Review

Pain Management

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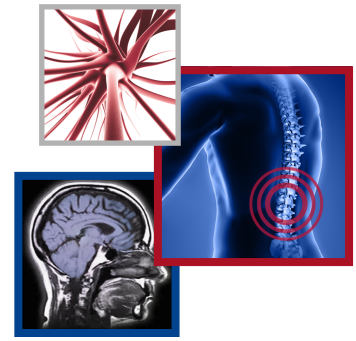

An overview of interventional strategies for the management of oncologic pain

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Practice points

- Pain is a ubiquitous part of the cancer experience.
- An isolated pharmacologic approach to cancer pain management commonly provides suboptimal relief and is limited by intolerable side effects.
- Pain signals can be interrupted at their site of generation, along the afferent nerve, within the sympathetic chain or in the neuroaxis.
- Local anesthetic can provide valuable diagnostic information in addition to temporary relief, while sustained relief can be achieved with the addition of corticosteroid or through neurolysis with cryoablation, chemical denervation or radiofrequency thermocoagulation.
- Precision for targeting nerves within fascial planes may be improved with ultrasound guidance.
- Sympatholysis can provide significant pain relief, improve quality of life and reduce the need for analgesic medication.
- Multidisciplinary collaboration is vital to maximizing treatment of the most refractory cancer pain.
- Neuromodulation is currently the most dynamic area within pain management, but more data are needed before these modalities can be safely and effectively applied to the patient suffering from cancer-related pain.
- There is a need for high-quality data regarding the use of many cancer pain interventions.

Pain is a ubiquitous part of the cancer experience. Often the presenting symptom of malignancy, pain becomes more prevalent in advanced or metastatic disease and often persists despite curative treatment. Although management of cancer pain improved following publication of the WHO's analgesic ladder, when used in isolation, conservative approaches often fail to control pain and are limited by intolerable side effects. Interventional strategies provide an option for managing cancer pain that remains refractory to pharmacologic therapy. The purpose of this review is to investigate these strategies and discuss the risks and benefits which must be weighed when considering their use. Therapies anticipated to have an increasingly important role in the future of cancer pain management are also discussed.

First draft submitted: 2 May 2018; Accepted for publication: 28 June 2018; Published online: 15 October 2018

Keywords: interventional pain management • oncology • pain

Once considered the fourth step of the WHO's analgesic ladder, interventional approaches have assumed a more prominent role in the management of cancer pain as evidence regarding the risk-benefit ratio of chronic opioid use has been elucidated. The WHO guidelines [1] state "neurolytic and neurosurgical blocks may be necessary as a supplementary approach in a small number of cases" but data suggest that conservative management may leave greater unmet need than previously estimated [2].

Pain signals can be interrupted at their site of generation, along the afferent nerve, within the sympathetic chain or in the neuroaxis. Augmenting nociception with local anesthetic can provide diagnostic information and temporary relief. Sustained relief can be achieved with corticosteroid or through neurolysis with cryoablation, chemical denervation or radiofrequency thermocoagulation. The choice of where and how to intervene is dependent on myriad variables, including pathoanatomic considerations, anticipated disease progression and practitioner experience. While reviews exist discussing the application of interventional strategies to cancer-related pain states [3,4] and evidence-based treatment algorithms have been proposed [5,6], novel approaches continue to emerge, obligating

Table 1. Ultrasonographic localization of commonly targeted peripheral nerves.

Nerve	Ultrasound localization
Maxillary (CN V2)	Probe is placed inferiorly to and parallel with the zygomatic arch to identify the pterygopalatine fossa. Care is taken to identify and avoid the internal maxillary artery. Alternatively, the nerve can be blocked distally as it exits the facial bone through the infraorbital foramen
Suprascapular	Probe is placed with an inferolateral inclination across the supraspinous fossa to visualize the suprascapular notch deep to the trapezius and supraspinatus muscles. Care is taken to identify and avoid the suprascapular vessels
Intercostal	Probe is positioned sagittal over the angle of the rib to identify the (superficial to deep) external, internal and innermost intercostal muscles as well as the pleura. The needle is advanced toward the inferior border of the rib until the tip lies in between the inner and innermost intercostal muscles
Intercostobrachial	Probe is positioned at the apex of the axillary fossa to visualize the axillary vein in cross section. The probe is then translated proximally toward the anterior axillary line, where the serratus anterior comes into view. A slight medial obliquity is applied to visualize the second intercostal space, pectoralis muscles, serratus anterior and pleura. The needle is advanced to the inferior edge of the second rib, between the pectoralis minor and serratus anterior. Care is taken to identify and avoid the axillary vasculature
Pudendal	Probe is positioned transverse near the gluteal fold to identify the ischial spine and overlying sacrospinous and sacrotuberous ligaments, between which the nerve is typically found. The needle is advanced lateral-to-medial until the plane between these structures is accessed. Care is taken to identify and avoid contact with the sciatic nerve, which runs lateral to this point
Saphenous	With the hip abducted and externally rotated, the probe is placed anteromedially at the level of the mid thigh to identify the nerve in the tissue plane between the sartorius and vastus medialis muscles. Care is taken to identify and avoid the femoral vessels

practitioners remain up-to-date to provide the highest quality care. This review aims to describe various anatomic targets of, and approaches to, interventional cancer pain management.

Peripheral nerves

As peripheral nerves branch to innervate their end-organ targets, their consistent location in reference to muscle, bone and soft tissue structures makes them amenable to interfascial blockade. Precision for targeting peripheral nerves demands a thorough understanding of neuromuscular anatomy, but accuracy may be improved with ultrasound guidance [7,8]. Common targets include the trigeminal [9], suprascapular [10], intercostal [11], intercostobrachial [12], ilioinguinal/iliohypogastric [13], pudendal [14] and saphenous [15] nerves. Table 1 describes ultrasonographic localization of common peripheral nerve targets. Multiple intercostal nerve branches can be blocked simultaneously using injections into the paravertebral space [3,16] or fascial planes surrounding the serratus anterior [17–20], transversus abdominis [21] or pectoralis [22] muscles, among others. Table 2 describes an approach to common fascial plane blocks.

While effective and generally safe, ultrasound-guided peripheral nerve blockade is not without risk. Visualization of vasculature reduces, but does not eliminate, the risk of hematoma. Direct contact with the nerve can elicit intense, albeit transient, pain. Optimizing technique reduces these ultimately innocuous consequences and minimizes the risk of a false-negative diagnostic block. Anesthesia dolorosa, or deafferentation pain, is characterized by persistent, painful hyperesthesia in a denervated region. It is estimated to occur in as many as 1.5% of patients following chemical neurolysis [22] and 3% of patients following thermocoagulation [23]. The resulting pain is often more severe and treatment refractory than the pain initially being treated. Motor blockade can also occur, although functional deficits are rare. Midline structures with paired innervation, such as bowel and bladder sphincters, may be resistant to dysfunction following unilateral denervation but are associated with the greatest morbidity if dysfunction occurs.

Sympathetic chain

Sympathetic ganglia, including the stellate ganglion, celiac plexus, superior hypogastric plexus, lumbar plexus and ganglion impar are common targets in the management of neuropathic and visceral pain. Proposed mechanisms for the effects of sympatholysis include inhibition of adrenergic hypersensitivity, interruption of positive nociceptive feedback circuits and reduction of central hyperexcitability [24].

Stellate ganglion

The stellate ganglion is formed by fusion of the inferior cervical and first thoracic sympathetic ganglia [25]. Located anterior to the seventh cervical and first thoracic transverse processes, between the scalene and longus colli muscles, it provides sympathetic input to the upper extremity, chest and face. Blockade is typically achieved by injecting local anesthetic along the anterior plane of the longus colli muscle at the level of C6, where the adjacent vertebral

Table 2. Approach to and target of common fascial plane blocks.

Block	Target	Approach
Serratus plane	Lateral cutaneous branches of the intercostal nerves, thoracodorsal nerve	Probe is placed in the mid-axillary line overlying the fifth rib to identify the latissimus dorsi (superficial) and serratus anterior (adjacent to the rib). The needle is inserted into the fascial plane superficial to the serratus anterior
Pecs I	Medial and lateral pectoral nerves	Probe is placed in the anterior axillary line overlying the fourth rib to identify the (superficial to deep) pectoralis major, pectoralis minor and serratus anterior overlying the rib. The needle is advanced from supero-medial to infero-lateral, into the plane between the pectoralis major and minor
Pecs II	Lateral cutaneous branches of the T2-4 intercostal nerves. May block the anterior branches if LA penetrates the external intercostal or the long thoracic nerve if LA spreads into the axilla through (surgically) disrupted lateral pectoral fascia	Probe is placed in the anterior axillary line overlying the fourth rib to identify the (superficial to deep) pectoralis major, pectoralis minor and serratus anterior overlying the rib. The needle is advanced from supero-medial to infero-lateral, aiming at the anterior surface of the fourth rib, deep to the serratus anterior
Paravertebral	Dorsal and ventral rami of the thoracic spinal nerves, sympathetic trunk	Probe is placed just lateral to the spinous process at the level of the transverse process. The probe is then translated inferiorly into the intercostal space to identify the paravertebral space, which is bordered by the superior costotransverse ligament posteriorly, the parietal pleura anteriorly and the vertebral body and intervertebral disk medially. The needle is advanced into this wedge-shaped space, where injection of LA is observed to cause anterior displacement of the pleura
Erector spinae plane	Dorsal and ventral rami of the thoracic spinal nerves. Possible involvement of the thoracic sympathetic fibers via LA spread into the thoracic paravertebral space	Probe is placed 2–3 cm lateral to the thoracic spinous process to identify (superficial to deep) the trapezius, rhomboid major and erector spinae overlying the transverse process. The needle is advanced cephalad-to-caudad, aiming at the plane between the erector spinae muscle and T5 transverse process
Transversus abdominis plane	Intercostal nerves, primarily T6–T12	Probe is placed in the mid-axillary line between the subcostal margin and the iliac crest, roughly at the level of the umbilicus. Three muscular layers are visualized: the external oblique superficially, the internal oblique and the deep transversus abdominis. The needle is advanced medial-to-lateral into the fascial plane between the internal oblique and the transversus abdominis muscles
Ilioinguinal and Iliohypogastric	Ilioinguinal and Iliohypogastric nerves	The anterior superior iliac spine is identified. The probe is translated 2 cm medially and superiorly to identify the abdominal muscular layers (superficial to deep): external oblique, internal oblique and transversus abdominis. The needle is advanced into the plane between the internal oblique and transversus abdominus muscles. Both nerves reside in this plane
Quadratus lumborum	T4-L1 spinal nerves via spread of LA into the paravertebral space	Probe is placed on the patient's flank, slightly cephalad to the iliac crest to visualize the 'shamrock sign' comprised of the L4 transverse process (stem), erector spinae (posterior leaf), quadratus lumborum (lateral leaf) and psoas major (anterior leaf). The needle is advanced posterior-to-anterior into the fascial plane between the quadratus lumborum and psoas major or erector spinae muscles (two approaches to consider)

LA: Local anesthetic.

artery is usually protected by the bony Chassaignac tubercle. Commonly performed using ultrasound guidance, this can also be accomplished using fluoroscopy, computed tomography or palpation. Stellate ganglion blocks can be utilized in the management of pain and other sequelae from cancers of the head and neck [26], esophagus [27] and breast [28]. Risks of the procedure include needle trauma to nearby structures, including the carotid, vertebral or inferior thyroid arteries, recurrent laryngeal or vagus nerves, brachial plexus, thyroid and trachea. Pneumothorax can be avoided by choosing a target cephalad to the first thoracic vertebra. Spinal or epidural blockade is possible if the needle is advanced or medication spreads into the neural foramen.

Celiac plexus

The celiac plexus is often at the level of the 12th thoracic or first lumbar vertebrae. It surrounds the anterior and lateral aspects of the aorta, near the takeoff of the celiac and superior mesenteric trunks. The plexus receives sympathetic fibers from the greater, lesser and least splanchnic nerves, parasympathetic fibers from the vagus nerve and sensory fibers from the phrenic and vagus nerves [29]. The primary indication for celiac plexus blockade is

visceral pain in the setting of pancreatic cancer, although pain from malignancies involving any of the upper abdominal viscera may be amenable [4,30].

There are several approaches to a celiac plexus block. The posterior, retrocrural approach utilizes computed tomography or fluoroscopy to place medication along the anterior border of the first lumbar vertebral body. While more appropriately termed a splanchnic nerve block, this method is effective and may be preferred when the plexus is distorted or displaced by lymphadenopathy [31]. Neurologic injury may occur via spread of the injectate to involve nearby somatic nerve roots or the epidural or subarachnoid spaces. With the posterior, transcrural approach, the needle is advanced through the diaphragmatic crus and medication is deposited in the potential space posterolateral to the aorta. If the aorta is penetrated, as often occurs, the needle is advanced through the anterior wall and medication is deposited directly within the plexus on its anterior surface. This approach reduces the risk of paravertebral spread and permits a single injection technique. Penetration of the muscular aorta is rarely of any significant consequence. Anterior approaches utilizing palpation or ultrasound guidance have also been described [32]. Another anterior approach utilizes endoscopic ultrasound to access the celiac plexus through the posterior gastric wall [33]. Performed concomitantly with diagnostic or therapeutic endoscopy, this approach permits fine control of needle placement through real-time visualization of needle movement but no approach has proven superior to another regarding safety or efficacy.

High-quality data support the efficacy of celiac plexus blockade, regardless of approach, for management of pain from upper abdominal cancers. Compared with placebo and active control groups, celiac plexus blockade has demonstrated superior pain relief, improved quality of life and diminished analgesic requirements [34]. It may even contribute to prolonged survival in patients with advanced pancreatic cancer [35], but the data are inconsistent [36,37].

Complications of celiac plexus blockade differ based on approach, but image-guided approaches are considered safe. Most complications are transient and minor, including injection site pain and diarrhea from unopposed parasympathetic activity. Orthostatic hypotension can occur due to dilation of the splanchnic vasculature following loss of sympathetic tone. Severe complications, including pneumothorax, vascular injury, hematuria, sexual dysfunction, pleuritis, pericarditis, and retroperitoneal abscess have been reported but are rare [29]. There are also several reports of spinal cord injury after celiac plexus blockade [38,39], attributed to occlusion or spasm of radicular arteries.

Lumbar sympathetics

The lumbar sympathetic plexus is located anterolateral to the second through fourth lumbar vertebral bodies. Blockade of the plexus, or the splanchnic nerves along which visceral afferent signals are transmitted from the plexus to the sympathetic trunk, is typically approached posteriorly using fluoroscopic guidance. Less commonly, computed tomography [40] or MRI [41] is employed. While a single, high-volume injection is often adequate, a multilevel approach may be more efficient [42].

Lumbar sympathetic blocks are used in the management of many painful conditions of the lower abdomen, pelvis and lower extremity [43]. High-quality evidence supporting this use of technique is sparse; however, and comes primarily from patients with lower extremity complex regional pain syndrome. In the complex regional pain syndrome population, radiofrequency denervation and injections of local anesthetic, saline, phenol and botulinum toxin have all been shown to provide relief, with only botulinum toxin proving more effective than others in comparative studies [44]. Risks of lumbar sympathetic blockade include injection site pain, motor or sensory deficits secondary to spread of medication into the epidural or subarachnoid space, visceral perforation, genitofemoral nerve injury and priapism [45–47].

Superior hypogastric plexus

The superior hypogastric plexus, which contains sympathetic, parasympathetic and visceral afferent fibers [48], is located anterior to the bifurcation of the abdominal aorta. It can be targeted in the management of pelvic pain secondary to genitourinary, gynecologic and colorectal cancers. Traditionally, fluoroscopic guidance is used to deposit local anesthetic, alcohol or phenol alongside the anterolateral fifth lumbar vertebral body [49]. Computed tomography is used for guidance in some centers [50]. More recently, transdiscal [51] and ultrasound-guided [52] approaches have been described. Pain relief on the order of 70% has been demonstrated [49,53], which can be improved to >90% when used as part of multimodal therapy [49]. There is no evidence than any one technique results in improved analgesia when compared with another technique.

Ganglion impar

The ganglion impar (Walther's ganglion) is located on the ventral surface of the coccyx. It supplies nociceptive and sympathetic fibers to the perineum, rectum, distal urethra, vulva, scrotum and distal vagina [54]. Ganglion impar neurolysis was initially described for management of pelvic malignancies [49] but is now commonly used for nonmalignant coccygodynia [24,55]. The fluoroscopically guided trans-sacrococcygeal approach is preferred for its ease and safety [55], but if the sacrococcygeal or intercoccygeal joints are fused, a paracoccygeal approach becomes necessary [56]. Computed tomography [57], ultrasound [58] and magnetic resonance [59] techniques also exist. The largest efficacy studies show success rates above 80%, albeit mostly for nonmalignant pain [60,61]. Evidence of the block's efficacy in the cancer pain population is limited to case studies and small case series. Complications are rare but can include motor, sexual or bowel/bladder dysfunction, rectal perforation and sciatic nerve impingement.

Neuraxial procedures

Neuraxial procedures include epidural injections or infusions; nerve root ablation or chemical neurolysis; electrical stimulation of the dorsal columns or dorsal root ganglion; intrathecal drug delivery (IDD) and stereotactic neurosurgical procedures such as cordotomy and myelotomy. Here, we will introduce treatment strategies involving the epidural space. Central neuroablative approaches will be discussed in more detail later.

Epidural interventions

Epidural injections are the most commonly performed procedure in the management of nonmalignant chronic pain. Their role in the care of patients with malignancy is increasing as improved disease-management strategies have created chronic diseases of cancers that were once imminently terminal. There is an extensive body of literature discussing the most appropriate approach (caudal, transforaminal or interlaminar) and injectate (local anesthetic with or without steroid, saline) but its results are far from conclusive [62–66]. The appropriateness of epidural injections has been questioned in light of its considerable risks, which include epidural abscesses or hematomas, dural tears and transient or permanent neurologic deficits from insult to the spinal cord or radiculomedullary arteries [67]. A thorough discussion of these considerations is beyond the scope of this review.

Less commonly utilized since the emergence of IDD systems, epidural infusion remains an effective alternative for management of pain at the end of life [68]. In patients too sick to undergo surgery or whose limited life expectancy brings the cost–effectiveness of intrathecal therapy into question, epidural analgesia may be considered. A catheter can be placed at the bedside under local anesthesia to provide days to weeks of relief; or tunneled under procedural sedation for longer use. With the option of patient-controlled boluses, epidural analgesia has advantages over intravenous patient-controlled analgesia or high-dose systemic opioids, including improved pain control and reduced side effects [69]. Limitations include a high rate of catheter migration, motor and bowel/bladder dysfunction, infection and concerns regarding monitoring and maintenance of the system outside of a healthcare setting.

Intrathecal neurolysis

Intrathecal dorsal rhizolysis via delivery of alcohol or phenol into the subarachnoid space preferentially destroys the sensory nerve rootlets, which occupy the area between the dorsal root ganglion and the dorsal horn of the spinal cord. Their greater surface portends increased susceptibility to neurolysis compared with the dorsal root ganglion or nerve root proper [70]. The anatomic separation of motor and sensory fibers within the intrathecal space theoretically permits destruction of sensory fibers without harm to motor function. Absolute sensory selectivity, however, is rarely achieved. A number of publications [71–74] suggest the technique may effectively control pain and reduce opioid requirements in patients with somatic pain, but the quality of evidence is low. Recently, the procedure has fallen out of favor given its potential for significant side effects and the boon of implanted IDD systems. Ideal candidates for intrathecal neurolysis have a life expectancy <12 months and severe, well-localized pain covering three or fewer dermatomes that is refractory to maximal-tolerated analgesic doses [70]. Response to a diagnostic local anesthetic block may also be considered a prerequisite for subarachnoid neurolysis, but evidence of superior relief in patients having undergone a positive block does not exist.

Little data support the choice of neurolytic agent. The duration of relief varies widely by patient, regardless of injectate, but alcohol may offer prolonged benefits compared with phenol [75]. Phenol, however, has a shorter onset of action, requires less volume (allowing greater dermatomal specificity) and does not cause intense burning upon injection as is typical of alcohol [70]. At low concentrations, phenol destroys nociceptive fibers with minimal motor

side effects. Above 6%, phenol can cause axonal degradation, nerve root damage, spinal cord infarcts, arachnoiditis and meningitis [76]. At even higher doses, phenol is frankly neurotoxic, causing CNS depression and cardiovascular collapse similar to local anesthetic toxicity [77]. Additionally, phenol can damage the neural tube, destroying the pathway along which neuronal regeneration would otherwise occur, increasing the risk of aberrant reinnervation and resultant neuropathic pain [78]. Regardless of neurolytic agent, side effects include sensory, motor and autonomic system derangements and dural tears. Safety concerns plus unproven efficacy have relegated this technique to use in only the most refractory cases.

Surgical & interventional radiologic approaches

When percutaneous treatment options fail, surgical techniques may offer relief. While some of these techniques fall under the purview of an adequately trained interventionalist, collaboration with surgical oncology, neurosurgery and interventional radiology is imperative to providing additional treatment options for the hardest-to-manage patients.

Intrathecal drug delivery

IDD is indicated when pain remains uncontrolled by an oral medication regimen whose further titration is limited by intolerable side effects. IDD provides direct access to receptor sites in the dorsal horn and reduces delivery to the brain via the blood–brain barrier [79]. IDD allows rapid dose titration at initiation or following disease progression. While drug abuse using an implanted IDD system has been described [80], the risk of medication misuse is less than with oral regimens. Follow-up appointments for pump management are generally less frequent and more streamlined than are those for chronic opioid management. Implanted IDD systems do not interfere with the ability to obtain an MRI or receive other oncologic care, although pump failure following direct exposure to a radiation field has been reported [81]. Medication delivery can be varied throughout the day based on a patient's needs and the pump allows patient-delivered rescue boluses within parameters set by the managing physician. There is even evidence that IDD can contribute to prolonged survival by reducing medication side effects and restoring eligibility for disease-modifying treatment [82].

The choice of IDD regimen is multifactorial and includes consideration of diagnosis, stage, pain type and location, prognosis, life expectancy and previous opioid exposure. Morphine was the first and remains the most commonly used medication in IDD systems. As one of three medications, and the only opioid, approved by the US FDA for intrathecal use, morphine is recommended as a first-line pump medication by the Polyanalgesic Consensus Conference [83]. Other opioids, such as fentanyl, sufentanil, hydromorphone and methadone are also used, alone or in combination with bupivacaine, clonidine, baclofen, midazolam, ketamine, octreotide and other adjuvants. When multiple medications are used in combination, stability of the admixture, priming bolus errors and permeability of the catheter tubing become concerns [84–86]. Leaching of medication from the pump tubing into the pump's rotor has been described as a cause of corrosion and premature failure. Despite this risk, the Polyanalgesic Consensus Conference supports the use of opioid–bupivacaine combinations as first-line IDD therapy for cancer pain [83].

Ziconotide, another first-line option [83], is unique in its requirement for intrathecal administration to maximize effectiveness and avoid sympatholysis [87]. A selective N-type voltage-sensitive calcium channel blocker, ziconotide can be highly effective at managing neuropathic pain [83,87–89]. Although studied in various admixtures [84–87,89], ziconotide is often utilized as first-in-pump monotherapy, for which it carries an FDA indication. Use of ziconotide is limited by cost and a slow titration schedule necessitated by neurologic, cognitive and psychological side effects seen with rapid dose escalation [88].

Additional considerations when initiating IDD include catheter tip location and drug concentration. Studies of cerebrospinal fluid (CSF) dynamics [90–92] suggest the catheter tip be placed at the spinal level corresponding to the area of greatest pain. Rather than laminar as was once postulated, CSF flow is now thought to be pulsatile, with oscillatory displacements creating eddy microcurrents but minimal net bulk flow [91]. Essentially, CSF radiates away from a source of disruption like water in a pond. Physiologically, disruption comes from changes in intrathoracic pressure during the cardiorespiratory cycle, changes in intra-abdominal pressure and spinal motion. In the presence of an IDD catheter, medication delivery provides this disruptive force, sending ripples of CSF away from the catheter tip, creating a concentration gradient across relatively few spinal levels. Factors influencing the degree of medication distribution remain incompletely understood, but include anatomic variation, pathoanatomic changes such as spinal stenosis or scoliosis, postural changes, solution density, binding characteristics of the drug to receptors in the dorsal horn and segmental variations in CSF volume and flow [91–94].

Intrathecal drug concentration is primarily determined by dose, which can be estimated based on the patient's oral opioid requirement and level of pain control. Two limiting factors must be considered, however, drug solubility, which changes based on the presence of other molecules in solution, and flow rate. Precipitation of medication within the pump, as is possible with high concentrations or unstable medication admixtures, can damage the pump tubing and corrode the pump's mechanics, causing device failure [84–86,95]. Flow rate is limited by the pump, which becomes less accurate as rates approach its limits in either direction, practical considerations regarding the frequency of refills, and the risk of catheter tip granuloma, which increases when highly concentrated opioids are delivered at a slow rate [96]. These noninflammatory masses can have a mass effect on nearby neural structures and obstruct the delivery of medication, potentially precipitating withdrawal. The potential for granuloma formation also plays into catheter tip placement, as some advocate placement below the conus medullaris to reduce the risk of adhesion to the spinal cord parenchyma, which can require an extensive and complicated resection [97].

The benefits offered by IDD come with substantial risks, including procedural risks and device-related complications. Procedural risks include those related to anesthesia as well as bleeding, neurologic injury, persistent CSF leaks and infections of the wound, pocket or catheter. Device-related complications include pump failure, pump migration, including erosion through the skin. Catheter-related complications include migration out of the subarachnoid space, kinking, tearing or adhering to the spinal cord or nerve roots. Optimizing medical comorbidities, such as obesity, tobacco use and diabetes, decreases the risk of surgical complications. Preimplant psychiatric evaluation can identify patients with undiagnosed psychotic or personality disorders, ensure optimal control of mood disorders and reinforce realistic expectations of the therapy. Patient education regarding the importance of pump refill appointments is vital, as missed appointments are costly for the healthcare system, can result in medication withdrawal and may even damage the pump, necessitating surgical revision. For the patient, consequences of withdrawal range from harmless (ziconotide) to unpleasant (opioids) to life threatening (clonidine and baclofen) [98–100] but universally increase healthcare utilization and are preventable.

Vertebral augmentation

Spinal metastases occur in up to 40% of patients with cancer [101], most commonly in the setting of multiple myeloma or from a primary lesion of the breast, lung, prostate or kidney. Each year, 5% of cancer patients will develop spinal metastases [102], which often present as pain following pathologic fracture. Average survival times in these patients is less than a year, so conservative treatment options are limited and often produce unsatisfactory results [103]. While surgical options can offer relief, many patients with end-stage disease are reluctant to pursue extensive surgery.

Vertebroplasty and kyphoplasty are image-guided percutaneous techniques which can be offered to these patients for palliative treatment of pathologic vertebral body fractures. They differ in that kyphoplasty uses a balloon tamponade to create a void prior to injection of the bone cement poly methyl methacrylate (PMMA), while vertebroplasty does not. Shared goals of the procedures include pain control, functional optimization, mechanical fracture stabilization and restoration of vertebral body height. The latter helps minimize the development of central or foraminal stenosis and their associated neurologic deficits, including paraplegia. Kyphoplasty is often combined with radiofrequency tumor ablation for additional pain relief [104,105].

Vertebral augmentation, with [104,105] or without [106–108] radiofrequency ablation, is a safe and effective alternative to surgical management of vertebral fractures but is not without risks. Complications most commonly result from cement extravasation, the rate of which varies widely in the published literature [101]. The risk likely increases with cement volumes >4 ml per level [109]. Although most cement leaks are clinically insignificant, severe neurologic or cardiorespiratory compromise from extravasation of PMMA into the central canal, neural foramen, vasculature or pleural cavity occurs at a rate of 1–2% [110]. Kyphoplasty theoretically reduces this risk by establishing a cavity into which PMMA can be injected under relatively low pressure, but there is no evidence that kyphoplasty provides superior safety or efficacy versus vertebroplasty. Other procedural risks include bleeding, infection, fracture, fat emboli, radiculopathy and hypotension [111]. An increased incidence of both remote and adjacent level fractures has been noted after cement augmentation of an index lesion [112]. Alterations in spine biomechanics are the most likely explanation for this finding, but a definitive causal relationship has not been established.

Tumor ablation, osteoplasty & sacroplasty

Procedures most commonly performed by interventional radiologists for the management of malignant pain include tumor ablation, osteoplasty and sacroplasty. The former is an alternative to surgical resection that uses

computed tomography or magnetic resonance guidance for percutaneous radiofrequency, microwave, cryo- or chemical ablation of tumor cells. It is most effective for primary or secondary tumors involving the lung [113], thyroid [114], bone [115], liver [116] and kidney [117]. The risks are procedure and site specific, but also include risks of procedural sedation, often general anesthesia. These techniques offer the possibility for complete destruction of the tumor; however, making them viable alternatives in properly selected patients.

Osteoplasty and sacroplasty, similarly to vertebral augmentation, utilize bone cement to stabilize and relieve pain from lytic extraspinal bony lesions [3]. Unlike that supporting the use of kyphoplasty for vertebral fractures; however, evidence for the role of these techniques is generally of low quality, including only case reports [118–121] and small case series [6,122,123]. Despite the lack of high-quality evidence, the favorable safety profile of the procedure warrants its consideration for treatment-refractory cases and the technique has been incorporated into an evidence-based treatment algorithm for sacroiliac tumors [5].

Cordotomy

Percutaneous cordotomy involves computed tomography-guided radiofrequency thermocoagulation of the lateral spinothalamic tract in the upper cervical spinal cord. The lateral spinothalamic tract, which carries pain and temperature sensation from the contralateral extremities and trunk, is organized such that selective lesioning of fibers from a single extremity is possible when using appropriate myelographic confirmation, impedance measurements and sensory-motor dissociation testing. Benefits include the potential for complete resolution of pain in the affected extremity [124]. The most common complication is a headache in a C2 dermatomal distribution [125]. Other complications include transient motor weakness or dysesthesias, bleeding, infection, sensorimotor changes from inadvertent injury to neighboring spinal tracts, bowel or bladder dysfunction, hypotension and Horner's syndrome. Bilateral procedures, especially those done using an open surgical approach without sensory testing, are not recommended as involvement of the neighboring reticulospinal tract can disrupt a patient's subconscious respiratory drive, resulting in sleep-induced respiratory arrest and death [126]. Overall, however, cordotomy is felt to be a safe procedure, with the risk of major complications being <1% [127].

Destruction of trigeminal pathways

Trigeminal tractotomy/nucleotomy involves destruction of descending trigeminal nerve fibers in the medulla (tractotomy) or nucleus caudalis (nucleotomy). Alternatively, dorsal root entry zone lesioning involves destruction of the entire substantia gelatinosa at the level of the nucleus caudalis [128,129]. Pain fibers from cranial nerves VII, IX and X descend with the spinal tract of the trigeminal nerve into the upper cervical cord. Reliable topographic localization of these cranial nerve nociceptive fibers makes them an attractive target for intervention. Destruction of these tracts can treat dysesthetic, neurogenic, or deafferentation types of craniofacial pain, including pain from cancers of the head and neck, and anesthesia dolorosa following neurolysis [129]. In large case series [126,129–131], as many as 85% of patients with pain from craniofacial malignancies responded favorably to one or more of these procedures. The most important complication is ataxia, which is caused by lesioning of the dorsal spinocerebellar tract and is usually transient [130]. The authors of the largest case series to date [130] opined that, in light of its efficacy and safety, computed tomography-guided trigeminal tractotomy, nucleotomy and nucleus caudalis dorsal root entry zone lesioning should be considered early in the treatment of refractory facial pain.

Myelotomy

Extralemniscal myelotomy involves stereotactic lesioning of the central canal, typically at the occiput-C1 level. Experience with this procedure dating back to 1968 suggests efficacy in relieving pain in the upper extremities, lower extremities and trunk, including visceral pain, pain in the anatomic midline and even central pain [126], but large randomized controlled trials are lacking. Schvarcz, who coined the term in 1977 [132], reported the goal of the procedure to be disruption of a 'nonspecific, extralemniscal, polysynaptic ascending system'. Al-Chaer later posited that interruption of dorsal column fibers may 'tip the balance' away from pain perception [133]. This explanation accounted for the clinical observation of pain relief without significant sensory loss. Another theory claims that a pathway responsible for transmitting visceral pain exists in the dorsal funiculus and that destruction of this pathway disrupts 'extensive cross connections within the propriospinal system' therein [134].

Ideal candidates for myelotomy have intractable visceral pain due to pelvic or abdominal malignancies, including gastric, pancreatic, renal, colon and rectal carcinomas. Reported efficacy in the available case studies and case series is significantly less than with previously discussed procedures, but complications were rare and included transient

hypoesthesia [126]. Following description of the procedure in the upper cervical cord, others reported lesioning of the central cord at various spinal levels, with similar results [135,136].

Future perspective

Neuromodulation is the most rapidly evolving aspect of pain management. Despite significant growth, however, evidence of these techniques for the management of oncologic pain is sparse. The most common application, transcutaneous electrical nerve stimulation, is inexpensive, safe and simple to use. Although Cochrane reviews [137,138] were unable to find high-quality data supporting the use of transcutaneous electrical nerve stimulation in patients with cancer pain, case series-level data provide evidence that this technology can be an effective nonpharmacologic adjunct for the management of cancer-related pain [139], fatigue [140] and lymphedema [141] as well as chemotherapy-induced myelosuppression [142], peripheral neuropathy [143] and nausea/vomiting [144].

Dorsal column stimulation, although first described in a patient with pain from bronchogenic carcinoma [145], likewise has only low-quality data supporting its use in patients with malignant pain [146,147]. Resolution of MRI compatibility issues and emergence of paresthesia-free stimulation paradigms should make possible conduction of high-quality, large-scale, randomized, placebo-controlled trials in patients with malignant pain. A similar role may be seen in the future for peripheral nerve stimulation.

Perhaps the fundamental improvement in interventional pain medicine is developing new guidelines or algorithms to implement the aforementioned therapies. Establishing anatomic criteria for the interventional techniques will standardize the pain treatment for emerging cancer pain syndromes. One consideration is improvement in cancer treatment is increasing survival rates. Hence, where once neurolytic options were first-line treatment, now consideration for long-term sequelae should be discussed. Nerve-sparing techniques such as neuromodulation may play more prominent role as survivorship increases. Finally, as survivorship improves, chronic noncancer pain syndromes will be more commonplace in the oncologic population (i.e., osteoarthritis). This will redirect our efforts for pain treatments in the future.

Conclusion

Pain is a common experience among patients with cancer. Interventional approaches offer the ability to control pain, improve function and enhance quality of life, both through direct analgesic effects as well as reduction or elimination of medication side effects. As the survivability of cancer continues to improve and as the dangers of long-term opioids are further elucidated, nonpharmacologic alternatives will play a more important role in the treatment of these patients. To serve this role, interventions must be applied by practitioners with a thorough understanding of the options and proper training in performing the techniques. This review seeks to fulfill the former, but only through the latter can the safety and efficacy of these interventions be optimized in an effort to improve delivery of care for patients with pain of oncologic origin.

Authors' contributions

Both the authors contributed to the literature review, composition and editing of the manuscript.

Financial & competing interests disclosure

A Gulati serves as a consultant for Medtronic and Flowonix. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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