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### Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Neuroablative Procedures for Patients With Cancer Pain

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## Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Neuroablative Procedures for Patients With Cancer Pain

**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 were reviewed by 2 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.

**CONCLUSION:** 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.

The full guidelines can be accessed at <https://www.cns.org/guidelines/browse-guidelines-detail/guidelines-on-neuroablative-procedures-patients-wi>.

**KEY WORDS:** Cancer pain, Central nervous system Ablation, Cordotomy, Guidelines, Myelotomy

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### 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

**ABBREVIATIONS:** AANS, American Association of Neurological Surgeons; CNS, Congress of Neurological Surgeons; DREZ, dorsal root entry zone; RF, radiofrequency

cordotomy, DREZ, thalamotomy, mesencephalotomy, and Rhizotomy that indicate efficacy of pain control?

### **Craniofacial Cancer Pain**

- 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?
- 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**

- For patients with midline subdiaphragmatic visceral cancer pain, is myelotomy effective for pain control and reducing risk of potential complications?
- In patients with midline subdiaphragmatic visceral cancer pain, what are the outcome(s) following myelotomy that indicate efficacy of pain control?

### **Disseminated Cancer Pain**

- For patients with disseminated cancer pain, is cingulotomy effective for pain control and reducing risk of potential complications?
- 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 radiofrequency (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 mo. 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-diaphragmatic 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 vs 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. While the general trend

in the last few decades of the twentieth century has been a departure from ablation of the nervous system, central nervous system ablation for cancer pain has been re-introduced as a treatment option in select instances, such as cordotomy for mesothelioma.<sup>1</sup>

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. A total of 131 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 ( $\geq 18$  yr 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."<sup>2</sup> In addition, the task force will confirm within 5 yr 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, and disseminated cancer pain. A total of 58 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.

### Rhizotomy

Seven reports of rhizotomy for cancer-related neuropathic pain were identified (Table 4A),<sup>3-9</sup> all of which were case series and, therefore, determined to provide Class III level of evidence.

### DREZ Lesioning

Three Class III case series were identified (Table 4B).<sup>10-12</sup> One manuscript addressed only deafferentation cancer pain, and two included cancer and noncancer pain. Most patients experienced long-term pain relief, but heterogeneous outcome metrics and times of evaluation precluded adequate conclusions about effectiveness.

### Thalamotomy

Two reports of thalamotomy for cancer-related chronic neuropathic pain were identified (Table 4C),<sup>13,14</sup> both of which were determined to provide Class III evidence.

### Mesencephalotomy

Two reports of mesencephalotomy for cancer pain were identified (Table 4D).<sup>15,16</sup> Both of these studies provide Class III evidence and include 40 and 202 patients respectively.

### Cordotomy

Thirty reports of cordotomy for cancer pain were identified (Table 4E),<sup>7,17-45</sup> suggesting that it is the most studied and commonly performed ablative procedure for cancer pain. Three studies were prospective,<sup>17,18,31</sup> and many included a large number of patients (over 100 in some cases), or followed all patients until death.

## 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<sup>46</sup> reported that fluoroscopy-guided pulsed RF ablation of the glossopharyngeal nerve could be an effective therapy for patients with craniofacial cancer pain in the distribution of the glossopharyngeal nerve.

### 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<sup>12</sup> reported that open nucleus caudalis DREZ could be an effective treatment for craniofacial cancer pain, including posterior fossa lymphoma,

lacrimonasal carcinoma, temporal meningioma, craniopharyngioma, and orbital fibrosarcoma.

### 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<sup>47</sup> reported that percutaneous CT-guided trigeminal tractotomy-nucleotomy could be an effective treatment for craniofacial cancer pain.

## Midline Subdiaphragmatic Visceral Cancer Pain

### Myelotomy

Nine class III studies support the use of myelotomy for immediate effective pain control for patients with midline subdiaphragmatic visceral cancer pain (Table 6).<sup>41,48-52,53,54</sup>

## 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).<sup>42,55,56</sup> All studies were case series and therefore class III evidence.

## DISCUSSION

Surgical neuroablation was introduced around the inception of neurosurgery as a specialty.<sup>57,58</sup> 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.<sup>59</sup> Neuroablation has been reemerging as a treatment option with increasingly frequent publications. 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.

## FUTURE RESEARCH

A multicenter randomized placebo-controlled blinded study is needed and is currently in process. Alternatively, case control or matched cohort studies could be developed to obtain Class II evidence. 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 pre- and postprocedure, NASS patient

satisfaction, caregiver burden, pain score (numerical rating scale, visual analog scale, etc), and a functional outcome measure (eg, patient-reported outcomes measurement information system, EQ-5D) at multiple time points so Kaplan-Meier curves can be developed. Cost effectiveness should also be studied (emergency room visits, cost of procedure, etc).

## CONCLUSION

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.

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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 guideline update may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in this guideline 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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