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Cordotomy in mesothelioma-related pain: a systematic review

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ABSTRACT

Background Cordotomy can be effective in relieving pain for patients with mesothelioma, but the evidence to support continued provision is limited. This review forms part of the Invasive Neurodestructive Procedures in Cancer Pain pilot study: The role of cordotomy in mesothelioma-related pain in the UK.

Aim/design We report on the results of the first comprehensive systematic review of the use of cordotomy in mesothelioma-related pain, with specific reference to effectiveness in relieving pain and safety. The review was conducted according to guidelines reported in the NHS Centre for Reviews and Dissemination and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses.

Data sources 14 databases from inception to March 2012 were searched, with no limitations on language or publication type.

Results Nine studies met the inclusion criteria, all of which were case series of percutaneous cervical cordotomy (PCC) involving 160 patients. All studies demonstrated good pain relief in the majority of patients. Initial post-procedure measurements showed the greatest reduction in pain. Some side effects (headache, mirror pain, motor weakness) occurred relatively frequently but were mostly transient. Respiratory dysfunction post-PCC was rare. No deaths were directly ascribed to cordotomy.

Conclusions The available evidence is significantly limited in quantity and quality. Although it seems to suggest that cordotomy might be safe and effective in this setting, more reliable evidence is needed to aid decision making on continued provision. A national registry for cordotomy would be a valuable first step in this process.

INTRODUCTION

In the UK in 2008, 2400 people were diagnosed with mesothelioma.[1] The incidence is still rising and is expected to peak around 2020.[1 2] More patients die of mesothelioma than cervical cancer, malignant melanoma or endometrial carcinoma.[3] Between 2006 and 2020, up to 30 000 people will die of mesothelioma in the UK.[3] Palliative care and symptom control is central to the management of patients as the disease is often associated with difficult pain syndromes and other symptoms that may respond inadequately to pharmacological approaches alone. The National Mesothelioma Framework suggested that patients should have access to services that offer cordotomy as a palliative intervention to provide relief from challenging pain syndromes.[4] However, great inequity exists in the provision of services offering cordotomy; new services are being established, while others have closed (Makin, unpublished data, 2012). For a small group of patients the procedure may yield significant analgesic benefit, yet there is an unquantified associated morbidity.

There seems to be little published evidence to support continued provision and commissioning of cordotomy, a fact that is supported by the findings of Raslan *et al*[5] who concluded that 'evidence needs to meet the current evidence-based standards through clinical trials.' In an attempt to consolidate all available evidence, the Invasive Neurodestructive Procedures in Cancer Pain (INPiC) pilot study was designed to focus on the use of cordotomy in mesothelioma-related pain (Makin, unpublished data, 2012). This review was conducted as part of the INPiC pilot study. This article reports on the results of the first comprehensive systematic literature review, with specific reference to safety and effectiveness of cordotomy in mesothelioma-related pain.

METHODS

This systematic review was conducted and reported according to NHS Centre for Reviews and Dissemination (CRD) Report 47 and Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[6 7] A preliminary scoping search showed a limited evidence base; the search strategy was therefore designed for sensitivity rather than specificity. A search strategy developed for Medline was adapted for 13 other databases; all were searched from inception until March 2012 (table 1). Reference lists from previous reviews and included studies were hand searched.

Inclusion criteria were as follows:

- Participants: patients with mesothelioma where the intention was to perform cordotomy (open or percutaneous) as a treatment for the control of intractable pain.
- Intervention: cordotomy: the creation of a permanent (often heat created by radiofrequency technique) lesion in the lateral spinothalamic tract in the anterolateral spinal cord.
- Control: treatment for pain using other modalities (pharmacotherapy or other neuroinvasive or neuroablative procedures).
- Outcomes: effectiveness in relieving pain and side effects.
- Study design: any, except reviews and single case reports.

There were no limits on language, year of publication or publication status. Two reviewers independently screened the titles and abstracts for relevancy. Disagreements were resolved by discussion or, if necessary, a third reviewer.

In studies that reported data on multiple diseases (including mesothelioma), only information relevant to mesothelioma was extracted. In studies where this was not possible (n=11), we wrote to the corresponding author and asked if they could supply us with separate data for mesothelioma patients.[8–18] One author forwarded individual patient data.[14]

Quality assessment was performed using criteria based on the CRD quality assessment guideline for case series.[19] Data were extracted into predesigned forms.

Data synthesis

Data were described using a narrative synthesis. As sample sizes of included studies were small and data potentially skewed, results were reported as median plus IQR. There were insufficient studies to assess the possibility of publication bias by funnel plots or related statistics. Outcomes were evaluated according to four follow-up periods: immediately post-procedure until 2 days, at 2 weeks, at 28 days and more than 28 days.

We included data on all patients where the intention was to perform cordotomy, meaning the patients went to theatre to have the procedure, whether they actually had a permanent (heat) lesion created or not.

The findings for 'overall pain relief at up to 2 days post-procedure' were pooled to produce a weighted average effect (meta-analysis). The analysis using a fixed-effect model (inverse-variance weighted method)[20] resulted in heterogeneity and therefore a random-effects model (DerSimonian and Laird) was also used. The analysis was consolidated using Stata V.9 and with pooled estimates of log odds converted to probability (or risk) of complete pain relief.

Table 1 Search strategy

For Medline:	
1	**Expcordotomy/**
2	chordotomy.mp
3	cordotomy.mp
4	tractotomy.mp
5	myelotomy.mp
6	1 or 2 or 3 or 4 or 5
7	limit 6 to humans

Adapted for: MEDLINE in-process, EMBASE, CINAHL, PsychINFO, British Nursing Index, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, NHS Economic Evaluation Database, BIOSIS, Science Citation Index, Social Science Citation Index, Index to Scientific and Technical proceedings and System for Information on Grey Literature.

RESULTS OF SYSTEMATIC REVIEW

The results are presented under the following headings:

- Study selection (also refer to figure 1, table 2 and see online supplementary table S1)
- Study characteristics (see online supplementary table S1)
  - Participants
  - Procedure
- Quality assessment (table 3)
- Synthesis of reported outcomes (see online supplementary table S2)
  - Effectiveness of cordotomy for pain relief (table 4)
  - Adverse effects (table 5)

Study selection

The results of the literature searches are illustrated in figure 1. An overview of the nine studies that met the inclusion criteria is listed in online supplementary table S1. All the studies were case series recorded between 1983 and 2011 involving a total of 160 participants (sample size ranging from 3 to 53)[21 22](Antrobus, unpublished data, 2011). Follow-up times ranged from 24 h post-procedure to 6 months or until death (table 2). All studies were in secondary care settings. Five of the included studies were prospective[14 17 23 24] (Sharma, unpublished data, 2011), three were retrospective[22 25] (Antrobus, unpublished data, 2011) and one study may have been prospective, but this remains unclear.[21] Two studies were unpublished (Antrobus, unpublished data, 2011, Sharma, unpublished data, 2011) (see online supplementary table S1).

Study characteristics

Participants

Participants were adults where the intention was to perform percutaneous cervical cordotomy (PCC) as a treatment for the control of severe or intractable pain

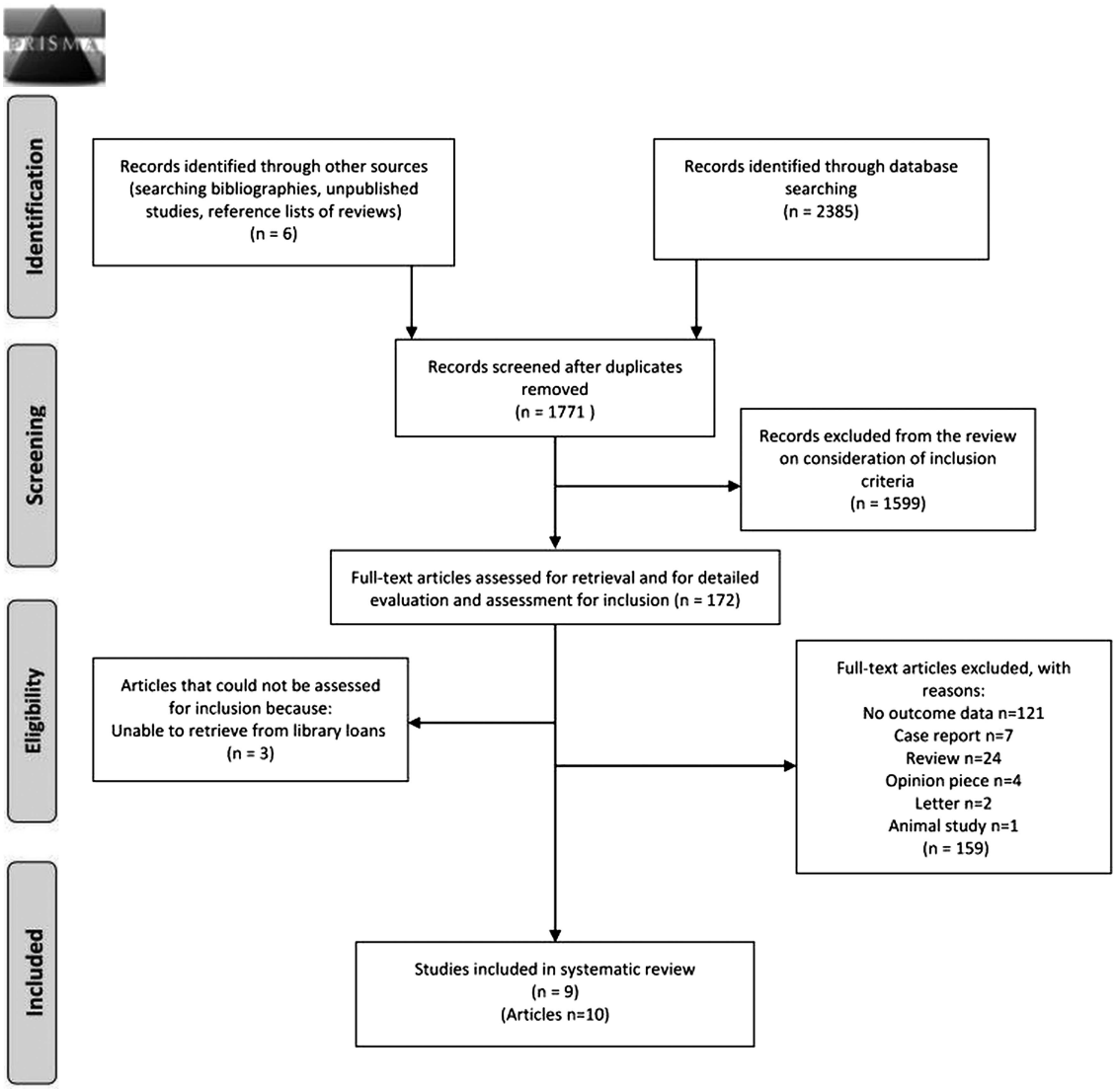

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

due to mesothelioma (see online supplementary table S1). All studies reported on the maximum intended follow-up after the procedure (range 2–365 days). Only Jackson *et al*[22] reported detailed information regarding the stage of the disease (Butchart[26] Stage 2 or above, or Tumour Node Metastasis (TNM)[27] Stage 4). All studies, except Sharma (2011), reported age of participants (range 18–89 years). Six studies reported gender involving a total of 107 participants, 80/107 (74.77%) were men and 27/107 (25.23%) women[14 21–24] (Antrobus, unpublished data, 2011).

Pre-procedure pain descriptors were reported under four headings: site of pain, nature/type of pain, pain intensity (score) and analgesia use. All nine included studies stated that the pain was unilateral. Six studies explained more about the nature or type of pain[14 17 22 23 25] (Sharma, unpublished data, 2011). Three stated that pain was 'intractable'[17 22 23] with Jackson *et al*[22] adding that pain was typical of chest wall involvement. Raslan(a) described pain as somatic or visceral,[14] Sharma (2011) as nociceptive or mixed and Crul *et al*[25] as either 'continuous somatic', 'continuous visceral', 'continuous neuropathic' or 'incident neuropathic'.

Six studies reported on pre-procedure pain intensity. Five used 11 point scales (patient self-report measures of pain ranging from no pain=0 to worst pain ever=10). Three of these reported a median pre-procedure pain intensity score which ranged from 7.5 to 9.[14 24 25] The other two reported a score for the maximum and average pain experienced in a pre-procedure interval: Antrobus (2011) noted pain during the last week (worst: median=10, average: median=7) and Sharma (2011) reported pain in last 24 h (maximum: mean=8.71, average: mean=6.76). Nicosia *et al*[21] and Raslan(a) reported a median pain score of four on their respective five-point scales.[14]

Pre-procedure analgesic and opioid use was recorded in five studies[23 25] (Antrobus, unpublished data, 2011, Sharma, unpublished data, 2011), and three reported on coanalgesic use[22 25] (Antrobus, unpublished data, 2011). Almost all patients were on strong opioids (range

Table 2 Reported outcomes (at clearly specified reporting time points)

Outcome	Immediately post-procedure until 2 days	At 2 weeks	At 28 days	More than 28 days	Unclear
Global measure of pain relief	Antrobus Kanpolat Nicosia Price Raslan 2005 Raslan 2008 Sharma	Raslan 2005	Raslan 2008 Sharma	Kanpolat Nicosia Raslan 2008	
Pain intensity	Crul Raslan 2005 Raslan 2008 Sharma	Raslan 2005	Raslan 2008 Sharma	Crul Raslan 2008	
Opioid use	Antrobus Crul Jackson Price	Price Raslan 2005		Jackson Nicosia	Kanpolat Sharma
Analgesic level	Kanpolat Price	Price Raslan 2005			
Performance status	Kanpolat Raslan 2008				
Total sleeping hours	Raslan 2008		Raslan 2008	Raslan 2008	
Patient satisfaction	Sharma		Sharma		
Adverse effects: Procedure specific	Price Raslan 2005 Raslan 2008 Sharma	Price Raslan 2008	Sharma		Antrobus Crul Jackson Kanpolat Nicosia
Adverse effects: General	Price				Jackson Raslan 2005

98.11% to 100%)[22 23 25] (Antrobus, unpublished data, 2011, Sharma, unpublished data, 2011), with doses reported in three studies (in morphine equivalents over 24 h) as median=410 mg,[25] median=100 mg[22] and mean=153.13 mg (Sharma, unpublished data, 2011). Coanalgesic use: Crul *et al*[25] noted that some patients were on neuropathic agents and Jackson *et al*[22] reported that 36 patients (36/53,67.92%) were on morphine and coanalgesics.

Four studies used likely prognosis as one of their inclusion criteria, although none specified the criteria used to estimate prognosis[14 21] (Antrobus, unpublished data, 2011, Sharma, unpublished data, 2011). Survival post-procedure was recorded in four studies (range 227–36 527 days) [17 22 25] (Antrobus, unpublished data, 2011).

Five studies reported performance status: four[14 21 23 25] used the Karnofsky Performance Status (KPS) Scale, where 100 is perfect health and 0 is death (median ranged from 55 to 75)[14 25] and one (Antrobus, unpublished data, 2011) the Brief Pain Inventory for interference in aspects of daily life (general activity median=9). Three studies gave descriptors of respiratory function.[17 23 25]

Procedure

All studies reported on PCC and none on open cordotomy. Six used X-ray control[17 21 22 25] (Antrobus, unpublished data, 2011, Sharma, unpublished data, 2011) employing the standard Lipton technique (with cervical vertebrae [C]1/2 foramen entry, lateral approach).[28] Two studies used water-soluble contrast,[17 22] while others used lipid-soluble contrast. Although there were differences in the starting temperature and duration, all authors titrated the heating of the cordotomy probe to an observed effect on pain relief or sensory examination. Sedation in small doses was used in some of the studies. Three studies used CT guidance.[14 23 24] Raslan(b), in his 2005 study, employed an anterior transdiscal approach at C4/5 or C5/6 level using water-soluble contrast.[24] Four studies reported on staff performing or assisting in the procedure[14 24] (Antrobus, unpublished data, 2011, Sharma, unpublished data, 2011). All procedures were performed by a pain specialist assisted by others, including a radiographer and theatre support staff (Antrobus, unpublished data, 2011, Sharma, unpublished data, 2011). Five patients in three studies did not have heat lesions due to needle or electrode placement difficulties[17 24] (Antrobus, unpublished data, 2011).

Quality assessment

Based on the quality assessment presented in table 3, the reviewers felt equal importance could be assigned to the evidence in the included studies as all had one or more limitations: loss to follow-up of more than 10%[17 23] (Sharma, unpublished data, 2011), non-consecutive series,[22] retrospective[22 25] (Antrobus,

Table 3 Quality assessment

Author, year n=number of mesothelioma patients	Was this a prospective study?	Are the criteria for inclusion explicit?	Is the study based on a representative sample?	Were patient characteristics described?	Did all individuals enter at a similar point in their disease progression?	Was loss to follow-up <10%?	Was follow-up long enough for important events to occur? (as specified by authors)*	Were outcomes assessed using objective criteria or was blinding used?†	If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors
Antrobus 2011 n=3	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No subseries
Crul *et al*,[25] 2005 n=4	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No subseries
Jackson *et al*,[22] 1999 n=53	No	Yes	No‡	Yes	Yes	Yes	Yes	No	No subseries
Kanpolat *et al*,[23] 2002 n=19	Yes	Yes	Yes	Yes	Yes	No§	Yes	Yes¶	No subseries
Nicosia *et al*,[21] 1983** n=3	Unclear	Yes	Yes††	Yes	Yes	Yes	Yes	No	No subseries
Price *et al*,[17] 2003 n=32	Yes	Yes	Yes	Yes	Yes	No‡‡	Yes	Yes§§	No subseries
Raslan(b),[24] 2005 n=5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes¶¶	No subseries
Raslan(a),[14] 2008 n=24	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No subseries
Sharma 2011 n=17	Yes	Yes	Yes	Yes	Yes	No***	Yes	No	No subseries

*The follow-up should be at least 4 weeks for pain relief and at least 2 weeks for adverse effects: based on the consensus opinion of cordotomy practitioners across the UK (agreed at a cordotomy registry meeting at Liverpool on 8 March 2012).
†The reviewers defined blinding as using an independent person to do data collection, that is, the data collector is not aware that they are evaluating cordotomy outcomes per se. None of the included studies specified that this method of data collection was used.
‡The authors could not obtain five sets of notes (out of 53 consecutive patients).
§Loss to follow-up of 19 patients (6/19, 31.57%) after 2 days post-PCC, with no clear reasons given as to why this happened.
¶Used an objective measure to assess analgesic level (dermatomal).
**This study has been translated for data extraction, which may have resulted in the misinterpretation of some data.
††It is likely that the sample is a consecutive series as they state that 20 adults came to their attention during the year 1982. We have recorded it as such with the proviso that this remains unclear.
‡‡Loss to follow-up at 2 weeks of 17 (of 35) patients, four had died (4/35, 11.43%) and 13 (13/35, 37.14%) chose not to attend due to distance to travel.
§§Used objective measures to assess analgesic level (dermatomal)and respiratory function.
¶¶Used an objective measure to assess analgesic level (dermatomal).
***Maximum loss to follow-up of five (of 17) patients at 28 days, three had died (3/17, 17.65%) and two were uncontactable (2/17, 11.76%).
PCC, percutaneous cervical cordotomy.

unpublished data, 2011), more than 20 years old[21] and included less than 10 patients[21 24 25] (Antrobus, unpublished data, 2011).

Synthesis of reported outcomes

Effectiveness of cordotomy for pain relief

The reported outcomes are presented under the following headings (see online supplementary table S2):

- Overall pain relief (table 4)
- Pain intensity
- Analgesic interventions
- Analgesic level (dermatomal)
- Performance status
- Total sleeping hours
- Patient satisfaction (see online supplementary table S2)

Overall pain relief

Seven studies assessed overall improvement in pain immediately (and until 2 days) post-procedure[14 17 21 23 24] (Antrobus, unpublished data, 2011, Sharma, unpublished data, 2011).

Outcomes in six studies could be grouped into complete, partial or poor pain relief[14 17 21 23 24] (Antrobus, unpublished data, 2011). Complete pain relief ('complete' or 'pain free' or 'no pain') was attained in 80.22% (73/91) of patients where the intention was to perform PCC. In patients who actually received a heat lesion, complete pain relief was recorded in 84.88% (73/86). Partial pain relief ('partial' or 'partial satisfactory' or 'initial or satisfactory' or 'significant') was achieved in 14.29% (13/91) where PCC was intended (vs heat lesion 13.95% [12/86]). Poor pain relief ('poor' or 'none') was reported in 5.49% (5/91) (heat lesion 1.16% [1/86]). Most patients were still on some form of oral analgesia post-procedure (see online supplementary table S2), so that 'overall pain relief' reflected patients' views on the effectiveness of their full analgesic regimen.

These six studies were included in the meta-analysis (table 4), where the ordinal data were dichotomised to complete versus partial/poor pain relief[14 17 21 23 24] (Antrobus, unpublished data, 2011). In patients where PCC was intended (n=91), the proportion with complete pain relief ranged from 20% to 100%, with a weighted average of 75% based on a random-effects model (95% CI=52% to 89%). There was a moderate level of between-study heterogeneity (I^2=57%) which appeared to be affected by two studies that had small sample sizes and event rates[24] (Antrobus, unpublished data, 2011). In patients who had heat lesions (n=86), the proportion with complete pain relief ranged from 33% to 100%, with a weighted average of 83% based on a fixed-effect model (95% CI=72% to 90%; I2=32%).

The seventh study reported pain data on a continuous scale which could not be dichotomised (Sharma, unpublished data, 2011).

At 2 weeks' follow-up, Raslan(b) reported that three patients (3/5,60%) continued to have satisfactory to complete pain relief.[24]

Two studies reported on overall pain relief at 28 days post-procedure. Raslan(a) noted that 23 patients (23/24,95.83%) had pain relief, of whom 20 (83.33%) had complete pain relief.[14] Sharma (2011) reported a mean of 4.45 (4='about the same' to 5='slightly better') on their seven-point 'Global Impression of Change Scale'.

At more than 28 days follow-up, Kanpolat *et al*[23] stated that 13 patients (13/13, 100%) were recorded as being pain free after an average follow-up period of 5.9 months and in Nicosia *et al*[21] three (3/3, 100%) had complete pain relief at an average of 3 months follow-up. Raslan(a) reported that at 3 months follow-up 23 patients (23/24, 95.83%) had pain relief, of which 17 (70.83%) experienced complete pain relief, and that at 6 months follow-up 22 (22/24, 91.67%) had pain relief, of which eight patients (33.33%) had complete pain relief.[14]

Pain intensity

Four studies reported on this outcome using either the Numerical Rating Scale (NRS) or Visual Analogue

Table 4 The results of the analysis of the probability of complete pain relief at 2 days

	Number of studies	Range of proportion*	Meta-analysis of proportion (95% CI)	Heterogeneity
Intention to have cordotomy	6 [Refs. 14 17 21 23 24 Antrobus, unpublished data, 2011]	0.20–1.00	Fixed-effect model† 0.79 (0.68 to 0.87)	I^2=56.9% (95% CI 0% to 82.67%) τ^2=0.80
			Random-effects model‡ 0.75 (0.52 to 0.89)	
Had heat lesion	6 [Refs. 14 17 21 23 24 Antrobus, unpublished data, 2011]	0.33–1.00	Fixed-effect model 0.83 (0.72 to 0.90)	I^2=32.3% (95% CI 0% to 72.7%) τ^2=0.34
			Random-effects model 0.81 (0.66 to 0.91)	

*The studies reported data on pain relief as ordinal data; these were dichotomised to complete pain relief versus partial or no pain relief.
†Inverse-variance weighted method.
‡DerSimonian and Laird method.

Scale (VAS) [14 24 25] (Sharma, unpublished data, 2011). All studies reported an improvement immediately post-procedure. In three the median score ranged from zero to three (vs median pre-procedure range of 7.5–9).[14 24 25] The remaining study reported an average pain relief score of 0.52 in the last 24 h and a maximum of 0.52 (vs pre-procedure average score of 6.76 and a maximum of 8.71) (Sharma, unpublished data, 2011).

At 2 weeks' follow-up, Raslan(b) reported a mean NRS score of 3.1.[24] At 28 days, Raslan(a) noted a median overall VAS score of two.[14] Sharma (2011) reported an average pain relief score of two in last 24 h and a maximum of 2.16.

The two studies which reported pain intensity at more than 28 days both noted a median of two (Crul *et al*[25] using NRS and Raslan[a][14] using VAS).

Analgesic interventions (including oral analgesic use and invasive procedures for pain management)

Three studies gave details on the percentage of patients who had a reduction in opioid dose ranging from 66.67% to 82.69%[22 25] (Antrobus, unpublished data, 2011).

Post-procedure opioid doses were reported in two studies. In Crul *et al*[25] the median dose of morphine was 120 mg (vs pre-procedure 410 mg) and Jackson *et al*[22] reported the lowest daily dose as a median of 20 mg (vs pre-procedure 100 mg). Price *et al*[17] stated that 'opioid dose was halved following successful PCC '.Jackson *et al*[22] reported that 43 patients (43/52, 82.69%) had more than 50% reduction in opioid dose, and 20 (20/52, 38.46%) stopped taking opioids altogether. Antrobus (2011) described the reduction as 'significant' with one patient (1/3,33.33%) requiring 'fewer interval doses in the first 24 h' and another (1/3, 33.33%) developed opioid toxicity immediately post-procedure. In the Crul *et al*[25] study one patient (1/4, 25%) needed an increase in opioid dose post-procedure.

At 2 weeks' follow-up, Raslan(b) reported 'stabilization of […] pain medication dosages or even reduction of the dose', but didn't specify the number of patients in whom this was the case.[24] In the Jackson *et al*[22] study, 18 patients (18/52, 34.62%) had recurrence of pain requiring increase in opioid dose after median of 9 weeks (range 0.71–26). Nicosia *et al*[21] reported that two patients (2/3, 66%) required additional oral or intramuscular morphine to reach complete pain relief at an average follow-up of 3 months.

Two other studies commented on opioid use, but did not specify clear time points of follow-up. Kanpolat *et al*[23] stated that 'in cases receiving opioid medication, doses of the drug were slowly decreased, and none of the cases received opioid treatment in their follow-up'. Sharma (2011) reported a mean percentage reduction in opioid use of 53.57% (data on 14 patients).

Two papers reported coanalgesic use: Crul *et al*[25] stated that 'in virtually all cases non-opioids such as acetaminophen and NSAIDS were continued following successful PCC' and Jackson *et al*[22] stated that 18 patients (18/53, 33.96%) continued on coanalgesics (vs pre-procedure 67.92%).

The use of repeat cervical cordotomy or other invasive procedures was deemed necessary in nine patients (9/160, 5.63%).[17 21 22]

Analgesic level (dermatomal)

Immediately post-procedure, Kanpolat *et al*[23] noted that 15 patients (15/19, 78.95%) had selective pain relief (ie, segmental block) and in four patients (4/19, 21.05%) the block involved all segments below the highest level of anaesthesia. Price *et al*[17] stated that the maximum height of the blockade at 24 h ranged from C3 to T1 dermatome. This remained the same at 2 weeks. Raslan(b) reported that all three patients who had heat lesions had a recorded level of anaesthesia at T1 dermatome at 2 weeks' follow-up.[24]

Performance status

Kanpolat *et al*[23] reported a 10% increase in the median KPS score immediately post-procedure and Raslan(a)[14] found a 25% increase in the median score.

Total sleeping hours

In one study, patients' sleeping time showed an improvement immediately post-procedure (median of seven vs pre-procedure median of three), although this did decrease over the follow-up period (6 months median of five).[14]

Patient satisfaction

Sharma (2011) reported data on 14 patients (14/17, 82.35%) at 2 days post-PCC. All 14 said it had been worthwhile having the procedure. At 28 days, eight patients (8/9, 88.89%) felt it was worthwhile.

Adverse effects

The reported outcomes are presented under the following headings (table 5):

- Procedure specific
- General
- Deaths following the procedure

Most studies did not specify clear follow-up time points of specific adverse events, and three studies pooled data on patients with mesothelioma as well as other diagnoses.[14 17 21]

Procedure specific

All included studies detailed procedure-specific adverse events, noting either events that occurred (some specifying the duration of impairment) or

Table 5 Summary of adverse events and details of deaths following cordotomy

Author, year Number of participants*	Procedure specific	General	Details of deaths following (not necessarily due to) cordotomy
Antrobus 2011 N=8 n=3	'No patient suffered neurological complication or other lasting harm'		
Crul *et al*[25] 2005 N=43 n=4	Mirror pain in one (1/4, 25%) patient, transient, with minimal impact on well-being		
Jackson *et al*[22] 1999 N=53 n=53	Dysaesthesia in two patients (2/53, 3.77%) Persistent motor weakness in four patients (4/53, 7.55%), in one graded as MRC 4/5; in three 'not regarded as severe', no data on duration of weakness, no hemiplegia or inability to walk No incontinence due to sphincter disturbance, no impotence or postural hypotension	Chest infection with pyrexia in two patients (2/53, 3.77%)	Six deaths within 2 weeks of procedure, five had successful procedures; three within 1 week, three within 2 weeks; none had a second procedure Two died due to presumed chest infections Two 'severely disabled by dyspnoea at rest because of pleural encasement from their tumours' One had 'marked cachexia and a very short life expectancy due to the mesothelioma itself' No information available regarding sequence of events leading to death in one patient
Kanpolat *et al*[23] 2002 N=19 n=19	Dysaesthesia in one patient (1/19, 5.26%)		'No mortality due to procedure' Seven died 'due to progression of malignancy'
Nicosia *et al*[21] 1983 N=20 n=3 POOLED DATA	Urine retention in one (1/20, 5%) case resolved within 4 days after repeated catheterisations 'Weakness–ataxia' in seven cases (7/20, 35%) resolved spontaneously in 2–7 days Respiratory failure in one case (1/20, 5%) 'needed assistance' Postoperative hypotension in one case (1/20, 5%) resolved with sympathomimetics in 2–3 h All complications were post-surgical and temporary		
Price *et al*[17] 2003 N=37 n=32 POOLED DATA	Ipsilateral leg weakness in three (3/37, 8.11%) patients, MRC 4/5, resolved after physiotherapy at 2 -week follow-up 'No significant change in $FEV_{1.0}$ at 24 h or 2 weeks' (mean=1.5 L baseline, 1.5 L at 24 h, 1.6 L at 2 weeks) 'No significant change in FVC at 24 h or 2 weeks' (mean=1.9 L baseline, 2.0 L at 24 h, 2.14 L at 2 weeks), 'Improvement in FVC immediately' in 16 patients (16/35, 45.71%), 'mean FVC improved by 13% at 2 weeks' (mean=1.9–2.14 L) 'Improvement in FVC immediately' in 16 patients, 'mean FVC had improved by 13% at 2 weeks' (data on 18 patients) 'mean PEFR was reduced' at 24 h(315 l/min to 247 l/min), 'but had returned to baseline values at 2 weeks' 'Mean partial pressures for oxygen and carbon dioxide did not alter from baseline significantly' (mean PaO_2=10.3 kPa baseline, 10.7 kPa at 24 h) (mean $PaCO_2$=5.1 kPa baseline, 5.2 kPa at 24 h)	Confusion in three patients (3/35, 8.57%) improved after 24 h Worsening of left ventricular failure following a blood transfusion in one patient (1/35, 2.86%) 'No patients experienced postoperative pneumonia'	Four early deaths (3–14 days) Two due to 'cerebrovascular accidents' Two due to 'advanced thoracic malignancy' No relationship between the maximum height of the blockade as defined by pinprick testing and survival
Raslan(b)[24] 2005 N=8 n=5	No reports of sleep-induced apnoea syndrome at 24 h	No complications reported	

Continued

Table 5 Continued

Author, year Number of participants*	Procedure specific	General	Details of deaths following (not necessarily due to) cordotomy
Raslan(a)[14] 2008 N=41 n=24 POOLED DATA	All complications were 'transient and not severe' Dysaesthesia in two (2/41, 4.88%) patients: in one it persisted for 3 days and in the other for 2 weeks Hypotension in two cases (2/41, 4.88%), but resolved after parenteral intravenous fluid administration, patients discharged without event Headaches in three patients (3/41, 7.32%) resolved after treatment with analgesics and fluids for 48 h, patients discharged without event No reported complications of weakness/change in motor power, sleep apnoea or respiratory depression		
Sharma 2011 N=35 n=17	At 2 days: headaches in 10 cases (10/17, 58.82%), mirror pain in 3 (3/17, 17.65%), no adverse events in 4 At 28 days: 'nerve damage' in 1 case (1/17, 5.88%), mirror pain in 2 (2/17, 11.76%), no adverse events in 14		

*N=Number of patients in the study (all diagnoses) where the intention was to perform cordotomy; n=number of patients with a diagnosis of mesothelioma where the intention was to perform cordotomy.
FEV 1.0, forced expiratory volume in 1 sec; FVC, forced vital capacity; MRC, Medical Research Council Scale for Grading Muscle Function; PEFR, peak expiratory flow rate.

potentially significant adverse events that did not occur.

Motor weakness: Two studies[14] (Antrobus, unpublished data, 2011) (44 patients) noted no patients with weakness or change in motor power but in four studies neurological deficit was recorded in 15 patients (15/127, 11.81%)[17 21 22] (Sharma, unpublished data, 2011). Deficit was described as 'persistent motor weakness', 'transient ipsilateral leg weakness', 'transient weakness-ataxia' and 'nerve damage'.

Dysaesthesia: Three studies reported dysaesthesia in five patients (5/113, 4.42%).[14 22 23] Raslan(a) noted it was temporary.[14]

Mirror pain: Crul *et al*[25] reported transient mirror pain in one patient (1/4, 25%). Sharma (2011) noted mirror pain in three patients (3/17, 17.65%) at 2 days post-procedure, and in two patients (2/17, 11.76%) at 28 days.

Urinary dysfunction/impotence: Jackson *et al*[22] reported no incontinence due to sphincter disturbance and no impotence in 53 patients post-PCC. Nicosia *et al*[21] noted short-lived urine retention in one case (1/20, 5%), which resolved after repeated catheterisations.

Respiratory dysfunction: Three studies (81 patients) reported no respiratory dysfunction post-PCC.[14 17 24] Nicosia *et al*[21] noted respiratory failure in one case (1/20, 5%) who 'needed assistance'.

Headaches: Two studies described transient headaches in 13 patients (13/58, 22.41%)[14] (Sharma, unpublished data, 2011).

Hypotension: One study reported no cases of postural hypotension in 53 patients.[22] Two studies noted three cases (3/61, 4.92%).[14 21]

General

Price *et al*[17] noted short-lived confusion in three patients (3/35, 8.57%) and one patient (1/35, 2.86%) with worsening left ventricular failure following a blood transfusion. Jackson *et al*[22] reported chest infection with pyrexia in two patients (2/53, 3.77%).

Deaths following the procedure

Three studies gave details on deaths following the procedure, but none were specifically ascribed to the procedure.[17 22 23]

DISCUSSION

Key findings

Our review found the evidence base for the use of PCC in mesothelioma-related pain to be small. All the included studies reported case series where unilateral PCC was offered for patients suffering intractable pain due to mesothelioma. Although multiple techniques were described to perform PCC, X-ray guided techniques were most commonly used. The studies used different measures to describe effectiveness of the procedure.

All nine case series demonstrated good pain relief in the majority of patients. This was derived from using overall pain relief measures, pain intensity scores, opioid use and dermatomal analgesic levels. Initial post-procedure measurements showed the most effect, and although the improvement in pain levels tended to lessen over time, it did not revert to pre-procedure levels. Other outcome measures also showed beneficial effect, including increased performance status and increased total sleeping hours. The majority of patients seemed to be satisfied with the procedure. A minority of patients did not have significant benefit from the procedure and required further pain blocks or repeat cordotomy.

The included studies described a range of adverse effects. Some side effects (headache, mirror pain, motor weakness) occurred relatively frequently (more than 10% of reports) but were mostly transient. Respiratory dysfunction post-PCC was rare. A number of deaths were described within 12 months of the procedure, all attributed to disease progression rather than PCC.

Strengths and limitations

The strengths of the review lie in the fact that we conducted the first comprehensive systematic review specifically on the use of cordotomy in mesothelioma-related pain. The review was not limited by either language or publication type.

The results of the review should be regarded in the context of its significant limitations, chiefly due to the low quantity and poor quality of the available evidence. All studies were case series, which are generally placed at the bottom of the evidence hierarchy.[29 30 31] The included studies either had small sample sizes, were retrospective and/or used a variety of outcome measures at different reporting intervals. Two of the studies are as yet unpublished. Also of note is that the three single author studies where all procedures were conducted by the author (who is likely to be an advocate of the procedure with high expectations of the procedure and carefully selected patients) might be seen as less reliable and generalisable than those with a reporting team.

Many of the authors of included studies described the reason for PCC as intractable or severe or uncontrolled pain, and some added more pain descriptors as well as prognostication to the criteria. The studies did not, however, all use directly comparable definitions of these criteria and hence the collated evidence did not give a clear indication of when the procedure should be considered, neither in terms of distinct pain parameters, nor the point in the disease trajectory or performance status of the patient.

We were unable to obtain independent patient data from eight studies, although most of these studies were at least 10 years old.[8–10 12 13 15 16 18]

CONCLUSION

The available evidence is significantly limited in quantity and quality. Although it seems to suggest that cordotomy might be a safe and effective procedure for patients with intractable pain due to mesothelioma, in isolation it does not aid the decision making on whether continued provision of cordotomy services is warranted.

There is another consideration at play—the procedure is performed by only a handful of practitioners (Makin, unpublished data, 2012) and this skill will be lost if the weight of evidence does not tip the balance in favour of continued provision. This would be devastating for the small group of patients in whom it yields significant analgesic benefit. It is therefore imperative that good quality evidence is provided soon by well-designed primary studies so that firm conclusions can be drawn on its effectiveness and safety.

A UK-wide registry for cordotomy could be the first step in achieving this. The comprehensive reporting will not only aid benchmarking and lead to improved patient outcomes but will also crystallise questions for further research. Parallel qualitative research into patient experiences would augment our understanding of the impact of the procedure.

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Supplementary Table 1: General patient characteristics of included studies

<table>
<tr><th>Author, year
Number of participants[a]
Country of origin</th><th>Study design/
Maximum follow-up (days)</th><th>Stage of disease /
Disease descriptors</th><th>Age(years)/
gender(M or F)</th><th>Pre-procedure pain descriptors</th><th>Expected prognosis (inclusion criteria) / survival (days)</th><th>Other patient descriptors / Other exclusion criteria</th></tr>
<tr><td>Antrobus 2011
N = 8
n = 3
United Kingdom</td><td>Retrospective case series
(audit)

Median = 62
(IQR = 37)
(range 26-100)</td><td></td><td>Median age = 67
(IQR = 9.5)
(range 56-75)

Gender
Male = 1
Female = 2</td><td>Site of pain: Unilateral in all cases (chest)
Nature/type of pain: Not stated
Pain intensity (score)
▪ Brief Pain Inventory (BPI): 0=no pain, 10= pain as bad as you can imagine over the past week
<table><tr><th></th><th>Worst</th><th>Least</th><th>Average</th><th>Now</th></tr><tr><td>Median</td><td>10</td><td>4</td><td>7</td><td>6</td></tr><tr><td>IQR</td><td>0</td><td>1.5</td><td>0.5</td><td>1</td></tr><tr><td>Range</td><td>-</td><td>2-5</td><td>6-7</td><td>5-7</td></tr></table>Analgesia
▪ All patients at WHO Analgesic Ladder Step 3 i.e. Strong opioid +/- Non-opioid; +/- Adjuvant</td><td>Prognosis ‘sufficiently long to justify the investment in treatment’

Median survival = 62
(IQR = 37)
(range 26-100)</td><td>Performance status
▪ BPI for interference in aspects of daily life: 0=does not interfere, 10= completely interferes
<table><tr><th></th><th>General Activity</th><th>Mood</th><th>Walking Ability</th><th>Normal Work</th><th>Relation-ships</th><th>Sleep</th><th>Enjoyment of Life</th></tr><tr><td>Median</td><td>9</td><td>8</td><td>8</td><td>9</td><td>7</td><td>6</td><td>10</td></tr><tr><td>IQR</td><td>1</td><td>3</td><td>0</td><td>1</td><td>2</td><td>0</td><td>1</td></tr><tr><td>Range</td><td>8-10</td><td>2-8</td><td>-</td><td>8-10</td><td>3-7</td><td>-</td><td>8-10</td></tr></table></td></tr>
<tr><td>Crul et al.[25]
2005
N = 43
n = 4
Netherlands</td><td>Retrospective case series
Consecutive series

Median = 104
(IQR = 90.25)
(range 46-347)</td><td></td><td>Median age = 69.2
(IQR = 6.5)
(range 64-75)

Gender not reported specifically for mesothelioma</td><td>Site of pain: Unilateral pain below spinal segment C5
Nature/type of pain
▪ Continuous somatic: 2 cases
▪ Continuous visceral: 1 case
▪ Continuous neuropathic: 3 cases
▪ Incident neuropathic: 1 case
(3 patients had 2 types of pain)
Pain intensity(score)
▪ NRS[b]: Median = 7.5 (IQR = 1.63) (range 5-8.5)
Analgesia
▪ All patients on strong opioids
▪ Opioid dose (in morphine equivalents in milligrams): Median = 410 (IQR = 63) (range 300-492)
▪ Neuropathic agents: some on tricyclic antidepressants and anticonvulsants(pooled data)</td><td>Median survival = 104
(IQR = 90.25)
(range 46-347)</td><td>Performance status
▪ Karnofsky Performance Status (KPS)score: Median = 75 (IQR = 15) (range 50-80)

Exclusion criteria
▪ Respiratory function: FEV1<12 ml/kg body weight / bleeding tendency</td></tr>
</table>

Author, year Number of participants[a] Country of origin	Study design/ Maximum follow-up (days)	Stage of disease / Disease descriptors	Age(years)/ gender(M or F)	Pre-procedure pain descriptors	Expected prognosis (inclusion criteria) / survival (days)	Other patient descriptors / Other exclusion criteria
Jackson et al.[24] **1999** **N = 53** **n = 53** **United Kingdom**	Retrospective case series Median = 91 (range 2-365)	**Butchart Scale** ▪ Stage 2 or above **TNM** ▪ Stage 4 **Features at presentation:** ▪ Pleural effusion = 40/53 (75.47%) ▪ Pleural mass/thickening = 8/53 (15.09%) ▪ Pleural encasement by tumour = 1/53 (1.89%) ▪ Pleural involvement unclear = 4/53 (7.55%)	Median age = 64 (range 44-82) Gender Male = 52 Female = 1	**Site of pain:** Unilateral **Nature/type of pain** ▪ Onset of severe intractable pain typical of chest wall involvement (costopleural syndrome) ▪ 'Not to be confused with dragging discomfort of bulky tumour confined to the parietal pleura without chest wall invasion' **Analgesia** ▪ Opioid use: 48/53 patients (90.57%) taking controlled release morphine sulphate tablets, often with morphine elixir as required; 7/53 (13.21%) on diamorphine infusion; 1 patient not on opioids ▪ Daily opioid dose (oral morphine salt 10mg = 3 mg diamorphine intramuscular): Median =100mg (range 0-1000) ▪ Co-analgesics: 36/53(67.92%) on morphine and co-analgesics; 31/53 (58.49%) on NSAIDs as co-analgesic ▪ No patient had intercostal nerve block or intrathecal block or palliative radiotherapy as deemed inappropriate due to disease diffusely affecting the hemithorax	Median survival = 91 (range 2-365)	**Time from diagnosis to procedure (weeks)** ▪ Median = 21 (range 0.43–143)
Kanpolat et al.[22] **2002** **N = 19** **n = 19** **Turkey**	Prospective case series Consecutive series Median = 152.08 (IQR = 243.33) (range 30.42-365)		Median age = 53 (IQR = 14) (range 31-65) Gender Male = 10 Female = 9	**Site of pain:** Unilateral **Nature/type of pain** ▪ Intractable. In most cases, chest pain radiated to the neck, shoulder, scapula and arm ▪ Duration of pain 3-12 months **Pain intensity (score)** ▪ Not reported **Analgesia** ▪ 19 patients (100%) on opioids		**Performance status** ▪ KPS score: Median = 60 (IQR = 10) (range 40-70) **Exclusion criteria** ▪ Respiratory function: $Pa0_2$ level <80% mm Hg / reduced ventilatory function
Nicosia et al.[21] **1983** **N = 20** **n = 3** **Italy**	Unclear. Italian study. Translation does not clarify. Consecutive series Median = 121.67 (IQR = 45.63) (range 30.42-121.67)		Median age = 62 (IQR = 15.50) (range 47-78) Gender Male = 3 Female = 0	**Site of pain:** Unilateral **Nature/type of pain:** Not stated **Pain intensity** ▪ Score 1-5 (1 = absent, 5 = very strong): Median = 4 (IQR = 0.5) (range 3-4)	Prognosis of between 1 month and 1 year	**Performance status** ▪ KPS score: Median = 60 (IQR = 15) (range 50-80)

Author, year Number of participants[a] Country of origin	Study design/ Maximum follow-up (days)	Stage of disease / Disease descriptors	Age(years)/ gender(M or F)	Pre-procedure pain descriptors	Expected prognosis (inclusion criteria) / survival (days)	Other patient descriptors / Other exclusion criteria
Price et al.[17] **2003** **N = 37** **n = 32** **United Kingdom** **POOLED DATA**	Prospective case series Consecutive series 14	All patients underwent a chest radiograph preoperatively to gauge extent of the disease but no further information given	Mean age = 62 (range 44-89)	**Site of pain:** Unilateral **Nature/type of pain:** Intractable	Mean survival = 83 (range 3-360)	**Respiratory function (pre-procedure measurement)** Mean / SD FVC (l): 1.9 / 0.8 FEV 1.0 (l): 1.5 / 0.65 PEFR (l/min): 315 / 137 PaO2 (kPa): 10.3 / 2 PCO2 (kPa): 5.1 / 0.8 **Exclusion criteria** ▪ Evidence of bilateral malignant disease
Raslan(b)[23] **2005** **N = 8** **n = 5** **Egypt**	Prospective case series 182.5		Median age = 56 (IQR = 20) (range 42-68) Gender Male = 2 Female = 3	**Site of pain:** Unilateral (mammary/chest pain) **Nature/type of pain:** Not stated **Pain intensity (score)** ▪ NRS[b]: Median = 9 (IQR = 1) (range 8-9) **Analgesia** ▪ Pain medication – dose, type not specified	Prognosis should be more than 3 months	**Exclusion criteria** ▪ Respiratory function: Reduced ventilatory function
Raslan(a)[14] **2008** **N = 41** **n = 24** **Egypt**	Prospective case series Consecutive series 182.5		Median age = 50 (IQR = 15,25) (range 18 – 68) Gender Male = 12 Female = 12	**Site of pain** ▪ Unilateral somatic pain reaching to the midline and below dermatome C5, or ▪ unilateral visceral pain not reaching the midline **Nature/type of pain:** Somatic and visceral **Pain intensity** ▪ VAS[c]: Median = 9 (IQR = 1) (range 8-10) ▪ Degree of pain: I – V (I = no pain, V = great pain): Median = IV (range III-V)		**Performance status** ▪ KPS score: Median = 55 (IQR = 10) (range 50-70) **Total sleeping hours (TSH)** ▪ Median = 3 (IQR = 1) (range 2-5) **Exclusion criteria** ▪ Respiratory function: Parameters < 50% of normal / Bleeding tendency / KPS < 40 / Epidural catheter feasible
Sharma 2011 **N = 35** **n = 17** **United Kingdom**	Prospective case series Consecutive series 28	Authors state that patients would have been at different (radiological) stages of disease		**Site of pain:** Unilateral **Nature/type of pain** ▪ Nociceptive pain: 2 cases ▪ Mixed pain: 14 cases ▪ Missing data: 1 case **Pain intensity (n=17)** ▪ NRS[b]: ▪ Maximum pain last 24 hours: Mean = 8.71 (range 6-10) ▪ Average pain last 24 hours: Mean = 6.76 (range 4-9) **Analgesia** ▪ Conversion to morphine equivalent in mg over 24 hours: Oxycodone to morphine 2:1; Hydromorphone to morphine 7.5 to 1; Fentanyl patch 25mcg equivalent to 60mg morphine; Alfentanil to diamorphine 10:1 ▪ Opioids equivalence (n=16): Mean = 153.13mg (range 0-560)	Prognosis of between 3 and 12 months	

[a] N = Number of patients in the study (all diagnoses) where the intention was to perform cordotomy; n = number of patients with a diagnosis of mesothelioma where the intention was to perform cordotomy

[b] Numerical Rating Scale (NRS): 0=no pain, 10=worst pain ever

[c] Visual Analogue Score (VAS): 0=no pain, 10=worst pain ever

[d] Karnofsky Performance Status (KPS) scale: 0=death, 100=normal; no complaints; no evidence of disease; able to work

All results reported as median (IQR, range) unless reviewers were unable to calculate these from the reports

FEV 1.0 = Forced expiratory volume in 1 second, FVC = Forced vital capacity, PEFR = Peak expiratory flow rate, PaO2 = Partial pressure of oxygen, PaCO2 – Partial pressure of carbon dioxide

Supplementary Table 2: Summary of Effectiveness

Author, year Number of participants[a]	Global measure of pain relief	Pain intensity	Opioid use	Analgesic level or height of block	Other pain interventions	Performance status/ ADL's	Other outcomes (TSH etc)
Antrobus 2011 N = 8 n = 3	**Post-procedure[b]** ▪ 1/3 (33.33%) had complete pain relief ('excellent result, pain free') ▪ 1/3 (33.33%) had significant pain relief ('significant reduction') ▪ 1/3 (33.33%) had no pain relief (did not have a heat lesion due to difficulties in placing the electrode)		**Post-procedure** ▪ 2/3 (66.67%) had reduction in opioid use, of which: ▪ One had 'significant reduction' and 'fewer interval doses in first 24 hours' ▪ One developed opioid toxicity and hence had 'significant reduction'				
Crul et al.[25] 2005 N = 43 n = 4		**Post-procedure** ▪ NRS[c]: Median = 0 (IQR = 0.5) (range 0-2) (vs. pre-procedure median = 7.5) **More than 28 days (n=3)** ▪ NRS: Median = 2 (IQR = 1.5) (range 1-4)	**Post-procedure** ▪ 3 /4 (75%) had reduction in opioid dose ▪ 1/4 (25%) had an increase in opioid use ▪ Dose (in morphine equivalents in milligrams): Median = 120 (IQR = 180) (range 0-720) (vs pre-procedure median = 410)		'Most patients still on non-opioids (acetaminophen/NSAIDS) post-procedure'		
Jackson et al.[24] 1999 N = 53 n = 53			**Post-procedure up to at least two weeks (n=52)** ▪ 43/52 (82.69%) patients had more than 50% reduction in opioid dose, 20/52 stopped taking opioids ▪ Lowest daily dose of morphine (oral morphine salt 10mg = 3 mg diamorphine intramuscular): Median = 20mg (range 0-520mg) (vs pre-procedure median = 100mg) ▪ Recurrence of pain in 18/52 (34.62%) patients requiring increase in opioid dose after median = 9 weeks (range 0.71-26)		▪ 18/53 (33.96%) continued on co-analgesics (vs pre-procedure 67.92%) ▪ 4/53 (7.55%) required second cordotomy, with 3/4 being successful		
Kanpolat et al.[22] 2002 N = 19 n = 19	**Post-procedure** ▪ 18/19 (94.73%) complete and ▪ 1/19 (5.26%) partial pain relief **More than 28 days (n=13)** ▪ 13/13 (100%) recorded as being pain free		▪ 'In cases receiving opioid medication, doses of the drug were slowly decreased, and none of the cases received opioid treatment in their follow-up' ▪ 'Some cases had begun to take opioids in their terminal stage due to pain related to the other, non-denervated, side of their body'	**Post-procedure** ▪ 15/19 (78.95%) pain was relieved selectively (pain relief with hypalgesia[d] obtained in the painful part of the body) ▪ 4/19 (21.05%) had hemi-hypalgesia (the block involving all segments below the highest level of anaesthesia)		**Post-procedure** ▪ Karnofsky Performance Status(KPS)[e] score: Median =70 (IQR = 10) (range 60-90) (vs pre-procedure median = 60)	

Author, year Number of participants[a]	Global measure of pain relief	Pain intensity	Opioid use	Analgesic level or height of block	Other pain interventions	Performance status/ ADL's	Other outcomes (TSH etc)
Nicosia et al.[21] 1983 N = 20 n = 3	**Post-procedure** ▪ 3/3 (100%) had 'excellent' pain relief **More than 28 days** ▪ 3/3 (100%) had complete pain relief		**More than 28 days** ▪ 2/3 (66%) patients required the addition of oral or intramuscular morphine to reach complete pain relief		In addition to other routes of morphine, 1/3 had subarachnoid phenol and 1/3 had subarachnoid morphine to reach complete pain relief		
Price et al.[17] 2003 N = 37 n = 32 POOLED DATA	**Post-procedure** ▪ 31/37 (83.78%) had complete pain relief ▪ 3/37 (8.11%) had partial pain relief ▪ 1/37 (2.7%) had poor pain relief ▪ 2/37 (5.41%) did not have a heat lesion due to difficulties in placing the electrode, and no results are reported		**Post-procedure** ▪ 'Opioid dose was halved following successful percutaneous cervical cordotomy' **At two weeks (n=20)** ▪ 'If the procedure was found to be effective, then opioid analgesia was reduced in a standard step-wise fashion over the following two weeks'	**Post-procedure and at two weeks** ▪ Maximum height of the blockade at 24 hours ranged from C3 to T1 dermatome ▪ This remained the same at 2 weeks	3/37 (8.11%) with partial pain relief, 'further nerve blocks' were performed		
Raslan(b) [23] 2005 N = 8 n = 5	**Post-procedure** ▪ 1/5 (20%) had complete pain relief ▪ 2/5 (40%) had satisfactory pain relief ▪ 2/5 did not have a heat lesion due triangular cord shape ▪ 1 had no pain relief ▪ 1 had initial pain relief (but pain recurred at 2 weeks follow-up) **At two weeks** ▪ 3/5 (60%) continued to have satisfactory to complete pain relief ▪ 2/5 (40%) no pain relief	**Post-procedure** ▪ NRS: Median 3 (IQR = 6.75) (range 0-9) (vs pre-procedure median = 8) **At two weeks** ▪ NRS (pooled data for N=8): Mean = 3.1 (range 0-9)	**At two weeks** ▪ There was a 'stabilization of (their) pain medication dosages or even reduction of the dose'	**At two weeks** ▪ All 3 that had pain relief had recorded level of anaesthesia at T1 dermatome			
Raslan(a)[14] 2008 N = 41 n = 24	n = 24 / Post proc / At 28 days / At 3 months / At 6 months I: No pain — 19 (79.17%) / 20 (83.33%) / 17 (70.83%) / 8 (33.33%) II: Partial satisfactory pain relief — 5 (20.83%) / 3 (12.5%) / 6 (25%) / 14 (58.33%) III:Partial non-satisfactory pain relief — 0 / 0 / 0 / 1 (4.16%) IV: Same, no change in pain — 0 / 1 (4.16%) / 1 (4.16%) / 1 (4.16%) V: Worse pain — 0 / 0 / 0 / 0 **Median** — 1 / 1 / 1 / 2 **IQR** — 0 / 0 / 1 / 1 **Range** — 1-2 / 1-4 / 1-4 / 1-4	**Post-procedure** ▪ VAS[f]: Median = 1 (IQR = 2) (range 0-6) (vs pre-procedure median = 9) **At 28 days** ▪ VAS: Median = 2 (IQR = 1) (range 0-8) **More than 28 days** ▪ VAS at 3 months: Median = 2 (IQR = 1) (range 0-8) ▪ VAS at 6 months: Median = 2 (IQR = 1) (range 1-4)				**Post-procedure** ▪ KPS score: Median = 80 (IQR = 10) (range 60-90) (vs pre-procedure median = 55)	**Total Sleeping Hours (TSH):** **Post-procedure** ▪ Median = 7 (IQR = 1) (range 5-9) (vs pre-procedure median = 3) **At 28 days** ▪ Median = 6 (IQR = 1) (range 4-8) **More than 28 days** ▪ At 3 months: Median = 5 (IQR = 1) (range 4-8) ▪ At 6 months: Median = 5 (IQR = 1) (range 4-6)

Author, year Number of participants[a]	Global measure of pain relief	Pain intensity	Opioid use	Analgesic level or height of block	Other pain interventions	Performance status/ ADL's	Other outcomes (TSH etc)
Sharma 2011 **N = 35** **n = 17**	Global Impression of Change Scale: Pain is 1= very much worse 2=much worse 3=slightly worse 4=about the same 5=slightly better 6=much better 7 = very much better **Post-procedure** ▪ Mean = 6 (range 4-7) **At 28 days (n=11)** ▪ Mean = 4.45 (range 2-6)	**Post-procedure NRS:** ▪ Maximum pain last 24 hours: Mean = 0.52 (range 0-9) (vs pre-procedure mean = 8.71) ▪ Average pain last 24 hours: Mean = 0.52 (range 0-9) (vs pre-procedure mean = 6.76) **NRS at 28 days (n=12)** ▪ Maximum pain intensity: Mean = 2.16 (range 0-10) ▪ Average pain intensity: Mean = 2.00 (range 0-10)	▪ Percentage reduction in opioid use (n=14): Mean = 53.57 (range 0-100)				**Patient satisfaction:** Was it worthwhile to undergo the procedure? **Post-procedure (n=14)** ▪ Yes = 14 (100%) **At 28 days (n=9)** ▪ Yes = 8/9 (88.89%) ▪ No = 1/9 (1.11%)

[a] N = Number of patients in the study (all diagnoses) where the intention was to perform cordotomy; n = number of patients with a diagnosis of mesothelioma where the intention was to perform cordotomy
[b] Post-procedure = Follow-up ranging from immediately post-procedure until two days afterwards
[c] Numerical Rating Scale (NRS): 0=no pain, 10=worst pain ever
[d] Hypalgesia = Diminished sensitivity to pain
[e] Karnofsky Performance Status (KPS) scale: 0=death, 100=normal; no complaints; no evidence of disease; able to work
[f] Visual Analogue Scale (VAS): 0=no pain, 10=worst pain ever

Explanatory notes:
All results are reported as median (IQR, range) unless reviewers were unable to calculate these from the reports
The reviewers have used descriptors (quotes) from the included papers in an attempt to explain the quantitive data more fully
The reviewers have included salient pre-procedure results for ease of comparison for the reader