Pain Physician 2020; 23:349-363 • ISSN 1533-3159

Systematic Review

Evidence for the Efficacy of Scrambler Therapy for Cancer Pain: A Systematic Review

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Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 07-17-2019
Revised manuscript received: 10-29-2019
Accepted for publication: 12-18-2019

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Background: Certain types of cancer pain have remained hard to control even by highly skilled pain experts. Uncontrolled cancer pain can have severe effects on quality of life, physical functioning, and leads to psychological distress. From this perspective, nonpharmacologic modalities of treatment are important. Neuromodulatory techniques, such as transcutaneous electrical nerve stimulation and scrambler therapy (ST), have gained popularity in recent times. ST is a relatively new therapy that has been used for the management of cancer pain resistant to pharmacologic management. Several studies have shown that ST is an effective therapy for this type of pain.

Objectives: The aim of this study was to detect possible gaps in the literature regarding the efficacy of ST for cancer pain and formulate recommendations for research through a systematic review of the literature.

Study Design: A systematic review of the literature was performed following the recommendations of the PRISMA Statement.

Methods: PubMed and EMBASE were searched for studies that met the inclusion criteria using a predetermined search strategy. Reference list of retrieved studies and Google Scholar were used to verify that no relevant studies had been omitted. Data were extracted from the studies with a data extraction sheet. A qualitative analyses of the extracted data was undertaken.

Results: Twenty-seven studies were retrieved. Ten were articles that were categorized as literature reviews, including 7 general literature reviews not following a specific review methodology, 1 editorial, and 2 systematic reviews. Seventeen were original studies, including 2 single-arm trials, 1 randomized controlled trial, 4 pilot trials, 4 case reports, 2 retrospective studies, and 4 prospective studies. By and large, the available literature supports the use of ST as an effective therapy for the management of refractory cancer pain. However, the level of evidence for its application to cancer pain is not particularly strong, and improvement in pain with ST may even be owing to a placebo effect.

Limitations: This study was not a meta-review. Because of the limited number of clinical trials on ST in cancer pain, such a meta-review could not meaningfully be performed.

Conclusions: Methodologically sound, large randomized control trials are needed in this area. However at this stage, ST may be considered a good option for cancer patients suffering from pain that does not respond to pharmacologic treatment.

Key words: Scrambler therapy, cancer, cancer pain, neuropathic pain, Calmare therapy, evidence, noninvasive pain treatment, chronic pain

Pain Physician 2020: 23:349-363

Pain is a common feature in all types of cancers, despite tremendous efforts in pain management over the past 20 years. Overall, the prevalence of pain among cancer patients is estimated to be between 50% and 70%, with nearly one-third or more of the patients rating their pain as moderate or severe (1,2).

Notwithstanding many research efforts, opioids remain the most effective drug for many types of cancer pain (3). Morphine is the recommended treatment for severe pain, whereas tramadol should be used for mild to moderate pain, and nonsteroidal anti-inflammatory drugs and adjuvants for mild pain (4). Unfortunately, chronic opioid therapy has been associated with side effects, such as increased risk of depression, constipation, impaired wound healing, fuzzy headedness, nausea, sedation, dizziness, vomiting, immune modulations, hormonal changes, physical dependence, tolerance, and respiratory depression (2,5). Moreover, certain types of cancer pain have remained hard to control, even by highly skilled pain experts. This results in poor pain management and severe effects on quality of life, physical functioning, and increased psychological distress (2).

From this perspective, the importance of nonpharmacologic modalities of treatment will increase with time as more of these modalities become available and are proven effective. Neuromodulation, a rapidly expanding field, may prove effective in the treatment of neuropathic cancer pain (3). Neuromodulatory techniques, such as transcutaneous electrical nerve stimulation (TENS) and scrambler therapy (ST), have gained popularity in recent times (6,7).

ST was introduced as a method of chronic pain relief in 2003. In the same year, Giuseppe Marineo (8) published the results of a small clinical trial among 11 terminal cancer patients suffering from drug-resistant chronic visceral pain. All patients responded positively to the treatment with significant reductions in pain scores (8). In the second trial, 226 patients with neuropathic pain were treated. A total of 80% of patients reported 50% pain reduction (9). Since then, several case reports and studies describing the use of ST for various kinds of pain have been published.

As per the evidence provided in the case reports, ST is effective for the treatment of both acute and chronic pain of varying etiologies. Regarding acute pain, a child with acute mixed pain refractory to pharmacologic treatment experienced substantial pain relief after 4 sessions of ST, with pain reducing from 5/10 to 0/10 (10). A 52-year-old women who was diagnosed with right medullary acute hemorrhage was suffering from burning pain from foot to knee for 12 years. ST sessions resulted in immediate effect. On day 1 after the session, pain score decreased from 9/10 to 3/10 on the Visual Analog Scale (VAS), which on the second day further reduced to 0/10. Until the completion of 10 days of sessions the pain score remained less than 1 on the VAS scale (11).

Regarding chronic pain, there is a case in the literature of a patient who had restricted range of motion and pain in the shoulder joint. After 10 sessions of ST, pain had been substantially reduced in comparison to the pain that the patient had experienced on the first day of treatment, and shoulder range of motion also increased (12). ST has proven to be very promising in extreme cases of pain that are particularly hard to control, such as complex regional pain syndrome and even HIV-related pain (13-15).

As promising as these case studies may be, a higher level of evidence is required to prove the efficacy of ST. Such evidence can be found by extended clinical trials. These trials tend to focus on chronic pain. Besides the earlier mentioned studies by Marineo (8) and Sabato et al (9), several other trials have shown that ST is an effective therapy for various kinds of chronic pain. Published trials are indicative of the efficacy of ST for pain conditions as diverse as low back pain, postherpetic pain, and neuropathic pain. For instance, a prospective study of patients with chronic low back pain included patients who had been experiencing this pain for more than 3 months due to degenerative changes of spine with or without radiation to lower limb. Significant improvements of pain were observed. The mean VAS score reduced from 8.12 to 3.63 after the sixth day of treatment (16). In another trial, 10 patients suffering from postherpetic pain were treated with ST. Pain was measured before and after treatment. The average Numeric Rating Scale (NRS-11) score decrease from 7.64 to 1.46 at baseline, and 0.42 to 0.89 at 1 month. The significant effect of ST on postherpetic neuropathy pain continued after 2 and 3 months (17).

ST has shown tremendous promise in treatment of neuropathic pain. In a prospective study of 45 patients with more than 3 months of neuropathic pain, despite therapy, 28 patients saw a reduction in Douleur Neuropathique en 4 questions (DN4) pain scores. Four patients even discontinued treatment before completing 10 sessions due to complete resolution of pain. Mean baseline DN4 score was 5.67, which decreased to 2.82 at the end of treatment (18). Another pilot random-

ized trial on the efficacy of ST for the treatment of neuropathic pain included 52 patients. Out of 26 in the intervention arm, 21 patients experienced complete pain-relief (19).

When findings of these studies, as well as several others that have been systematically analyzed elsewhere (20), are considered, the evidence for the efficacy of ST initially seems overwhelming. However, a final verdict on the efficacy of the therapy has not yet been delivered. This was, at least, the conclusion of Majithia et al (20) who conducted a systematic review on ST for the management of chronic pain. The review attempted to investigate preliminary data to evaluate the therapy's efficacy. In line with the findings that were presented earlier, the reviewers found that overall, studies seem to indicate that ST leads to pain reduction, and there is a phenomenal benefit that lasts for a long time.

This article will assess the research needs regarding the use of ST for the management of cancer pain. Majithia et al (20) studied chronic pain across diseases and pointed toward particular shortcomings in the evidence. In contrast, this study will more specifically review the evidence on the efficacy of ST for cancer-related pain. The aim of this study was to detect possible gaps in the literature, and formulate recommendations for research through a systematic review of the literature. We were particularly interested in analyzing the kinds and levels of evidence that are available to support the use of ST for the management of cancer pain, and assess what kind of studies need to be conducted to strengthen the evidence.

Methods

This systematic review was performed following the recommendations of the PRSIMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (21,22). As per the PRISMA statement, a systematic review starts from a focused research question, using clearly stated methods to retrieve, assess, and analyze research on a specific topic of interest. PRISMA describes a rigorous method for conducting and presenting systematic reviews, including a 27-item checklist of facets that need to be reported in systematic reviews (22). In this systematic review, data collection, extraction, and analyses were done in 2 stages, which had been determined and described before the study began.

In the first stage, reports were retrieved and screened. On February 27, 2019, the databases PubMed and EMBASE were searched using the following search string: cancer AND (scrambler therapy OR Calmare). The search string consisted of 2 components connected with the Boolean "AND." The first component was cancer because pain related to cancer or its treatment is the focus of the current review. The second component was scrambler therapy OR Calmare (Calmare Therapeutics Inc. (OTCQB: CTTC) (CTI) Italy). Calmare is an alternative name for ST, which is sometimes used in research publications. Initially, all reports that were found in the databases on the date of search were included. Because ST has only been around for 15 years, we did not set a starting year for inclusion of studies in the review.

After screening the reports, those were retained if they met the following criteria. Reports had to be in English and published in a peer-reviewed journal. Conference abstracts and dissertations were excluded. Reports had to explicitly discuss the efficacy of ST for the management of pain related to cancer or its treatment. An overview of the inclusion and exclusion criteria can be found in Table 1. Relevant reports were first selected on the basis of a thorough reading of the titles and abstracts. Then the full texts of the retained reports were read, and a further selection was made. After this screening of the reports, missing reports were identified through checking the reference lists of the retrieved reports and searching Google Scholar. To make sure that no relevant reports were missing, the list of retrieved reports was presented to specialists in pain management who were requested to check whether the list was exhaustive and identify relevant gray literature. Figure 1 represents the outcome of the search.

In the second stage, data were extracted from the studies. For the purposes of this review, the publications were divided into 2 groups: reviews (which included editorials), and other studies (trials, case reports, retrospective studies). Data were extracted using a data extraction sheet. On these sheets the following

Table 1. *Inclusion and exclusion criteria.*

Inclusion Criteria	Exclusion Criteria
Available in the databases on February 27, 2019	Conference abstracts
Published in peer-reviewed journal	Dissertations
In English	
Explicitly discuss the efficacy of ST for the management of pain	

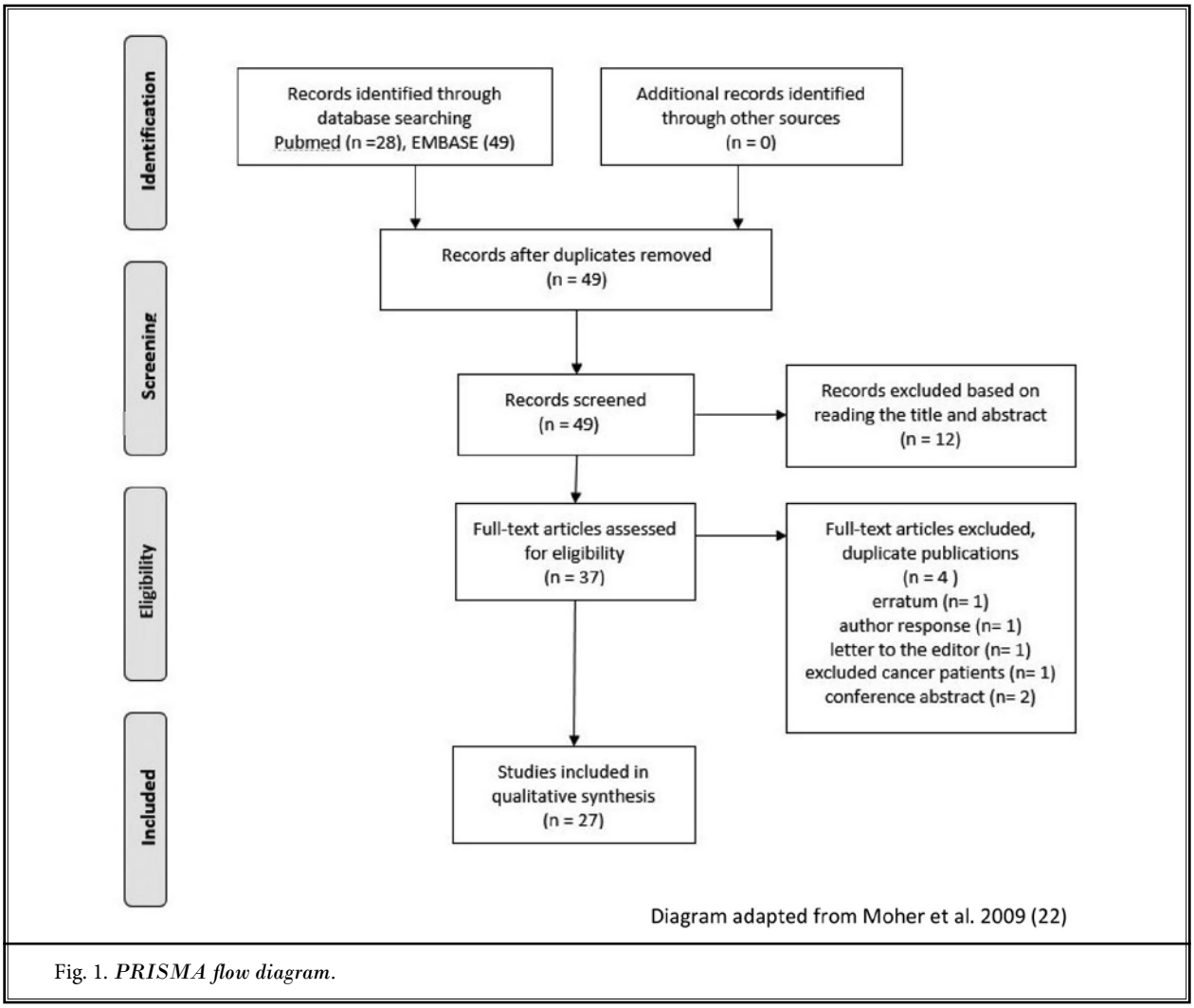

Fig. 1. *PRISMA flow diagram.*

data were recorded: goals and objectives, study design, studied patient population, and main findings. The first author (KK) performed the report search, report selection, and data extraction; the second author (SB) verified the output.

Results

Twenty-eight reports were found in the PubMed database and 49 in EMBASE. Twenty-eight duplicate entries were removed, after which 49 reports remained. Screening of the reports based on the title and abstract led to the exclusion of 12 studies that did not meet the inclusion criteria. Full texts of 37 studies were retrieved and assessed for eligibility. This led to the exclusion of 10 studies that did not meet the inclusion criteria for various reasons: 4 were duplicate publications; 1 was an erratum of an already included study; 1 turned out to be an author response, and 1 was a letter to the editor and not an original study; 2 were conference abstracts; and 1 explicitly excluded cancer patients. A search in Google Scholar and checking of the reference lists of the retrieved studies did not fetch new studies to result in the discovery of studies that had not been included. At the end, 27 studies were included in qualitative synthesis.

Out of these 27 studies, 10 were articles that were categorized as literature reviews, including 7 general literature reviews not following a specific review methodology, 1 editorial, and 2 systematic reviews. Seventeen were original studies, including 2 single-arm trials, 1 randomized controlled trial, 4 pilot trials, 4 case reports, 2 retrospective studies, and 4 prospective studies. Most of the retrieved publications only included patients suffering from cancer-related pain,

although 6 publications reported on patients suffering from noncancer-related pain besides patients suffering from cancer-related pain (20,23-27). An overview of the retrieved reviews and studies can be found in Tables 2 and 3.

In the presentation of the evidence described later,

Table 2. *Overview of the retrieved reviews on ST for cancer pain.*

Authors	Year	Title	Review Type	Most Important Findings
Al-Atiyyat and Obaid (41)	2017	Management of peripheral neuropathy induced by chemotherapy in adults with cancer: A review	Literature review	Effective therapies for decreasing CIPN were acupuncture and sweet bee venom pharmacopuncture. ST appeared to be a most promising therapy with significant decreases in level of CIPN.
Cathcart-Rake et al (23)	2017	Chemotherapy-induced neuropathy: Central resolution of a peripherally perceived problem?	Editorial	ST brings about changes in the central perception of the peripherally experienced CIPN, and it decreases pain, tingling, and numbness among patients.
Chwistek (3)	2017	Recent advances in understanding and managing cancer pain	Literature review	Cancer pain is most often managed with opioids. However, nonpharmacologic methods of cancer pain management will become more important, as they have shown significant promises in research and gradually become more easily available. One of these modalities is ST, which has been around since the early 2000s. The advantages of ST are its noninvasive nature, easiness to use, excellent safety profile, and effectiveness with significant and long-lasting pain relief.
Davis (42)	2018	Cancer-related neuropathic pain: Review and selective topics	Literature review	There is no substantive body of quality studies to back up the evidence for the efficacy of opioids in treating neuropathic pain. As per the available evidence, patients who do not respond to single analgesics should be treated with antidepressants and anticonvulsants together with opioids. In this context, ST may be helpful because it is low risk and noninvasive.
Fakhari et al (34)	2017	Post mastectomy pain syndrome	Literature review	For improving neuropathic pain and postmastectomy pain syndrome, ST has been found to be effective with positive outcomes.
Hou et al (44)	2018	Treatment of chemotherapy-induced peripheral neuropathy: Systematic review and recommendations	Systematic review	Twenty-six different treatment options were described for CIPN, which included pharmacologic therapy, light therapy, ST, magnetic field therapy, etc.
Majithia et al (20)	2016	Scrambler therapy for the management of chronic pain	Systematic review	Scrambler device is beneficial in pain reduction and there is a long-lasting phenomenal benefit. However, ST is an expensive treatment. Moreover, it is not yet widely available and some insurance companies in the United States will not pay for it due to lack of evidence. To further evaluate the efficacy of ST for chronic pain relief larger randomized studies are recommended.
Pachman et al (45)	2014	Therapeutic strategies for cancer treatment related peripheral neuropathies	Literature review	Duloxetine is the most effective treatment for CIPN. Other agents with significant benefit include gabapentinoids, venlafaxine, and tricyclic antidepressants; however, none of these have been proven to be beneficial. Other nonpharmacologic interventions, including acupuncture and ST, have been found to be effective with positive outcomes in initial smaller trials; however, further larger, placebo-controlled trials are needed to confirm their efficacy.
Scāunaæu et al (43)	2015	Neuropathic postoperative chronic pain syndrome following breast cancer surgery	Literature review	New modalities for pain management, including ST and electrical nerve stimulation, have shown encouraging results for the management of neuropathic postoperative chronic pain syndrome following breast cancer surgery.
Wilson et al (31)	2018	Physical agents for cancer survivors: An updated literature review	Literature review	Low-level laser therapy and intermittent pneumatic compression reduce breast cancer–related lymphedema without adverse effects. ST may be safe and beneficial for individuals post-CIPN. However, there has been no definitive conclusion regarding the efficacy of ST, and the generalizability of these findings is limited to specific populations.

Table 3. *Overview of the retrieved studies on ST for cancer pain.*

Authors	Year	Title	Study Type	Cancer Type	Most Important Findings
Coyne et al (6)	2013	A trial of scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy	Single-arm trial	39 patients with various types of cancer, resulting in moderate to severe pain	The investigators administered ST sessions of 45 minutes on 10 consecutive days. There was a monthly follow-up for the first 3 months after the ST treatment. Pain reduced from 6.6 before treatment to 4.5 after treatment at 14 days, 4.6 at 1 month, 4.8 at 2 months, and 4.6 at 3 months. The decrease in pain from baseline to day 14 was significant ($P = 0.0005$). Changes in the BPI pain scores between baseline and 30th day were also statistically significant ($P = 0.002$). The sensory component of the EORTC CIPN-20 also improved. The use of opioids did not change appreciably. No patient dropped out during the study.
Kashyap et al (30)	2017	Impact of scrambler therapy on pain management and quality of life in cancer patients: A study of twenty cases	Single-arm trial	20 patients with various types of cancer	The investigators administered ST sessions of 45 minutes on 12 consecutive days. There was a follow-up session 1 week later. Mean VAS scores at day 1 were 7.50, and it drastically reduced to 0.75 after completion of 10 sessions. Pain relief continued at second follow-up with VAS score reducing from 1.15 presession to 0.15 postsession. Pain scores decreased significantly ($P < 0.01$) from baseline until second follow-up. Similar results were observed for quality of life scores, with the mean domain scores in each domain showing significant improvement. The mean domain scores in each domain had significant improvement at second follow-up when compared with baseline scores ($P < 0.01$). No patient dropped out from this study.
Lee (32)	2018	Efficacy of scrambler therapy on breast cancer-related lymphedema	Case report	1 patient with breast cancer	The duration of treatment was 45 minutes, and the number of consecutive sessions were 10. The outcome of this case report was reduction in pain observed without an increase in lymphedema.
Lee et al (38)	2016	An exploratory study on the efficacy of "Calmare therapy" in patients with cancer-related neuropathic pain: A pilot study	Single-arm trial	20 patients with various types of cancer	The investigators administered ST sessions of 40 minutes on 10 consecutive days. There was a follow-up after 2 weeks post-ST treatment. Average NRS-11 score for all the 20 patients at baseline was 7.4, which was reduced to 4.3 at visit 1, 3.1 at visit 2, and finally 3.7 on the final visit. There was significant reduction in NRS-11 pain score at 1 month from baseline ($P < 0.001$). Three patients dropped out from this study.
Marineo (8)	2003	Untreatable pain resulting from abdominal cancer: New hope from biophysics?	Single-arm trial	11 patients with various types of cancer	The investigators administered 10 ST sessions in which duration and frequency depended on analgesia. Nine out of 11 patients reported discontinuation of painkillers. The remaining 2 patient's consumption of pain killers was very minimal, almost negligible. Pain intensity after the 10 sessions of ST therapy reduced significantly in comparison to baseline ($P < 0.001$). The study stated no limitations.
Moon et al (24)	2015	Predictive factors associated with success and failure for Calmare (scrambler) therapy: A multicenter analysis	Retrospective study	147 patients with CIPN with multiple types of cancer and other noncancer pain	The investigators administered 3-5 sessions of ST, which varied in length between 40-60 minutes, depending on pain. There were 2 monthly follow-ups. Efficacy of ST was not dependent on number of sessions, treatment compliance, etiology, or baseline pain score but the major factor was the type of pain. Having a neuropathic or mixed neuropathic-nociceptive pain condition was associated with a positive outcome of ST after 1 month when compared with baseline score ($P = 0.006$ and $P = 0.042$, respectively).
Notaro et al (29)	2016	Pilot evaluation of scrambler therapy for pain induced by bone and visceral metastases and refractory to standard therapies	Single-arm trial	25 patients with various types of cancer, including bone or visceral metastases	The investigators administered ST sessions of 30-40 minutes on 10 consecutive days. There were 2 monthly follow-ups. Pain relief was observed for 24 hours after daily treatment with the NRS-11 score prior to each session being lower in comparison to baseline scores. At the end of ST, more than 50% pain relief was observed by all the 25 patients. On average, pain scores reduced from 8.4 at baseline to 2.9 at day 10 ($P = 0.008$), with an average increase of 3 hours in sleeping time. ST was found to be effective in terms of safety and noninvasiveness for the treatment of cancer pain without any side effects. Fourteen patients dropped out from this study.

Table 3 (cont.). *Overview of the retrieved studies on ST for cancer pain.*

Authors	Year	Title	Study Type	Cancer Type	Most Important Findings
Pachman et al (37)	2015	Pilot study of scrambler therapy for the treatment of chemotherapy induced peripheral neuropathy	Single-arm trial	37 patients with CIPN with multiple types of cancer	The investigators administered ST sessions of 30 minutes on 10 consecutive days. The investigators found that ST lead to an improvement of tingling, numbness, pain symptom scores, and quality of life. This improvement persisted for 10 weeks of follow-up. At the end of 10 days of treatment, average pain decreased to 2.6 from baseline score of 5.7 ($P < 0.0001$). Sixteen patients dropped out from this study.
Park et al (35)	2017	Scrambler therapy for the treatment of neuropathic pain related to leukemia in a pediatric patient	Case report	1 patient with B-cell lymphoblastic leukemia	The investigators administered 4 ST sessions of 45 minutes. There was follow-up at 1 and 4 weeks after treatment. In this pediatric patient, ST was found to be effective for cancer-related neuropathic pain. No complications were observed, and the patient experienced no significant discomfort during treatment.
Park et al (28)	2013	Scrambler therapy for patients with cancer pain-case series	Case series	3 patients: breast cancer, uterine sarcoma, hepatocellular carcinoma	The investigators administered ST sessions of 40 minutes on 10 consecutive days. The follow-up varied for all 3 cases. For one case it was 1 month, for the other case it was 1 week, and for last case it was 2 months. ST effectively reduced pain in patients who had been suffering from cancer pain that had not reduced after nerve blocks or pain medication. ST was more effective than these other therapies, particularly considering treatment session duration.
Ricci et al (25)	2019	Scrambler therapy: What's new after 15 years? The results from 219 patients treated for chronic pain	Single-arm trial	219 patients with multiple types of cancer (83) and noncancer	The investigators administered ST sessions of 30 minutes on 10 consecutive days. There were 2 weekly follow-ups after the treatment. ST was given to 219 patients with chronic pain, with a mean NRS-11 value of 6.44. Eighty-three patients complained of cancer pain, and 136 patients were having noncancer pain. NRS-11 scores significantly improved in both groups. NRS-11 score reduced to 3.22 at the end of the treatment, and 3.19 at second follow-up. On average, cancer pain reduced by 3.35 from the beginning of treatment to the 10th day of treatment ($P < 0.0001$).
Ricci et al (26)	2012	Managing chronic pain: Results from an open-label study using MC5-A Calmare(R) device	Single-arm trial	73 patients: 41 patients with various types of cancer, and 32 patients with other diseases	The investigators administered ST sessions of 30 minutes on 10 consecutive days. There were 2 weekly follow-ups. At the beginning of treatment with ST, the mean pain value was 6.2. After the 10th day of treatment, this had fallen to 1.6. After the second week of follow-up, it had again increased to 2.9. Both cancer and noncancer showed a substantial pain reduction. However, in comparison to the cancer pain group, the outcomes were more impressive in the noncancer pain group. Mean pain scores for both groups combined fell significantly from baseline to day 10 ($P < 0.0001$).
Smith et al (33)	2017	Scrambler therapy for the treatment of chronic post-mastectomy pain (cPMP)	Case series	3 patients with breast cancer	The investigators administered ST sessions of 45 minutes and offered ST until patients no longer experienced pain. After treatment, all 3 patients had more than 75% pain reduction on VAS score, and sustained reduction of allodynia, hyperalgesia, and pain for many months.
Smith et al (39)	2010	Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A Calmare) for chemotherapy-induced peripheral neuropathy	Single-arm trial	18 patients with CIPN with various types of cancer	The investigators administered ST sessions of 60 minutes on 10 consecutive days. There were follow-ups 2 weeks after treatment, at 6 weeks, and at 10 weeks. ST was given to 16 enrolled patients with average NRS-11 score more than 5. Fifteen patients achieved 20% reduction in NRS-11 score by the end of the study. Pain reduced significantly from baseline to day 10 ($P < 0.0001$).

Table 3 (cont.). *Overview of the retrieved studies on ST for cancer pain.*

Authors	Year	Title	Study Type	Cancer Type	Most Important Findings
Smith et al (40)	2020	A pilot randomized sham-controlled trial of MC5-A scrambler therapy in the treatment of chronic chemotherapy-induced peripheral neuropathy (CIPN)	Pilot randomized sham controlled phase II trial	35 patients with colorectal cancer, breast cancer, and myeloma	The investigators administered ST sessions of 30 minutes on 10 consecutive days. ST was not found effective for CIPN with only few patients reporting enough pain relief. There were small, nonsignificant changes in pain scores over the study period in each arm at day 10, 28, 60, and 90. There was no difference between both arms in the pain drug use, BPI-CIPN total scores, and EORTC CIPN-20 scale. Difference in pain from baseline to 28 days was not much, and *P* value calculated was 0.80 The first follow-up duration was 28 days, then 2 follow-up sessions at 2 and 3 months after initial 10 days of therapy.
Sparadeo et al (27)	2012	Scrambler therapy: An innovative and effective treatment for chronic neuropathic pain	Single-arm trial	173 patients suffering from chronic neuropathic pain with various types of cancer with CIPN and noncancer	The investigators administered ST sessions of unspecified duration on 10 consecutive days. The follow-up duration was variable depending on pain and varied from 3 to 6 months. Average follow-up duration was 4.2 months. In the first session, the VAS score reduced from 7.24 on average before treatment to 3 after treatment, and in the last session of ST the VAS score showed improvement by a reduction from 3 before treatment to 1 after treatment. On average, mean VAS scores were halved in each session. At the end of treatment on day 10, the investigators observed significant improvement from baseline for variables BPI and VAS among single site, spine pain, and CRPS patients ($P < 0.01$). The mean BPI summary scores indicated statistically significant improvement across all 4 groups (spine pain, neuralgia, CRPS, and multisite) before and after the 10 ST treatment sessions ($P < 0.01$).
Tomasello et al (36)	2018	Scrambler therapy efficacy and safety for neuropathic pain correlated with chemotherapy-induced peripheral neuropathy in adolescents: A preliminary study	Single-arm trial	9 patients with CIPN with acute lymphoid leukemia, neuroblastoma, Hodgkin disease, acute promyelocytic leukemia, acute myeloid leukemia	The investigators administered ST sessions of 45 minutes and continued 10 sessions. Adolescent patients with chemotherapy-related neuropathic pain benefited from ST through significant improvement in pain relief. NRS-11 score at baseline was 9.22 on average for the 9 patients. This was reduced to 2.33 at the end of ST at day 10 ($P < 0.001$). The Lansky performance score significantly improved from an average of 26.7 at baseline to 57.8 after 10 days of ST. In 7 out of 9 patients, opioids were totally eliminated. Four patients completed ST within 10 days, 4 within 14 days, and 1 patient required 21 days.

our final 27 shortlisted articles were analyzed in 3 categories of studies. The first category is that of studies combining patients suffering from various kinds of cancer pain. The second category is that of studies specifically focusing on breast cancer–related pain. Breast cancer has been the only specific type of cancer that has received individual attention in research on the efficacy of ST. The third category is that of studies on neuropathic pain. A few publications in this category also include noncancer patients. In the description later, for each of these 3 categories, the evidence has been arranged in ascending order of strength. First are the case reports, second are retrospective studies and single-arm trials, third are randomized controlled trials, and finally fourth are reviews, which is the highest level of evidence if the reviews adhere to strict methodologic rigor. For 2 pain categories, across various cancer types and breast cancer, some evidence levels were not covered by the literature.

Evidence Across Various Cancer Types

Case Reports

Park et al (28) published a case series to investigate the efficacy of ST in patients diagnosed with cancer. Three cases were considered in this case series. Based on the outcomes of all 3 cases, the authors concluded that ST was an effective treatment in patients complaining

of severe cancer pain that could not be relieved through nerve blocks or medication therapy.

Single-Arm Trials

There have been 4 single-arm trials assessing the efficacy of ST across cancer types that did not explicitly focus on neuropathic pain. Notaro et al (29) undertook a single-center study to assess the efficacy of ST for cancer pain management. In this trial, 25 patients, 15 men and 10 women, were treated with ST. On average, pain scores reduced from 8.4 ± 1.4 to 2.9 ± 1.5, accompanied with an average increase of 3 hours in sleeping time, when compared with baseline scores (pretreatment sessions). Notaro et al (29) concluded that ST appeared effective in terms of safety and noninvasiveness for the treatment of cancer pain without any side effects. Moreover, scrambler sessions can be performed during anticancer treatment, such as chemotherapy, without interfering with the oncologic program, for both outpatients and inpatients.

Ricci et al (25,26) conducted 2 prospective studies on ST among cancer patients, the first in 2012 and the second in 2019. The first study included 73 patients of which 38 (52%) patients were men, and 35 (48%) were women. Forty-one patients had been diagnosed with cancer, and 32 patients had other diseases. The primary objective of the study was to assess efficacy and tolerability of ST. There was clear reduction in pain for both cancer and noncancer patients as shown by the decrease in pain scores. However, compared with the cancer pain group, the outcomes were more impressive in the noncancer pain group.

The second prospective study conducted by Ricci et al (25) aimed to evaluate the impact of ST on cancer patients who reported moderate to severe chronic pain. The investigators studied 219 patients involving 100 men and 119 women affected by chronic pain. The study consisted of 2 consecutive weeks of treatment with ST, 30 minutes duration each session for 5 days a week, and a 2-week follow-up. A reduction in the pain symptoms from the initiation of therapy to the end of the treatment was maintained through follow-up ($P < 0.0001$). From these findings, Ricci et al (25) concluded that ST represents a complementary perspective to analgesic control.

Kashyap et al (30) carried out another single-arm trial on the efficacy of ST for the treatment of cancer pain. Besides the impact of ST on chronic cancer pain, the study assessed change in quality of life (World Health Organization-Quality of Life brief questionnaire [WHOQOL-BREF domains]). This study was conducted on 20 patients with chronic pain due to cancer, not responding to oral analgesics. All patients successfully completed the therapy without adverse effects. VAS scores for pain decreased significantly after each session. Significant reduction in pain scores measured on the VAS was observed throughout the study. Similar results were observed for quality of life scores, with the mean scores in each domain showing significant improvement ($P < 0.05$) at the 10th day, first follow-up 1 week after the end of treatment, and second follow-up 2 weeks after the end of treatment when compared with baseline scores at the beginning of ST.

Marineo (8) aimed to investigate the efficacy of the recently developed noninvasive ST for the treatment of visceral and neuropathic cancer pain that was not totally curable by drugs. Eleven cancer patients who reported elevated drug-resistant visceral pain were included in this trial. Based on the response to ST, drugs were eliminated in a stepwise manner during the trial period. The VAS score was reduced significantly at the last day when compared with baseline score, despite the elimination of supporting painkillers. Marineo et al (8) observed that the results were highly promising with all patients showing positive results in the form of pain reduction. Nine out of 11 patients reported the discontinuation of painkillers, and for the remaining 2 patients consumption of pain killers reduced to very minimal, almost negligible, after the end of ST therapy sessions.

Literature Reviews

Three reviews have been published that include observations on the efficacy of ST for the treatment of cancer pain that is not specifically related to breast cancer or neuropathy.

The review by Chwistek (3) presents recent advances in management of cancer pain. The author observed that the noninvasive nature of ST, ease of use, and excellent safety profile make it a very desirable complementary technique in the treatment of cancer pain, which resulted in significant and long-lasting relief from cancer pain.

The review by Wilson et al (31) concluded that there has been no definitive conclusion as to whether TENS-based therapies, such as ST, are advantageous in controlling cancer-related pain. The generalizability of these findings is limited to specific populations, and the therapy may still have the potential to cause harm if applied incorrectly (31).

Evidence in Breast Cancer Pain

Case Reports

Lee (32) published a case report of an individual treatment outcome of a breast cancer–related lymphedema patient who was a 39-year-old woman, and had undergone a right-side mastectomy followed by radiology therapy and chemotherapy. VAS was used to measure pain at baseline, during the treatment of 10 days before and after the ST therapy, and also at follow-up. The patient did not receive any other treatment during this period. The outcome of this 10 day treatment was positive with clear indication of pain reduction, which was observed without an increase in lymphedema.

Smith et al (33) studied 3 female patients suffering from postmastectomy pain. ST was given for 45 minutes each day and continued until successful pain relief was achieved. The outcome was positive for all 3 patients with improvement of more than 75% on VAS, and sustained reduction of allodynia, hyperalgesia, and pain for many months. All patients reported improvements in their quality of life and normal function. One woman was able to stop chronic opioid use. No side effects were observed in all 3 cases.

Literature Review

Fakhari (34) undertook a review study on the symptoms, risk factors, etiology, prevalence rate, prevention, and treatment of breast cancer. Regarding ST, he reported that it is effective for improving postmastectomy pain syndrome, as well as neuropathic pain, which is discussed in the next section (34).

Evidence in Neuropathic Pain

Case Reports

There is only one case report on neuropathic cancer pain. Park et al (35) published a neuropathic pain study of an 11-year-old girl who was suffering from left groin and medial thigh pain after irradiation to the knee. ST was suggested and given as both patient and attendant were afraid of injections, which were required during preferred obturator nerve block. Immediately after the first session, NRS-11 score decreased from 8/10 to 3/10, and improvement in pain was observed in subsequent sessions also. NRS-11 score decreased to 0/10 with just 3 treatment sessions. Drugs were progressively reduced after pain relief and then prescribed when needed.

Retrospective Study and Single-Arm Trials

Moon et al (24) undertook a multicenter study to identify the factors associated with treatment outcome for ST. Study data were collected from 3 medical centers of 147 patients (105 men and 42 women) with various pain conditions, who had undergone either a minimum of 3 ST sessions consecutively or a total of 5 therapy sessions overall. The therapy was considered successful if an outcome of more than 50% pain relief was scored on NRS-11 and lasted for more than 1 month after the last session. The crucial factors associated with therapy success (in univariate analysis) included site of study, higher age, gender (female), patients with neuropathic pain, and chemotherapy-induced peripheral neuropathy (CIPN).

Sparadeo et al (27) undertook a prospective study involving 173 patients having chronic neuropathic pain. The goal was to study their pain relief by ST. Ninety-one patients agreed for re-evaluation. The authors did not provide an explanation as to why the remaining 82 patients did not agree to re-evaluation. Follow-up analysis was conducted after 3 to 6 months from the beginning of the ST therapy. The study consists of 49 women and 42 men. On the first day of session, the average VAS score reduced from 7.24 to 3, and in the last session of ST the average VAS score showed improvement by reduction from 3 to 1. In all 10 treatment sessions, the mean VAS ratings for each treatment dropped by well over 50%. The investigators concluded that, in their study, ST has proven to be effective.

Another single arm trial was conducted by Coyne et al (6), who included cancer patients suffering from CIPN with predominant numbness but no pain, postmastectomy pain, postsurgical pain, postherpetic neuropathy, and postradiation pain. For this study, 39 patients were included: 16 men and 23 women. The NRS-11 score change over time was significant ($P = 0.006$). Pain reduced from 6.6 before treatment to 4.5 at 14 days, 4.6, 4.8, and 4.6 at 1, 2, and 3 months, respectively ($P < 0.001$). Changes in the Brief Pain Inventory (BPI) pain scores were statistically significant ($P = 0.002$). The sensory component of the European Organization for Research and Treatment of Cancer (EORTC) CIPN 20-item scale (CIPN-20) also improved. The use of opioids did not change appreciably.

A total of 9 patients with CIPN with an average age of 14 years were enrolled in a prospective study that was performed to investigate the efficacy and applicability of ST to neuropathic pain in adolescents with CIPN, in which the pain was unresponsive to conven-

tional drug treatment (36). Five were male patients and 4 were female patients.

NRS-11 score at baseline was 9.22 on average for the 9 patients, which was reduced to 2.33 at the end of ST at day 10. The Lansky performance score significantly improved from an average of 26.7 at baseline to 57.8 after 10 days of ST. Similarly, the researchers observed significant improvement in quality of life considering multiple parameters, such as pain interference with general activity, mood, walking ability, sleep, and relations with other people. There was a significant reduction in drug consumption, including opioids and anticonvulsants. In 7 out of 9 patients, opioids were totally eliminated. Based on the study results, adolescent patients with chemotherapy-related neuropathic pain seem to benefit from ST through significant improvement in pain relief.

Pachman et al (37) undertook an open access pilot trial to further investigate the effect of ST for the treatment of CIPN. Thirty-seven patients were enrolled (12 men and 25 women). Average pain decreased by 53% as scored on NRS-11, tingling decreased by 44%, and numbness decreased by 37% at the end of 10 days of treatment. This study also shows that the numbness, tingling, and pain symptom scores improved daily during therapy session.

Lee et al (38) undertook an open-labeled and single-arm study for pain relief with the focus on patients who had cancer neuropathic pain or mixed neuropathic pain and received only conservative therapy for more than 6 months. Average NRS-11 score for all 20 patients at baseline was 7.4, which reduced to 4.3 at visit 1, 3.1 at visit 2, and finally 3.7 on the final visit. After 1 month of treatment out of total 20 patients, 6 patients (30.0%) reported more than 50% decrease in pain, 9 patients (45.0%) reported between 50 and 30% decrease in pain, and 5 patients (25.0%) reported less than 30% decrease in pain. Fifteen patients (75.0%) experienced more than 30% pain reduction.

Smith et al (39) undertook a pilot study to evaluate the impact of ST on CIPN in 18 patients with CIPN. The primary endpoint, which was a reduction in NRS-11 pain score of 20% by the end of the study, was met by 15 out of the 16 enrolled patients. The overall score for all patients fell 59% from 5.81 before starting treatment to 2.38 at the end of 10 days. No side effects were observed; however, for many patients, the pain returned to original intensity over the 2-month period after ST was completed.

Randomized Controlled Trial

There has been only one randomized controlled trial on the efficacy of ST for the management of neuropathic pain resulting from cancer. This study was undertaken by Smith et al (40). They conducted a randomized sham-controlled phase II trial of ST. Thirty-five patients suffering from CIPN for at least 3 months were included in the study. Seventeen patients were randomly assigned to the intervention group with ST, and 18 to the sham procedure group. There were small, nonsignificant changes in pain scores over the study period in each arm at day 10, 28, 60, and 90. There was also no difference between both arms in the pain drug use, BPI-CIPN total scores, and EORTC CIPN-20 scale.

Literature Reviews

The available reviews on neuropathy in cancer did not elaborately assess ST. The reviewers generally listed it as a promising approach for the management of neuropathic pain in cancer. Al-Atiyyat and Obaid (41) compared multiple agents and modalities for management of CIPN. They observed that nonpharmacologic treatments, such as ST, significantly reduced the level of CIPN. Of the 4 studied nonpharmacologic interventions, ST appeared to be most promising with significant decreases in level of CIPN.

Cathcart-Rake et al (23) described ST as a new approach that has shown tremendous potential, and has also been found to be effective to changes in the central perception of the peripherally experienced CIPN. In their view, the treatment given for pain relief using the scrambler device surely decreases pain, tingling, and numbness among patients.

Davis (42) described ST as a noninvasive modality with low risks. A similar observation had been made by Scãunaæu et al (43) who had concluded that ST had shown encouraging results for the treatment of neuropathic postoperative chronic pain syndrome following breast cancer surgery. Hou et al (44) described 26 different treatment options for CIPN, which included ST.

Pachman et al (45) observed that among nonpharmacologic treatments, ST has been found effective for the treatment of CIPN. Multiple but small trials have been done and all have shown positive outcomes. Because there are no studies with larger patient populations, the reviewers recommended that further trials with larger patients be conducted for validation of the full efficacy of ST (45).

Limitations of the Studies

In the trials, patients were excluded for different reasons: patients with heart stents or any form of metal devices, such as pacemakers and automatic defibrillators (8,25,30,36-40); patients having active reaction to previous use of TENS (30,36,38); pregnant women (12,30,37,39); patients having a history of epilepsy (25,30,36-38,40); and patients with skin conditions (30,36-39); psychiatric disorders (26); and those taking or having taken chemotherapy (26,37,39).

Several studies explicitly mentioned small sample size as a limitation (6,24,29,30,36-38,40). Other limitations were the heterogeneity of the sample leading to disparate effects (6,40); absence of a control arm, particularly a placebo arm (26,30,36,38,39); short follow-up (26,29,37-39); the retrospective nature of the study (24,29); nonstandardization of treatment (24,27,40); no statistical determination of sample size (24); and large number of dropouts (37).

Discussion

The description of the available evidence on the efficacy of ST in cancer pain is clearly indicative of its efficacy in the 3 categories: across cancer types, in breast cancer, and in neuropathic cancer pain. However, in all 3 categories, the evidence is not particularly strong. The highest level of evidence, that of well-designed systematic reviews, including strong randomized control trials (RCTs), are not reached for any of the categories. There is one systematic review for neuropathic pain (44). However, that systematic review does not explicitly assess ST, but rather describes an entire range of treatment options for CIPN. The systematic review by Majithia et al (20) focuses on ST and includes studies across cancer types, but also includes evidence for noncancer. Moreover, at the current state of research on ST, even systematic reviews cannot establish the highest level of evidence because of the absence of a substantial body of RCTs. The highest level of evidence in medicine consists of systematic review(s) "with homogeneity of RCTs" (46). Unfortunately, at present, only one RCT on ST for cancer pain is available (40), and thus homogeneity cannot be established.

Table 4 illustrates the lack of the strongest evidence for the treatment of cancer-related pain with ST. With the exception of the RCT by Smith et al (40), the evidence consists of case studies and single-arm trials. To this we need to add that the study by Smith et al (40), although well-designed pilot RCT, included 35 patients. Strikingly, they observed that the differences between the intervention and control arm were not significant.

The investigators offered multiple explanations for ST not being as effective for CIPN, as only few patients reported enough pain relief. The application of the ST treatments was not uniform, as it was performed by different practitioners, and also there was too much heterogeneity in the patients with CIPN to detect improvements in specific neuropathy symptoms. It was difficult for patients to describe the improvement because even when they felt that their pain had reduced, they still had numbness and tingling effect. Thus there is an urgent need for robust RCTs that can further establish the evidence of ST for the management of cancer-related pain. In particular, researchers should consider sham-controlled trials, to further assess the possibility that the improvements in pain observed among patients who are treated with ST are owing to a placebo effect.

The level of evidence for the application of ST to cancer pain is not particularly strong. Because this technique is novel, insufficient studies are available to establish a high level of evidence through a systemic review of the literature. The available studies include only a small number of studied patients, and only one is multicentric. The only available retrospective multicentric study on the efficacy of ST including cancer patients specifically focuses on CIPN (24). Furthermore, available studies on the efficacy of ST in cancer pain are single-arm trials (6,8,12,25-27,29,30,36,37,39), one pilot RCT (40), and case studies (28,32,33,35). The RCT included 35 CIPN patients, whereas the largest single-arm trial included 83 cancer patients (25). One of the single-arm trials (27) and a retrospective study (24) included both cancer and noncancer patients, and did not differentiate between the effect of ST on pain in both groups. Trials with substantially larger samples of cancer patients, distinguishing cancer patients from noncancer patients, would help to reduce the risk of bias in the future. Therefore a large, multicenter, randomized, sham-controlled, double-blinded trial, involving patients with a variety of cancer pain syndromes, would strengthen the conclusions from initial studies. Although designing the studies, investigators should carefully reflect on the exclusion criteria and make sure not to exclude patient populations that might benefit from the treatment. The descriptions of the studies' limitations showed that there was no consistency among the studies regarding the patients who need to be excluded for reasons of safety. Currently, no study has reported adverse effects of ST. Therefore ST may be

Table 4. *Overview level of evidence of ST in cancer patients.*

Level of Evidence	Author	Year	Title
1 Systematic review	Hou et al (44)	2018	Treatment of chemotherapy-induced peripheral neuropathy: Systematic review and recommendations
	Majithia et al (20)	2016	Scrambler therapy for the management of chronic pain
2 RCT	Smith et al (40)	2020	A pilot randomized sham-controlled trial of MC5-A scrambler therapy in the treatment of chronic chemotherapy-induced peripheral neuropathy (CIPN)
3 Literature review	Al-Atiyyat and Obaid (41)	2017	Management of peripheral neuropathy induced by chemotherapy in adults with cancer: A review
	Cathcart-Rake et al (23)	2017	Chemotherapy-induced neuropathy: Central resolution of a peripherally perceived problem?
	Chwistek (3)	2017	Recent advances in understanding and managing cancer pain
	Davis (42)	2018	Cancer-related neuropathic pain: Review and selective topics
	Fakhari (34)	2017	Post mastectomy pain syndrome
	Pachman et al (45)	2014	Therapeutic strategies for cancer treatment related peripheral neuropathies
	Scãunaæu et al (43)	2015	Neuropathic postoperative chronic pain syndrome following breast cancer surgery
	Wilson et al (31)	2018	Physical agents for cancer survivors: An updated literature review
4 Single-arm trial or retrospective study	Coyne et al (6)	2013	A trial of scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy
	Kashyap et al (30)	2017	Impact of scrambler therapy on pain management and quality of life in cancer patients: A study of twenty cases
	Marineo (8)	2003	Untreatable pain resulting from abdominal cancer: New hope from biophysics?
	Moon et al (24)	2015	Predictive factors associated with success and failure for Calmare (scrambler) therapy: A multicenter analysis
	Notaro et al (29)	2016	Pilot evaluation of scrambler therapy for pain induced by bone and visceral metastases and refractory to standard therapies
	Pachman et al (37)	2015	Pilot study of scrambler therapy for the treatment of chemotherapy induced peripheral neuropathy
	Ricci et al (25)	2019	Scrambler therapy: What's new after 15 years? The results from 219 patients treated for chronic pain
	Ricci et al (26)	2012	Managing chronic pain: Results from an open-label study using MC5-A Calmare(R) device
	Smith et al (39)	2010	Pilot trial of a patient-specific cutaneous electro-stimulation device (MC5-A Calmare) for chemotherapy-induced peripheral neuropathy
	Sparadeo et al (27)	2012	Scrambler therapy: An innovative and effective treatment for chronic neuropathic pain
	Tomasello et al (36)	2018	Scrambler therapy efficacy and safety for neuropathic pain correlated with chemotherapy-induced peripheral neuropathy in adolescents: A preliminary study
5 Case study	Lee (32)	2018	Efficacy of scrambler therapy on breast cancer-related lymphedema
	Lee et al (38)	2016	An exploratory study on the efficacy of "Calmare therapy" in patients with cancer-related neuropathic pain: A pilot study
	Park et al (35)	2017	Scrambler therapy for the treatment of neuropathic pain related to leukemia in a pediatric patient
	Park et al (38)	2013	Scrambler therapy for patients with cancer pain-case series
	Smith et al (33)	2017	Scrambler therapy for the treatment of chronic post-mastectomy pain (cPMP)

a safe treatment even for pregnant women. However, patients with active implanted metal devices should be excluded because the signal might interfere with the working of these devices.

Conclusions

Overwhelmingly, the current literature shows that ST is a promising intervention for the management of refractory cancer pain. However, this review of the literature has shown that the level of evidence for its application to cancer pain is not particularly strong. Particularly, methodologically sound large RCTs are needed in this area. Until then, ST may be considered as an option for cancer patients suffering from pain that does not respond to pharmacologic treatment, although clinicians should be aware that it is possible that the positive effect of ST is a placebo effect.

Acknowledgments

Author contributions: Komal Kashyap designed the study, collected the studies for the review, extracted and analyzed the data from the studies. She wrote the first draft of the manuscript and approved the final version. Sushma Bhatnagar provided revision for intellectual content throughout the process of conducting the review and writing the manuscript. She approved the final version of the manuscript.

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