Neurosurgical interventions for cancer pain

Alexander Alamri, Abteen Mostofi, and Erlick A.C. Pereira

Purpose of review
Half of all cancer patients will develop cancer-related pain, and a fifth of these patients will continue to experience pain refractory to maximal pharmacological therapy. This, together with the opioid crisis, has prompted a resurgence in neurosurgical treatments. Neuromodulatory or neuroablative procedures are largely used for various nonmalignant, chronic pain conditions, but there is growing evidence to support their use in cancer pain. This review aims to cover the main neurosurgical treatments that may prove useful in the changing sphere of cancer pain treatment.

Recent findings
Neuromodulation techniques for pain have largely replaced neuroablation in neurosurgical practice due to the higher risk of inadvertent permanent neurological deficits from the latter. When compared to neuroablative approaches for severe treatment-refractory cancer pain, neuromodulation is more expensive (largely due to implant cost) and requires more follow-up, with greater engagement needed from the health service, the patient and their carers. Furthermore, neuroablation has a more rapid onset of effect.

Summary
Neuromodulation techniques for pain have largely replaced neuroablation in neurosurgical practice due to the higher risk of inadvertent permanent neurological deficits from the latter. Whilst this approach is beneficial when treating nonmalignant pain, neuromodulation in patients with pain related to advanced cancer still has a limited role. Neuroablative procedures are less expensive, require less follow-up, and can have a lower burden on health services, patients and their carers.

Keywords
cancer pain, cingulotomy, intrathecal drug delivery, neurosurgery, spinal cord stimulation, thalamotomy

INTRODUCTION

Advances in cancer diagnosis and treatment have resulted in increasing numbers of cancer survivors. The prevalence of cancer pain ranges between 40 and 66% depending on the stage of the disease, with nearly 40% of patients reporting moderate to severe pain [1]. Although the implementation of the pharmacological analgesia step-ladder has had a major impact on the treatment of pain, it remains lacking in the area of cancer pain [2]. A significant proportion of cancer patients will develop cancer-related pain, yet between 10 and 30% of these patients will continue to experience pain refractory to maximal pharmacological therapy [2,3]. This, together with the opioid crisis, has prompted an expansion in neurosurgical treatments in an effort to tackle this unmet need.

Neurosurgical pain interventions aim to alter or disrupt the transmission or perception of neural signals mediating the sensation or experience of pain. Broadly, these can be classified as either 'neuromodulatory' or 'neuroablative'. Neuromodulation can be defined as 'the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites of the body' [4]. This collection of treatments is largely used for various nonmalignant, chronic pain conditions, but there are established and growing bodies of evidence to support their use in cancer pain [5–8]. Neuroablation, conversely, achieves its effect by making deliberate and focal lesions along one or more sites in neural pain pathways in the spinal cord or brain. The choice of a specific anatomical target depends upon each patient's pain generator and pain distribution. One advantage of many neuroablative interventions is that they can be performed under local anaesthesia, and the therapeutic effect is

Molecular and Clinical Sciences Research Institute, St George's University of London, Cranmer Terrace, London, UK

Correspondence to Alexander Alamri, St George's University of London, London SW17 0RE, UK.
E-mail: aalamri@sgul.ac.uk

KEY POINTS

- Neuroablative techniques are a cost-effective and rapid treatment modality for cancer pain patients.

- Spinal cord stimulation shows promise as a treatment modality but requires higher class evidence to be considered for cancer pain.

- Inrathecal drug delivery continues to be a viable and effective treatment option for cancer pain patients ineligible for neuroablative procedures.

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often immediate, in contrast to neuromodulation, which usually requires general anaesthesia and ongoing follow-up to titrate settings and optimise pain relief. The main drawback of neuroablation, however, is the risk of inadvertent damage to surrounding brain structures, causing potentially irreversible neurological deficits and disability.

This narrative review presents the current and evolving evidence for some common neuromodulatory and neuroablative interventions used in cancer pain. Indications, efficacy and safety are reviewed and discussed.

NEUROMODULATORY THERAPIES

Intrathecal drug delivery

Intrathecal drug delivery (ITDD) systems are indicated for those with inadequate pain management despite high doses of oral opioids. Oral opioid analgesia is also associated with intolerable dose-related adverse effects at higher doses, which limit its deployment in chronic cancer pain management [9]. A 2002 multicentre randomised controlled trial analysed 200 patients with refractory cancer pain despite at least 200 mg oral morphine equivalent opioid use [10]. The authors also compared comprehensive medical management (CMM) to ITDD and CMM. A significant reduction in opioid-related toxicity was achieved when ITDD was added to CMM. Pain scores and median systemic opioid use were also improved. This has been further ratified in a more recent prospective, long-term multicentre registry by Stearns *et al.* [11]. At 6 months, significant reductions in pain scores were reported as well as a significant improvement in quality of life. The predominant postoperative morbidity was surgical site infection at 3.2% requiring revision surgery.

Ongoing trials and observational studies in this field focus predominantly on combinations of intrathecal therapies such as morphine, ziconitide and levobupivacaine [12] or substitution with other opioid analogues such as hydromorphine [13]. The combinations and substitutions have shown persistent reductions in pain intensity, discontinuation of opioids and significant reductions in Karnofsky performance scores [14].

Spinal cord stimulation

Spinal cord stimulation (SCS) is an established treatment for persistent pain, particularly that which meets the definition of localised neuropathic pain. Surgically refractory spinal pain, previously known as 'failed back surgery syndrome' and complex regional pain syndromes are the most common indications. Stimulation of the dorsal columns of the spinal cord via implanted electrodes in the epidural space is thought to modulate neuronal function and disrupt the neuronal hyperactivity and maladaptive changes that occur in persistent pain states. This often results in the down-titration of analgesic use.

There is a limited evidence base for SCS in the management of cancer pain, despite positive outcomes reported in some observational studies. A 2015 Cochrane review identified only four case series and no randomised studies for inclusion [15▪]. There is only low-level evidence that SCS should be considered as an additional therapeutic option in cancer pain patients as opposed to level 1 evidence in noncancer patients. It is therefore clear that the pursuit of level 1 evidence will be crucial to allowing clinicians to explore SCS as a therapeutic option in cancer pain patients whose inadequately treated cancer pain may have a negative impact on their remaining quality of life.

NEUROABLATIVE PROCEDURES

Spinal cord lesions

Cordotomy

The greatest experience with neuroablative techniques for cancer pain is cordotomy. Cordotomy aims to destroy fibres running along the spinothalamic tract, abolishing the pain response below the level of the lesion [16]. The character of the pain must be considered carefully when assessing these patients. Certain pain modalities, such as visceral pain or deafferentation pain, will not respond particularly well to cordotomy.

For percutaneous cordotomy, radiofrequency electric current causes a thermal lesion in the spinothalamic tract. The entry point for the lesion is usually located over the C1/2 intervertebral foramen on the opposite side of the source of pain. Importantly, it can be performed under local anaesthesia, thus expanding the patient demographic that may safely undergo this procedure. The

mechanism is yet to be fully elucidated but may involve alteration of inhibitory descending impulses, dorsal horn modulation, damage to C fibres, and immunomodulatory effects [17]. The benefit is immediate, and there is the opportunity to perform the intervention even in the advanced stages of disease [18]. No further surgical follow-up is required, but the procedure can be repeated if pain recurs. CT-guided procedures, minimally invasive cordotomy and intraoperative neurophysiological monitoring have been shown to be safe and effective [19].

The diminishing analgesic effect that is often observed during follow-up is of less consequence in cancer pain patients, who likely have a reduced life expectancy. The side effect of contralateral pain seen in some case series could be attributable to pre-existing mild contralateral pain masked by more severe other pain prior to the procedure or could be, in those patients with no contralateral pain generator present, a 'mirror pain' phenomenon, hypothesised to arise from modulation of the central pain mechanism after disconnection of the spinothalamic tract. Regardless of the cause, it is usually well controlled with oral analgesia.

Myelotomy

The technical aim of myelotomy is to disrupt ascending fibres in the dorsal columns as well as decussating second-order neurons of the spinothalamic tract, specifically the postsynaptic dorsal column. As the postsynaptic dorsal column is a more medial pathway in the dorsal columns, the lesion is usually performed 1 mm to either side of the columns. Spinothalamic tract transmission of visceral signals is predominantly affected, leading myelotomy to be a procedure of choice for patients with refractory abdominal and pelvic cancer pain [20].

Performing myelotomy on cancer patients can be effective for visceral/abdominal pain [21,22]. Several different techniques have been utilised, but outcome data for these remain sparse. It is currently unknown whether percutaneous or open limited thoracic is more successful. Despite the lack of randomised, controlled trial data, it is possible to state that the most common side effects include small risk of bowel and bladder dysfunction, proprioceptive loss, transient paraesthesia and weakness.

Dorsal root entry zone lesions

Dorsal root entry zone lesion (DREZotomy) has a limited role in the treatment of cancer pain, specifically symptoms secondary to Pancoast tumour, and in some cases, radiation-induced plexopathy. DREZotomy destroys the lateral portions of the dorsal rootlets, the hyperactive neurons of the dorsal horn and the excitatory part of Lissauer's tracts. Different techniques have been used to accomplish this, including microsurgical, radiofrequency, ultrasonic and laser ablation [23–25]. A conventional approach involves hemilaminectomy with conservation of the spinous processes to preserve stability and limit postoperative pain. When compared to subjects with brachial plexus avulsion, the nerve rootlets of those with cancer pain are intact with fewer atrophic and gliotic changes which can distort the anatomy, thus accurate identification of the DREZ is less challenging, potentially minimising inadvertent lesioning of adjacent structures [25].

Brain lesioning

Brain lesions can be performed in a number of ways, but the greatest experience dating back many decades is with stereotactic radiofrequency lesions. Stereotactic neurosurgery concerns the accurate targeting of brain structures using three-dimensional coordinate systems defined relative to an external frame of reference. Radiofrequency lesions are made with an electrical probe delivered via a predefined trajectory to a target brain structure using a stereotactic frame. At the target, radiofrequency alternating current is passed through the probe, causing heating of the tip and thermocoagulation of the surrounding tissue. The two most common brain lesions for cancer pain are cingulotomy and thalamotomy. Important relative contraindications to brain lesions in the cancer setting include anticoagulation and abnormal brain anatomy from metastases.

Cingulotomy

The cingulate gyrus is located on the medial part of each cerebral hemisphere around the corpus callosum. It is broadly divided into anterior and posterior divisions. The anterior cingulate cortex (ACC) is part of the 'medial' central pain processing pathway, which concerns the affective-motivational aspect of pain. Specifically, the ACC can be thought of as assessing the emotional significance or reaction to pain (its valency or salience), rather than the perception or sensation of pain in itself.

The representation of pain in the ACC does not appear to be clearly lateralized. Cingulotomy therefore involves making one or two contiguous lesions of the ACC and its underlying white matter tract, the cingulum, bilaterally. The therapeutic effect often involves a reduction in emotional awareness of pain. In other words, patients become 'bothered' less by it.

Cingulotomy is indicated where there is medically refractory diffuse whole or hemibody pain, pain from head and neck malignancies, and axial or

bilateral pain which cannot be targeted more se-lectively with other interventional procedures, as well as significant associated emotional distress. Patients with dyspnoea may also benefit from cin-gulotomy, as reported in cases of improvement in the subjective sensation of 'air hunger' [26].

Cingulotomy is relatively uncommon and case series are few and heterogeneous in patient pop-ulations, specifics of technique, indications and duration of follow-up. However, in recent studies ~60–70% of patients experienced some meaningful benefit which persisted for 3 months or more, with the likelihood that pain relief tended to decline over time [27].

Reported adverse effects of cingulotomy include transient confusion or apathy, akinetic mutism, dysphasia or disinhibited speech, and urinary in-continence, which usually resolve fully within a few days [28–30]. Significant persistent neurocognitive effects are uncommon. There are rare reports of transient global aphasia and seizures. Procedural complications include symptomatic intracerebral haematoma related to probe insertion, which can rarely be fatal, and surgical site infection.

Thalamotomy

The thalamus is an important structure in ascending pain pathways. Spinothalamic fibres terminate mainly in the ventral posterior nucleus (VP), from which third-order thalamocortical neurons convey pain information to cerebral cortical areas, including the somatosensory cortex. VP has a somatotopic organ-isation with the head and face representation medially in the ventral posteromedial nucleus and the upper and lower limb representations located progressively lateral in the ventral posterolateral nucleus [31,32].

Spinoreticulothalamic and a small proportion of spinothalamic fibres terminate in the more medial centromedian-parafascicular complex (CM-PF) within the intralaminar group of thalamic nuclei [33]. CM-PF has reciprocal connections with the basal ganglia and cerebral cortex, including so-matosensory cortex and ACC, and is an important structure in the paleospinothalamic system and as-sociated 'medial' pain pathways mediating the affective components of pain.

Thalamotomy can target both VP and CM-PF but is usually performed unilaterally since bilateral tha-lamic lesions have a higher incidence of neurological adverse effects [32]. Indications for VP thalamotomy include medically refractory regional contralateral pain, especially of neurogenic origin, where the painful area is restricted to somatotopically con-tiguous body parts. As such, it can be considered an alternative to cordotomy for leg or arm pain and is particularly useful for unilateral head, neck and face

pain. Patients must be able to tolerate the procedure awake under local anaesthesia as intraoperative test stimulation and assessment is essential. The ability of patients to communicate effectively on the operating table is paramount for such assessment and warrants consideration when assessing patient suitability [34].

Data on outcomes is restricted to small histor-ical case series with heterogeneous patient pop-ulations, variable follow-up and inconsistent definition of thalamic target nuclei. Around 50% of patients will experience meaningful pain relief that lasts more than 2–3 months, with around 20% reporting complete resolution [32,33,35–37]. In common with many neuroablative procedures, pain relief usually declines over time.

Risks of thalamic lesions are mitigated by metic-ulous intraoperative assessment. However, transient sensorimotor deficits, dysphasia and confusion last-ing a few days are not uncommonly seen. Patients with VP lesions may be left with permanent sensory deficits and occasionally with dysaesthesia. For this reason, some practitioners prefer CM-PF over VP thalamotomy, though somatotopic discrimination is less of a feature with CM-PF thalamotomy. As with cingulotomy, surgical complications include intracerebral haematoma and surgical site in-fection [36,37].

DISCUSSION

Neuromodulation techniques for pain have largely replaced neuroablation in neurosurgical practice due to technological advancements in neuromodulation. Whilst this approach is beneficial when treating nonmalignant pain, neuromodulation in patients with pain related to advanced cancer still has a limited role, predominantly due to poor cost-effectiveness. When compared to neuroablative ap-proaches for severe treatment-refractory cancer pain, neuromodulation is more expensive (in part due to implant cost) and requires more follow-up, with greater burden on the health service, the patient and their carers. Furthermore, neuroablation has a more rapid onset of effect. When compared to the option of up-titrating the dose of opioids and other systemic medications, ablative procedures may provide enduring analgesia with a greater quality of life, both through decreased pain and avoidance of the risk of potential drug side effects, including drowsiness, confusion and respiratory depression. Additionally, ablation is arguably more beneficial from a health-economic perspective. Compared to the relatively costly and labour-intensive implantable pumps, whose drug reservoirs require regular refills, the one-time neuroablative procedure may be more suitable for patients with a short life expectancy (< 6–12 mo).

Although it is thought that pain relief affected by neuroablative procedures diminishes over time, this is not as relevant for the oncological population, who commonly have a more limited life expectancy.

CONCLUSIONS

There are ethical issues surrounding sham lesioning and the use of controls in studies involving cancer patients with refractory pain, who may have a compromised quality of life. It is also challenging to recruit and follow-up patients for long periods; this may explain why there is little evidence supporting the use of neuroablative techniques. However, an emerging body of research suggests that there is a need for better-quality trials comparing conventional medical therapy to SCS.

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Conflicts of interest
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