CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED GUIDELINE ON NEUROABLATIVE PROCEDURES FOR PATIENTS WITH CANCER PAIN

Sponsors: Congress of Neurological Surgeons (CNS) and the Section on Pain

Endorsement: Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

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Abbreviations:
BPI: Brachial Plexus Injury
CNS: Central nervous system
CT: Computed tomography
DREZ: Dorsal root entry zone
ELM: Extralemniscal myelotomy
RF: Radiofrequency
TN: Trigeminal neuralgia
VAS: visual analog scale
WBPQ: Wisconsin Brief Pain Questionnaire (WBPQ)

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ABSTRACT

Background: Managing cancer pain, once it is refractory to conventional treatment, continues to challenge caregivers committed to serving those who are suffering from a malignancy. Although

neuromodulation has a role in the treatment of cancer pain for some patients, these therapies may not be suitable for all patients. Therefore, neuroablative procedures, which were once a mainstay in treating intractable cancer pain, are again on the rise. This guideline serves as a systematic review of the literature of the outcomes following neuroablative procedures.

Objective: To establish clinical practice guidelines for the use of neuroablative procedures to treat patients with cancer pain.

Methods: A systematic review of neuroablative procedures used to treat patients with cancer pain from 1980 to April 2019 was performed using the United States National Library of Medicine PubMed database, EMBASE, and Cochrane CENTRAL. After inclusion criteria were established, full text articles that met the inclusion criteria was reviewed by two members of the task force and the quality of the evidence was graded.

Results: In total, 14,646 relevant abstracts were identified by the literature search, from which 189 met initial screening criteria. After full text review, 58 of the 189 articles were included and subdivided into 4 different clinical scenarios. These include unilateral somatic nociceptive/neuropathic body cancer pain, craniofacial cancer pain, midline subdiaphragmatic visceral cancer pain and disseminated cancer pain. Class II and III evidence was available for these 4 clinical scenarios. Level III recommendations were developed for the use of neuroablative procedures to treat patients with cancer pain.

Conclusions: Neuroablative procedures may be an option for treating patients with refractory cancer pain. Serious adverse events were reported in some studies, but were relatively uncommon. Improved imaging, refinements in technique and the availability of new lesioning modalities may minimize the risks of neuroablation even further.

KEY QUESTIONS

Unilateral somatic nociceptive/neuropathic body cancer pain

a) For patients with unilateral somatic nociceptive/neuropathic body cancer pain, is cordotomy, dorsal root entry zone lesioning (DREZ), thalamotomy, mesencephalotomy or rhizotomy most effective for pain control and reducing risk of potential complications?

b) In patients with unilateral somatic nociceptive/neuropathic body cancer pain, what are the outcome(s) following cordotomy, DREZ, thalamotomy, mesencephalotomy and rhizotomy that indicate efficacy of pain control?

Craniofacial cancer pain

a) For patients with craniofacial cancer pain, is trigeminal tractotomy, rhizotomy (cranial nerves) or nucleus caudalis DREZ most effective for pain control and reducing risk of potential complications?

b) In patients with craniofacial cancer pain, what are the outcome(s) following trigeminal tractotomy, rhizotomy (cranial nerves) and nucleus caudalis DREZ that indicate efficacy of pain control?

Midline subdiaphragmatic visceral cancer pain

a) For patients with midline subdiaphragmatic visceral cancer pain, is myelotomy effective for pain control and reducing risk of potential complications?

b) In patients with midline subdiaphragmatic visceral cancer pain, what are the outcome(s) following myelotomy that indicate efficacy of pain control?

Disseminated cancer pain

a) For patients with disseminated cancer pain, is cingulotomy effective for pain control and reducing risk of potential complications?

b) In patients with disseminated cancer pain, what are the outcome(s) following cingulotomy that indicate efficacy of pain control?

RECOMMENDATIONS

Unilateral somatic nociceptive/neuropathic body cancer pain

Rhizotomy

Rhizotomy, both in its percutaneous RF/chemical and open surgical forms may be used to treat patients with unilateral body cancer pain and occasionally bilateral cancer pain, but outcomes, such as sensory deficit (as a result of rhizotomy) and occasionally a motor or autonomic deficit (depending on the nerve(s) ablated), should be considered.

Strength of Recommendation: Level III

DREZ

There is insufficient data to make recommendations regarding the efficacy of DREZ for unilateral body cancer pain.

Thalamotomy

Mediodorsal and basal thalamotomy (RF or radiosurgical) may be used to treat patients with unilateral somatic nociceptive/neuropathic body cancer pain. Potential complications, such as transient diplopia, confusion or delirium, should be considered.

Strength of Recommendation: Level III

Mesencephalotomy

Mesencephalotomy may be used to treat patients with unilateral somatic nociceptive/neuropathic body cancer pain, especially as an alternative to cordotomy when pain involves dermatomes above C5. Potential complications should be considered including gaze palsy and 0.5% risk of mortality when performed bilaterally.

Strength of Recommendation: Level III

Thalamotomy may be used to treat patients with unilateral somatic nociceptive/neuropathic body cancer pain, and may be more effective for pain involving the face and upper body.

Strength of Recommendation: Level III

Cordotomy

Percutaneous image guided cordotomy may be used for the treatment of patients with unilateral somatic nociceptive/neuropathic body cancer pain with an expected durability of at least 6 months. Potential complications, including temporary paresis, should be considered.
Strength of Recommendation: Level II

Craniofacial cancer pain

Cranial nerve rhizotomy may be used for pain control in patients with craniofacial cancer pain.
Strength of Recommendation: Level III

Nucleus caudalis DREZ may be used for pain control in patients with craniofacial cancer pain.
Strength of Recommendation: Level III

Trigeminal tractotomy-nucleotomy may be used for pain control in patients with craniofacial cancer pain.
Strength of Recommendation: Level III

There is insufficient evidence to recommend one procedure over the other (trigeminal tractotomy, cranial nerve rhizotomy, or caudalis DREZ) for pain control in patients with craniofacial cancer pain.

Midline subdiaphragmatic visceral cancer pain

Myelotomy (open or percutaneous) may be used to treat patients with midline sub-diaphragmic visceral cancer pain.
Strength of Recommendation: Level III

There is not enough evidence in literature to suggest a size of the myelotomy lesion or to favor open versus percutaneous method.

Disseminated cancer pain

Cingulotomy may be used in patients with diffuse cancer pain associated with metastatic disease. Risks of postoperative cognitive and behavioral problems should be considered.
Strength of Recommendation: Level III

INTRODUCTION

Rationale

Cancer-related pain is a significant problem worldwide. Pain adversely affects functional status as well as quality of life, and shortens survival in patients with cancer. An estimated 60-85% of those patients with advanced cancer have pain. Furthermore, cancer pain is either not diagnosed or inadequately treated in approximately 40% of patients. One-third of those patients using hospice services reported pain at the last care visit before death.[1] Additionally, in a study of 106,500 hospice decedents, 5-7% of patients desired better pain control, independent of length of stay.[2] Unfortunately, patients with cancer reported worse pain control between 1998 and 2010, even as efforts to improve end-of-life care were being addressed.[3] As a result, the American Society of Clinical Oncology (ASCO) has included pain assessment and treatment as part of its Quality Oncology Practice Initiative (QOPI).[4]

Central nervous system (CNS) ablation for pain has been an integral part of neurosurgical practices since the inception of the subspecialty of neurological surgery and has evolved from accounts first published in the early twentieth century.[5] Spiller et al[6] described sectioning the spinothalamic tract to control neuropathic pain in a cancer patient in 1914. In a later report, Sjoqvist et al[7] cut the trigeminal tract fibers as they coursed through the medulla to alleviate trigeminal neuralgia pain. Dr. Harvey Cushing, in what would be one of his many lasting legacies that would usher in modern neurosurgical care, developed a technique resecting the trigeminal ganglion in 1900.[8]

While the general trend in the last few decades of the twentieth century has been a departure from ablation of the nervous system, CNS ablation for cancer pain has been re-introduced as a treatment option in select instances, such as cordotomy for mesothelioma.[9]

On this basis, this clinical practice guideline for the use of neurosurgical ablation for cancer pain was developed. This guideline will be updated as imaging improves, technical expertise expands and lesioning modalities continue to evolve.

This guideline is organized into four clinical cancer pain scenarios for ease of use and applicability in real clinical settings. The search, however, was approached by procedure, due to the nature of organization of relevant literature, which is procedure based.

METHODS

Writing Group and Question Establishment

Members of the Evidence-Based Clinical Practice Guideline Taskforce, the Joint Section on Pain of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) have prioritized the development of guidelines for neuroablative procedures for cancer pain. Authors for the development of guidelines related to neuroablative cancer pain were identified and screened for conflict of interest. The final author group agreed on a set of questions addressing the topic and conducted a systematic review of the literature relevant to neuroablative procedures for cancer pain treatment.

Literature Search

The task force members collaborated with a medical librarian to search the US National Library of Medicine PubMed database, EMBASE, and Cochrane CENTRAL for the period from January 1, 1980, to April 24, 2019, using the search strategies provided in Table 1. The literature search yielded 14,646 unique results. The task force selected 189 full-text articles for review. Of these, 131 were rejected for not meeting inclusion criteria or for being off-topic.

Study Selection and Eligibility Criteria

A total of 189 articles were manually reviewed by the authors with specific inclusion and exclusion criteria, as outlined below. One hundred thirty-one studies did not meet inclusion criteria below and were therefore excluded. A total of 58 studies were included for definitive analysis. Two independent reviewers evaluated and abstracted full-text data for each article, and the 2 sets of data were compared for agreement by a third reviewer. Articles with inconsistencies between reviewers were re-reviewed, and disagreements were resolved by consensus. To be included in this preparation of the guidelines, an article had to meet the following criteria:

- Describes ablative neurosurgical procedures for cancer pain (studies describing other pathology in addition to cancer pain were not excluded);
- Includes at least 5 adult human patients (≥18 years of age) treated for cancer pain;

- Was published in the English language between January 1, 1980 and April 24, 2019;
- Presents quantitative results;
- Analyzed clinical outcome data rather than *in vitro* analysis (such as studies of patient samples for molecular markers, biomechanical studies, cadaver studies, etc.);
- Was not an in vitro study (for novel molecular markers, in vitro studies were included on patient samples);
- Was not a biomechanical study;
- Was not performed on cadavers;
- Was published in English.

The authors did not include systematic reviews, guidelines, meta-analyses conducted by others, or, manuscripts with unclear underlying pathology of cancer pain. These documents were examined if their abstract suggested that they might address one of the recommendations, and their bibliographies were searched for additional studies. Meeting abstracts, editorials, letters, and commentaries were also excluded.

Data Collection Process

Abstracts that met the selection criteria mentioned above were retrieved in full-text form. Each article's adherence to the selection criteria was confirmed. To determine how the data should be classified, the information in the full-text articles was evaluated to determine whether they provided results of therapy or focused on diagnostic/prognostic information. Agreement on these assessments, on the salient points regarding the type of study design and objectives, conclusions and data classification was reached by exchanging e-mail correspondence. The information was then used for construction of evidence tables.

Rating Quality of Evidence

The quality of evidence was rated using an evidence hierarchy for therapeutic studies. The hierarchy is shown in Table 3: Rating Evidence Quality. Additional information regarding the hierarchy classification of evidence can be located here: https://www.cns.org/guidelines/guideline-development-methodology.

Revision Plans

In accordance with the Institute of Medicine's standards for developing clinical practice guidelines, the task force will monitor related publications following the release of this document and will revise the entire document and/or specific sections "if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations."[10] In addition, the task force will confirm within 5 years from the date of publication that the content reflects current clinical practice and the available technologies for neuroablative procedures for cancer pain.

RESULTS

Four clinical scenarios were identified for this guideline including: unilateral somatic nociceptive/neuropathic body cancer pain, craniofacial cancer pain, midline subdiaphragmatic visceral cancer pain and disseminated cancer pain. Fifty-eight studies met inclusion criteria and were included in this systematic review. The included studies were graded as Class II or III evidence.

Unilateral somatic nociceptive/neuropathic body cancer pain

For patients with unilateral somatic nociceptive or neuropathic pain, several options for procedure exist including cordotomy, DREZ, thalamotomy, mesencephalotomy and rhizotomy.

The particular choice of procedure relates to anatomic distribution of pain as well as pain characteristics. Cordotomy is the most commonly performed procedure and is usually selected in situations where pain is somatic and involves a large area of one side of the body, such as entire limb, entire side of the chest or trunk, or a combination of both. This is usually associated with soft tissue sarcomas and mesotheliomas. Mesencephalotomy is usually selected as a treatment when the pain involves a dermatome higher than C5 or when sleep apnea is a significant concern (previous contralateral cordotomy and/or poor pulmonary function tests). DREZ is often used to treat cancer pain with strong neuropathic component and relatively smaller area that can be treated by ablating a finite number of dermatomes. Rhizotomy can be used as an alternative to cordotomy when the area affected by pain is smaller and can be covered by resecting or ablating

a finite number of dermatomes (usually 3). Thalamotomy (medial not sensory) is usually selected when a non-invasive option is desired, because it can be performed using Gamma Knife, or when a mixed neuropathic and somatic pain exists, because it targets the affective component of pain.

Rhizotomy

Seven reports of rhizotomy for cancer-related neuropathic pain were identified (Table 4A),[11-17] all of which were case series and, therefore, determined to provide Class III level of evidence. Two studies evaluated percutaneous radiofrequency ablation of the glossopharyngeal nerve, with or without the trigeminal nerve, for glossopharyngeal neuralgia secondary to nasopharyngeal or orofacial cancer pain.[16,17] They will be considered in the later section on craniofacial pain. Three studies evaluated spinal percutaneous rhizotomy via neurolytic agents, primarily phenol, either through an epidural or intrathecal approach for lung cancer,[11] rectal cancer,[12] and pelvic cancer.[15] The remaining 2 studies assessed the effects of open rhizolysis for cancer pain of the chest wall[13] as well as coccodynia due to cancer pain.[14]

The effectiveness of rhizotomy did not depend on the type of cancer, as long as the malignancy produced pain of neuropathic origin, nor did efficacy depend on the type of rhizotomy performed. However, 1 study found improved benefits in phenol rhizotomies using higher concentrations (10-15%) of the phenol solution.[15] All procedures were associated with a neurological deficit in the distribution of affected nerve, such as urinary retention for sacral rhizotomy or swallowing difficulty for glossopharyngeal rhizotomy, trading off pain relief for neurological deficit.

The largest case series included 73 patients treated using a percutaneous approach for cancer pain related to pelvic malignancy.[15] Researchers used phenol rhizotomy and/or unilateral cervical percutaneous cordotomy. In the patients who underwent phenol rhizotomy, an L5/S1 block was done for perineal pain of malignant origin, and higher concentrations of phenol, ranging from 10-15% phenol solutions, provided long-lasting, with the only side effects of urinary retention. The remaining studies ranged from 5 to 20 patients, with follow-up ranging from 6 weeks to 102 months.[11-14,16,17]

Dorsal Root Entry Zone (DREZ) Lesioning

Three Class III case series were identified (Table 4B).[18-20] One manuscript addressed only deafferentation cancer pain, and 2 included cancer and non-cancer pain. Most patients

experienced long-term pain relief, but heterogeneous outcome metrics and times of evaluation precluded adequate conclusions about effectiveness. Sindou et al[18] reported 87% of patients were operated on at the cervical or the cervico-thoracic level and 78% of patients operated on at the lumbar and/or sacral levels had a "good result." The best candidates were those with topographically limited pain caused by local lesions, as found in Pancoast syndrome, circumscribed invasion of the thorax or the abdomen wall, limited neoplastic involvement of lumbar-sacral roots/plexuses, or of the perineal floor. There is some controversy as to whether the lesions need to be limited to the dermatomes in which the patient has pain[19] or if it should extend to adjacent levels.[18] All procedures were performed open. It is difficult to parse out the complications associated with DREZ for cancer pain, because all series reported overall complications for cancer and non-cancer pain. Complications included cerebral spinal fluid leak (4.4%), weakness (4.4%)[18,19] or death. Complications were more likely in cases with thoracic lesion due to the smaller diameter of the spinal cord with less room for error.[19] Reported techniques included radiofrequency with a curved electrode with a 2-3 mm exposed tip measuring 0.25 mm in diameter[19] or with a bipolar and knife.[18] Monitoring of somatosensory evoked potentials was thought to be helpful and used in both studies.

Thalamotomy

Two reports of thalamotomy for cancer-related chronic neuropathic pain were identified (Table 4C),[21,22] both of which were determined to provide Class III evidence. One report[21] described radiosurgical Centromedian (CM-pf) thalamotomy using radiosurgery. Out of 52 patients with cancer pain, only 8 achieved excellent pain relief, 20 patients achieved satisfactory pain relief, and 24 were without substantial pain relief. Patients with pain in the face and upper body were more likely to experience pain relief. Two patients (out of 52, or 3.8%) treated with radiosurgery developed hemiparesis following treatment. The study did not include the time to pain relief using radiosurgery.

The second study[22] compared radiofrequency basal (sensory) thalamotomy to centromedian thalamotomy. The outcome of RF thalamotomy for cancer pain in these patients was good regardless of the technique used since 96 and 87.5 % of patients experienced pain relief respectively. Centromedian thalamotomy was slightly more successful than sensory

thalamotomy, but statistical significance was not reported. Transient alteration of consciousness was common in this series: affecting 53% and 36 % of patients undergoing centromedian and basal thalamotomy respectively. Ocular dysfunction including permanent dipolopia was more common in basal thalamotomy (14%) compared to centromedian thalamotomy (4.2%).

Mesencephalotomy

Two reports of mesencephalotomy for cancer pain were identified (Table 4D).[23,24] Both of these studies provide Class III evidence and include 40 and 202 patients respectively. Mesencephalotomy refers to mesencephalic spinothalamic tractotomy. The procedure was used as an alternative to cordotomy to provide pain relief above the cervical dermatomes. The procedure requires stereotactic intracranial guidance. Both reports used Leksell frame and radiofrequency ablation.

The larger of the 2 reports[24] included 202 patients with cancer pain. The authors abandoned cordotomy for mesencephalotomy. There was 1 (0.5%) mortality and gaze palsy occurred in 19 (9%) patients. The most commonly treated cancer pain location was the chest wall. The second report[23] treated 33 patients with cancer pain. There was one mortality in a patient who underwent bilateral mesencephalotomy. Interestingly, the initial pain relief rate was very similar in both studies (85%[24] and 87.9%[23]) and there was a delayed recurrence of pain in 5%.

Cordotomy

Thirty reports of cordotomy for cancer pain were identified (Table 4E),[15,25-53] suggesting that it is the most studied and commonly performed ablative procedure for cancer pain. Three studies were prospective,[25,26,39] and many included a large number of patients (over 100 in some cases), or followed all patients until death.

Three of the reports of cordotomy for cancer pain were prospective.[25,26] There was one prospective randomized trial for cordotomy versus best palliative therapy that showed statistically significant superiority of cordotomy over palliative therapy. The vast majority of palliative therapy group crossed over to cordotomy after a week. Due to the lack of randomization and the small size, the level of evidence was downgraded to level II based on this

study. One study[26] used a standardized outcome measure (visual analogue scale), Karnofsky performance scale, activities of daily living, and total sleeping hours. In this study, there was a statistically significant improvement of all outcome measures comparing post-procedure to baseline pain levels. The other series[25] reported average pain scores using the numeric rating scale (NRS) immediately preoperatively, 2 days postoperatively, and 28 days postoperatively and found them to be 7, 0, and 0, respectively.

Despite the heterogeneity of outcome measures, the vast majority reported excellent lasting relief (≥80% of patient with complete or satisfactory pain relief) for several months within the context of patients with diminished life expectancy. Reported cordotomy outcomes in cancer pain patients contrasts with outcomes for non-cancer pain patients, where pain relief was moderate, short-lived, and often complicated with dysesthesias.

The most commonly reported complication of cordotomy was weakness, which was mostly mild and temporary. However, this was more commonly noted in the older studies in which the procedure was performed using fluoroscopy and not CT guidance. Mirror pain, due to either a bilateral pain syndrome that is masked by marked severity on one side or due to bilateral projection of dorsal roots in both spinothalamic tracts was observed rarely.[40] Ondine's curse was not reported in any of the studies.

Craniofacial cancer pain

Cranial Nerve Rhizotomy

There is class III evidence to support the use of cranial nerve rhizotomy for pain control in patients with craniofacial cancer pain (Table 5A). A single prospective observational study[54] reported that fluoroscopy-guided pulsed radiofrequency ablation of the glossopharyngeal nerve could be an effective therapy for patients with craniofacial cancer pain in the distribution of the glossopharyngeal nerve. Of the 25 patients treated, 23 (92%) had >50% pain relief at the 3-month post-treatment time point. These patients also exhibited a significant reduction in opioid consumption. No complications were reported. A single retrospective study[16] reported that percutaneous radiofrequency rhizotomy of the glossopharyngeal nerve (1 patient with pain in the glossopharyngeal nerve distribution) and combined percutaneous radiofrequency rhizotomy of the glossopharyngeal and trigeminal nerves (4 patients with pain in the glossopharyngeal and

trigeminal nerve distributions) were effective. All patients had oropharyngeal carcinoma. Pain outcomes were defined as "pain-free", "great improvement", "improvement", or "unchanged". Of the patients treated, 4/5 (80%) were pain-free during the study period and 1/5 (20%) was pain-free in the glossopharyngeal distribution and had improvement in the trigeminal distribution during the study period, which ranged from 4 months to 3 years. Complications included painful hypesthesias of the cornea, face, and pharynx; palatal weakness; and changes in voice. A single retrospective study[17] reported that percutaneous radiofrequency rhizotomy of the glossopharyngeal nerve was effective for pain from craniofacial cancer, including cancer of the tongue base, tonsil, larynx, and pyriformis sinus. Pain outcomes were defined as "complete" or "partial". Follow-up duration was not reported. Of the patients treated, 11/15 (73%) reported complete pain relief while 4/11 (27%) reported partial pain relief. Complications included glossopharyngeal nerve dysfunction in all patients, and included reduced gag reflex, oropharyngeal hypesthesia, and increased swallowing difficulties.

Nucleus Caudalis DREZ

There is class III evidence to support the use of nucleus caudalis DREZ for pain control in patients with craniofacial cancer pain (Table 5B). A single retrospective study[20] reported that open nucleus caudalis DREZ could be an effective treatment for craniofacial cancer pain, including posterior fossa lymphoma, lacrimal carcinoma, temporal meningioma, craniopharyngioma, and orbital fibrosarcoma. Postoperative results were graded as excellent (complete pain relief), good (pain decreased, activity not limited), fair (pain present, but less than before surgery, activity limited), and poor (pain same or worse than before surgery). Of the patients treated, 5/5 (100%) reported excellent or good pain relief immediately following surgery. On later follow-up (mean = 14.4 mo), 3/5 (60%) patients reported excellent or good pain relief, and 2/5 (40%) reported fair pain relief. There was only one complication: CSF leak requiring lumbar drain placement.

Trigeminal tractotomy-nucleotomy

There is class III evidence to support the use of trigeminal tractotomy-nucleotomy for pain control in patients with craniofacial cancer pain (Table 5C). A single retrospective study[55]

reported that percutaneous CT-guided trigeminal tractotomy-nucleotomy could be an effective treatment for craniofacial cancer pain. Postoperative results were graded as Grade I, no pain; Grade II, partial satisfactory pain relief; Grade III, partial non-satisfactory pain relief; and Grade IV, no change in pain. Of the treated patients, 11/13 (85%) achieved Grade I pain relief and 2/13, (15%) achieved Grade III pain relief. Both of these Grade III patients underwent nucleus caudalis DREZ as a salvage procedure. One patient had pain control and one did not and later committed suicide. The reported complications were listed for the whole group of 65 patients were not listed separately for the subgroup of cancer patients. A single retrospective study[56] reported that open C1-2 rhizotomy combined with trigeminal tractotomy and partial vertical nucleotomy could be an effective treatment for craniofacial cancer pain, including squamous cell carcinoma, laryngeal carcinoma, epipharyngeal carcinoma, and malignant hemangioma. Postoperative results were graded as "pain free" or "partial improvement." Follow-up duration was not specifically reported. Of the treated patients, 3/6 (50%) were reported as "pain free for the rest of their lives" and 3/6 (50%) were reported as "partial improvement."

Regarding trigeminal tractotomy, cranial nerve rhizotomy, or caudalis DREZ, there is insufficient evidence to recommend one procedure over the other for pain control in patients with craniofacial cancer pain. There were no published studies that compared these studies that also met the inclusion criteria for this guideline. Given the refractory nature of cancer pain in this population and the lack of available treatment options for these patients, cranial nerve rhizotomy, nucleus caudalis DREZ, and trigeminal tractotomy-nucleotomy may be reasonable treatment options, alone or in combination, in these patients who fail to respond to less invasive pain management strategies.

Midline subdiaphragmatic visceral cancer pain

Myelotomy

Nine class III studies support the use of myelotomy for immediate effective pain control for patients with midline sub-diaphragmic visceral cancer pain (Table 6). Eiras et al[57] and Gildenberg et al[58] first explored percutaneous cervical[57] and open thoracic[58] myelotomy, respectively, to treat cancer (unspecified type) and found that patients had significant reduction in pain immediately after surgery. Some had a late recurrence of pain years later.[57,58] Goedhart et

al demonstrated that 8 of 10 patients benefited with open myelotomy at the conus for sub-diaphragmic midline cancer pain.[59] Kanpolat et al found that over 70% of the cohort (n=10) received pain relief after percutaneous cervical myelotomy.[60] Between 2000-2004, Nauta et al,[61] Kim et al[62] and Hwang et al[63] explored the use of open myelotomy at the thoracic class ranging between T1-8 to treat the same and demonstrated significantly reduced pain and opioid use.[61-63] In 2010, Viswanathan et al found that of 11 abdominopelvic and spinal cancer patients, 8 had excellent to good relief with one failure.[64] In 2018, Vedantam et al[49] explored the use of open and mechanical and radiofrequency myelotomy in a variety of cancer and non-cancer patients. The study found that 5 out of 8 patients had significant decrease in visual analog scale (VAS) pain scores.[49] Of the 9 Class III studies discussed, 4 used the following outcome metrics to measure improvement and pain relief: VAS[49,63], NRS[49], Brachial Plexus Injury (BPI)[61], and Wisconsin Brief Pain Questionnaire (WBPQ).[62] Three of these also recorded opioid use.[61-63] Others used the Gildenberg/Hirchberg scale or a modification of it.[49,57,59,60,62,64]

Complications range from temporary[49,57-60,62] or permanent[62,64] sensory findings to gait disturbance/paraparesis[57,59] to none.[63] Other less common complications included post-operative sepsis[61] and urinary retention.[64] Given the lack of a control group, it is not clear whether the risk of these complications was higher in patients who underwent myelotomy versus those that did not undergo myelotomy. Recurrent pain also occurred.[57-59,61-64]

There is one class III study which addresses the smaller size of the tip used in percutaneous myelotomy as a possible etiology of less pain relief.[60] Specifically, the authors speculate less pain relief before making a methodological change to a 0.45mm diameter probe. However, there is not enough evidence in the literature to make a recommendation.

Disseminated Cancer Pain

Cingulotomy

Among ablative procedures, cingulotomy can be considered for patients with diffuse cancer pain, given that it targets pain processing networks rather than specific ascending pathways. There were 3 studies detailing the results of cingulotomy (Table 4).[50,65,66] All studies were case series and therefore class III evidence. The largest case series included 15 patients with an average follow-up of 6 months.[65] All series included mixed cancer types. Four studies

used radiofrequency to create bilateral cingulate gyrus ablations.[65,66] Two studies showed a substantial mean decrease in pain scores (50% reduction of pain rating scales),[50,66] whereas one study showed improvement in most patient initially (first month), but by 6 months 50% of patient had only 25%.[65] None of the studies recorded postoperative opioid use. All studies reported side effects related to personality changes, such as flat affect, perioperative confusion or paranoia.

DISCUSSION

Surgical neuroablation was introduced around the inception of neurosurgery as a specialty.[6,7] The decline in the use of neuroablation was concurrent with the discovery and increased utilization of opioids through multiple formulations and routes. Throughout its history, neuroablation's popularity has waxed and waned.[5] Neuroablation has been reemerging as a treatment option with increasingly frequent publications. There are several reasons for this resurgence: 1) One-third of those patients using hospice services reported pain at the last care visit before death. At present, the current WHO ladder (a three-step process to approach cancer pain relief in adults) does not adequately control pain in many patients,[2] 2) The increase in concern about opioid-induced hyperalgesia,[67] which has also become more evident given the present day opioid crisis, 3) the need for development of cost-effective procedures across patient populations,[68] 4) clinical scenarios that would not lend itself suitable for the neuromodulation alternative, such as presence of infection or need for MRI when the neuromodulation option is not MRI-compatible, 5) the potential for increased safety, accuracy, and precision of cordotomy and other ablative procedures, given more recently developed technology, including endoscopy, intraoperative monitoring and neuronavigation,[69] and 6) the resurrection of ablation in newer technologies such as laser ablation. Given the renewed interest in neural ablation, a thorough review of the literature and development of clinical practice guidelines on this topic is timely and necessary.

It is important to note that while there are many ablative procedures of the central nervous system for pain management, very few are utilized on a consistent basis. It also has received the highest attention in terms of structured reviews and analysis.[9,70] The guidelines task

force elected to include literature starting in 1980 to reflect practices close to contemporary practices.

The central nervous system ablative procedures are not equivalent in their intended effect, therefore, they have a preferential effect on certain types and/or locations of cancer pain. Table 2 outlines the ablative procedure for common indications.

Cordotomy is the procedure that received the highest level of recommendation in this review (level II). Kanpolat introduced CT guidance for percutaneous spinal cord ablation in the late 1980's, which greatly reduced the invasiveness of these procedures, contributing to its popularity. There are no reported mortalities using CT-guided cordotomy, compared to a 6.25% mortality rate when fluoroscopy alone was used.[71] There have been no reports directly comparing fluoroscopic to CT-guided cordotomy. Most recent reports exclusively used CT guidance. Multiple studies have examined the physiologic effects of interruption of the spinothalamic tract using quantitative sensory testing or using high resolution imaging.[72] Cordotomy was found to be most effective in unilateral somatic pain. Malignancies that produce this type of pain, such as mesothelioma, were most commonly treated using cordotomy. In addition, 2 studies[9,48] highlighted the extensive experience with cordotomy and large number of patients treated. There have also been recent reports regarding technical advances in this procedure.[38,70]

All other procedures received a level III recommendation and are considered options in the treatment of cancer pain based on the particular clinical scenario with which patients present.

FUTURE RESEARCH

A multicenter randomized placebo-controlled blinded study[73] is needed and is currently in process. However, this is not an easy task, given the ethical issue of randomizing a severe cancer pain patient with severe pain to non-surgical option and the number of patients needed to power a study.

Many other surgical procedures that have proven efficacy are subject to this ethical scrutiny. For example, Class I evidence of temporal lobectomy for epilepsy was only created in an environment where a 12-month waitlist was naturally imposed on all patients. Prior to this study, patients were only randomized to medical treatment when it was determined surgical

indication was challenging.[74] Alternatively, case control or matched cohort studies could be developed to obtain Class II evidence.

The alternatives to neuroablation are limited and usually exhausted prior to resorting to neuroablation. Intrathecal opioid therapy or spinal cord stimulation are reasonable alternatives, but are not effective or suitable in many cases. Neuroablation may be an alternative to intrathecal opioid therapy in certain subsets of cancer patients. Furthermore, the majority of papers are prospective series without control groups. Future studies should include randomized controlled trials to further evaluate the efficacy of cordotomy and other ablative procedures.

Guidelines are also an opportunity to identify gaps in evidence and needs for future research. Neurosurgeons specializing in the treatment of cancer pain should also report and/or include the following in future studies: self-reported morphine milligram equivalents (MMEs) pre- and post procedure, NASS patient satisfaction, caregiver burden, pain score (NRS, VAS, etc.), and a functional outcome measure (e.g., PROMIS, EQ-5D) at multiple time points so Kaplan-Meier curves can be developed. Cost effectiveness should also be studied (ER visits, cost of procedure, etc.).

CONCLUSIONS

Review of the data available for 8 neuroablation procedures demonstrated class II evidence for cordotomy effectiveness on the short term and therefore it should be considered as a treatment option in patients with unilateral somatic pain (level II recommendation). All other procedures except DREZ had class III evidence supporting these procedures as an option for the treatment of the particular type of cancer pain each procedure is effective against (level III recommendations). Currently there is not sufficient evidence to recommend DREZ as a treatment option for unilateral cancer pain.

Conflicts of Interest

All Guideline Task Force members were required to disclose all potential conflicts of interest (COIs) prior to beginning work on the guideline update, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee. The CNS Guidelines Committee and

Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs. Please see table 8 for all COIs.

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Disclaimer of Liability

This clinical, systematic, evidence-based clinical practice guideline update was developed by a multi-disciplinary physician volunteer taskforce and is provided as an educational tool based on an assessment of the current scientific and clinical information regarding the management and treatment of pediatric patients with hydrocephalus. This guidelines update is disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a physician should be sought. The proposals contained in this guidelines update may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in this guidelines update must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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Figure 1. PRISMA Article Flow Chart

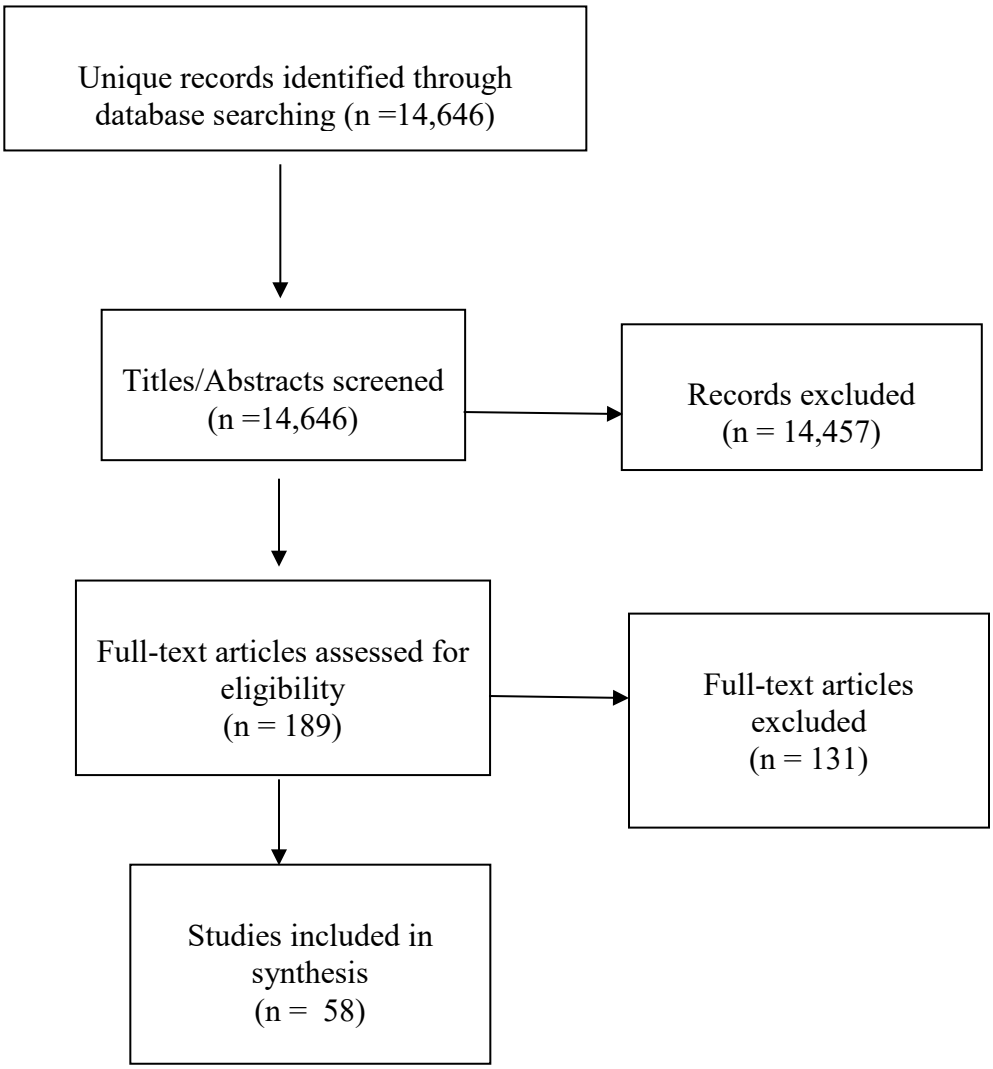

Table 1. Literature Search

Search Strategies

PUBMED Search	
1	Cordotomy [MeSH] OR Ganglionectomy [MeSH] OR Rhizotomy [MeSH] OR Sympathectomy [MeSH] OR Gyrus Cinguli/surgery [MeSH] OR Mesencephalon/surgery [Mesh] OR thalamus/surgery [MeSH]
2	Ablation [tiab] OR neuroablat* [tiab] OR "neurosurgical ablation" [tiab] OR "dorsal root entry zone" [tiab] OR DREZ [tiab] OR drezotomy [tiab] OR cingulotomy [tiab] OR cordotomy [tiab] OR chordotomy [tiab] OR ganglionectomy [tiab] OR gangliectomy [tiab] OR mesencephalotomy [tiab] OR myelotomy [tiab] OR neurotomy [tiab] OR neurectomy [tiab] OR rhizotomy [tiab] OR sympathectomy [tiab] OR thalamotomy [tiab] OR tractotomy [tiab]
3	1 OR #2
4	pain [Mesh]
5	pain [tiab]
6	#4 OR #5
7	#3 AND #6
8	#7 AND English [Lang]
9	(animals [MeSH] NOT humans [MeSH])
10	#8 NOT #9
11	#10 AND ("1966/01/01"[PDAT] : "2015/12/31"[PDAT])

EMBASE Search	
1	‘ablation therapy’/de OR ‘cordotomy’/de OR ‘ganglionectomy’/exp OR ‘neurectomy’/de OR ‘rhizotomy’/exp OR ‘sympathectomy’/exp OR ‘thalamotomy’/de OR 'cingulate gyrus'/exp/dm_su OR 'mesencephalon'/exp/dm_su
2	(Ablation OR neuroablat* OR ‘neurosurgical ablation’ OR ‘Dorsal root entry zone’ OR DREZ OR drezotomy OR cingulotomy OR cordotomy OR chordotomy OR ganglionectomy OR gangliectomy OR mesencephalotomy OR myelotomy OR neurotomy OR neurectomy OR rhizotomy OR sympathectomy OR thalamotomy OR tractotomy):ab,ti
3	#1 OR #2
4	pain’/exp
5	Pain:ab,ti
6	#4 OR #5
7	#3 AND #6
8	#7 AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1966-2015]/py
9	#8 NOT ‘conference abstract’/de
Cochrane CENTRAL Search	
1	MeSH descriptor: [Cordotomy] explode all trees

2	MeSH descriptor: [Ganglionectomy] explode all trees
3	MeSH descriptor: [Rhizotomy] explode all trees
4	MeSH descriptor: [Sympathectomy] explode all trees
5	MeSH descriptor: [Gyrus Cinguli] explode all trees and with qualifier(s): [Surgery - SU]
6	MeSH descriptor: [Mesencephalon] explode all trees and with qualifier(s): [Surgery - SU]
7	MeSH descriptor: [Thalamus] explode all trees and with qualifier(s): [Surgery - SU]
8	Ablation OR neuroablat* OR "neurosurgical ablation" OR "dorsal root entry zone" OR DREZ OR drezotomy OR cingulotomy OR cordotomy OR chordotomy OR ganglionectomy OR gangliectomy OR mesencephalotomy OR myelotomy OR neurotomy OR neurectomy OR rhizotomy OR sympathectomy OR thalamotomy OR tractotomy):ti,ab,kw
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10	Neoplasms [Mesh]
11	(neoplas* OR cancer* OR carcino* OR tumor* OR tumour* OR malignan*):ti,ab,kw
12	#10 OR #11
13	pain [Mesh]
14	pain [tiab]
15	#13 OR #14
16	#9 AND #12 AND #15

Table 2. Neuroablative procedure by clinical scenario

Clinical Scenario	Procedure
Disseminated cancer pain	Cingulotomy
Unilateral somatic nociceptive/neuropathic body cancer pain	Rhizotomy, Thalamotomy, Mesencephalotomy, Cordotomy
Craniofacial cancer pain	Trigeminal tractotomy, Rhizotomy (cranial nerves) or nucleus caudalis DREZ
Midline subdiagphragmatic visceral cancer pain	Midline myelotomy

Table 3. Classification of Evidence on Therapeutic Effectiveness and Levels of Recommendation

Class I evidence: Level I recommendation	Evidence from ≥1 well-designed, randomized, controlled clinical trials, including overviews of such trials
Class II evidence: Level II recommendation	Evidence from ≥1 well-designed comparative clinical studies, such as nonrandomized cohort studies, case-control studies, and other comparable studies, including less well designed randomized, controlled trials
Class III evidence: Level III recommendation	Evidence from case series, comparative studies with historical controls, case reports, and expert opinion, as well as significantly flawed randomized, controlled trials

Tables 4A-E. Unilateral somatic nociceptive/neuropathic body cancer pain

Table 4A. Rhizotomy

Author, Year	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
El-Sayed, 2007	III	20/20 patients in this study had cancer pain. Follow-up duration was 3 months. All cancers were lung cancer and included: bronchogenic CA, mesothelioma. Surgery type was percutaneous IT catheter. Complications included 1 non-responder. Opioid use was not recorded. Significant improvement in VAS but slow loss of efficacy up to 3 months was demonstrated. There was no survival analysis.
Rodriguez-Bigas, 1991	III	11/11 patients in this study had cancer pain. Follow-up duration was not explicit, but the longest recorded was 102 months. The study included survival analysis. All cancers were unresectable rectal adenocarcinoma. Surgery type was percutaneous IT injection. Complications included: 5- poor response. Opioid use was reported: Average: 333 MME/135 MME. Outcomes: 3 good, 3 fair, 5 poor.
Arbit, 1989	III	14/14 patients in this study had cancer pain consisting of intractable chest wall pain. Follow-up duration was 6 to 45 weeks, median 22 weeks. This study included survival analysis (median 22 weeks). Types of cancer included squamous, adenocarcinoma, and sarcoma. Surgery type: open thoracic rhizotomy. Complications included 1 unsatisfactory pain relief, 3 minor infections. Opioid use was not recorded. A total of 93% of patients had excellent or good pain relief.
Saris, 1986	III	This study evaluated cancer pain and non-cancer pain consisting of coccydynia. The number of patients with cancer pain out of the total patients was 19/28. Follow-up duration was 3 years (average). There was no survival analysis. Types of cancer included colorectal, prostate, bladder, cervical, and uterine. Surgery type: open selective rhizolysis. Complications included numbness, erectile dysfunction, bladder dysfunction, and wound infection. Opioid use was not recorded. Good pain relief in 53% of patients with malignant pain versus 22% of patients in non-malignant pain.

Author, Year	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Ischia, 1984	III	73/73 patients had cancer pain consisting of perineal and/or pelvisacral pain. Follow-up duration was 56 weeks. There was no survival analysis. Types of cancer included pelvic malignancies. Surgery type: percutaneous phenol injection with or without unilateral cervical cordotomy. Complications included urinary retention. Opioid use was not recorded. Intrathecal phenol rhizotomy effective 10-15% solution, but causes urinary retention.
Giorgi, 1984	III	This study evaluated cancer pain consisting of glossopharyngeal neuralgia. The number of patients with cancer pain out of the total patients was 5/14. Follow-up duration was 2 months to 20 years. There was no survival analysis. All types of cancer included nasopharyngeal. Surgery type was percutaneous radiofrequency ablation of the glossopharyngeal nerve with or without the trigeminal nerve (open surgery done only in the non-malignant cancer patients). Complications included reduced oropharyngeal sensation, dysphagia, ageusia. Opioid use was not recorded. Complete pain relief with percutaneous glossopharyngeal rhizotomy.
Pagura, 1983	III	15/15 patients had cancer pain consisting of glossopharyngeal neuropathic pain. Follow-up duration was not stated. There was no survival analysis. Types of cancer included tongue base, tonsil, larynx, and pyriformis sinus. Surgery type was percutaneous glossopharyngeal radiofrequency. Complications included reduced gag reflex, oropharyngeal hypesthesia, and increased swallowing difficulties. Opioid use was not recorded. 11/15 patients had complete pain relief and 4/15 partial pain relief.

Abbreviations: CA: Cancer; CSF: Cerebrospinal fluid; IT: Intrathecal; MME: Morphine milligram equivalent

Table 4B. DREZ

Author, Year	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Sindou, 1995	III	This case series evaluated cancer pain. The number of patients with cancer pain out of the total patients was 81/367. Follow-up duration was 1-4 months. There was no survival analysis. Types of cancer were not specified. Surgery type was open. Complications included infection and death (surgery precipitant). Opioid use was not recorded. 83% of cancer patients had "good" outcomes.
Kanpolat, 2008	III	This case series was mixed. The number of patients with cancer pain out of the total patients was 7/44 DREZ; 3/11 NC-DREZ. Follow-up duration was mean 6 years (0.5-20), but not specified for cancer pain patients. There was no survival analysis. Types of cancer was not specified. Surgery type was open. Complications included ARF, weakness, and CSF leak (DREZ); death - PE, ataxia, and hemiparesis (NC-DREZ). Opioid use was not recorded. Grade I-IV (VAS). There was "success" in 77% of patients (DREZ) and 72.5% of patients (NC-DREZ); cancer pain subgroup was not specified.
Rossitch, 1989	III	This case series evaluated cancer pain. The number of patients with cancer pain out of the total patients was 5/5. Follow-up duration was 14.4 (mean) months. There was no survival analysis. Types of cancer included posterior fossa lymphoma, lacrimal carcinoma, temporal meningioma, craniopharyngioma, and orbital fibrosarcoma. Surgery type was open. Complications included CSF leak. Opioid use was not recorded. There was significant improvement in 3/5 patients.

Abbreviations: CSF: Cerebrospinal fluid; DREZ: Dorsal root entry zone; NC-DREZ:

Table 4C. Thalamotomy

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Steiner, 1980	III	This case series evaluated cancer pain. There were 52 patients. Follow-up duration was 24 months. There was a survival analysis. Types of cancer were

		mixed and stage was not stated. Surgery type was GK. Complications included 2 patients with hemiparesis, 1 patient with subdural hematoma and a "few" patients with hypoesthesia. Opioid use was not recorded. 27 patients had good or moderate improvements and 23 patients with slight or no improvement.
Hitchcock, 1981	III	This was a case series. There were 14 cancer patients out of 43 total patients. Follow-up duration was 42 months. There was a survival analysis. Types of cancer were mixed and stage was not stated. Surgery type was RF. Complications included transient worsening of consciousness and transient weakness or occulomotor changes. Opioid use was not recorded. CM/Pf thalamotomy resulted in initial complete pain relief and satisfactory pain relief in most patients until death.

Abbreviations: CM/Pf: Centromedian/Parafasicular; GK: Gamma knife; RF: Radiofrequency

Table 4D. Mesencephalotomy

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Bosch, 1991	III	This was a case series that evaluated cancer pain. There were 40 cancer patients. Follow-up duration was >6 weeks in the cancer group. There was no survival analysis. Types of cancer: multiple. Surgery type was stereotactic. Complications: 1 mortality, 2 dysthesia, and 1 rubral myoclonus. Opioid use was not recorded. Effective in nociceptive pain relief.
Frank, 1989	III	This was a case series that evaluated cancer pain. There were 202 cancer patients. Follow-up duration was >6 weeks in the cancer group. There was no survival analysis. Types of cancer: multiple. Surgery type was stereotactic. Complications: 1 mortality, 7 dysesthesias, and 3 gaze palsies. Opioid use was not recorded. 81% of patients reported persistent pain relief.

Table 4E. Cordotomy

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Viswanathan 2019	II	A small prospective randomized controlled trial of 16 patient, 7 randomized to minimally invasive (percutaneous CT guided) cordotomy, 9 to best multidisciplinary palliative management. Follow up was for one week for all participant and up to 6 months depending on survival. The primary outcome was 33% reduction of pain intensity. Six of 7 patients (85.7%) randomized to cordotomy experienced >33% reduction in PI (median pre-procedure PI = 7, range 6–10; 1 week after cordotomy median PI = 1, range 0–6; p =.022). Zero of nine patients randomized to palliative care achieved a 33% reduction in PI. Seven patients (77.8%) randomized to palliative care elected to undergo cordotomy after 1 week. There were 3 complications: urinary retention, mild temporary limb weakness of 4+/5 and temporary dysesthetic pain on the previously painful side. Due to small sample size and the lack of blinding downgraded this study to level II.

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Honey 2019	III	Retrospective study examining the somatotopic organization of the spinal cord during percutaneous CT guided cordotomy. The clinical follow up was only for one week. Maximal daily pain reduced from average of 9.3 ± 0.5 (mean ± SD measured on a visual analog scale) to 0.5 ± 1.2 on the first postoperative day. 12 of the 18 palliative care patients were able to leave the hospital and be cared for at home or in a hospice. The average reduction in opiate medications, as measured by morphine equivalents, was 75% over 1 week (range 40%–98%). Two patients had a permanent complication: 4+/5 Medical Research Council grade weakness in the ipsilateral arm of a patient who was able to ambulate and go home, and urinary retention requiring an indwelling catheter in a patient with bladder cancer. Temporary complications included urinary retention (1 patient), ipsilateral weakness (2), and bilateral sixth nerve palsy from CSF leakage (1).
Vedantam 2018	III	Retrospective study examining the somatotopic organization of the spinal cord during percutaneous CT guided cordotomy. The study included 12 patients. Pain intensity was measured at day 1. 9/12 patients reported VAS between 0-1 at day 1. There were no reported complications.
Strauss 2017	III	Retrospective study examining outcomes after percutaneous cordotomy with O-arm (Medtronic, Dublin, Ireland) guidance. FU was up to 3 months (5/17 operated patients available for outcome), 2/19 patients developed delirium and procedure was aborted. 16/17 patients had excellent immediate pain relief, 15/17 had excellent pain relief at 1 months, only 5 patients were available for FU at 3 months, all experienced pain relief. 6/17 patients developed mirror pain, but only 1 was severe. 3/17 developed headache, 1/17 patients developed hemiparesis/Brown Sequard syndrome due to contrast injection

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Bekar, 2017	III	Retrospective review of 48 patients who underwent percutaneous CT guided cordotomy for cancer pain between 2004-2013. FU was up to 6 months and outcome included VAS, KPS, sleeping hours and Pain relief. 93% of patients showed either complete or satisfactory pain relief at 6 months. KPS improved from mean of 78 to 95 after surgery. 1/48 patients developed transient mild weakness, 7/48 patients reported dysesthesia initially and only 5 continued to report a mild dysesthesia later. 1/48 patients reported urinary retention.
Raslan, 2008	III	This is a prospective case series that evaluated cancer pain. There were 41 cancer patients. Follow-up duration was 6 months. There was no survival analysis. Types of cancer: varied. Surgery type was CT guided. Complications: 2 patients with dysesthesia; 2 with hypotension. Opioid use was not reported. VAS (8.5 preop, 2.3 at 6 months); KPS (56 preop, 77 postop); sleeping hours (3.2 to 7.1 postop).
Raslan, 2005	III	This is a case series that evaluated cancer pain. There were 8 cancer patients. Follow-up duration was 2 weeks. There was no survival analysis. Types of cancer: varied. Surgery type was CT guided. Complications: none (no lesion in 2 patients). Opioid use was not reported. 2 patients had complete pain relief; 4 satisfactory pain relief; 2 no pain relief; mean pain 3.1, 2 weeks postop
Crul, 2005	III	This is a case series that evaluated cancer pain. There were 43 cancer patients. Follow-up duration was 118 days (2-1460 days). There was no survival analysis. Types of cancer: varied. Surgery type was fluoroscopy-guided. Complications: 11 patients (7 mirror pain). Opioid use was reported: preop mean 190 mg MME; postop median 60 mg. Patients had a preoperatively mean VAS 7.2; postop to mean 1.1 postoperatively; end of life mean 2.9 months.

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Yegul, 2003	III	This is a case series that evaluated cancer pain. There were 9 cancer patients. Follow-up duration was not available. There was no survival analysis. Types of cancer: not available. Surgery type was CT guided. Complications: mild complications (headache, nausea, dysesthesia). Opioid use was not reported. There was a mean reduction of VAS 8.4 to 1.6 postop.
Jones, 2003	III	This is a case series that evaluated cancer pain. There were 9 cancer patients. Follow-up duration was 107 days (median). There was no survival analysis. Types of cancer: varied- pelvic cancer. Surgery type was open thoracic. Complications: none. Opioid use was reported: 8/9 decreased opioids; mean 560 mg preop; mean 160 mg postop. All patients had near complete pain relief.
McGirt, 2002	III	This is a case series that evaluated cancer pain treated by MRI-guided cordotomy versus percutaneous cervical cordotomy PCC. There were 38 cancer patients. Follow-up duration was (MRI group) 7 months (mean); (PCC group) 6 months (mean). There was no survival analysis. Types of cancer: varied. Surgery type was frameless stereotaxy and fluoroscopy. Complications: 16% MRI; 18% PCC. Opioid use was not reported. MRI group: excellent 100% postop; 83% last follow-up PCC group: 78% excellent postop; 55% last follow-up
Kanpolat, 2002	III	This is a case series that evaluated cancer pain. There were 19 cancer patients. Follow-up duration was 5.9 months (mean). There was no survival analysis. Types of cancer: mesothelioma. Surgery type was CT guided. Complications: 1 patient with dysesthesia. Opioid use was reported: 15 patients stopped opioids postoperatively. 18 patients had complete pain relief; 1 patient had partial pain relief.

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Jackson, 1999	III	This is a case series that evaluated cancer pain. There were 53 cancer patients. Follow-up duration was 2 days - 1 year (mean 13 weeks). There was no survival analysis. Types of cancer: mesothelioma. Surgery type was fluoroscopically-guided. Complications: 2 patients with dysesthesia; 4 with motor weakness. Opioid use was reported: mean 100 mg MME preop; mean 20 mg postop. 83% with pain relief allowing 50% reduction in opioids.
Sanders, 1995	III	This is a case series that evaluated cancer pain. There were 62 cancer patients. Follow-up duration was mean 6 months (3 weeks - 18 months). There was no survival analysis. Types of cancer: varied (most lung). Surgery type was fluoroscopically-guided. Complications: 13/62 (urinary retention, hemiparesis, mirror image pain). Opioid use not reported. 87% satisfactory; 9.7% partial; 2 none
Fenstermaker, 1995	III	This is a case series that evaluated cancer pain. There were 6 cancer patients. Follow-up duration was 4-10 months. There was no survival analysis. Types of cancer: multiple. Surgery type was 6 CT-guided transdiscal; lateral cordotomy unspecified. Complications: transient bladder dysfunction N=1. Opioid use not reported. Excellent 3 patients; Good 2 patients; Fair 1 patient; very limited details
Cowie, 1982	III	This is a case series that evaluated cancer pain. There were 43 cancer patients out of 56 total patients. Follow-up duration was 3 years. There was survival analysis. Types of cancer: multiple. Surgery type was open. Complications: 15/56 (urinary retention, ataxia, hemiparesis, respiratory failure, dysesthesia). Opioid use not reported. Grade I-IV (no pain to severe pain); 95% grades 1 or 2 postop; 73% grades I or II at 6 months; 55% grades I or II at 1 years

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Lahuerta, 1994	III	This is a case series that evaluated cancer pain. There were 140 cancer patients out of 146 total patients. Follow-up duration was long term. There was survival analysis. Types of cancer: multiple. Surgery type was percutaneous, fluoroscopy-guided. Complications: 6% Mortality, 100% Horner's syndrome, 69% weakness, and 20% retention. Opioid use not reported. 96 patients had complete pain relief, 33 patients had partial relief, 16 patients had no relief; 69% of cancer patients had complete pain relief
Collins, 2013	III	This is a case series that evaluated cancer pain. There were 6 cancer patients. Follow-up duration was 12 months. There was survival analysis. Types of cancer: multiple. Surgery type was percutaneous using O-arm. Complications: not reported. Opioid use not reported. Patients experienced 90% to 100% initial pain relief, with 50% to 100% sustained pain relief at the time of death at 2 to 12 months.
Bain, 2013	III	This is a prospective case series that evaluated cancer pain. There were 45 cancer patients. Follow-up duration was 28 days. There was no survival analysis. Types of cancer: multiple. Surgery type was percutaneous, fluoroscopy-guided. Complications: Mirror pain persisted in 8/45 patients, headache, worse pain. Opioid use was reported. Average pain score (Numerical Rating Scale: NRS) immediate preoperative, two days postoperative and 28 days postoperative was 7, 0, 0 respectively. Reduction of opioid use by 56%

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Kanpolat, 2013	III	This is a prospective case series that evaluated cancer pain. There were 210 cancer patients. Follow-up duration was not available. There was no survival analysis. Types of cancer: multiple. Surgery type was percutaneous CT guided. Complications: 2.4% temporary weakness, 2.4% temporary ataxia. Opioid use not reported. Median preoperative VAS score was 8 (6-9), which dropped postoperatively to 0 (0-8).
Higaki, 2015	III	This is a case series that evaluated cancer pain. There were 26 cancer patients. Follow-up duration was 57 days. There was no survival analysis. Types of cancer: multiple. Surgery type was percutaneous fluoroscopy guided in 21/26, CT guided in 5/26, and Bilateral in 3. Complications: mirror pain and motor weakness were fairly common. Opioid use was reported. 73% with new mirror pain, target pain improved in 100%. Weakness in about 40%.
Ischia, 1985	III	This is a retrospective cohort of prospectively collected data (survival analysis) that evaluated cancer pain. There were 119 cancer patients. Follow-up duration was until death (survival analysis). Types of cancer: Pancoast and thoracic. Surgery type was percutaneous, fluoroscopy-guided. Complications: Ipsilateral temporary weakness in 30%. Opioid use was not reported. 92% of patients had initial pain relief declines to as low as 30% at the time of death (around 12 months)
Ischia, 1984	III	This is a retrospective cohort of prospectively collected data that evaluated cancer pain. There were 69 cancer patients. Follow-up duration was 5 months (median). There was no survival analysis. Types of cancer: Neoplastic spinal. Surgery type was percutaneous fluoroscopy guided. Complications: not reported. Opioid use was not reported. 71% of patients had pain relief, some patients may be included elsewhere.

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Ischia, 1984	III	This is a retrospective cohort of prospectively collected data that evaluated cancer pain. There were 36 cancer patients. Follow-up duration was until death. There was survival analysis. Types of cancer: multiple. Surgery type was percutaneous fluoroscopy guided, bilateral. Complications: 12.5% mortality, 36% weakness. Opioid use was not reported. Bilateral cases only, 47% of patients had complete pain relief, and 12.5 % of patients had pain relief. Patients might be included in other studies.
Ischia, 1984	III	73/73 patients had cancer pain consisting of perineal and/or pelvisacral pain. Follow-up duration was 56 weeks. There was no survival analysis. Types of cancer included: pelvic malignancies. Surgery type: percutaneous phenol injection with or without unilateral cervical cordotomy. Complications included urinary retention. Opioid use was not recorded. Intrathecal phenol rhizotomy effective 10-15% solution, but causes urinary retention.
Stuart, 1993	III	This is a case series that evaluated cancer pain. There were 273 cancer patients. Follow-up duration was up to 5 years. There was no survival analysis. Types of cancer: multiple with majority mesothelioma. Surgery type was percutaneous fluoroscopy guided. Complications: 3.3 % mortality, 1.5% hemiparesis, 0.7 % dysesthesia, 1.1 % urinary retention. Opioid use not reported. Patient outcomes: 219 successful, 1 partially successful, 3 effective cordotomy without pain relief, 26 unsuccessful but repeat cordotomy successful, 1 unsuccessful but repeat cordotomy partially successful, 23 failed without repeat attempt.

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Amano, 1991	III	This is a case series that evaluated cancer pain. There were 198 cancer patients out of 221 total patients. Follow-up duration was up to 3 months. There was no survival analysis. Types of cancer: multiple. Surgery type was percutaneous, fluoroscopy-guided, bilateral in 60/221. Complications: urinary retention in 4 bilateral cordotomy patients. Opioid use not reported. Bilateral cordotomy had superior results. "Clinically acceptable" pain relief in 95% of bilateral and 82% of unilateral patients.
Hogberg, 1989	III	This is a case series that evaluated cancer pain. There were 24 cancer patients. Follow-up duration was up to 111 days (median). There was no survival analysis. Types of cancer: gynecologic. Surgery type was open. Complications: no "serious" complication. Opioid use was incompletely reported. Patient outcomes: 19 pain free, 4 moderate or no relief, 1 not evaluable.
Palma, 1988	III	This is a case series that evaluated cancer pain. There were 145 cancer patients out of 163 total patients. Follow-up duration was >2 weeks, up to 8 years for non-cancer patients. There was no survival analysis. Types of cancer: multiple. Surgery type was percutaneous, fluoroscopically-guided in all but 2 patients (open). Complications: 10 transient bladder dysfunction, 5 transient paresis, 4 transient respiratory failure, 2 transient ataxia, 1 prolonged respiratory failure, and 2 death (one respiratory, one coronary); "high frequency" of Horner's syndrome; bilateral did not have special complications (no death among bilateral). Opioid use not reported. Patient outcomes: 94 (52%) cervico-dorsal, 60 (33%) high dorsal, 28 (15%) dorsal-lumbar. All patients reported immediate and complete pain relief.

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Meglio, 1981	III	This is a case series that evaluated cancer pain. There are 52 cancer patients. Follow-up duration was 11 weeks (mean). There was no survival analysis. Types of cancer: multiple. Surgery type was percutaneous fluoroscopy guided, 1 had a repeat open. Complications: 3 respiratory dysfunction, 4 non-incapacitating paresis, 2 bladder dysfunction, 1 hypotension, and 1 astenia. Opioid use not reported. Patient outcomes: excellent results in 92% immediately, 73% after one week, 63% after 15 weeks; only considered complete relief because of difficulties rating partial relief.

Abbreviations: CT: Computed tomography; HA: Headache; KPS: Karnofsky performance status; MRI: Magnetic resonance imaging; NRS: Numerical Rating Scale; PCC: Percutaneous Cervical Cordotomy; VAS: Visual analog scale

Table 5A-C. Craniofacial cancer pain

Table 5A. Cranial Nerve Rhizotomy

Author, Year	Class of Evidence	Summay, Outcomes, complications and rationale for evidence grading
Bharti, 2018	III	This prospective observational study included 25 patients treated with percutaneous pulsed radiofrequency ablation of the glossopharyngeal nerve for cancer pain in the territory of the glossopharyngeal nerve. The patients had oropharyngeal carcinoma. Outcome measures included pain relief, nausea/vomiting, opioid consumption, and sleep disturbance. Follow-up duration was 1 year. There was no survival analysis. There were no major complications. Of the patients treated, 25/25 (100%) had $\geq$50% pain relief at the 2-week post-treatment time point and 23/25 (92%) had $\geq$50% pain relief at the 3-month post-treatment time point. The average duration of effective pain relief was 5 to 9 months. These patients also had decreased opioid consumption, lesser nausea/vomiting, and improved sleep.
Giorgi, 1984	III	This retrospective study included 5 patients, 1 patient with pain confined to the glossopharyngeal nerve treated with percutaneous radiofrequency rhizotomy of the glossopharyngeal nerve and 4 patients with pain in both the glossopharyngeal and trigeminal nerve distributions treated with percutaneous radiofrequency rhizotomy of the glossopharyngeal and trigeminal nerves. All patients had oropharyngeal carcinoma. Pain outcomes were defined as "pain-free", "great improvement", "improvement", or "unchanged". Follow-up duration ranged from 4 months to 3 years. There was no survival analysis. Of the patients treated, 4/5 (80%) were pain-free during the study period and 1/5 (20%) was pain-free in the glossopharyngeal distribution and had improvement in the trigeminal distribution during the study period. Complications included painful hypesthesias of the cornea, face, and pharynx; palatal weakness; and changes in voice. Opioid use was not reported.

Author, Year	Class of Evidence	Summay, Outcomes, complications and rationale for evidence grading
Pagura, 1983	III	This retrospective study included 15 patients with pain confined to the glossopharyngeal nerve treated with percutaneous radiofrequency rhizotomy. Types of cancer included tongue base, tonsil, larynx, and pyriformis sinus. Pain outcomes were defined as "complete" or "partial". Follow-up duration was not reported. There was no survival analysis. Of the treated patients, 11/15 (73%) reported complete pain relief while 4/11 (27%) reported partial pain relief. Complications included glossopharyngeal nerve dysfunction in all patients, and included reduced gag reflex, oropharyngeal hypesthesia, and increased swallowing difficulties. Opioid use was not reported.

Table 5B. Nucleus Caudalis DREZ

Author, Year	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Rossitch, 1989	III	This retrospective case series included 5 patients treated with open nucleus caudalis DREZ for craniofacial cancer pain. Postoperative results were graded as excellent (complete pain relief), good (pain decreased, activity not limited), fair (pain present, but less than before surgery, activity limited), and poor (pain same or worse than before surgery). Follow-up duration was immediately after surgery and "later follow-up" (mean of 14.4 months). There was no survival analysis. Types of cancer included posterior fossa lymphoma, lacrimal carcinoma, temporal meningioma, craniopharyngioma, and orbital fibrosarcoma. Complications included CSF leak. Opioid use was not recorded. Immediately after surgery, 5/5 (100%) of patients reported "excellent" or "good" pain relief. At later follow-up, 3/5 (60%) reported "excellent" or "good" pain relief while 2/5 (40%) reported "fair" pain relief.

Abbreviations: CSF: cerebrospinal fluid; DREZ: dorsal root entry zone

Table 5C. Trigeminal Tractotomy-Nucleotomy

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Kanpolat, 2008	III	This retrospective case series, which included a total of 65 patients, included 13 patients treated with percutaneous CT-guided trigeminal tractotomy-nucleotomy for craniofacial cancer pain. Postoperative outcomes were Grade I, no pain; Grade II, partial satisfactory pain relief; Grade III, partial nonsatisfactory pain relief; and Grade IV, no change in pain. There was no survival analysis. Types of pain were not reported. Opioid use was not recorded. Of the treated patients, 11/13 (85%) achieved Grade I pain relief and 2/13, (15%) achieved Grade III pain relief. Of these two patients, both underwent nucleus caudalis DREZ as a salvage procedure. One patient had pain control and one did not and later committed suicide. The reported complications were listed for the whole group of 65 patients were not listed separately for the subgroup of cancer patients.
Plangger, 1987	III	This retrospective case series, which included 20 patients treated with open rhizotomy (C1-C2) as well as tractotomy and partial vertical nucleotomy for craniofacial pain, included 6 patients with cancer-related pain. Malignancies treated included squamous cell, larynx and epipharynx carcinoma and malignant hemangioma. Outcomes were defined as "pain free" or "partial improvement." Follow-up duration was not specifically reported. There was no survival analysis. Opioid use was not reported. Of the treated patients, 3/6 were reported as "pain free for the rest of their lives" and 3/6 with "partial improvement."

Abbreviations: CT: computed tomography, DREZ: dorsal root entry zone

Table 6. Midline subdiaphragmatic visceral cancer pain

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading

Vedantam et al, 2018	III	This was a case series that evaluated cancer pain. There were 7 cancer patients and 1 non-cancer patient who underwent myelotomy. Follow-up duration was 2-54 weeks. There was no survival analysis. Types of cancer: melanoma, pancreatic, sarcoma, hemangio-endothelioma, and prostate. Surgery type was open limited, percutaneous radiofrequency, and percutaneous mechanical. Complications: minor sensory; cold feeling or tingling in feet. Opioid reports were used to determine outcome categorizations. There was significant reduction in VAS scores in patients who underwent open limited myelotomy categorizing them as having excellent outcomes. Mechanical and radiofrequency percutaneous patients had fair or poor outcomes.
Hwang, 2004	III	This was a case series that evaluated cancer pain. There were 6 cancer patients. Follow-up duration was 12-18 weeks. There was no survival analysis. Types of cancer: abdominal. Surgery type was open, T2-3 laminectomy with fluoro, microscope; punctate lesion with needle. Complications: none. Opioid use was recorded. There was significant reduction in VAS and opioid use.
Nauta, 2000	III	This was a case series that evaluated cancer pain. There were 6 cancer patients. Follow-up duration was 3-31 months. There was no survival analysis. Types of cancer: Midline visceral and somatic cancers. Surgery type was open laminectomy with fluoro and microscope at T7-8 in 2, T8 in 2, T7 in 1, T3-4 in 1. Complications: sepsis. Opioid use was recorded. There was significant reduction in BPI and opioid use.
Kim, 2000	III	This was a case series that evaluated cancer pain. There were 8 cancer patients. Follow-up duration was 3-18 months. There was no survival analysis. Types of cancer: stomach. Surgery type was open, T1-2 laminectomy, dorsal midline myelotomy. Complications: Permanent (1 patient) and temporary (2 patients) paresthesias. Opioid use was recorded. Patients had a reduction in pain and opioid use.

Eiras, 1980	III	This was a case series that evaluated cancer pain. There were 12 cancer patients. Follow-up duration was 2-22 months. There was no survival analysis. Types of cancer: not reported. Surgery type was frame-based percutaneous cervical. Complications: Temporary gait disturbance and paresthesias. Opioid use was incomplete. Patients had initial good results with late recurrence of pain in 5 patients.
Gildenberg, 1984	III	This was a case series that evaluated cancer pain. There were 20 cancer patients, including 4 patients with combined cordotomy. Follow-up duration was 2-13 months. There was no survival analysis. Types of cancer: not reported. Surgery type was open; T9-10 laminectomy. Complications: Paresthesias that improved with time. Opioid use was not reported. Majority of patients had marked reduction of pain, with late decay of the effect.
Goedhart, 1984	III	This was a case series that evaluated cancer pain. There were 10 cancer patients. Follow-up duration was 2 months-20 years. There was survival analysis. Types of cancer: Sub-diaphragmatic midline. Surgery type was open microscopic midline myelotomy at conus at L1- down to S5- short as possible. Complications: Paraparesis in 3, paresthesias in 5. Opioid use was not reported. 5 patients had benefit until death, 3 patients had meaningful relief, 2 patients had temporary relief.
Kanpolat, 1997	III	This was a case series that evaluated cancer pain. There were 14 cancer patients. Follow-up duration was 43 days (median). There was no survival analysis. Types of cancer: Sub-diaphragmatic midline. Surgery type was percutaneous cervical. Complications: hypesthesia in 1 patient. Opioid use was not reported. In six of the cases, total pain relief was achieved (42.8%); partial, satisfactory pain relief was attained in four cases (28.5%), and no pain control was achieved in four cases (28.5%).
Viswanathan, 2010	III	This was a case series that evaluated cancer pain. There were 11 cancer patients. Follow-up duration was long term. There was no survival analysis. Types of cancer: Abdominopelvic and spinal tumors with neural

		infiltration. Surgery type was open microscopic T10-L1. Complications: 3 patients had proprioception problems post op; 1 patient needed a urinary catheter. Opioid use was not reported. Gildenberg/Hirschberg- 5 excellent, 3 good, 2 fair 1 poor; 1 had relief for only 2 weeks. No change to KPS. Frankel grade: 5 frankel E- preop- post op 2 E, 1 C, 2 D. 1 D and 4 C all stayed the same.

Table 7. Disseminated Cancer Pain

Authors	Class of Evidence	Summary, Outcomes, complications and rationale for evidence grading
Yen, 2005	III	This case series evaluated cancer pain. There were 15 patients. Follow-up duration was 6 months. There was a survival analysis. Types of cancer were mixed and stage IV. Surgery type was RF. Complications included transient confusion, GI bleeding, loss of efficacy. Opioid use was not recorded. 2 of 10 patients had >75% improvement. 5 patients had <25% improvement at 6 months
Pillay, 1992	III	This case series evaluated cancer pain. There were 8 patients. Follow-up duration was 6 months. There was no survival analysis. Types of cancer were mixed and stage IV. Surgery type was RF. Complications were not stated. Opioid use was not recorded. Verbal pain scale dropped from mean 7 to mean 3.4.
Strauss, 2017	III	This was a case series of 13 patients with advanced metastatic disease and pain, with limited survival prognosis. Patients underwent two cingulotomy ablations per side. 9 of 11 patients reported good pain relief after one month and 5 of 7 patients reported relief at 3 months.

Table 8. Conflicts of Interest

Guideline Author	COI Disclosure
André G. Machado, MD, PhD	Grants/Research Support: NIH Consultant Fee: St. Jude, Functional Neuromodulation Other Financial Support: Medtronic Board/Trustee/Officer Position: Enspire DBS Other: ATI, Cardionomics, Enspire
Jonathan Miller, MD	Nothing to Disclose
Julie G. Pilitsis, MD, PhD	Grants/Research Support: Medtronic, Boston Scientific, Abbott, Nevro, TerSera, NIH 2R01CA166379-06 and NIH U44NS115111 Consultant: Boston Scientific, Nevro, TerSera, Medtronic, Saluda and Abbott Medical Advisor/stock equity: Aim Medical Robotics and Karuna
Ahmed M. Raslan, MD	Grants/Research Support: Medtronic, St. Jude Medical, Boston Scientific, Integra, Cyberonics; Consultant Fee: St. Jude Medical
William S. Rosenberg, MD	Consultant Fee: Medtronic, Nevro
Jason M. Schwalb, MD	Research funding: Boston Scientific, Medtronic, Neuros, StimWave Salary support: Blue Cross Blue Shield of Michigan (co-Director of the Michigan Spine Surgery Improvement Collaborative)
Jennifer Sweet, MD	Grants/Research Support: KL2 NIH award Other Financial Support: Scientific Advisory Board-Helius Medical Technologies
Ashwin Viswanathan, MD	Grants/Research Support: NIH Consultant Fee: Boston Scientific, Medtronic

Guideline Author	COI Disclosure
Christopher J. Winfree, MD	Nothing to disclose
Sharona Ben-Haim, MD	Nothing to disclose
Steven M. Falowski, MD	Consultant: Abbott, Medtronic, Saluda, Vertiflex, Boston Scientific, Vertoss Equity: Thermaquil, SPR Therapeutics, Saluda, CornerLoc, PainTeq, Stimgenics, AGR, Neural Integrative Solutions, SpineThera, Celeri Research: Medtronic, Abbott, Vertiflex, Saluda, CornerLoc, Boston Scientific, Biotronik, Stimgenics
Joshua Rosenow, MD	Consultant: Boston Scientific Neuromodualtion Grant/Research Support: NIH, DoD, VA, SPR, Boston Scientific Neuromodulation, Voyager Therapeutics

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