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Treatment of chest wall pain syndrome from oncologic etiology with neuromodulation: A narrative review

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ABSTRACT

Pain affects 50% of patients with cancer. Cancer-related pain occurs from tumor invasion as well as a sequela from cancer treatment. Despite numerous and often significant side effects, opioid, and neuropathic pain medications remain the mainstays of treatment for cancer-related pain. Neuromodulation-based treatment approaches including SCS, DRGS, and PNS are becoming increasingly common in the cancer pain landscape. In this narrative review, we present 11 case reports and case series that highlight the usefulness of neuromodulation for the treatment of chest wall pain from various cancer-related pathologies. Of the 34 patients included in these reports, 30 patients (88.25%) derived meaningful pain relief with the use of neuromodulation-based approaches. In addition, a majority of patients were able to reduce or eliminate their opioid requirements. This review provides early evidence that neuromodulation can be an effective treatment option for the treatment of cancer-related chest wall pain and set the backdrop for future clinical trials.

1. Introduction

Based on data from the American Cancer Society, there were 16.1 million Americans living with cancer in 2019 and this population is expected to surpass 22.1 million by 2030 [1]. It is estimated that pain affects over 50% of patients with cancers of all stages and 39.1% of patients after curative treatment [2]. With the trend towards improvement in cancer survivorship, the proportion of patients who will suffer from cancer-related pain after curative treatment will likely increase. According to the World Health Organization guidelines, opioids and non-opioid adjunct medications are recommended first for the treatment of pain in cancer patients [3]. However, side effects from these medications, including nausea, vomiting, sedation, constipation, fatigue, and cognitive impairment, often compromise the quality of life and limit escalation to effective doses in this population.

Neuromodulation techniques such as dorsal column spinal cord stimulation (SCS), dorsal root ganglion stimulation (DRGS), and peripheral nerve stimulation (PNS) are interventional options for the treatment of various painful conditions including failed back surgery syndrome, painful peripheral neuropathy, complex regional pain syndrome and other neuropathic pain conditions [4–6]. The adoption of these procedures for cancer-related pain has been cautious due to concerns over magnetic resonance imaging (MRI) conditionality, risks of device infection in an immunocompromised patient population, and the higher incidence of coagulopathy and anticoagulation among patients with active malignancies. With improvements in MRI-compatible devices and the efficacy of neuromodulation, these procedures are increasingly being utilized in cancer patients.

Chest wall pain from tumor extension or from cancer treatment can occur in many patients whose cancer originates in the thoracic cavity. Breast, lung, mesothelioma, and esophageal cancer can extend into the brachial plexus resulting in neuropathic pain in the form of plexopathy. They can also invade into the pleural tissue or the rib cage producing nociceptive chest wall pain. Surgical removal of the tumor can lead to tissue trauma that can manifest as various forms of neuropathic chest wall pain such as intercostal neuralgia from thoracotomy to post-mastectomy pain syndrome from breast surgery. Chemotherapy and radiation therapy can lead to nerve damage which can present as either chemotherapy or radiation-induced plexopathy of the brachial plexus. Numerous case reports and case series have been published that demonstrate the use of neuromodulation for the treatment of chest wall pain of oncologic etiology. The goal of this manuscript is to provide a narrative review of the usefulness of neuromodulation for the treatment of chest wall pain of oncologic etiology.

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Table 1
Studies highlighting the use of dorsal column spinal cord stimulation for the treatment of thoracic wall pain from various oncologic etiology.

Study	Type of Study	Number of subjects	Age	Sex	Cancer type	Pain type	Duration (mon)	Neuromodulation System	Waveform	Lead location	Outcome
1	Case report	1	71	M	Esophageal	Right-sided post-thoracotomy pain syndrome	NR	SCS	Traditional	T3 superior endplate (slightly right of the midline)	The patient's pain score improved from 8/10 at baseline to complete resolution of pain at 3 months follow-up. The patient also experienced functional improvement and improvement in sleep.
2	Case report	1	58	F	Lung	Right-sided post-thoracotomy pain syndrome	3	SCS	Traditional	T6 and T7 (slightly right of the midline)	The patient reported 9/10 pain at baseline. The patient experienced a 75% improvement in pain with the trial. The pain scores improved to 2/10 during the trial. At 24 months follow-up after implantation, the patient continued to experience a 75% reduction in pain. Additionally, the patient experienced functional improvement.
3	Case series	14	NR	M (10) F (4)	Lung	Post-thoracotomy pain syndrome and post-radiation pain syndrome	9–23	SCS	Traditional	T3, T4, and T5 (position varied based on the patient)	The patients' pains score ranged between 6 and 9 out of 10. The pain score improved for all patients and ranged between 1 and 3 out of 10 at 12 months after SCS implantation. Ten patients stopped opioids and 4 patients decreased opioid use.
4	Case series	6	56	F	Breast	Right arm pain from brachial plexopathy (tumor invasion)	NR	SCS	BurstDR	Top of C2 and C3	The patient experienced >75% pain relief during the trial and continued at a 1-year follow-up. The patient took opioids at baseline which she progressively lowered after SCS implantation.
			54	F	Breast	Right-sided post-mastectomy pain syndrome		SCS	BurstDR	Both lead slightly right paramedian at the top of T3 and T1	The patient experienced 80% pain relief during the trial. The patient discontinued all opioids at 15-month follow-up. Complications: Lead migration after a mechanical fall
			64	F	Breast	Right-sided post-mastectomy pain syndrome		SCS	BurstDR	Top of C4 (single lead trial)	The patient experienced 30% pain relief during the trial and did not proceed to implantation.
			65	F	Breast	Left-sided post-mastectomy pain syndrome		SCS	Traditional	Top of C2 (single lead)	The patient experienced >50% pain relief during the trial and proceed to implantation. The patient discontinued

(*continued on next page*)

Table 1 (*continued*)

Study	Type of Study	Number of subjects	Age	Sex	Cancer type	Pain type	Duration (mon)	Neuromodulation System	Waveform	Lead location	Outcome
											all opioids after the implantation until passing away within a year of disease progression.
			61	F	Breast	Right-sided post-mastectomy pain syndrome		SCS	Traditional	One lead at T3/4 interspace and second lead at T5/6 interspace	The patient experienced >75% pain relief during the trial but passed away prior to implantation.
			53	F	Breast	Right-sided post-mastectomy pain syndrome		SCS	Traditional	Top of T1 and T2	The patient experienced >60% pain relief during the trial and proceeded to implantation. The patient continued to derive pain relief for the post-mastectomy pain syndrome; however, opioid use continued due to CIPN from the feet.
5	Case report	1	66	M	Mesothelioma	Tumor invasion of the left chest wall	NR	SCS	BurstDR	Top of T1 and top of T3; slightly left of midline	The patient's NRS pain score improved from 8 at baseline to 4 after the trial; therefore, the patient underwent permanent implantation. The patient was able to reduce opioid use by 180 OME and experienced improved function. The author does not report the time point when the patient experienced reduced opioids.
6	Case report	1	55	M	Lung	Multifocal pain (Right post-thoracotomy pain, chronic lower back pain and bilateral lower extremity pain)	NR	SCS	Traditional	Top of T5 and Top of T8	The patient experienced a 60% improvement in pain after the trial and continued the same benefit at 1-year follow-up. The patient discontinued all opioids at the follow-up.

Legend: M – male, F- female, NR – not reported, SCS – spinal cord stimulation.

2. Methods

This is a review of the literature highlighting the usefulness of SCS, DRGS, and PNS for the treatment of chest wall pain from oncologic etiology. We performed a librarian-assisted literature search of the EMBASE and Google Scholars databases. Search terms used were "chest wall pain", "post-thoracotomy pain syndrome", "post-mastectomy pain syndrome", "thoracic pain", "cancer", "neuromodulation", "spinal cord stimulation", "dorsal root ganglion stimulation", and "peripheral nerve stimulation". A total of 815 results were found which were manually reviewed and excluded if they were in a non-English language, meta-analysis, review articles, poster presentations, or not relevant to the topic of interest.

3. Results

A manual review of the results led to the identification of 11 relevant manuscripts. Of these, 6 were on the use of SCS, 2 were on the use of DRGS and 3 were on the use of PNS for chest wall pain originating from cancer.

3.1. SCS for chest wall pain

A total of 6 case reports and case series were published on the usefulness of SCS for the treatment of chest wall pain from oncologic etiology [7–12]. Table 1 shows the demographics, cancer type, pain type, duration of pain prior to neuromodulation use, neuromodulation specifications, and outcomes of 24 patients who were treated with SCS in these reports. In this cohort of 24 patients, 54.17% were male and 45.83% were female. Age was reported for 10 patients and ranged between 53 and 71 years. Cancer types in this patient population included breast, lung, esophageal, and mesothelioma. Pain types treated with SCS included post-thoracotomy pain syndrome (75.0%), post-mastectomy pain syndrome (20.83%), and chest-wall pain from direct tumor invasion (8.33%). A traditional tonic SCS waveform was used in 20 patients and BurstDR (Abbott Neuromodulation, Plano, Texas) waveform was used in four patients. Lead position varied based on the specific pain location and ranged from C2 to T8. With regards to outcome, 22 patients were reported to have derived meaningful pain relief after permanent implantation at variable follow-up time points. In all these studies,

Table 2
Studies highlighting the use of dorsal root ganglion stimulation for the treatment of thoracic wall pain from various oncologic etiology.

Study	Type of Study	Number of subjects	Age	Sex	Cancer type	Pain type	Duration (months)	Neuromodulation System	Waveform	Lead location	Outcome
1	Prospective study	4	68	F	Lung	Post-thoracotomy pain syndrome	NR	DRGS	NA	Left T6 and T8	The patient's NRS pain score improved from 7 at baseline to 2 at 90 days and 1-year follow-up. The patient's DN4 pain score improved from 8 at baseline to 3 at 90 days and 1-year follow-up. The patient discontinued all opioids at 90 days follow-up.
			49	F	Thymus	Post-thoracotomy pain syndrome		DRGS		Left T6 and T8	The patient's NRS pain score improved from 6 at baseline to 2 at 90 days and 1-year follow-up. The patient's DN4 pain score improved from 9 at baseline to 2 at 90 days and 1-year follow-up. The patient discontinued all opioids at 90 days follow-up.
			37	M	Lung	Post-thoracotomy pain syndrome		DRGS		Left T4 and T6	The patient's NRS pain score improved from 8 at baseline to 3 at 90 days and 1-year follow-up. The patient's DN4 pain score improved from 8 at baseline to 2 at 90 days and 1-year follow-up. The patient discontinued all opioids at 90 days follow-up.
			70	M	Chondro-sarcoma	Post-thoracotomy pain syndrome		DRGS		Left T4 and T6	The patient's NRS pain score improved from 8 at baseline to 3 at 90 days and 1-year follow-up. The patient's DN4 pain score improved from 8 at baseline to 2 at 90 days and 1-year follow-up. The patient discontinued all opioids at 90 days follow-up.
2	Case series	6	55	F	Breast	Post-mastectomy pain syndrome	36	DRGS	NA	Bilateral T4, T5, T6 and T7	The patient's VAS pain score improved from 8 at baseline to 2 at the 2-week follow-up. The patient discontinued all opioids at the 2-week follow-up.
			72	F	Breast	Post-mastectomy pain syndrome	36	DRGS		Left T2, T3 and T4	The patient's VAS pain score worsened from 7 at baseline to 8 at the end of the trial; therefore, the patient did not undergo permanent implantation.

Legend: M – male, F- female, NR – not reported, NA – not applicable. DRGS – dorsal root ganglion stimulation.

meaningful pain relief was defined as at least greater than >50% pain relief. One patient did not have a successful trial and did not proceed to implantation. One patient had a successful trial but expired prior to implantation. Four of the studies consisting of a total of 22 patients reported on the impact of neuromodulation on opioid use and showed that 21 patients were able either discontinue or reduce opioid requirements.

3.2. DRG for chest wall pain

A total of two case reports were published on the usefulness of DRGS for the treatment of chest wall pain from oncologic etiology [13,14]. Table 2 shows the demographics, cancer type, pain type, duration of pain prior to neuromodulation use, and outcomes of six patients included in these case reports. In this group of six patients, 33.33% were male and 66.67% were female with age ranged between 37 and 72 years. Cancer types in this patient population included lung, breast, thymus and chondrosarcoma. Four patients (66.67%) were treated for post-thoracotomy pain syndrome and two patients (33.33%) were treated for post-mastectomy pain syndrome. Lead placement varied depending on the location of the pain and ranged from T2 to T8 dorsal root ganglia. However, it is worth noting that DRG technology is currently FDA-approved to stimulate T7 to S2 dorsal root ganglion. Five

Table 3
Studies highlighting the use of peripheral nerve stimulation for the treatment of thoracic wall pain from various oncologic etiology.

Study	Type of Study	Number of subjects	Age	Sex	Cancer type	Pain type	Duration (mon)	Neuromodulation System	Waveform	Lead location	Outcome
2	Case report	1	83	M	Lung	Brachial plexopathy	NR	PNS	NA	Inferior trunk of brachial plexus	The patient's pain improved from 8/10 at baseline to 0/10 immediately after PNS implantation. On day 2, the patient experienced a 60% improvement in his pain. In the following weeks, the patient was able to titrate off all of his neuropathic pain medications and solely relied on his PNS.
3	Case series	1	46	F	Breast	Post-mastectomy pain syndrome	96	PNS	NA	T2 and T4 spinal nerve	The patient's pain score improved from 10/10 to 1/10 at the time of lead extraction. The patient continued to experience pain relief for 6 weeks followed by a return to baseline pain.
12	Case series	11	NR	F	Breast	Post-mastectomy pain syndrome and CRPS II	NR	PNS	NA	Right T2 and T4	The patient's patient score improved from 10 at baseline to 1 during stimulation and 1 at lead extraction. The patient experienced 6 weeks of analgesia after lead extraction.
			NR	F	Breast	Post-mastectomy pain/ intercostobrachial neuritis	NR			C8 and T	The patient's patient score improved from 10 at baseline to 8 during stimulation and 10 on day two of trial when lead was extracted secondary to rash.

Legend: M – male, F- female, NR – not reported, NA – not applicable. PNS – peripheral nerve stimulation.

out of six patients experienced improvement in their pain score from DRGS and one patient experienced worsening of their pain score during trial and did not undergo permanent implantation. Of these five patients with improved pain score, four patients had improvement in pain score that persisted beyond one year. Five patients were able to discontinue all opioids; after two weeks for one patient and 90 days for four patients.

3.3. PNS for chest wall pain

A total of three case reports consisting of four patients were published on the usefulness of PNS for the treatment of chest wall pain from oncologic etiology [15–17]. All these studies used SPR system. Table 3 shows the demographics, cancer type, pain type, duration of pain prior to neuromodulation use, and outcomes of four patients included in these case reports. In this group of four patients, 25.0% were male and 75.0% were female. Age was reported for two of the four patients and was 46 and 83. Cancer types in this group included breast and lung cancer. In this cohort, one patient had brachial plexopathy from tumor extension where the PNS lead was placed over the inferior trunk of the brachial plexus, two patients had post-mastectomy pain syndrome where the PNS leads were placed over T2 and T4 spinal nerve roots, and one patient had combined post-mastectomy pain syndrome and intercostobrachial neuralgia where the PNS lead was placed over C8 and T1 spinal nerve roots. With regards to outcome, two patients experienced significant improvement in pain score during the 60 days trial that persisted at six weeks follow-up. One patient experienced 60% pain relief during the 60 days trial and was able to titrate off all neuropathic pain medications at the time of trial. However, the duration of pain relief after PNS lead extraction is not reported for this patient. One patient could not complete the trial due to the development of a rash at the site of lead insertion.

4. Discussions

Cancer-related pain due to tumor extension, mass effect or secondary to treatment can cause a range of pain syndromes. Unfortunately, around 50% of patients with cancer experience pain related to their treatment [18]. Cancer-related pain can be categorized as neuropathic or nociceptive, and may be accompanied by central sensitization. Symptoms more indicative of central sensitization include allodynia, pressure hyperalgesia, pain mediated by low threshold mechanoreceptors (Aβ fibers), and the spread of pain and sensitivity into areas with no identifiable pathology.

When conservative treatments and medication management are not effective at relieving cancer-related pain, neuromodulation may be considered as an option, even for non-traditional locations such as the thorax and chest. As we described in our literature review, there have been 11 published manuscripts, entirely comprised of case reports and case series, that reported on the use of neuromodulation for chest and thoracic pain syndromes from cancer-related origins. In total, 34 patients were included in the studies, of which 30 patients (88.24%) found meaningful pain relief of at least a few months. An additional patient had a successful trial, but passed away before implantation occurred. This preliminary evidence suggests that in those patients that have chest and thorax cancer-related pain, neuromodulation may be a viable option for pain relief.

5. Future direction

Cancer-related pain is a significant and growing issue, not only in terms of patient related quality of life, but also in terms of the number of people impacted and the subsequent healthcare costs. Most patients with

cancer-related pain are treated with a combination of opioid and non-opioid medications, but many continue to experience poorly controlled pain and a marked reduction in quality of life. The side effects of these pain medications, particularly those affecting the central nervous system and gastrointestinal system, can also significantly impact patient well-being and limit effective dose escalation.

Spinal cord stimulation received approval from the US Food and Drug Administration in 1989 for the treatment of chronic pain in the trunk and limbs [19]. Over the past decade, advancements in SCS technology, particularly advancements in waveform and pulse programming, have significantly improved patient outcomes [20]. SCS has been shown in numerous randomized controlled trials to be more effective at controlling pain than conservative medical management in several chronic neuropathic pain conditions, including chronic spine and extremity pain after surgery, painful diabetic neuropathy, complex regional pain syndrome, and pain related to peripheral vascular disease [21]. However, there is a dire need for additional studies on the use of SCS in cancer-related pain, as the current published literature in this area is very limited. As we described above, small studies and case reports suggest it is likely that neuromodulation may be an effective therapeutic modality for several challenging cancer-related neuropathic pain syndromes, such as post-mastectomy pain syndrome, post-thoracotomy pain syndrome, and intercostobrachial neuralgia [7–17]. However, larger well-designed studies are necessary before formal recommendations can be provided to medical providers and more specific guidance offered to patients. These future studies should focus on comparing optimal conservative medical management (CMM) to CMM and neuromodulation techniques. Additionally, specific patient and disease characteristics require further analysis to identify subgroups that may be more likely to benefit from these techniques. These factors may include age, gender, cancer type, cancer stage, type of pain (ex. neuropathic vs nociceptive; somatic vs visceral), type of treatment, pre-surgical opioid intake, and associated comorbidities. This information may one day allow us to more confidently tailor specific treatment plans to each individual patient in this heterogenous patient population.

Lastly, as cancer treatment improves and patients continue to live longer, healthier lives during and after their cancer treatment, it is imperative that pain specialists continue to advance our field to support this vulnerable patient population. We have the potential to dramatically improve the lives of these patients who suffer immensely during their cancer journey.

6. Conclusion

Cancer-related chronic pain of the chest and thorax affects a large number of cancer patients and is likely to continue to increase as oncologic therapies advance. While these symptoms are most often managed with medications, injections, and neuraxial therapies, there is some evidence to suggest that SCS and PNS should be considered as additional treatment options. There is Level 1 evidence, based on studies in non-cancer pain, to support the use of SCS and PNS in chronic neuropathic pain states. As many cancer patients experience similar types of pain, it is important to consider the use of SCS, DRGS, and PNS as a therapeutic option for cancer-related pain, and for the pain medicine community to further research these treatment options for this specific patient population.

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Declaration of competing nterest

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