Case Report

CONSIDERATIONS FOR THE USE OF DORSAL COLUMN STIMULATION FOR LUMBOSACRAL RADIATION NEURITIS OF THE NERVE ROOT IN THE SPINE TUMOR PATIENT (A CASE SERIES)

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Background: Radiation therapy (RT) has become a mainstay in the treatment of various malignancies. Unfortunately, a potential side effect of this modality is radiation-induced neuritis. The time-course is varied and the emergence of pain syndromes can be delayed by several years after the completion of treatment. Risk factors include the total radiation dose, fractionation schedule, and radiation field size. Spinal cord stimulation (SCS) may have an important role in attenuating the symptoms of radiation-induced neuritis.

Objectives: We aim to characterize a case series of oncologic patients who underwent SCS to treat iatrogenic radiation neuritis of the lumbosacral nerve roots.

Study Design: This is a retrospective review of 4 cases of patients who were eligible for either intrathecal drug delivery or SCS (magnetic resonance imaging [MRI] conditional devices for spine surveillance), of which each patient elected to have a SCS trial and possible permanent implantation.

Setting: The data were collected at a major cancer center in the US.

Methods: In this case series, we present 4 patients with radiation-induced neuropathy. For each patient, we describe the use of SCS, which uses electric impulse generation, in an effort

to treat the patient's symptoms. To assess for efficacy, we compare pre- and post-procedure numerical rating scale (NRS) pain scores and post-procedure pain medication requirements.

Results: Each patient had marked improvement in their pain (> 50%) during the trial lead placement and proceeded to the permanent implant. In subsequent months and years, the patients decreased their opioid utilization and reported an improvement in their overall pain.

Limitations: This case series is a small sample size of heterogeneous malignancies with radiation treatment to the spine.

Conclusions: Radiation-induced neuritis remains a severe and limiting outcome that some patients must live with after RT. Survivors of malignancy have often found this pathology to severely impact their quality of life, and it is difficult to treat. We have described the utilization of spinal cord neuromodulation as an effective treatment modality in the spine tumor patient population. Further research is needed to maximize the benefit and ensure appropriate case selection in the future.

Key words: Radiation neuritis, radiation neuropathy, oncologic lumbar radiculopathy, spinal cord stimulation, neuromodulation, dorsal column stimulation, spinal tumor pain, MRI conditional spinal cord stimulation

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Therapeutic radiation therapy (RT) is based on the premise that cancer cells have impaired DNA repair abilities and are thus less able to withstand the energy transfer provided by the directed radiation, though surrounding “normal” tissue may still be damaged (1,2). Over half of all cancer patients will receive radiation during their treatment (3). Unfortunately, the rise of this modality has led to increasing radiation-induced pain syndromes in the cancer patient population. A meta-analysis found that approximately one-third of patients with cancer experience chronic pain even after curative therapy (4,5). Radiation-induced nerve damage often manifests several years after the completion of RT, and the diagnosis may be complicated by concern for local cancer recurrence (6-8).

Risk factors for nerve damage include the large total dose (> 50 Gy to plexus, > 60 Gy to cranial nerves), large dose per fraction (> 2.5 Gy, stereotactic radiosurgery), salvage RT of previously treated areas, and intracavitary radium source, among others (9). With regards to neuropathies and plexopathies, common risk factors include the total radiation dose, fractionation schedule, and radiation field size; in regard to the patient, common risk factors include advanced age, obesity, and/or co-morbidity factors, particularly those involving impaired vascularity such as hypertension or diabetes (10,11). In patients with radiation-induced brachial plexopathies, patients report paresthesias (100%), hypoesthesia (74%), weakness (58%), and pain (47%) (12). The incidence and chronicity is highly dependent on the factors discussed above and newer technologies targeting tumors with better accuracy (12).

Paradigms for treatment options in patients with neuropathic pain induced by RT are lacking. Opioids and adjuvant analgesics are often a mainstay of therapy, though this approach is not based on clinical trials. Chemical sympathectomy has been helpful in a small case series, whereas amputation was found to exacerbate the overall pain due to development of phantom pains (6). Cervical dorsal root entry zone lesions in the cervical spinal cord may be effective in selective patients (13). Intrathecal drug delivery may be the mainstay for uncontrolled pain in the oncologic population. Recently, due to the availability of magnetic resonance imaging (MRI) conditional systems, spinal cord stimulation (SCS) may prove to be a use-

ful modality for patients suffering from RT-induced neuropathy in terms of reduced self-reported pain as well as decreased opioid utilization (14,15). This is especially important in the spinal tumor population as MRI surveillance of the spine is needed to note disease progression.

We describe 4 patients, who underwent therapeutic and/or palliative RT of the spine and subsequently developed radiation-induced neuritis of a lumbosacral nerve root, who were successfully treated with SCS. Each patient presented with poor pain control with conservative medication management in our pain clinic. Each patient's oncologic disease was stable and not progressing with RT, thus, they had an expected lifespan greater than one year. Finally, each patient was offered an intrathecal drug trial and possible delivery system (as is standard in our practice). The patients decided to undergo an SCS trial, rather than an intrathecal trial with opioids and/or local anesthetic or ziconotide.

METHODS

This retrospective review was approved via a waiver for informed consent by the Memorial Sloan Kettering Cancer Center (MSKCC) Internal Review Board and supported by the MSKCC Support Grant (P30 Core Grant) and the Department of Anesthesiology and Critical Care. A chart review of each patient with radiation neuritis who underwent a trial and permanent implant of SCS was performed. For each case we outlined the clinical history and pain symptoms and severity, before and after the SCS implantation. For each trial, we utilized a Medtronic SureScan® (Medtronic, Minneapolis, MN) with 2 leads and 8 contacts per lead. Medtronic was chosen for each case because at the time of implantation they offered the only MRI conditional device of the full body, and each of our patients may require future MRI scans to monitor the status of their respective oncologic diseases.

Technique

Trial SCS Lead Placement

All trial lead placements were performed in a hospital operating room. The patients were given the choice of conscious sedation by a trained anesthesiologist or

nurse anesthetist under the supervision of an anesthesiologist. In cases of spinal fusion, an intact epidural space was confirmed with MRI and the previous operating surgeon. The position of the percutaneous leads in the epidural space was confirmed by fluoroscopy in both the anteroposterior (AP) and lateral positions. The position of the leads was confirmed on fluoroscopy and through test stimulation. If the patient had received sedation, the anesthetic depth was lightened in order for the patient to be appropriately responsive to the stimulation questions. Intermittent programming occurred throughout the trial period.

Permanent SCS Lead and Generator Placement

If the patient reported 50% improvement on the pain scales or functional improvement, a permanent implant was offered. All procedural techniques were similar to the temporary placement, with the exception of the following: patients were given the option for general anesthesia for placement. If the patient chose this option, the placement of leads was similar to the final trial lead locations. In these cases, neuromonitoring, using somatosensory evoked potentials under the supervision of a neurologist, was

used to ensure adequate coverage of the affected areas during lead placement in the manner outlined above (to confirm appropriate laterality).

Case One

An 83-year-old woman with a history of metastatic breast cancer (1992), status post-lumbar fusion (2005 for spinal stenosis) and status post-radiation to L2 (2014), presented with worsening left L3 radicular pain. Her neuropathic pain worsened for the following 6 months after radiation, requiring an escalating dosage of opioids (including fentanyl patch 100 mcg/hr and morphine 15 mg every 4 hours as needed) and anti-neuropathic therapy (gabapentin 900 mg/day), until a SCS trial was recommended. A percutaneous device was trialed and implanted and 8-contact leads were inserted at the T12-L1 interspace and advanced to T7 (Fig. 1). Her settings are pulse width 450 microseconds at 450 Hz. The patient reported significant relief (50% improvement in numerical rating scale [NRS] score of 8/10 to 4/10) with an improved ability to ambulate from a few steps to being able to walk around her home and perform household chores) and the decision was made to proceed to the permanent implant in 2 weeks after the 5-day trial.

Following the implant, her fentanyl patch was reduced to 37 mcg/hr, in addition to taking minimal breakthrough-pain medications. After decreasing her

Fig. 1. (A) AP view of the SCS leads at the T7-T8 interspace. (B) Sagittal MRI of the lumbar spine showing disease at L3 (*).

opioid and gabapentin doses, the patient reported improvement of her iatrogenic constipation and sedation. Ten months post-implant, the patient complained of severe axial low back pain, and subsequent MRI of the spine showed multiple lumbar vertebral body fractures. Her pain returned to baseline after multiple kyphoplasties. Of note, the SCS was not able to improve her axial pain during the discovery of the vertebral fractures. As of this publication acceptance, she is baseline in improvement of pain and 20 months post-implant.

Case 2

A 68-year-old woman with breast cancer, status post-mastectomy and chemotherapy in 1996, presented with low back pain in 2014; she was treated conservatively at an outside facility. In 2015, a mass lesion in the sacrum abutting the S1 and S2 nerve

roots was discovered during imaging after her pain escalated. A biopsy confirmed the mass to be follicular thyroid metastases. The patient underwent total thyroidectomy and stereotactic RT in 2015 (30 Gy with 3 fractions) and re-irradiation (35 Gy in 5 fractions). Despite treatment, she continued to have sacral back pain radiating into the right groin and buttocks and down the leg. Her pain become more difficult to manage and she became intolerant to opioids and anticonvulsants due to the side effects. Prior to the SCS trial, she had been relying on long-acting oral hydromorphone 12 mg every 12 hours and oral dilaudid 4mg every 4 hours as needed.

The patient was admitted in pain crisis and given a hydromorphone PCA. A SCS trial was offered and performed, with the entry being at the L1-L2 interspace and threaded to T7 (Fig. 2). The trial resulted in 60% improvement of pain (NRS score of 10/10 to

Fig. 2. (A) AP view of the SCS leads placed at the T7 T8 interspace. (B) CT scan of the pelvis at the level of the sacrum and ilium (axial cuts).

(*) shows a right sacral mass invading the right S1 foramen. For comparison, the left S1 nerve and foramen are intact (arrow).

4/10) during the day with ambulation (she was unable to ambulate beyond one to 2 steps) and 100% pain relief at night (with the ability to sleep on her back which she could not do previously). The settings are 500 milliseconds pulse width at 80 Hz (though throughout the management she uses multiple programs). She discontinued her hydromorphone IV PCA and was comfortable ambulating with an assistive device, and after a 2-day trial she proceeded to the permanent implant the following week.

Post-implant, she was weaned off all opioids. Seven months after implant, she had an acute exacerbation of her pain, and MRI of the spine showed no disease progression, but increased swelling of the S1 nerve root. Steroid therapy reduced her pain symptoms; however, the daytime coverage of her pain decreased to 40% improvement, while the nighttime pain was still 100% resolved. She was restarted on hydromorphone therapy, and 15 months post-implant, an intrathecal pump was implanted (hydromorphone only) as she developed intractable nausea to systemic opioid therapy. As of the acceptance of this publication, she continues to use SCS programs for 100% pain relief at night, and intrathecal boluses during the day for additional day-time pain relief.

Case 3

The patient in this case is a 77-year-old woman diagnosed with a chordoma in the lumbar spine, who underwent surgical decompression in 2012 (mass at L3) and RT (24 Gy with one fraction). The patient was taking hydrocodone-acetaminophen combination pills approximately 4 times daily, as well as gabapentin 1800 mg per day for worsening radicular pain (beginning in 2014) of her right thigh, which was presumed to be radiation-induced since the pain was not present after surgical treatment. In 2015, she underwent a trial of SCS because she could no longer tolerate opioid therapy (multiple regimens were initiated prior to trial, including methadone) and epidural steroid injections were ineffective in improving her pain.

Her leads were staggered at T8 and T10 to improve the likelihood of adequate coverage (Fig. 3). The trial improved her pain by 50% (NRS score of 8/10 to 4/10) and her opioid dosage was reduced to one to 2 tablets of hydrocodone (a 50% improvement in dosage) both during the trial and permanent implan-

tation 3 weeks after trial. Of note, she was able to ambulate without assistance (multiple steps) with the SCS device active. During discontinuation of stimulation, she would sit and not ambulate due to pain. Her settings are 500 microseconds at 500 Hz up to 1.6 V. As of the acceptance of this publication, she is 16 months post-implant and currently uses her SCS for back pain (NRS score of 5–6/10) and oral opioids for left knee osteoarthritis-related pain, which has exacerbated in the last year.

Case 4

The patient in this case is a 63-year-old woman diagnosed with rectal carcinoma in 2000, who underwent chemotherapy and pelvic RT (45 Gy with 9 fractions). She subsequently developed a high grade sacral sarcoma (presumably radiation-related and was diagnosed in 2013) with lumbar and sacral nerve root involvement, for which she was treated with chemotherapy, RT, and proton therapy in 2014 (75.6 CGE [cobalt gray equivalents] with 42 fractions). Her pain went from a NRS score of 10/10 to 0/10, however, within one year, her pain returned and escalated with a presumed diagnosis of S1 radiation neuritis (Fig. 4). The patient used long-acting morphine sulfate 60mg every 12 hours prior to SCS implantation. Her pain was rated as a 10/10 on a NRS, prior to implantation.

In 2016, a SCS trial was recommended with the leads placed at T10 for adequate coverage. She had a decrease of pain to a NRS score of 5/10 and was able to discontinue all opioids after the permanent implant. Her settings are 500 microseconds at 500 Hz with maximum 1.8 V. As of the acceptance of this publication, she is 10 months post-implantation and states similar pain relief at 50% improvement (NRS score of 5/10), and she states a subjective improvement in mobility.

DISCUSSION

These cases above demonstrate the potential value that SCS can have for patients affected by RT-induced neuritis. RT has grown significantly over the decades since its inception and is now widely employed in a large spectrum of malignancies. SCS has matured over a similar time-course and has become well-established for its efficacy (16) and has been utilized as a treatment modality for a growing

Fig. 3. (A) AP view of the SCS leads at T8. (B) Sagittal MRI of the lumbar spine with the epidural extension at L3 (*).

range of painful conditions (17). This case series emphasizes radiation neuritis of the lumbosacral nerve root as an evolving pain syndrome. As part of routine monitoring, MRI conditional systems are necessary for continued imaging of the spine, and at the time of these case series, devices available were limited to the ones described above.

These patients present with radiation neuritis of a particular nerve root, and the pain syndrome may be akin to lumbar radiculopathy of a degenerative disease. The selection of lead placement may be similar to locations chosen for failed back syndrome. Of concern is the effect of radiation to the epidural space. In cases 1 and 3, lead placement in the epi-

dural space was more difficult due to either changes in the epidural space (case one with fibrotic changes felt during lead placement) or fusion (case 3 required placement between surgical rods and scar tissue was encountered during needle placement). In this population, changes to soft tissue are expected at and near the radiation field and may extend beyond the borders of the tumor. Thus, we expect a more difficult placement of SCS leads in this population and have chosen to perform these cases in the operating room, due to the potentially increased length of procedure time. Furthermore, the tactile feel of placing these leads may be different in patients with previous radiation in the spine, and practitioners should be aware

Fig. 4. (A) SCS leads placed at T10, AP view. (B) Axial CT scan with calcification and tumor in the sacrum (*). Calcification is also noted in the S1 foramen (arrow).

of the possible complications of bleeding and dural puncture as a result (none of our patients had a known dural puncture during placement).

Interestingly, the patients in cases 2 and 4 present with similar pain syndromes (right S1 radicular pain symptoms), however, the lead placement varied in each case (T8 and T10, respectively). The trials were based on paresthesia settings and thus, it may be expected that stimulation may occur at different locations for each patient. It may be inferred that oncologic pain may be complex, involving not only the nerve root but also treated tissue which may encompass additional structures. As radiation is delivered to tumor, adjacent structures also receive radiation doses (albeit lower Gy as the distance from a tumor increases) (Fig. 5). Newer radiation techniques, using protons, reduce adjacent radiation exposure and perhaps the incidence of pain syndromes.

Additionally, newer high-frequency technologies may provide pain relief at different locations along the spinal cord and may be investigated in the oncologic population. Though not available at the time of the publication, MRI conditional systems that include the spine have become available from multiple manufacturers. Furthermore, ultra high frequencies > 1000 Hz and variations of burst stimulation may prove to be more efficacious in the treatment of pain syndromes in this population. In case 2, the patient has multiple programs with multiple paresthesia and sub-paresthesia settings, which she rotates to provide optimal pain relief, and our newer trials involve multiple platforms for the use of SCS in the oncologic population.

However, as noted in case 3, radiation neuritis is an evolving syndrome. An acute exacerbation of pain may be resultant of an advancing disease or the changing condition of neuritis. The neuritis begins

Fig. 5. Shown here are the radiation dosage fields for the patient in case 2 (photon-based radiation). (A) This area of the field receives maximum radiation dosage calculated to treat the tumor. (B) Tissue in this field receives 50% of the dosage to the tumor. The contour encompasses the sacral plexus. (C) Illustrates 30% dosage and exposure to the bowel. (D) Illustrates 20% of the treatment dose and exposure to the patient's skin.

as an inflammatory process, though it may become a fibrotic process over time. More importantly, the pain symptoms may present themselves at anytime of the continuum of neuritis. In case 2, the patient had a significant change in the quality and characteristic of her pain, presenting with intense "burning." Of concern is disease progression, and if this is not occurring, consideration to worsening neuritis may be a cause of worsening pain. The patient was responsive to oral and intravenous steroids, further supporting inflammatory neuritis as a cause of the patient's pain. Because the pain syndrome may change, it is reasonable to assume that the stimulation settings would need to change as well. Furthermore, if disease progression or changes in the neuritis pattern are expected, SCS may not be the most appropriate choice for pain control over time.

In each of these cases, the patients preferred a SCS trial rather than intrathecal drug delivery for pain control. In general, intrathecal drug delivery is probably a more accepted modality for pain control in this population (18). However, as technology improves, we need a better understanding of the effects of neurostimulation in the dorsal column and whether this modality

would be helpful in the oncologic population (19). At our institution, our paradigm involved the stability of the pain syndrome. Patients are given the option of a SCS trial if we believe the pain syndrome is unlikely to evolve or change, or they are offered intrathecal drug delivery if disease progression or pain evolution is likely to occur (or if the SCS trial is insufficient in managing a patient's pain) (19-20).

In an oncologic pain practice, we are attempting to define the paradigm for the use of SCS. It is generally accepted that in the oncologic population, intrathecal drug delivery may be a preferred option for neuroaxial pain control (18). Though as our understanding of pain syndromes in the oncologic population become better identified, neuropathic pain syndromes may be better treated with stimulation. Furthermore, patient preference may drive whether to offer SCS as a treatment option. Three of the 4 patients preferred not to have "regular" maintenance of their pain therapy. Moreover, one patient (case 2) wanted to eliminate all opioids from her pain treatment and elected for a SCS trial. Finally, a SCS trial more closely resembles the permanent system, whereas intrathecal drug delivery trialing remains controversial. We tend to select

a SCS trial for neuropathic pain syndromes that tend to remain stable over time in the oncologic population (i.e., for acute and active diseases, intrathecal drug delivery may be better indicated).

An important concern in the oncologic population is the use of MRI for both the detection of cancer and surveillance. For example, MRI screening for breast cancer is becoming better studied and more accepted in the high-risk population (21). In our subset of patients, MRI of the spine was a requirement prior to considering a SCS implant, though as technology changes, newer devices may be available for consideration. As MRI indications increase, practitioners should consider which device is best for an oncologic patient. We advise working with radiology departments to ensure that patients may have MRIs under the conditions specified by the SCS manufacturer. In our 4 cases, 2 patients needed MRI of the spine to evaluate for disease progression (case 2) and a new pain syndrome (case 3 for lumbar vertebral fracture). In both cases, MRI of the lumbosacral spine was obtained without incident.

Limitations

As a case series, the presented data only represents the potential of SCS in the oncologic population suffering from symptoms of radiation neuritis. Further studies should be considered in the form of rigorous trials and studies.

CONCLUSION

We present 4 cases of successful placement of a SCS in patients with distinct radiculopathy of the lumbosacral spine resulting from radiation neuritis. As newer technologies become available, it is thought that electrical neuromodulation may become a wider accepted option for pain control in the oncologic population. However, conditional MRI systems may still be necessary in this population as MRI indications continue to expand in this population. Special attention for MRI surveillance in the spine may determine the appropriate devices needed in the spinal tumor population.

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