and efforts are currently being undertaken to evaluate the necessity and best practices of trialing to establish more uniform practice habits.

Managing Chronic Opioid Therapy in the Setting of a Trial Procedure

In the non-cancer pain population, it has been suggested that tapering of systemic opioids prior to intrathecal pump implant may improve outcomes.[112,116] However, in the patient with cancer-associated pain, it is impractical and unethical to withhold analgesics prior to initiating IDD. The literature supporting IDD for cancer pain does not discuss tapering systemic opioids prior to implantation.[102,105,117] Recent studies have demonstrated the ability to safely and effectively discontinue systemic opioids in the perioperative period and transition exclusively to IDD.[118]

In a situation where systemic opioids are causing a concerning level of sedation hospital admission should be arranged for monitoring and consideration for interventional pain management options that may permit improved pain control with reduced systemic opioid doses. There may be instances when the patient is on extraordinarily high doses of opioids with concern for opiate-induced hyperalgesia in whom the intent of initiating IDD will be to reduce systemic opioid levels while introducing nonopioid analgesics such as ziconotide,[119] local anesthetics, or clonidine.

Implant Considerations

Variable rate intrathecal pumps consist of a battery and integrated microelectronic circuits that control drug delivery. These pumps allow drug delivery rates to be changed as needed, and for the provision of patient-administered bolusing. The two most popular commercially available variable rate pumps are peristaltic continuous pumps (Synchromed II Pump, Medtronic Inc., Minneapolis, MN, USA) and valve-

Table 4 Recommended Intrathecal Catheter Tip Location Based on Pain Location

Pain Location	Vertebral Body Catheter Tip Location
Brachial plexus	C3-5
Arm	C3-5
Breast	T1-2
Upper chest wall	T3-4
Visceral abdomen	T5-6
Lower chest wall	T6-7
Abdominal wall	T6-7
Pelvis	T9-12
Leg	T10
Sacral	Vertebral body at level of conus

Note: Reproduced from Chen GH, Spiegel MA, Magram YC, et al. Evaluation of fixed intrathecal bupivacaine infusion doses in the oncologic population. *Neuromodulation*. 2020;23(7):984–990. © 2020 International Neuromodulation Society, with permission from John Wiley and Sons.[121]

gated pumps (Prometra Intrathecal Drug Delivery System, Flowonix Medical Inc., Mount Olive, NJ, USA). Peristaltic pumps consist of a roller geared rotor system that delivers reservoir medications by a peristaltic sequence to an intrathecal catheter.[116] A low-pressure reservoir and its rollers occlude the plastic tubing at multiple points along the catheter to control flow of fluid. The pump reservoir is called a metal bellows reservoir, which contains medications, and there is pressurized gas surrounding these bellows. The pressurized gas exerts pressure on the bellows, changing the volume depending on the volume of the drug present.

Valve-gated pumps use a positive-pressure design with two microvalves (inlet and outlet), a dosing chamber, and a flow-activated valve.[120] Medications are delivered through a precision dosing system not susceptible to external factors like pressure or temperature. It is hypothesized that this positive pressure, valve-gated system reduces granuloma formation and prevents corrosion with combination therapy within the drug reservoir.

The location of the catheter tip for different cancer pain generators is often debated. The 2017 PACC guidelines recommend placing the tip around the spinal dermatome associated with the source of the pain.[116] A recent publication provided level-specific bupivacaine dose recommendations based on the pain location (Table 4).[121]

Intrathecal Medications

The Food and Drug Administration (FDA) has approved three medications for intrathecal use: morphine, ziconotide, and baclofen. However, other medications are commonly and safely used within the intrathecal space such as fentanyl, sufentanil, hydromorphone, bupivacaine, and clonidine. The 2017 PACC guidelines recommend that off-label drugs should be tried after FDA-approved drugs are attempted and failed or are contraindicated.[117] It is important to note that these guidelines were not specific for cancer-associated pain and many centers utilize a combination of opioid and local anesthetic often at a ratio of 1:2 or 1:3 to optimize analgesia for poorly controlled malignant pain.

Total Daily Dose of IT Medication

Starting intrathecal opioid doses may vary widely depending on the patient's baseline opioid intake. Sindt et al suggest that the initial daily intrathecal dose following implantation of a permanent system be calculated using a ratio of 100:1 of the patient's daily oral morphine equivalent dose prior to implant assuming all systemic opioids are discontinued.[118] If appropriate, demand doses

can also be programmed at 10% of the daily intrathecal dose for up to 24 additional hourly doses while the patient is admitted, which is then decreased to a maximum 12 daily activations upon discharge. The PACC guidelines recommend that the daily initiating intrathecal dose be 50% or less of the successful trial dose if an intrathecal trial was performed, with demand dosages of 5–20% of the total daily dose.[116] Other factors that should be considered when determining initial intrathecal doses include risks of cardiopulmonary depression and whether the patient will be admitted to the hospital for observation. Based on clinical experience, a conversion of 10:1 can be considered for epidural trial to intrathecal dosing. Regardless, conservative dosing strategies are typically recommended.

Intrathecal Drug Delivery: Complications, Management, and Considerations

Pharmacological complications include cardiopulmonary depression, anaphylaxis, and meningitis with introduction of contaminated solution. While complication are rare, potential complications include catheter tip granuloma formation, bleeding complications, infection risks, and complications related to surgical management. Other adverse effects include opioid-induced hyperalgesia, hypotension, inflammatory mass, hypogonadotropic hypogonadism, immunologic compromise, headaches, seromas, hygromas, and bacterial meningitis. Risk factors that lead to higher complication rates include underlying psychological issues, obstructive sleep apnea, immunosuppression, smoking, diabetes mellitus, active infections, bleeding disorders, and anticoagulation therapy. The annual rate for IDDS complication requiring surgical intervention is 10.5%, with 35% being pump related and 65% catheter related.[102,116,122]

Cancer Pain–Specific IDD Considerations

Cancer patients are likely to undergo radiation and chemotherapy that may impact IDD. However, there are many factors to consider when ensuring patient safety, such as absolute neutrophil count greater than 500/μL and platelet counts greater than 80,000/uL when addressing candidacy for pump placement with concurrent chemotherapy.

A single-center retrospective review of 88 patients with IDDS receiving radiation therapy (0–18.0 Gy) demonstrated no incidence of IDDS malfunction related to RT.[123] While there is limited evidence demonstrating adverse effects of radiation exposure on IDD systems,

there are reports of battery drain or electric failure of the implanted device if the pump is directly within the field of radiation.[102,116,122]

Epidural or spinal metastases are not an absolute contraindication to placement of IDDS, but these lesions may affect device efficacy and increase complication rates of neuraxial treatments.

Intrathecal Catheter Tip Granuloma Formation

Intrathecal catheter tip granulomas can produce potentially irreversible neurologic sequelae. The prevalence of granuloma formation may be as high as 8%. Medications shown to cause catheter tip granulomas include morphine, hydromorphone, sufentanil, bupivacaine, and baclofen. Granuloma formation is more likely to occur with low flow rates and has been demonstrated to be dose and concentration dependent. Ziconotide has not been shown to cause intrathecal granuloma. MRI with and without contrast, CT myelogram, or a dye study into the catheter side-port can detect a granuloma typically by identifying a filling defect around the catheter tip.[102,116,122,124,125]

Bleeding Considerations

Intrathecal catheter and pump implant is defined as a high-risk procedure for potential serious neuraxial bleeding.[126] The incidence of spinal hematoma associated with intrathecal therapy is not well defined.[102,116,122,124,125] However, epidural hematoma has a reported incidence of 0.75% for percutaneous placement of SCS. In regards to the pump pocket site, we extrapolate from the cardiac device literature, where 2.2% of implantable cardioverter defibrillators demonstrated clinically significant pocket hematoma.[102,116,122,124,125]

Infection

Pocket and lumbar site infection, meningitis, and encephalitis are primary infection concerns with IDD. Factors associated with surgical site infections (SSI) include anemia, tobacco smoking, diabetes mellitus, cancer, malnutrition, obesity, cardiovascular disease, and immunosuppression. Cancer treatments, including corticosteroids and chemotherapy, may cause increased risk for SSI. The incidence of infections in IDD has been found to be 0.7–3.2% per year.[102,116,122,124,125] A recent retrospective review in a large cancer center showed an infection incidence of 0.9% despite frequent concurrent cancer treatment and leukopenia.[127] In other studies, the incidence of infection in the cancer patient population was 2.7–3.2%.[128,129]

Table 5 IDDS Pump-Related Complications

Causes of Pump Failure
Change in performance or failure of the catheter • Micro-fracture • Pinhole leak • Disconnection • Breakage • Migration • Partial occlusion • Tip fibrosis/granuloma • Inflammatory mass
Unexpected battery depletion
Component or motor failure
Catheter access port failure

Note: Reproduced with permission from Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol.* 2002;20(19):4040–4049[102] https://ascopubs.org/journal/jco.

Table 6 Diagnostic Approach to IDDS Failure

Initial evaluation, including patient history will often identify the source of the problem
Verification of pump contents, volume and pump setting is the critical initial step
Plain x-ray (PA and Lateral to visualize the entire catheter)
Serial x-ray or fluoroscopy to confirm that the pump roller is moving at the expected rate
Magnetic resonance imaging (MRI) study
Catheter access port aspiration
Nuclear medicine scan
Fluid collection assay

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Surgical and Technical Complications

Post-dural puncture headache (PDPH) occurs in 15.5% of the patients and CSF hygromas (pseudomeningocele) occur in 1.5%.[102,116,122,124,125] Pocket site seroma is another possible complication. Seroma formation following IDD may be managed conservatively by using a pressure dressing and an abdominal binder for a number of weeks with serial follow-up to assess for resorption. If without improvement,

sterile aspiration may be performed. Diagnostic glucose testing and fluid analysis can help differentiate between third space fluid due to seroma formation versus CSF accumulation. In rare cases, surgical evacuation and revision may be necessary for definitive treatment.[102,116,122,124,125]

Catheter and Pump Complications

The most common complications of IDD are catheter-related malfunctions. This includes catheter tip migration, kinking, occlusion, fracture, and loosening of connections. Studies have shown the incidence of catheter migration is 7.3%, catheter tear 6.4%, and catheter occlusion 1.8%.[122] Pump-related complications such as motor stalls, over or under infusion, corrosion, and gear wear may occur to a lesser degree. The incidence of a motor stall has been reported to be 0.28% at 48 months and 0.69% at 84 months post-implantation.[122] The risk of IDD over-infusion is 0.16%.[122]

An algorithmic approach to pump and catheter dysfunction as well as subsequent interrogation is demonstrated in Tables 5 and 6.

MRI Following IDDS Implantation

Magnetic resonance imaging is often necessary with ongoing cancer treatments or for other non-cancer-related issues. The two commonly utilized intrathecal pump systems (Medtronic SynchroMed II and Flowonix Prometra II) have MRI Conditional labelling.[130] They are considered compatible with MRI when specific parameters are followed as specified by the device manufacturers. MRI safety profiles are found on each manufactures website and in online searchable databases. It is important to recognize that device malfunction can still occur during scanning and may pose a potential safety hazard for medication overdose or withdrawal.

The Medtronic SynchroMed II is labeled MRI conditional at 1.5 and 3.0 Tesla. Before MRI, the therapy should be discontinued, and restarted after the scan. If therapy is not discontinued, a "motor stall event" will occur with automatic restart within 30 minutes of the scan. It is recommended to interrogate the system within 24 hours after MRI to ensure the pump has restarted appropriately.[131]

The Prometra II pump is labelled MRI conditional at 1.5 Tesla and it requires pre-MRI discontinuation of therapy, emptying the medication from the pump reservoir, followed by a post-MRI interrogation, pump reservoir refill and re-initiation of therapy.[132]

Evidence Evaluation and Best Practice Statement

One multicenter, randomized controlled trial of programmable IDDS added to comprehensive medical management (CMM) versus CMM alone was analyzed, consisting of a six-month follow-up period.[102] Evidence from this study suggested that the use of IDDS plus CMM reduces overall drug toxicity over a 12-week period when compared with CMM alone; however, no statistically significant difference was observed in pain scores. For the composite outcome of reduction in pain and drug toxicity, evidence favoured the use of IDDS.

A retrospective review of cancer patients compared the economic burden CMM to targeted drug delivery with CMM over a seven-year period. The IDDS plus CMM group had significant reduction in healthcare utilization due to intractable pain as reflected by fewer inpatient visits and shorter hospital stays, and overall cost savings. A total of 536 patients met criteria for review, 268 patients in TDD and CMM and 268 patients in CMM group. A mean total cost savings of $15,142 was found at 2 months and $64,498 at 12 months. The use of CMM alone was also associated with higher dose of opioid use at 12 months.[13]

In another study on cost-effectiveness, Brogan et al assessed patients with cancer-related chronic pain before pump placement and 4–6 weeks after pump implant.[133] Patients were stratified into high-cost drug therapy (ie, parenteral drugs, high-dose opioids), and low-cost drug therapy (all others). With an average cost of pump placement estimated to be $35,601, economic evidence suggested that IDDS had the potential to be more cost-effective than high-cost oral therapy if administered for 7 months or longer.

- Intrathecal drug delivery using an implantable pump should be strongly considered in patients with cancer-related pain that is not responding to, or who develop side effects from conventional medical management. I-A
- Trialing before intrathecal pump implantation for cancer-related pain should be at the discretion of the physician and patient. It is not a requirement. III-C

Spinal Cord Stimulation
Indications for Use

The most common indications for SCS are complex regional pain syndrome (CRPS) Types I and II, post-

laminectomy syndrome, chronic radiculopathy, intractable neuropathic pain, and visceral pain.[134] While treatment of cancer-related pain is often focused on symptoms explicitly related to the primary malignant diagnosis, true supportive care and palliative care should include all treatments that may improve QOL.[135] Cancer patients remain susceptible to all non-cancer-related pain pathologies. With the increase of MRI compatible technologies, we must ensure that patients are not excluded from evidence-based therapies because of their malignant diagnosis. This includes access to evidence-based use of neuromodulation for non-cancer-related syndromes.[136]

In addition, adverse effects of many cancer treatments are amenable to SCS. With five-year cancer survival rates for all cancer diagnoses increasing from 50.3% to 67% over the past 20 years, more patients are living with the chronic pain resulting from effective cancer treatments.[137] Fifty-two percent of patients exposed to neurotoxic chemotherapeutic agents develop chemotherapy-induced peripheral neuropathy (CIPN) with median time to symptom development of 71 days.[138] Many case reports demonstrate effective treatment of CIPN with SCS, but currently there are no RCTs demonstrating efficacy.[139–141] Early bench research has shown the role of SCS in preventing CIPN. Sivanesan et al demonstrated that SCS may attenuate CIPN pain-related behavior in rats prior to treatment with paclitaxel.[142] While more studies are needed, with few proven effective pharmaceutical treatments and continued improvements in technology, SCS is a viable treatment option for refractory CIPN.

Many patients with abdominal, gynecologic, and orthopedic cancer require surgical treatment which may result in nerve damage and subsequent neuropathic pain, post-surgical pain, or peripheral causalgia. A recent publication by Hagedorn et al reviewed the use of SCS for cancer-related pain, both cancer- and treatment-related pain.[17] In general, the literature regarding SCS for the treatment of cancer-related pain is largely represented by case reports and small case series. In 2010, Yakovlev et al reported on 14 patients with lung cancer who underwent SCS for post-surgical pain. At 12 months post-implant, all patients had greater than 50% VAS pain reduction, and all patients had decreased or discontinued pain medications.[143] In 2012, Yakovlev et al described 15 patients with treatment-related low back

pain after undergoing treatments for metastatic colon cancer, anal cancer, or angiosarcoma of the sacrum. At 12 months post-implant, all patients had greater than 50% pain relief and 86% had decreased or discontinued pain medications. In the largest patient cohort to date, Shimoji et al published a retrospective review of 52 patients with carcinoma or sarcoma of the head/face, neck/upper extremities, trunk, or lower extremities. The authors reported that while the subjects obtained 80% pain relief initially, this decreased to 20% pain relief at 1 year.[144]

Extrapolating from non-malignant pain data, both SCS and DRG-S are effective for refractory neuropathic, postsurgical and peripheral causalgia-related pain.[145–148] Also, many patients with primary spinal tumors or metastasis may require laminectomy, decompression, and fusion. Since approximately 30% of the patients develop pain worse than or equal to their pain prior to spine surgery, many of these patients may require treatment for failed back surgery syndrome (FBSS).[149] With high-quality evidence for the treatment of this condition in both post-surgical lumbar and cervical radicular pain, SCS should be considered early in the treatment algorithm for these patients.[150,151]

Device Selection

Cancer patients may require screening MRI for progression of disease or evaluation of new symptoms. With regard to device selection, it is imperative to understand the MRI conditionality of the devices.[130] In the non-cancer population, Desai et al found that 82–84% of SCS-implanted patients were expected to need at least one MRI within 5 years of implant. Within 10 years of implantation, 59–74% of all patients implanted were likely to require non-spine MRI.[152] Additionally, consideration should be given to the degree of patient comfort in maintaining, charging, and programming the implantable pulse generator (IPG).

Evidence Evaluation and Best Practice Statement

- Spinal cord stimulation may be considered in patients with refractory cancer pain. II-3-C
- Spinal cord stimulation may be considered on a case-by-case basis for pain that is related to cancer treatment such as chemotherapy induced peripheral neuropathy. III-C

Vertebral Augmentation and Radiofrequency Ablation

In the United States, it is estimated that up to 30% of all newly diagnosed cancers displayed vertebral metastasis at presentation. Approximately 30–70% of cancer patients will present with back pain complaints related to metastasized spinal tumors often involving multiple levels. This is thought to be due to the high vascularity with anterograde spread and retrograde seeding through the valveless extradural Batson's venous plexus. These tumors cause severe pain via several different mechanisms. Tumor growth within the vertebral body increases pressure on the endosteum triggering an inflammatory cascade. This inflammation, due to chemical mediators, activates nociceptive impulses via intraosseous basivertebral nerves. The vertebral body can also weaken with continued tumor growth resulting in painful pathologic compression fractures.

The clinical manifestations of spinal tumors include localized pain with or without radicular pattern, neurological deficits, and spinal deformities with some patients experiencing no symptoms at all. Appropriate management of spinal metastasis requires a multi-disciplinary approach assessing cancer staging, tumor involvement, spinal instability/deformities, neurological function, number of involved levels, radio- and chemo-sensitivity of the tumor, and patient prognosis.[153]

Vertebral augmentation should be considered for patients with severe pain secondary to pathological vertebral compression fractures.[154] A multicenter, randomized controlled trial of kyphoplasty versus conservative management showed improved function and pain in cancer-related vertebral compression fractures.[155,156] Systematic reviews have also demonstrated improvements in subsequent pain scores, opioid use, and pain-related disability.[157,158] There is little data to suggest the superiority of either kyphoplasty versus vertebroplasty when treating malignant vertebral compression fractures; however, kyphoplasty has a lower risk of cement extravasation and results in greater kyphosis correction.[159]

The use of percutaneous radiofrequency ablation (RFA) with or without cement augmentation is indicated for treatment of back pain from spinal tumors and has proven to be a safe and effective palliative therapy for painful spinal metastasis.[160] The application of RFA in osseous lesions was first described by Rosenthal et al in

1992.[161] Radiofrequency ablation is a well-established percutaneous thermal energy that causes localized necrosis of targeted tissue. The mechanism of pain relief is believed to be due to destruction of the pain transmitting neural tissue and periosteal nociceptors. Levy et al reported data on 100 patients undergoing RFA with cementoplasty for painful spinal metastases in the prospective multicenter international OPuS One Study. There was significant improvement in pain (8.2 ± 1.7 at baseline to 3.5 ± 3.2 at 6 months), pain interference and QOL.[162] The increasing number of prospective studies utilizing RFA with or without cement augmentation continue to demonstrate the safety and efficacy of this treatment with a more rapid rate of pain relief (0–2 weeks) compared to conventional fractionated radiotherapy (4–6) weeks.[163] Current therapies and treatments involve a combination of analgesics, bisphosphonates, and radiotherapy with variable results and many patients experiencing inadequate pain relief. Conventional surgery is associated with high complication rates.[164] Evidence supporting the efficacy of RFA includes retrospective and prospective series demonstrating it to be effective and safe in achieving short- to mid-term (from 1 week to 6 months) analgesia in patients affected by painful spinal metastasis.[165] Vertebral RFA with or without cement augmentation allows for safe, effective, rapid pain reduction, and also enables quick initiation of adjuvant therapies.

Evidence Evaluation and Best Practice Statement

- Vertebral augmentation should be strongly considered for patients with symptomatic vertebral compression fractures from spinal metastases. 1-A
- Percutaneous radiofrequency ablation with or without cement augmentation is indicated for treatment of severe back pain from spinal tumors and has proven to be a safe and effective palliative therapy for painful spinal metastasis. II-2 B

Radiofrequency Lesioning and Nerve Blocks

Radiofrequency ablation and nerve blocks are techniques commonly used and most studied in the treatment of nonmalignant pain. The former involves the application of heat generated from an electrical current to disrupt innervation from a painful anatomic site. In the cancer literature, there are case reports/series of pain relief efficacy in conditions arising from metastatic brachial plexus tumor, head and neck cancer, thoracic vertebral body metastases

and glossopharyngeal neuralgia.[166] The only RCT concluded superior efficacy of RFA lesioning over steroid treatment when applied to the dorsal root ganglion in patients experiencing axial thoracic pain from vertebral metastases.[167] Nerve blocks using corticosteroids targeting the glossopharyngeal nerve in patients with tongue cancer can be considered if the pain is refractory to conventional medical therapy.[168]

Evidence Evaluation and Best Practice Statement

- Consider radiofrequency lesioning of the dorsal root ganglion in the treatment of axial thoracic back pain from vertebral malignant metastases. I C
- For cancer pain unresponsive to medical management, application of nerve blocks using corticosteroid or radiofrequency lesioning to a peripheral nerve can be considered. II-2 C

Surgical Options: CT Guided Radiofrequency Cordotomy, Myelotomy, DREZ-Otomy, and Cingulotomy

Surgical interventions in carefully selected patients remain a valid tool in the management of refractory cancer pain.[169,170]

Surgical cordotomy interrupts the spinothalamic tract and is effective in unilateral nociceptive pain related to direct tissue involvement. It was described by Kanpolat, who performed the procedure percutaneously under CT guidance at the C1-C2 level.[171] Kanpolat also explains that cordotomy can be performed between the occiput and C1 for the lesion of the nucleus tractus to improve head and neck–related malignant pain.[171,172] The procedure is offered to patients with life expectancy of more than 3 months, with no intracranial metastasis or suspicious high intracranial pressure, and intact autonomic nervous system. Procedure complications are mild and transient and may include dysesthesia, mirror pain, motor weakness, urinary retention, and ataxia. The procedure is performed by using RFA between 60°C and 80°C for 60 seconds under intraoperative sensory and motor monitoring. Alternatively, a double channel endoscopic technique has been described with similar efficacy and safety.[173] A recent RCT assessed pain relief in patients with unilateral somatic pain undergoing CT guided cordotomy when compared to palliative care. Primary outcome was pain reduction of 33% or greater.

A total of 85.7% of the patients in the cordotomy group achieved greater than 33% pain relief compared to zero patients in the palliative group. At 1 week, 77.8% of the patients randomized to palliative care opted to cross over to cordotomy and all achieved greater than 33% reduction in pain.[174] According to different case series, the overall pain control was high with up to 80–100% reporting no pain at one month.[175] In another report of 51 patients with cancer-related body or face pain, the initial pain reduction was 98% with 80% sustained pain relief at 6 months.[176] A recent prospective observational case series has demonstrated both reduction in pain and opioid consumption post cordotomy.[177] The incidence of new pain was variable and the underlying pathophysiology is still poorly understood, but progression of the disease and interruption of descending inhibitory pathways may play a role.

Myelotomy is used for abdominal or pelvic visceral pain by interrupting the dorsal columns. It can be performed either open or percutaneous.[178] The open technique is performed under general anesthesia, where T3-T4 levels are approached for upper abdominal pain and T6-T8 for lower abdominal and pelvic pain. Laminectomy and dural opening are the initial steps. A 16-gauge angiocatheter is used to create a 0.5 mm lesion bilaterally from the midline with 5 mm depth.

The percutaneous technique is performed under CT guidance at the occiput-C1 level or at thoracic level using RFA at 70–80 °C for 60 seconds. Complication rate is low.[178] In case series, myelotomy was found to be effective in reducing pain and opioid consumption.[178]

Dorsal root entry zone lesioning or DREZ-otomy is used for limited limb pain. The most common indication is Pancoast tumours, but its indication expands to lumbosacral plexopathy. The procedure is performed via an open technique with intradural approach. A 2–3 mm curved RFA needle is placed under somatosensory evoked potential monitoring.[179] It can provide up to 80% pain relief.

Finally, at late stages of disease and pain control, and if all therapeutic options have failed, stereotactic anterior cingulotomy has shown to be effective in controlling pain.[180,181] It carries cerebral risks, in addition to psychological side effects and cognitive impairment.[182]

Evidence Evaluation and Best Practice Statement

- Cordotomy should be considered for uncontrolled unilateral nociceptive pain after failure of more conservative options. II-B
- Myelotomy is used for infra-diaphragmatic visceral pain for pain control and decrease opioid consumption. III-C
- DREZ-otomy is indicated for focal limb pain and in Pancoast tumors. III–Insufficient
- Cingulotomy is indicated for late-stage and uncontrolled pain refractory to other therapies. III-C

Future Direction: Intrathecal Resiniferatoxin (RTX)

Resiniferatoxin (RTX) is derived from the Euphorbia Resinifera plant and is a potent agonist for transient receptor potential vanilloid 1 (TRPV1) expressed on Aδ and C nerve fibers. Receptor binding prolongs cation channel activation, leading to a large and rapid influx of intracellular calcium. This results in axonal destruction in TPRV1 expressing primary afferent spinal and dorsal root ganglion neurons while effectively sparing motor, proprioceptive and sensory cell bodies that do not express the TPRV1 receptor.[183] Initial animal trials were conducted in a rat model,[184] followed by a study in companion dogs afflicted with advanced bone cancer pain and showed favorable effects.[185]

The first human study of RTX was a single-center, Phase Ib, non-randomized, open-label, dose-escalation study to determine its safety and efficacy in patients with severe refractory pain due to advanced malignancy at or below the level of the chest.[186] In all patients, intrathecal RTX was injected under propofol sedation to prevent the acute pain associated with excitotoxic destruction of TRPV1 neurons. Pre- and post-injection Numeric Rating Scale (NRS) scores, quality of life, quantitative thermal sensation, and safety data were observed. The lower doses of 3–13 µg demonstrated variable pain relief but permitted dose escalation with patients receiving up to 26 µg of RTX into the intrathecal space. Patients who received either 13 µg (n=3) or 26 µg (n=3) injections of RTX reported less pain and improved mobility. Numeric rating scale scores trended lower compared to pretreatment, although the NRS change was statistically insignificant at these doses. Thermal perception reduction was consistent with cell death of the TRPV1 neurons. There were no other sensory or motor changes post-treatment and no changes in EKG, MRI, or eye examination were noted.[186]

This paved the way for the currently ongoing multicenter, open-label, phase 1b trial to assess the safety and establish the maximally tolerated dose of epidural RTX injection for the treatment of intractable pain associated with cancer. Fourteen subjects with intractable cancer pain received a single epidural injection ranging from 0.4 to 35 µg.[187] The primary outcome is to determine the dose limiting toxicity and the maximum tolerated dose. Secondary outcomes include NRS, Brief Pain Inventory-Short Form, and daily analgesic consumption, among others. Interim analysis presented at an annual conference in 2020 reported positive outcomes at doses of 8 µg with no dose limiting toxicity. The most common treatment-related adverse event was transient procedural pain described as a burning sensation in the lower extremities that subsided over several hours.[187] Initial RTX human safety and efficacy data are promising in reducing the burden of cancer-associated intractable pain with minimal adverse effects. As of this publication, a multicenter, blinded, control, Phase 3 clinical is ongoing.

Evidence Evaluation and Best Practice Statement

- RTX is still undergoing safety and efficacy trials. Grade for this treatment class is insufficient

Conclusion

This work provides a succinct clinical overview of conservative medical management for cancer-related pain including opioids, adjuvant mediations, and radiotherapy. We performed a detailed systematic review of all relevant literature for the interventional management of cancer and treatment-associated pain. Limitations of the current manuscript include being confined to the limitations of the available data and methodological differences between studies, including study design and heterogeneity of study populations. However, we have appropriately assessed the quality of evidence, and provided grading and recommendation levels using USPSTF criteria. Best practice statements with grading were made after critical evaluation of the literature (Table 7). The existing best practice and guidelines for therapies such as IDDS and[116] SCS[136] are not specific to cancer-associated pain. This paper bridges the gap between conservative medical management and recently published surgical neuroablative guidelines.[170] We provide clear evidence-based guidance and recommendations on how interventional techniques should be integrated into the management of

Table 7 Best Practices

Therapy	Statement	Evidence Level	Grade
Opioids for cancer pain	Opioids should be considered for moderate to severe cancer-related pain.	I	A
	Opioid agent selection should be individualized to account for the variance in pain presentations and co-existing medical comorbidities.	III	B
Methadone	Methadone should be considered when other opioids are ineffective, or additional NMDA or serotonin receptor modulation is desired.	II-3	C
	Dosing initiation is dependent on opioid tolerance with low introductory doses for naïve patients.	II-3	B
	For opioid tolerant patients a conservative approach is recommended starting at 75–90% less than the calculated equianalgesic dose using 1:15 to 1:20 conversion factor.	II-3	A
Ketamine	Ketamine therapy for cancer pain should be considered on a case-by-case basis for refractory neuropathic, bone, and mucositis-related pain.	II-1	B
Radiotherapy, radioisotopes, and bone-modifying agents for metastasis	External beam radiation therapy with short, fractionated regimens are favored over conventional protracted schedules for painful metastatic bone disease. Stereotactic body radiation therapy may be preferred for radio-resistant cancers or oligometastatic disease.	I	A
	There is evidence for the use of osteoclast inhibitors, though it has not been found to be effective for some cancers, such as metastatic non-small cell lung cancer. Therefore, these agents should be used as an adjuvant treatment and considered on a case-by-case basis	II-1	B
Blocks and neurolysis	Celiac plexus neurolysis should be performed for pancreatic cancer-related abdominal pain.	I	A
	Splanchnic nerves neurolysis should be considered in patients with intractable abdominal cancer-related pain due to advanced body and tail located pancreatic CA.	I	B
	Early neurolysis is associated with better outcomes	II-3	B
	Superior hypogastric plexus neurolysis should be considered in patients with intractable pelvic cancer-related pain.	II	B
	Ganglion impar neurolysis should be considered in patients with intractable perineal cancer-related pain.	III	B
Targeted drug delivery	Intrathecal drug delivery using an implantable pump should be strongly considered in patients with cancer-related pain that is not responding to conventional medical management	I	A
	Trialing before intrathecal pump implantation for cancer-related pain should be optional and at the discretion of the physician and patient.	III	C
Spinal cord stimulation	Spinal cord stimulation may be considered in patients with refractory cancer pain.	II-3	C
	Spinal cord stimulation may be considered on a case-by-case basis for pain that is related to cancer treatment such as chemotherapy induced neuropathy.	III	C
Vertebral augmentation and radiofrequency ablation	Vertebral augmentation should be strongly considered for patients with symptomatic vertebral compression fractures from spinal metastases.	I	A
	Percutaneous radiofrequency ablation with or without cement augmentation is indicated for treatment of severe back pain from spinal tumors and has proven to be a safe and effective palliative therapy for painful spinal metastasis.	II-2	B
Radiofrequency lesioning and nerve blocks	Consider radiofrequency lesioning of the dorsal root ganglion in the treatment of axial thoracic back pain from vertebral malignant metastases.	I	C

(*Continued*)

Table 7 (Continued).

Therapy	Statement	Evidence Level	Grade
	For cancer pain unresponsive to medical management, application of nerve blocks using corticosteroid or radiofrequency lesioning to a peripheral nerve, brachial plexus can be considered.	II-2	C
Surgical options	Cordotomy should be considered for uncontrolled unilateral nociceptive pain after failure of more conservative options.	II	B
	Myelotomy is used for infra-diaphragmatic visceral pain for pain control and decrease opioid consumption.	III	C
	DREZ-otomy is indicated for focal limb pain and in Pancoast tumors.	III	I
	Cingulotomy is indicated for late-stage and uncontrolled pain refractory to other therapies	III	C

cancer-associated pain. When necessary, development of best practice statements in the setting of limited high-quality data is given based upon clinical expertise and scientific discourse between the authors.

Disclosure

MMA is a consultant for Abbott, Bioness, Vertos Medical. TD is a consultant for Abbott, Vertos, Axonics, Flowonix, SpineThera, Saluda Medical, Nalu, Medtronic, Nevro, SI Bone, Stimgenics, SPR Therapeutics, Cornerloc, Boston Scientific, PainTeq, Ethos, and Vertiflex. TD is a member of the advisory board for Abbott, Vertos, Flowonix, Nalu, SPR Therapeutics and Vertiflex. TD has stock options in Bioness, Vertiflex, Axonic, Vertos, SpineThera, Nalu, Cornerloc, PainTeq and SPR Therapeutics. TD has common stock in Saluda Medical. He is a research consultant for Abbott, Vertos, Mainstay Medical, Saluda Medical, SPR Therapeutics, Boston Scientific and Vertiflex. TD has a patent pending for the DRG paddle lead with Abbott. DS is a consultant for Flowonix, Medtronic, Merit, Abbott, Nevro, PainTeq, ans Vertos. JMH is a consultant for Abbott, Boston Scientific, and Nevro. SEB is a consultant for Medtronic. VS is a consultant for Releviate LLC. AG is a consultant for Medtronic, SPR therapeutics, Nalu Medical and serves on the Advisory Board for AIS HealthCare (advisory board) and Spark medical. NHS is a consultant for Abbott. JSW is a consultant for Abbott, Medtronic, Boston Scientific, Vertos, Saluda, PainTeq, Omnia Medical. Research Consultant for Abbott, Saluda. JHG is a consultant for Abbott and Stratus. JHG receives research support from SPR Therapeutics. AV is a consultant for CornerLoc, Vertos, Guidepoint Global. Research consultant for SPR. AEH is consultant for Abbott. AE is a consultant for Abbott, Boston Scientific, Medtronic, Nevro and Vertos Medical. KS is a consultant for Abbott, Boston Scientific, Flowonix, Nevro, Vertos Medical. JS is a consultant for Abbott labs, Executive leadership council for Vertos Medical, Shareholder and Medical Advisory Board for Celeri Health. SN is a consultant for Medtronic and AIS. The authors report no other conflicts of interest in this work.

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