**Neuroablative Surgical Treatments for Pain due to Cancer**

Farrell SM1,2\*, Pereira EAC3, Brown MRD4,5, Green AL1, Aziz TZ1

1Nuffield Department of Clinical Sciences, John Radcliffe Hospital, Oxford, UK.

2The Royal Free London NHS Foundation Trust, UK.

3Neurosciences Research Centre, Molecular and Clinical Sciences Institute, St George's University of London, London, UK.

4The Royal Marsden Hospital NHS Foundation Trust, London, UK.

5The Institute of Cancer Research, London, UK.

\*Corresponding author: sarahmariefleurfarrell@gmail.com; sarah.farrell2@nhs.net

**Abstract:**

 Cancer pain is common and challenging to manage - it is estimated that approximately 30% of cancer patients have pain that is not adequately controlled by analgesia. This paper discusses safe and effective neuroablative treatment options for refractory cancer pain. Current management of cancer pain predominantly focuses on the use of medications, resulting in a relative loss of knowledge of these surgical techniques and the erosion of the skills required to perform them. Here we review surgical methods of modulating various points of the neural axis with the aim to expand the knowledge base of those managing cancer pain. Integration of neuroablative approaches may lead to higher rates of pain relief, and the opportunity to dose reduce analgesic agents with potential deleterious side effects. With an ever increasing population of cancer patients, it is essential that neurosurgeons maintain or train in these techniques in tandem with the oncological multi-disciplinary team.

**Key words: ‘cingulotomy’, ‘cordotomy’, ‘myelotomy’, ‘neuroablation’, ‘pain’, ‘thalamotomy’ .**

1. **Introduction**

It is a fundamental clinical responsibility to minimise patient distress, and the provision of effective analgesia forms a key aspect of managing patients with advanced cancer. Despite the development of novel analgesics and updated pain guidelines, cancer associated pain is often severe and poorly controlled [1]. Additionally, effective pain control brings wide-ranging benefits in the form of lower rates of hospital readmission, shorter length of stay and less interruption in cancer therapy [2]. The situation is complicated by the fact that pain is often viewed as a ‘non-life-threatening’ issue and subsequently deprioritised.

Over 90% of patients with cancer develop pain attributable to their disease [3], yet unrelieved pain remains a significant problem. The estimates of refractory cancer pain vary, with some sources suggesting 5-10% [4] and others approximately 30% of patients experiencing pain despite maximal medical therapy [5]. Conservative pain management commonly starts by adopting the approach advocated in the WHO pain ladder (step 3 = strong opioids) (World Health Organization: Cancer Pain Relief: With a Guide to Opioid Availability, ed 2. Geneva: World Health Organization, 1996 (<http://www.who.int/iris/handle/10665/37896> )). Options outside this ladder include adjuncts such as anti-neuropathic agents and NSAIDs, physical therapy and the management of psychological, sociocultural and spiritual factors. In some instances surgery is indicated, for example to prophylactically stabilise bony metastasis or reduce pathological fractures. For other pain generators (headache from brain or meningeal involvement, pain due to localised nerve involvement or visceral pain) radiotherapy may be an option. A number of distinct administration routes may be used to deliver analgesia, including oral preparations, transdermal patches and syringe drivers - a multimodal pharmacological approach is often adopted. Many of the analgesic drugs are associated with unpleasant side effects further reducing patients’ quality of life. The delivery of drugs into the intrathecal space using implantable or external intrathecal drug delivery systems may be indicated in some patients [6]. When pain is refractory to multimodal therapies a neuroablative procedure could potentially be considered.

Here we describe the evidence surrounding neurosurgical ablative procedures; myelotomy, cordotomy, dorsal root ganglion entry zone lesioning (DREZotomy), thalamotomy and cingulotomy to manage cancer pain. These interventions modulate the transmission of pain signals along a number of sites in its central nervous system pathway. This approach permits the targeting of different anatomy depending upon the patient’s pain generator. Some of these procedures are minimally invasive, can be done under local anaesthesia and have immediate, long-lasting effects. Indications, efficacy and safety are reviewed and discussed. This review does not cover other possible interventional techniques to treat cancer-related pain.

1. **Methodology:**

A PubMed search of the literature was conducted (October 2019-March 2020) using search terms ‘pain’ , ‘cancer’ and ‘cingulotomy’, then ‘pain’, ‘cancer’ and ‘thalamotomy’, then ‘pain’, ‘cancer’ and ‘cordotomy’, then ‘pain’, ‘cancer’ and ‘myelotomy’, then ‘pain’, ‘cancer’ and ‘dorsal root entry zone lesioning’ or ‘DREZotomy’. All references found were scanned for relevance, and then reviewed in more detail. The relevant references found in these articles were also added to the list. No unpublished material was included in this work.

1. **Cordotomy**

The greatest experience with neuroablative techniques for cancer pain is of cordotomy. Cordotomy aims to destroy fibres running along the spinothalamic tract, abolishing pain response below the level of the lesion. 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, see Figure 1, and may only be suitable to treat pain below the level of C4 dermatome [7]. The detailed surgical technique for cordotomy can be found elsewhere [8]. Importantly it can be performed under local anaesthetic, thus expanding the patient demographic who 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 of C fibres and immunomodulatory effects [9]. The benefit is immediate and there is the opportunity to perform the intervention even in the advanced stages of disease. No further surgical follow up is required but the procedure can be repeated if pain recurs. CT-guided procedures have been shown to be safe and effective [10, 11].

A systematic review of 9 case series (n=160) fell weakly in favour of cordotomy for effective pain relief[12] with further retrospective, uncontrolled studies showing a decrease or cessation of opioid use [10, 11, 13]. 45 retrospective and 5 prospective case studies of cancer related pain showed cordotomy to be effective, either alone or when combined with intrathecal pumps [14, 15]. Berger et al. recently conducted a retrospective review of patients undergoing neurosurgical interventions for advanced cancer with limited life expectancy and intractable pain [4]. The main technique used was O-arm (intra-operative CT) guided radiofrequency percutaneous cervical cordotomy (PCC) (for procedural technique see Strauss et al. [16]). 93% had immediate and excellent post-operative pain relief. After one month, this improvement was maintained in 30/36 patients (83%) available for follow up. Pain intensity was measured using the 11-point Numerical Rating Scale (NRS). Patient pain intensity averaged 9/10 pre-operatively, and was significantly lower at 1 month follow-up (mean NRS 0, range 0-5; p=0.001) with 27 of 31 surviving patients free of original pain. At 3 months, 9 out of 11 (81%) who survived and were included in 3 month follow-up were still pain free (mean 0, range 0-9, p=0.001). Two patients developed intraoperative delirium after midazolam sedation and the procedure aborted. Major complications included one case of hemiparesis, side effects included transient gait ataxia (n=3) and transient positional headaches (n=10). Although contralateral pain was described in 10 patients (30%) for ‘a few days’ after the procedure, this was mild and controlled with analgesia. Three patients (9%) developed severe disabling contralateral pain.

Until recently there was a paucity of prospective randomized controlled trials (RCT) of cordotomy., but the first RCT showed promising results [17]. Patients were included if they experienced one-sided, somatic pain caused by tumour below shoulder level (C5 dermatome) and with a >3 month life expectancy. A patient’s pain was determined to be refractory if the patient had a pain intensity ≥4 on NRS.

Sixteen patients were enrolled and assigned to either the neuroablative procedure or the interdisciplinary treatment team for optimal opioid therapy. The primary outcome success was set as a 33% improvement in pain intensity (PI) as measured by the Edmonton Symptom Assessment Scale at one week after cordotomy or study enrolment. Six out of seven patients randomized to cordotomy reached the primary outcome compared to zero out of the nine patients randomized to conservative care. Subsequently, seven patients from the medical arm underwent cordotomy after one week and all achieved at least a 33% reduction in pain intensity. Three complications occurred in the cordotomy group; urinary retention (resolved with treatment), subjective ipsilateral leg weakness lasting two weeks, and dysesthetic sensations for one week on the previously painful side of the body. These results are promising, with cordotomy shown to be effective and safe although the study was unblinded with a small number of participants. The study justifies a larger RCT, the protocol of which was published earlier this year [18], and should encourage the patient’s oncological MDT to explore the option of cordotomy for those patients in whom it may be indicated.

The first UK prospective data repository of adult patients undergoing PCC for pain control recently published data between 2012-17 of 159 patients from three centres [19]. This data consisted of 57% mesothelioma patients with a mean time from diagnosis to PCC assessment of 13.3 months (range 6.2-23.2) and further demonstrates PCC to be an effective treatment. Mean pain intensity scores on NRS dropped from 6 (s.d 2) to 2 (s.d.2) at a follow up of 8-25 days post-procedure, with only 4% experiencing adverse events; urinary retention (2 patients), opioid toxicity (1), impaired balance (1), dyspnoea (1) and pain at PCC site (1).

See Table 1: Post-operative outcomes of cordotomy for cancer pain: Key Studies.

The cordotomy literature demonstrates this technique to be effective and safe for treating unilateral cancer -related pain below C4. The diminishing analgesic effect over subsequent months is a general phenomenon of interventional pain procedures and is less problematic in those patients with limited 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 is present, a ‘mirror pain ‘ phenomenon, hypothesised to arise from modulation of the central pain mechanism after disconnection of the Spinothalamic tract [20, 21]. Regardless of the cause, it is usually well controlled with analgesia.

1. **Myelotomy**

Technically, myelotomy involves partially severing the spinal cord in the midline, interrupting ascending fibres of the postsynaptic dorsal column (PSDC) pathway in the dorsal columns [22, 23]. This lesion interrupts only the medial most aspects of dorsal columns; 1mm to each side. The PSDC pathway ascends along the midline of the dorsal columns and plays an important role in spinothalamic tract visceral signal transmission [23-29]. Thus, myelotomy is generally used for otherwise intractable abdominal and pelvic cancer pain [6, 22, 30, 31].

Open approach to myelotomy has been described [22, 31, 32]. However, the development of a minimally invasive technique with less disturbance of the spinal structure means that procedures can be performed under local anaesthesia, with a reduction in associated anaesthetic risk, and shorter hospital length of stay (discharge at 12-24 hours post-procedure).

Hong et al. [30] reviewed all published clinical series from 1997-2004 [6, 22, 31, 33-35]. The studies show in general that the procedure is successful, with most patients achieving either significant reduction in, or complete cessation of opioid intake. Although some studies showed that pain recurred (albeit at lower intensity) both in the original area and at distant sites, this was often due to disease progression [6, 22, 35]. The major complications included risk of bowel and bladder dysfunction, and loss of proprioception due to damage of dorsal columns. Postoperative paraesthesia has been reported but out of 4 patients only one was permanent [6].

Additional side effects of myelotomy have been demonstrated in later studies. Viswanathan studied a series of 11 patients from 1992-2009. 8 patients experienced successful pain relief (either complete or significantly reduced, some with cessation of analgesic medications), with a low incidence of postoperative urinary retention (1 patient), and decrease in leg strength (3 patients) [36]. This motor weakness did not necessarily limit functional levels as most of the patients in this series were bedbound by the severity of their pain. Importantly, weakness was regarded by the patients as a valid trade-off for the very significant pain relief and reduction in pain medications. A comparison of different myelotomy techniques [37] appears to favour open approach over percutaneous, with all four of the latter patients switching to open for better pain results.

See Table 2: Postoperative outcomes of myelotomy for cancer pain: Key Studies

Performing myelotomy on cancer patients can be effective for visceral/abdominal pain. Several different techniques have been utilized but outcome data for these remain sparse. It is currently unknown whether percutaneous or open limited thoracic is more successful. Despite the lack of RCT 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.

1. **Dorsal Root Ganglion Entry Zone lesions**

Dorsal Root Ganglion Entry Zone lesion (DREZotomy) has a limited role in the treatment of cancer pain, specifically Pancoasts tumour, and possibly localised radiation induced plexopathy, Gadgil et al. 2012 provides a comprehensive review of the subject [38]. DREZotomy destroys the lateral portions of the dorsal rootlets, the hyperactive neurons of the dorsal horn, and the excitatory part of Lissauer’s tracts [39]. Different techniques have been used to accomplish this, including microsurgical, radiofrequency, ultrasonic and laser ablation [40-43]. A popular 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 minimizing inadvertent lesioning of adjacent structures.

Sindou’s work provides the largest evidence supporting the use of the DREZotomy in cancer patients. In 1982, a series of 13 patients with Pancoast tumours were treated with microsurgical DREZotomy [44]. Although 2 died postoperatively due to disease progression, 10 of the 11 survivors experienced good results. The same author has described a series of cases from 1972 onwards [45], of 367 patients, 81 were treated for cancer pain; it is not clear whether this group includes patients in the previously mentioned study. A good result ( 75% reduction in pain intensity) was obtained in 87% of patients operated at the cervicothoracic level and 78% of the patients operated at the lumbosacral level. The median postoperative survival was 13 months. The authors report 2 postoperative surgical site infections and 2 procedure associated deaths.

A number of studies have investigated the use of DREZotomy to treat radiation-induced plexopathy. The largest cohort was described by Teixeira *et al.,* reporting resolution of pain in 5 of 6 patients with a median follow-up of 12 months and a preoperative rating between 8 and 10 on VAS [46]. Two other studies each included 2 patients with radiation-induced plexopathy: 3 became pain free and 1 had recurrence of pain 8 months after the procedure [47, 48]. Though these studies are small, the results are encouraging, and suggest longevity of pain relief may trump that of myelotomy and cordotomy for those patients in whom DREZ is an appropriate procedure.

The heterogeneity of the cancer patient population and surgical techniques used makes outcome analysis for DREZotomy difficult, and thus indications for patient selection equivocal.

Particularly good results are found for those with Pancoast Tumour. Unlike myelotomy and cordotomy, DREZotomy is not effective in relieving pain below the level of the lesion [39, 47, 49].

1. **Thalamotomy**

As a relay for several components of the pain perception system, the thalamus has been a promising target for surgical intervention. The first thalamotomies using irradiation (gammathalamotomy) for intractable pain were performed by Leksell [50] and Forster [51]. Procedures can be performed under local anaesthetic, are quick to perform, and the patient experiences a good recovery with low morbidity and mortality rates. See Figure 2a.

Steiner et al. examined a series of 52 patients undergoing thalamotomy with varying types of cancer pain. They performed gamma irradiation creating medial lesions (focusing on centromedian and parafascicular nuclei) that were produced either contra-, ipsi- ,or bilaterally. Immediate pain relief was experienced by 2/3 of subjects in the following 2 weeks, some of which may be attributed to placebo effect. Over a greater time period, 8/52 subjects experienced good pain relief lasting at least 3 months or until death (13, 10, 4, 4 and 1 months). Another 18 patients experienced moderate pain relief, lasting 1-19 months. The remaining 24 patients did not experience significant pain relief [52]. The authors noted better results in patients with face, arm or shoulder pain, compared to pain in the lower half of the body. They concluded this method could be used as a last resort in treatment of cancer pain in selected patients with short life expectancy.

Successful cases of pain reduction outside this ‘face, arm, shoulder’ distribution have previously been described. Kudo *et al*., described 3 thalamotomy cases, one pertaining to lower abdominal pain stemming from inoperable carcinoma of the uterus. Pain was relieved with bilateral medial thalamotomy with a transient complication of ‘excitability’ lasting only one day [53]. Whittel and Jenkinson describe two cases of thalamotomy for cancer pain, one left sided brachialgia and the other, left leg, thigh and low lumbar pain with primaries from follicular thyroid carcinoma and iliac chondrosarcoma respectively. In both cases the procedures (targeting anteromedial pulvinar and centromedian parafascicular nuclear regions of the thalamus) were well tolerated, devoid of complications and resulted in decreased pain and reduced analgesic medication requirements for the remainder of the patients’ lives [54].

More recently, a comparison of mesencephalotomy and thalamotomies for treatment of cancer pain compared two case series at different institutions [55]. After 2-7 month follow up, the authors conclude thalamotomy had no mortality and only slight morbidity, however antalgic benefit may not be as effective as other ablative modalities.

Jeanmonod studied 96 patients with intractable pain including 5 with cancer pain (results for which are not separated in their paper). Although it is not possible to delineate which follow up data relates specifically to these individual cancer patients, it is perhaps still useful to see the general use of thalamotomy for a variety of pain aetiologies whether malignant or not, given the sparsity of cancer- specific data. The localisation of the pain included the face (23.9%), the head and neck (7.3%), the upper and lower limb (69.8%), the thoracoabdominal and the perineal areas (20.8%) or the entire hemi corpus (8.3%). The authors classified pain into continuous, intermittent, or allodynic with follow up ranging between 2 weeks (cancer patient) to 10 years 5 months, with a mean of 3 years and 5 months. Results were mixed but promising, with 53% of patients estimating their pain relief to be greater than 50%, and 18.7% of patients experiencing complete relief [56]. It was noted that results were very good for those patients experiencing intermittent pain and allodynia, but less convincing for continuous pain.

11 patients experienced complications including intraventricular bleeding, reversible thalamic oedema, short-lasting sensorimotor deficits, reversible pretectal and motor manifestations and irreversible trigeminal deficits. A further patient experienced anterior thalamic vasospasm causing verbal deficits, this only partially recovered and represents the only serious complication. The conclusion we can draw from this study is that centrolateral thalamotomy is a useful surgical option for all forms of intractable neurogenic pain, including that resulting from malignancy. The authors note this pain relief likely arises through reduction of the hypersynchronization of low frequencies in the posterior portion of the centrolateral thalamic nucleus.

Evidence to date is confined to descriptions of case reports and series, but nonetheless demonstrate thalamotomy to be an inviting target for cancer patients with intractable pain of somatotopic origin, particularly in the face, arm and shoulder but also extending outside this to the legs. It is a viable alternative to cordotomy, effective for segmental pain, and, whilst risking numbness and weakness is not commonly associated with significant morbidity and mortality. The choice of thalamotomy over cordotomy is often based on individual clinicians’ experiences. For pain interventionalists who usually represent the first port of call for referrals, they are often limited to percutaneous cordotomy whereas for functional neurosurgeons, thalamotomy is a safer option with which they have more translatable experience with.

1. **Cingulotomy**

Cingulotomy involves severing fibres passing through an area of the brain which contributes to the affective component of nociceptive processing, the anterior cingulate gyrus. See Figure 2b. Patients with diffuse pain, especially abdominal metastasis, respond well to the procedure. More detailed information regarding this procedure can be found elsewhere [57] [58, 59].

Foltz and white 1962 conducted one of the earliest studies of cingulotomy for pain. Six patients with pain that involved strong emotional factors associated were included. Areas of pain included face and neck (n=3), back and hip (n=2), shoulder and arm (n=1) [60]. Outcomes were deemed to be excellent for 2 of the patients, good for 3, and fair for 1 patient. Patients were able to stop opioid analgesia without withdrawal symptoms. A similar study by Faillace et al. in 1971 demonstrated less favourable results with only 3 out of 7 patients improved at 3 days, all of whom lost this benefit by 3 month follow up [61]. Possible cognitive decline was indicated with a decrease in nonverbal ordering tests, however this was not significant from baselines. A larger series of 32 patients (with advanced cancers including lung, GI, head and neck, melanoma, sarcoma) showed 32% complete or marked pain relief, 19% moderate pain relief, and 44% slight or no relief [62]. No deaths were reported but side-effects included transient headache and fever, less commonly bladder and bowel dysfunction and confusion. These did not persist beyond 2 weeks after the postoperative period. A longer follow-up (1-12 months) of bilateral cingulotomy in five patients demonstrated all experienced pain relief until death [63]. Another series of 9 patients saw the NRS drop from 9 to 4 and analgesia dose decreasing after procedure. Side effects included one case of global aphasia, resolving 10 days after surgery. This study saw improved cognition, especially concentration and perception, and no changes in or flattening of affect [64]. Wong and colleagues observed flattened affect and paranoid ideation in 1 out of 3 cases with the remaining two patients experiencing excellent outcomes [65].

A retrospective study assessing patients from 2001-2002, demonstrated 53% (n=8) to experience significant pain relief, 27% (n=4 patients) meaningful relief, and 20% (n=3) showing little improvement [59]. The same group repeated the process for the years 2002-2004, finding 40% had >75% pain relief, and two others between 25-75% [66]. At 1 month follow-up 66% showed definitive pain relief, decreasing to 50% at 6 months. No noticeable effects were seen on language, memory, intellect and motor-visual constructional skills 1 day before, 1 week or 1 month post operatively. The early post-operative period did show decline in focussed attention performance on the Stroop interference test. Additionally 2 patients with good pain relief had transient and self-resolving inappropriate and disinhibited speech for two days.

A more recent retrospective review of double stereotactic cingulotomy for cancer pain studied patients (2015-2018) with metastatic cancer with a prognosis of >1 year. All patients experienced diffuse pain refractory to other targeted treatment, medical treatment and radiotherapy. 13 patients were assessed. Out of 6 patients that were preoperatively bed ridden, 3 were ambulating shortly after. At one month follow up the mean VAS scores decreased from 9 +/- 0.9 to 4+/- 2.7 [57]. During the 1 to 2 month follow up visits, 9 out of 11 patients (82%) and 5 out of 7 patients (71%) available for follow up reported substantial pain relief. Neuropsychological analyses of 6 patients showed stable cognitive functions with a mild nonsignificant decline in focused attention. Adverse events included transient confusion or mild apathy in 5 patients (38%) lasting 1-4 weeks [57]. The study concluded double stereotactic cingulotomy is safe and effective in alleviating refractory oncological pain. A further study by the same group examined 20 patients with diffuse pain undergoing stereotactic cingulotomy (technical details of procedure found in: [57]). 18/20 (90%) reported substantial pain relief immediately after operation. At one month, good pain relief was reported for 13/17 (76% of those available for follow-up, mean NRS score 3 out of 10, range 6-9, p=0.001). At 3 months, good pain relief was found for 7/11 (64% median NRS score 4, range 1-10;p=0.012)[4]. The paper reported no major morbidity and mortality, though transient confusion was reported as a common side effect.

See Table 3: Post-operative outcomes of cingulotomy for cancer pain: Key Studies

Studies of cingulotomy for intractable cancer pain demonstrate that this procedure is effective for diffuse pain syndromes, head and neck malignancies or significant emotional distress. The procedure is safe, performed under local anaesthetic, and whilst side effects are minimal may include some cognitive effects.

1. **Discussion**

Neurosurgical ablative procedures afford opportunities to treat cancer pain intractable to current medical methods in an efficacious, safe way. Using CT guidance has further increased the accuracy of these techniques. The undeniable limitation to their use is the lack of randomized control trials comparing to best medical therapy. The success of cordotomy in a recent small RCT should pave the way for larger scale RCTs and the inclusion of  cordotomy as a treatment modality in subsequent guidelines for cancer pain management.

Neuromodulation techniques for pain has replaced ablation in many neurosurgical centres, and whilst this approach is beneficial when treating non-malignant pain, its use in patients with pain related to advanced cancer has in general been limited to intrathecal pumps. When compared to neuromodulatory approaches for severe treatment-refractory cancer pain, ablative procedures are less expensive and require less follow up, thus reducing the burden on the health service, the patient, and their carers. 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 arguable more beneficial from a health-economic perspective. Berger states in their recent review (2019) that 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 months). Although it is thought that pain relief effected by neuroablative procedures diminishes over time, this is not as relevant for the oncological population who commonly have a limited life span.

Neuroablative procedures for cancer pain currently sit at a tipping point in regard to their future development. Pain management in advanced cancer has witnessed a reliance on strong analgesic agents such as opioids and anti-neuropathic adjuvant drugs. Concurrently the role of neuroablation has been deemphasized by the neurosurgical population who often lack the necessary surgical knowledge of these procedures. Unfortunately in the UK, the lack of expansion in the provision of these ablative procedures has been, in part, due to conflation of psychosurgery and pain relief amongst some healthcare teams; their vocal expression leading to loss of funding. As some ablative procedures, particularly cingulotomy, target the affective component of pain processing, there is confusion over whether this treatment is psychosurgery; a therapy which has gained a sense of taboo due to historic misuse of the practice. We would argue that not only does the very necessary practice of informed consent and the patient-doctor relationship reduce this fear [67], but cingulotomy for pain relief does not class as a psychosurgery. Mood effects are not usually observed in these patients beyond pain relief. Regardless of how the treatment is labelled, patients report to be less bothered by their pain, thus experiencing an increased quality of life. Education about these surgeries which highlights the relative ease with which they can be performed, minimal follow up requirements, their safety profile, and their efficacy might help reduce neurophobia amongst patients and their clinicians, offering an opportunity of effective pain control to the significant number of patients with advanced cancer who experience severe pain. This is particularly important in light of the coronavirus pandemic, which is anticipated to result in increased numbers of patients receiving delayed or suboptimal oncological care and who may experience severe pain. For this population access to and provision of timely, effective pain-relieving interventions will make a subjective difference to quality of life and are of high importance.

Judicious use of any therapy is key to its success. It can be challenging to decide when a patient is an appropriate candidate for any of the neurosurgical interventions offered. What exactly is intractable pain and when does the patient qualify for the surgery? What therapeutic approaches must they have tried first? Given the patients are often at the end-stage of their disease process, how does this effect their performance status and fitness for surgery? The general consensus is to use the following selection criteria which specifies 5 domains which must be satisfied prior to consideration for an ablative procedure [4]: 1) advanced oncological disease with limited life expectancy; 2) options for radiotherapy have been exhausted; 3) best medical treatment have a. failed to cause pain relief or b. incurred the development of intolerable side effects; 4) pain has failed to respond adequately to any targeted interventions (for example, nerve blocks); and 5) absence of technical limitations or medical contraindications to the procedures offered.

Figure 3 shows a basic algorithm for selection of appropriate procedure for a patients pain presentation as an adapted version of that proposed by Berger and colleagues [4]. Put simply, cordotomy or thalamotomy may benefit those intractable pain patients with unilateral nociceptive pain, myelotomy if visceral midline pain is present, and cingulotomy in subjects presenting with diffuse pain, head and neck malignancy, and with elements of significant emotional distress.

1. **Conclusion**

Interventional and surgical procedures for pain are often neglected or simply forgotten despite their ability to effectively mitigate patient’s pain and distress, in some cases obviating or reducing the need to take strong analgesic medication. The relative ease with which these ablative procedures are performed, commonly under local anaesthesia, their short recovery time and rapid effects on pain relief, increases the attractiveness of these procedures to patients and clinicians alike. Additionally neuroablation often represents a cost-effective intervention for these patients and so from a health-economic viewpoint is also favourable.

For these reasons, neuroablative procedures offer a means to narrow the gap between patients’ expectations for adequate symptom management, and our capability to achieve this. Creating and maintaining a knowledgeable treatment team who can select the right patient to receive the right treatment, heavily involving patients during this decision process, is vital for successful outcome.

**Authors contribution**

SMF performed original draft preparation; EACP, MRDB, ALG, TZA and SMF performed writing (reviewing and editing).

**Acknowledgments**

The authors acknowledge the NHS funding to the Oxford NIHR Biomedical Research Centre and the Royal Marsden/Institute of Cancer Research NIHR Biomedical Research Centre.

We acknowledge Sean Farrell for assistance with schematics and graphics.

**Declarations of Interest**

No interests declared.

**Funding**

Research for this review article received no external funding.

**References**

1. Kwon, J.H., *Overcoming barriers in cancer pain management.* J Clin Oncol, 2014. **32**(16): p. 1727-33.

2. Gunn, G.B., et al., *High symptom burden prior to radiation therapy for head and neck cancer: a patient-reported outcomes study.* Head Neck, 2013. **35**(10): p. 1490-8.

3. Caraceni, A. and R.K. Portenoy, *An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain.* Pain, 1999. **82**(3): p. 263-74.

4. Berger, A., et al., *Neurosurgical ablative procedures for intractable cancer pain.* J Neurosurg, 2019: p. 1-8.

5. van den Beuken-van Everdingen, M.H., et al., *Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis.* J Pain Symptom Manage, 2016. **51**(6): p. 1070-1090.e9.

6. Kim, Y.S. and S.J. Kwon, *High thoracic midline dorsal column myelotomy for severe visceral pain due to advanced stomach cancer.* Neurosurgery, 2000. **46**(1): p. 85-90; discussion 90-2.

7. Feizerfan, A., Antrobus, J.H.L., *Role of percutaneous cervical cordotomy in cancer pain management*. 2014: Continuing Education in Anaesthesia Critical Care & Pain. p. 23-26.

8. Reddy, G.D., et al., *Percutaneous CT-guided cordotomy for the treatment of pediatric cancer pain.* J Neurosurg Pediatr, 2013. **12**(1): p. 93-6.

9. Scott-Warren, J., Bhaskar, A., *Cancer pain management: Part II: Interventional techniques.*. 2015: C*ontin. Educ. Anaesth. Crit. Care Pain*p. 68-72.

10. Raslan, A.M., *Percutaneous computed tomography-guided radiofrequency ablation of upper spinal cord pain pathways for cancer-related pain.* Neurosurgery, 2008. **62**(3 Suppl 1): p. 226-33; discussion 233-4.

11. Kanpolat, Y., et al., *Computed tomography-guided percutaneous cordotomy for intractable pain in malignancy.* Neurosurgery, 2009. **64**(3 Suppl): p. ons187-93; discussion ons193-4.

12. France, B.D., et al., *Cordotomy in mesothelioma-related pain: a systematic review.* BMJ Support Palliat Care, 2014. **4**(1): p. 19-29.

13. Jackson, M.B., et al., *Percutaneous cervical cordotomy for the control of pain in patients with pleural mesothelioma.* Thorax, 1999. **54**(3): p. 238-41.

14. Bain, E., H. Hugel, and M. Sharma, *Percutaneous cervical cordotomy for the management of pain from cancer: a prospective review of 45 cases.* J Palliat Med, 2013. **16**(8): p. 901-7.

15. Bentley, J.N., et al., *Treatment of medically refractory cancer pain with a combination of intrathecal neuromodulation and neurosurgical ablation: case series and literature review.* Pain Med, 2014. **15**(9): p. 1488-95.

16. Strauss, I., et al., *O-Arm-Guided Percutaneous Radiofrequency Cordotomy.* Stereotact Funct Neurosurg, 2017. **95**(6): p. 409-416.

17. Viswanathan, A., et al., *Minimally Invasive Cordotomy for Refractory Cancer Pain: A Randomized Controlled Trial.* Oncologist, 2019. **24**(7): p. e590-e596.

18. Viswanathan, A., et al., *Percutaneous Cordotomy for Pain Palliation in Advanced Cancer: A Randomized Clinical Trial Study Protocol.* Neurosurgery, 2020.

19. Poolman, M., et al., *Percutaneous cervical cordotomy for cancer-related pain: national data.* BMJ Support Palliat Care, 2020.

20. Higaki, N., et al., *Usefulness of cordotomy in patients with cancer who experience bilateral pain: implications of increased pain and new pain.* Neurosurgery, 2015. **76**(3): p. 249-56; discussion 256; quiz 256-7.

21. Nagaro, T., et al., *New pain following cordotomy: clinical features, mechanisms, and clinical importance.* J Neurosurg, 2001. **95**(3): p. 425-31.

22. Nauta, H.J., et al., *Punctate midline myelotomy for the relief of visceral cancer pain.* J Neurosurg, 2000. **92**(2 Suppl): p. 125-30.

23. Al-Chaer, E.D., et al., *Pelvic visceral input into the nucleus gracilis is largely mediated by the postsynaptic dorsal column pathway.* J Neurophysiol, 1996. **76**(4): p. 2675-90.

24. Al-Chaer, E.D., et al., *Visceral nociceptive input into the ventral posterolateral nucleus of the thalamus: a new function for the dorsal column pathway.* J Neurophysiol, 1996. **76**(4): p. 2661-74.

25. Willis, W.D., et al., *A visceral pain pathway in the dorsal column of the spinal cord.* Proc Natl Acad Sci U S A, 1999. **96**(14): p. 7675-9.

26. Al-Chaer, E.D., Y. Feng, and W.D. Willis, *A role for the dorsal column in nociceptive visceral input into the thalamus of primates.* J Neurophysiol, 1998. **79**(6): p. 3143-50.

27. Houghton, A.K., S. Kadura, and K.N. Westlund, *Dorsal column lesions reverse the reduction of homecage activity in rats with pancreatitis.* Neuroreport, 1997. **8**(17): p. 3795-800.

28. Houghton, A.K., C.C. Wang, and K.N. Westlund, *Do nociceptive signals from the pancreas travel in the dorsal column?* Pain, 2001. **89**(2-3): p. 207-20.

29. Feng, Y., et al., *Epigastric antinociception by cervical dorsal column lesions in rats.* Anesthesiology, 1998. **89**(2): p. 411-20.

30. Hong, D. and A. Andrén-Sandberg, *Punctate midline myelotomy: a minimally invasive procedure for the treatment of pain in inextirpable abdominal and pelvic cancer.* J Pain Symptom Manage, 2007. **33**(1): p. 99-109.

31. Nauta, H.J., et al., *Surgical interruption of a midline dorsal column visceral pain pathway. Case report and review of the literature.* J Neurosurg, 1997. **86**(3): p. 538-42.

32. Gildenberg, P.L. and R.M. Hirshberg, *Limited myelotomy for the treatment of intractable cancer pain.* J Neurol Neurosurg Psychiatry, 1984. **47**(1): p. 94-6.

33. Vilela Filho, O., et al., *CT-guided percutaneous punctate midline myelotomy for the treatment of intractable visceral pain: a technical note.* Stereotact Funct Neurosurg, 2001. **77**(1-4): p. 177-82.

34. Cowie, R.A. and E.R. Hitchcock, *The late results of antero-lateral cordotomy for pain relief.* Acta Neurochir (Wien), 1982. **64**(1-2): p. 39-50.

35. Hwang, S.L., et al., *Massive cerebral air embolism after cardiopulmonary resuscitation.* J Clin Neurosci, 2005. **12**(4): p. 468-9.

36. Viswanathan, A., et al., *Commissural myelotomy in the treatment of intractable visceral pain: technique and outcomes.* Stereotact Funct Neurosurg, 2010. **88**(6): p. 374-82.

37. Vedantam, A., et al., *Limited Midline Myelotomy for Intractable Visceral Pain: Surgical Techniques and Outcomes.* Neurosurgery, 2018. **83**(4): p. 783-789.

38. Gadgil, N. and A. Viswanathan, *DREZotomy in the treatment of cancer pain: a review.* Stereotact Funct Neurosurg, 2012. **90**(6): p. 356-60.

39. Sindou, M., P. Mertens, and M. Wael, *Microsurgical DREZotomy for pain due to spinal cord and/or cauda equina injuries: long-term results in a series of 44 patients.* Pain, 2001. **92**(1-2): p. 159-71.

40. Nashold, B.S. and R.H. Ostdahl, *Dorsal root entry zone lesions for pain relief.* J Neurosurg, 1979. **51**(1): p. 59-69.

41. Sindou, M. and D. Jeanmonod, *Microsurgical DREZ-otomy for the treatment of spasticity and pain in the lower limbs.* Neurosurgery, 1989. **24**(5): p. 655-70.

42. Dreval, O.N., *Ultrasonic DREZ-operations for treatment of pain due to brachial plexus avulsion.* Acta Neurochir (Wien), 1993. **122**(1-2): p. 76-81.

43. Young, R.F., *Clinical experience with radiofrequency and laser DREZ lesions.* J Neurosurg, 1990. **72**(5): p. 715-20.

44. Sindou. M., L., C., *Neurosurgical treatment of pain in the Pancoast-Tobias syndrome: selective posterior rhizotomy and open antero-lateral C 2 -cordotomy*in *Advances in Pain Research and Therapy: Management of Superior Pulmonary Sulcus Syndrome.*, J. Bonica, Editor. 1982, Raven Press: New York. p. 199-209.

45. Sindou, M., *Microsurgical DREZotomy (MDT) for pain, spasticity, and hyperactive bladder: a 20-year experience.* Acta Neurochir (Wien), 1995. **137**(1-2): p. 1-5.

46. Teixeira, M.J., E.T. Fonoff, and M.C. Montenegro, *Dorsal root entry zone lesions for treatment of pain-related to radiation-induced plexopathy.* Spine (Phila Pa 1976), 2007. **32**(10): p. E316-9.

47. Rath, S.A., et al., *Results of DREZ coagulations for pain related to plexus lesions, spinal cord injuries and postherpetic neuralgia.* Acta Neurochir (Wien), 1996. **138**(4): p. 364-9.

48. Zeidman, S.M., E.J. Rossitch, and B.S. Nashold, *Dorsal root entry zone lesions in the treatment of pain related to radiation-induced brachial plexopathy.* J Spinal Disord, 1993. **6**(1): p. 44-7.

49. Friedman, A.H. and B.S. Nashold, *DREZ lesions for relief of pain related to spinal cord injury.* J Neurosurg, 1986. **65**(4): p. 465-9.

50. Leksell, L., *Cerebral radio surgery, gamma thalamotomy in two cases of intractable pain.* 1968: Acta Chir, Scand. p. 585-595.

51. Forster, D.M.C., Meyerson, B.A., Leksell, L., Steiner, L., *Stereotaxic radio surgery in intractable pain. In: Pain, pp. 194-198 (Janzen, R., ed).* 1972: London: G. Thieme.

52. Steiner, L., et al., *Gammathalamotomy in intractable pain.* Acta Neurochir (Wien), 1980. **52**(3-4): p. 173-84.

53. Kudo, T., Yoshii, N., Shimizu, S., Aikawa, S., Nakahama, H., *Effects of stereotaxic thalamotomy to intractable pain and numbness.* 1966: Kelo Journal of Medicine.

54. Whittle, I.R. and J.L. Jenkinson, *CT-guided stereotactic antero-medial pulvinotomy and centromedian-parafascicular thalamotomy for intractable malignant pain.* Br J Neurosurg, 1995. **9**(2): p. 195-200.

55. Frank, F., et al., *Stereotactic mesencephalotomy versus multiple thalamotomies in the treatment of chronic cancer pain syndromes.* Appl Neurophysiol, 1987. **50**(1-6): p. 314-8.

56. Jeanmonod, D., Magnin, M., Morel, A., Siegemund, M., *Surgical control of the human thalamocortical dysrhythmia: I. Central lateral thalamotomy in neurogenic pain.* 2001: Thalamus & Related Systems. p. 71-79.

57. Strauss, I., et al., *Double Anterior Stereotactic Cingulotomy for Intractable Oncological Pain.* Stereotact Funct Neurosurg, 2017. **95**(6): p. 400-408.

58. Viswanathan, A., et al., *Cingulotomy for medically refractory cancer pain.* Neurosurg Focus, 2013. **35**(3): p. E1.

59. Yen, C.P., et al., *Stereotactic bilateral anterior cingulotomy for intractable pain.* J Clin Neurosci, 2005. **12**(8): p. 886-90.

60. FOLTZ, E.L. and L.E. WHITE, *Pain "relief" by frontal cingulumotomy.* J Neurosurg, 1962. **19**: p. 89-100.

61. Faillace, L.A., et al., *Cognitive deficits from bilateral cingulotomy for intractable pain in man.* Dis Nerv Syst, 1971. **32**(3): p. 171-5.

62. Hurt, R.W. and H.T. Ballantine, *Stereotactic anterior cingulate lesions for persistent pain: a report on 68 cases.* Clin Neurosurg, 1974. **21**: p. 334-51.

63. Voris, H.C. and W.W. Whisler, *Results of stereotaxic surgery for intractable pain.* Confin Neurol, 1975. **37**(1-3): p. 86-96.

64. Pillay, P.K. and S.J. Hassenbusch, *Bilateral MRI-guided stereotactic cingulotomy for intractable pain.* Stereotact Funct Neurosurg, 1992. **59**(1-4): p. 33-8.

65. Wong, E.T., et al., *Palliation of intractable cancer pain by MRI-guided cingulotomy.* Clin J Pain, 1997. **13**(3): p. 260-3.

66. Yen, C.P., et al., *Impact of bilateral anterior cingulotomy on neurocognitive function in patients with intractable pain.* J Clin Neurosci, 2009. **16**(2): p. 214-9.

67. Grant, R.A., et al., *Ethical considerations in deep brain stimulation for psychiatric illness.* J Clin Neurosci, 2014. **21**(1): p. 1-5.