

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

### Interventional procedure overview of percutaneous image-guided cryoablation of peripheral neuroma for chronic pain

Neuromas are thickenings of tissue around a nerve. Peripheral neuromas affect nerves outside the brain and spinal cord that can carry pain signals between the brain and the rest of the body. Neuromas can cause chronic pain. In this procedure, a needle-like probe is inserted through the skin (percutaneous). Ultrasound, CT or MRI imaging is used to guide the probe near to the neuroma. The probe freezes the nerve to destroy a small part of it (cryoablation) and stop the pain signals. The nerve will slowly recover and the pain can come back, so the procedure may need to be repeated.

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## Abbreviations

Word or phrase	Abbreviation
Confidence interval	CI
Visual analogue scale	VAS

## Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

## Date prepared

This overview was prepared in April 2022 and updated in October 2022.

## Procedure name

- Percutaneous image-guided cryoablation of peripheral neuroma for chronic pain

## Professional societies

- British Society of Neuroradiologists
- British Peripheral Nerve Society
- Association of British Neurologists
- British Orthopaedic Foot and Ankle Society
- The Society of Chiropractors and Podiatrists
- The British Pain Society
- Faculty of Pain Medicine of the Royal College of Anaesthetists
- Royal College of Radiologists.

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## Description of the procedure

### Indications and current treatment

Neuromas are thickenings of tissue around a nerve, which can occur after injuries to the nerve, such as a cut, a crushing injury, nerve compression, or an excessive stretch. They are often associated with amputations. Peripheral neuromas affect nerves outside the brain and spinal cord that can carry pain signals between the brain and the rest of the body. This can cause chronic pain. Initial treatment may involve physical therapy, medication, or local anaesthetic and corticosteroid injections. [NICE's guideline on neuropathic pain in adults](#) describes pharmacological management in non-specialist settings. Surgical options include decompression and nerve removal.

A common type of neuroma is Morton's neuroma, which affects a nerve that lies between 2 metatarsal bones of the foot. It causes pain in the ball of the foot and sometimes the toes. Conservative management includes measures such as soft pads or insoles to take pressure off the painful area of the foot, wearing shoes with plenty of room in the toes, weight loss, and pain medication. If these measures do not work, non-surgical treatments include [radiofrequency ablation](#) and injection of corticosteroid or alcohol. If symptoms persist, the affected nerve can be surgically removed.

### What the procedure involves

Image-guided cryoablation of a peripheral neuroma for chronic pain is a percutaneous treatment, which is usually done as an outpatient procedure under local anaesthesia. Using image guidance (MRI, CT or ultrasound), a needle-like probe is inserted through the skin and near to the neuroma. Inside the probe, gas flows from a high- to low-pressure chamber creating an extremely cold temperature at the tip. The extreme cold causes reversible destruction of the nerve axon, which disrupts the pain signals. Unlike surgical or heat-mediated ablation, cryoablation does not disrupt the acellular epineurium or perineurium, which may allow eventual nerve regeneration. The time to total regeneration is related to the rate of axonal regrowth and the distance of the lesion from the end organ, so duration of symptomatic relief varies. The procedure can be repeated if necessary.

The main aim of the procedure is to relieve pain but it can also reduce swelling associated with the neuroma.

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## Efficacy summary

### Pain relief

In a case series of 20 patients with Morton's neuroma, the mean pain score measured on a VAS from 0 to 10 (higher scores indicating worse pain) was 3.0 after a mean follow up of 19.7 months (Cazzato 2016).

In a case series of 21 patients with refractory phantom limb pain (including 13 with an identified neuroma), the mean pain score reduced from 6.2 (95% CI 5.2 to 7.3) before treatment to 5.4 (95% CI 4.2 to 6.6;  $p$ =not significant) at 7 days, 2.3 (95% CI 1.6 to 3.0;  $p$ <0.0001) at 45 days and 2.0 (95% CI 0.9 to 3.0;  $p$ <0.0001) at last follow up (mean 194 days; Prologo 2017).

In a case series of 7 patients with a symptomatic stump neuroma after limb amputation, the mean pain score reduced from 8.3 before treatment to 2.1 at 1 week ( $p$ =0.004) after treatment and 3 at last follow up (mean 27 months;  $p$ =0.004). There was no correlation of pain decrease with patient age, duration of pain before ablation or time interval between amputation and ablation (von Falck 2022).

In a case series of 22 patients with refractory peripheral neuropathic pain (3 with plantar neuromas), the mean pain score reduced from 8.3 before treatment to 2.3 at 1 month ( $p$ =0.0001), 3.2 at 3 months ( $p$ =0.0002), 4.7 at 6 months ( $p$ =0.002) and 5.1 at 12 months ( $p$ =0.03). The mean time to pain recurrence was 9.3 months (Yoon J 2016).

In a case series of 20 patients with painful neuromas or peripheral neuritis, 75% (15/20) of people had some pain relief after the treatment. Of these 15 patients, 11 had marked or total pain relief, 3 had moderate relief and 1 had mild relief (Friedman 2012).

In a case series of 221 patients with persistent pain after microsurgical denervation of the spermatic cord who had transient pain relief after a spermatic cord block, 75% of patients reported a greater than 50% reduction in pain after cryoablation, measured on a VAS. When an objective pain index questionnaire (PIQ-6) was used, pain reduction was reported after 59 to 65% of procedures at 1 to 5 year follow up; the number of procedures followed up at 1, 2, 3, 4 and 5 years was 279, 275, 232, 128 and 53 respectively. The differences between baseline and follow up were statistically significant for all time periods ( $p$ <0.001; Calixte 2019).

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## Functional score

In the case series of 21 patients with refractory phantom limb pain, the mean functional score (range 0 to 24) improved from 11.3 (95% CI 8.8 to 13.9) before treatment to 9.4 (95% CI 7.3 to 11.5;  $p$ =not significant) at 7 days and 3.3 (95% CI 2.2 to 4.4;  $p$ <0.001) at 45 days follow up (Prologo 2017).

## Patient satisfaction

In the case series of 20 patients with Morton's neuroma, complete satisfaction was reported for 78% (14/18) of neuromas, and satisfaction with minor reservations was reported for 17% (3/18) of neuromas, after a mean follow up of 19.7 months. None of the patients reported that they were dissatisfied (Cazzato 2016).

In the case series of 7 patients with a symptomatic stump neuroma after limb amputation, the mean satisfaction score was 69% (range 10 to 100%) at last follow up (mean 27 months). Of the 7 patients, 1 was not satisfied with the treatment outcome and reported that they would not be willing to have the procedure again (von Falck 2022).

## Technical success

In the case series of 20 patients with Morton's neuroma and the case series of 7 patients with a symptomatic stump neuroma after limb amputation, technical success was 100% (Cazzato 2016, von Falck 2022).

## Repeat procedures

In the case series of 21 patients with refractory phantom limb pain, 4 had a second cryoablation treatment, all of which were technically successful. Pain intensity scores decreased by a mean of 4.25 points ( $p$ =0.0013) compared with baseline of the first procedure after a mean follow up of 165 days (Prologo 2017).

In the case series of 22 patients with refractory peripheral neuropathic pain, 1 patient had repeat cryoablation within the first month, 2 had repeat cryoablation at 3 months, 3 at 6 months, 6 at 12 months and 5 people had repeat cryoablation between 13 and 18 months after the initial procedure. One person chose to have a neurectomy 9 months after the cryoablation procedure (Yoon 2016).

## Safety summary

### Infection

Local cellulitis around the cryoprobe entry point was reported in 1 patient in the case series of 20 patients with Morton's neuroma. This fully resolved after 5 days of oral antibiotic therapy (Cazzato 2016). Wound infection was reported in 1 patient in the case series of 221 patients with persistent pain after microsurgical denervation of the spermatic cord (Calixte 2019).

### Pain

Pain that needed additional anti-inflammatory prescription medication was reported in 29% (6/21) of patients during the initial days after the procedure in the case series of 21 patients with refractory phantom limb pain (Prologo 2017). Penile pain was reported in 2% (4/221) of patients in the case series of 221 patients; all 4 patients were in the initial 20 patients to be treated. All subsequent procedures were done with a spacer and there were no further incidences of penile pain (Calixte 2019).

### Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events that they have heard about) and about theoretical adverse events (events that they think might possibly occur, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse events: worsening pain and fat necrosis around the procedure site. They listed the following theoretical adverse events: persistent pain, bruising and generation of scar tissue, which might make revision surgery more challenging.

## The evidence assessed

### Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous image-guided cryoablation of peripheral neuroma for chronic pain. The following databases were searched, covering the period from their start to 22 August 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the [literature search](#)

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[strategy](#)). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The [inclusion criteria](#) were applied to the abstracts identified by the literature search. If selection criteria could not be determined from the abstracts the full paper was retrieved.

### Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with chronic pain caused by peripheral neuroma.
Intervention/test	Percutaneous image-guided cryoablation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

### List of studies included in the IP overview

This IP overview is based on about 300 patients from 6 case series (Cazzato 2016, Friedman 2012, von Falck 2022, Prologo 2017, Yoon 2016, Calixte 2019).

Other studies that were considered to be relevant to the procedure but were not included in the main [summary of the key evidence](#) are listed in the [appendix](#).

## Summary of key evidence on percutaneous image-guided cryoablation of peripheral neuroma for chronic pain

### Study 1 Cazzato R (2016)

#### Study details

<b>Study type</b>	Case series
<b>Country</b>	France
<b>Recruitment period</b>	2011 to 2015
<b>Study population and number</b>	n=20 (24 neuromas) Patients with Morton's neuroma
<b>Age and sex</b>	Mean age 50.3 years; 75% (15/20) female
<b>Patient selection criteria</b>	Patients were included if they presented with typical clinical features (forefoot pain exacerbated by walking and relieved by rest and shoe removal); typical ultrasound and MRI findings; failure of conservative treatments (orthotic assessment, physical therapy) and ultrasound-guided corticosteroid injection; chose not to have surgery. Patients were excluded if they had contraindications to MRI (such as a pacemaker or claustrophobia).
<b>Technique</b>	All procedures were done under local anaesthesia on an outpatient basis. Patients were positioned in a large-bore 1.5 T MRI unit. After a small skin incision, a 2-cm active tip cryoprobe (Ice-Seed, Galil Medical Inc., US) was advanced into the centre of the lesion using an inter-metatarsal approach. A single therapeutic freezing cycle lasting 150 seconds was done, and ice-ball growth was monitored throughout the procedure. The cryoprobe was repositioned (with an additional 90-second freezing cycle for each repositioning) if the target lesion was not completely covered by the ice-ball. Finally, a short thawing cycle was applied to enable cryoprobe withdrawal.
<b>Follow up</b>	Mean 19.7 months
<b>Conflict of interest/source of funding</b>	3 authors are proctors for Galil Medical Inc.

#### Analysis

Follow up issues: Patients were followed up by telephone survey. Follow-up data was only available for 75% (18/24) of neuromas. The remaining patients could not be contacted.

Study design issues: Single centre, retrospective case series. Clinical outcomes (patient satisfaction and local pain scores) were evaluated using retrospective chart review and results of the telephone survey. Technical success was defined as an accurate cryoprobe placement in the centre of the lesion, homogeneous ice-ball growth with full lesion coverage, and limited involvement of the adjacent metatarsal bones and plantar fat pad.

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Complications were classified as minor or major according to the Society of Interventional Radiology grading system.

Study population issues: The mean Morton's neuroma size was 12.7 mm (range 8 to 34 mm). Four patients had bilateral lesions. The most common location of the Morton's neuroma was the third web-space (92% [22/24]).

## Key efficacy findings

Number of patients analysed: 20 (24 Morton's neuromas)

- Technical success=100%
- Patient satisfaction on per-lesion basis
  - Completely satisfied=77.7% (14/18)
  - Satisfied with minor reservations=16.6% (3/18)
  - Satisfied with major reservations=5.7% (1/18)
  - Dissatisfied=0% (0/18)
- Mean pain score at last follow up (visual analogue scale [VAS] 0 to 10) = 3.0

## Key safety findings

There was 1 minor complication: local cellulitis around the cryoprobe entry point. This fully resolved after 5 days of oral antibiotic therapy.

There were no cases of 'stump neuroma'.

## Study 2 Friedman T (2012)

### Study details

<b>Study type</b>	Case series
<b>Country</b>	US
<b>Recruitment period</b>	2007 to 2011
<b>Study population and number</b>	n=20 (5 Morton's neuroma, 12 stump neuromas secondary to surgery or trauma, 3 peripheral neuritis with no visible lesion) Patients with painful neuromas or peripheral neuritis
<b>Age and sex</b>	Mean age 49 years (range 18 to 79); 75% (15/20) female
<b>Patient selection criteria</b>	All patients who had sonographically guided cryoneurolysis for painful neuromas or peripheral neuritis were included. The patients were referred for pain that was refractory to multiple conservative measures, including physiotherapy and steroid injections. All patients had at least moderate pain improvement after anaesthetic injection.
<b>Technique</b>	Cryotherapy machine: Frigitrionics CE 2000 (Cooper Surgical Inc., US). At their request, 1 patient had spinal anaesthesia and 1 had intravenous sedation. An ultrasound scan was used to identify the target nerve or neuroma and to plan the trajectory of the cryoprobe. A proximal nerve block was done in most patients at the start of the procedure to provide regional anaesthesia for the duration of the procedure and short-term periprocedural pain relief. A small amount of 1% lidocaine was used as a local anaesthetic. A trochar tip cryoprobe was advanced under sonographic visualisation until just proximal to the nerve or into the neuroma. A sheath was left around the cryoprobe to protect the skin and nontarget tissues. When there was no visible lesion, an electric stimulator was used to confirm correct positioning. Once in position, the cryoprobe was activated and 2 to 4 ice balls were created, until the lesion was surrounded. The probe was repositioned slightly to create contiguous ice balls.
<b>Follow up</b>	Morton's neuroma: mean follow up=14 weeks (range 6 weeks to 14 months) Stump neuromas: mean follow up=6.3 months (range 2 weeks to 38 months) Peripheral neuritis: mean follow up=5.6 months (range 4 to 8 months)
<b>Conflict of interest/source of funding</b>	Not reported

### Analysis

Follow up issues: Patients were scheduled for routine clinical follow up at 4 to 6 weeks after the procedure. After this time, follow up was variable.

Study design issues: Retrospective case series. The same anaesthesiologist who initially assessed the patients and helped administer treatment did the follow-up. A VAS pain score was used and categorised into mild (1 to 3), moderate (3 to 6) or severe (7 to 10). When a VAS score was unavailable, the patient's own

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descriptors of pain were used to categorise the pain as mild, moderate, or severe. Response to treatment was categorised as no, mild, moderate, and marked pain relief.

Study population issues: patients with different indications were included.

Other issues: The authors noted that only the superficial margin of the ice ball was evident on imaging because of dense posterior acoustic shadowing.

## Key efficacy findings

Number of patients analysed: 20

### Clinical outcome in patients with Morton's neuroma

Patient	Pain before treatment	Treatment response	Duration of follow up
1	Severe	Marked	6 weeks
2	Severe	Marked	14 months of pain relief
3	Moderate	Moderate	4 weeks
4	Moderate	Marked	10 weeks
5 (both feet)	Moderate	None	4 weeks

### Clinical outcome in patients with lesions secondary to trauma or surgery

Patient	Pain before treatment	Treatment response	Duration of follow up
1 (stump neuroma)	Severe	None	2 weeks
2 (plantar nerve scar)	Moderate	Mild	7 weeks
3 (stump neuroma)	Moderate	Marked	17 weeks
4 (sural nerve scar)	Moderate	Marked	6 months of relief, returned for repeat treatment
5 (plantar nerve scar)	Moderate	Moderate	6 weeks
6 (sural nerve scar)	Moderate	Moderate	Moderate relief at 3 weeks, no relief at 4 months
7 (plantar nerve scar)	Moderate	Marked	8 months of relief, returned for repeat treatment
8 (stump neuroma)	Moderate	None	1 month
9 (saphenous neuroma)	Severe	Marked	38 months of relief, returned for repeat treatment
10 (plantar nerve scar)	Severe	None	3 weeks
11 (stump neuroma)	Moderate	Marked	6 months of relief, returned for repeat treatment
12 (plantar nerve scar)	Severe	Marked	11 weeks

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### Clinical outcome in patients with no visible lesion

Patient	Pain before treatment	Treatment response	Duration of follow up
1 (left medial nerve)	Moderate	Marked	5 months of relief, returned for repeat treatment
2 (Baxter nerve neuritis)	Severe	None	4 months
3 (Medial plantar nerve neuritis)	Moderate	Marked	8 months of relief, returned for repeat treatment

- Overall, 75% (15/20) of patients had a positive response to treatment and 5 patients had no pain relief (including 1 who had both feet treated).
- Of those with a positive response, 11 patients had marked or total pain relief, 3 had moderate relief and 1 had mild relief.
- Of the 5 patients who had no pain relief, 3 had further surgical procedures. No information was available for the other 2 patients.

### Key safety findings

The only adverse event was minor bleeding at the puncture site. There were no cases of infection, thrombosis or skin necrosis.

## Study 3 von Falck C (2022)

### Study details

<b>Study type</b>	Case series
<b>Country</b>	Germany
<b>Recruitment period</b>	2018 to 2020
<b>Study population and number</b>	n=7 (8 neuromas) Patients with a symptomatic stump neuroma after limb amputation
<b>Age and sex</b>	Mean age 42 years (range 25 to 55 years); 43% (3/7) female
<b>Patient selection criteria</b>	Inclusion criteria: patient aged 18 years or over, adequate coagulation status, on imaging recognisable painful stump neuroma and decrease of pain after probatory perineural infiltration. Prior to ablation, all patients had typical neuropathic pain in the stump, restricting them in their daily living activities. Additional complaints were local cramps, phantom pain and an inability or limitation in wearing their limb prosthesis.
<b>Technique</b>	Cryoablation was done as an inpatient procedure under analgosedation and ultrasound guidance (Visual Ice System, Galil Medical Inc., US). A single cryoprobe (IceSphere or IceSeed) was advanced to the previously identified neuroma and ablation started (2 cycles of 6 minutes freezing separated by a 4-minute thaw cycle). The ablation zone and surrounding structures were continuously monitored with ultrasound. Care was taken that the resulting ice ball covered the whole neuroma without extending less than 0.5 cm to the skin surface. In addition, skin was protected with warm gel cushions. Patients were discharged the next morning, after follow-up ultrasound.
<b>Follow up</b>	Mean 27 months (range 6.8 to 40 months)
<b>Conflict of interest/source of funding</b>	None

### Analysis

Follow up issues: Outpatient clinical follow-up was scheduled 6 weeks after the ablation. No losses to follow up were described.

Study design issues: Retrospective observational study of prospectively collected data. Pain intensity before and after cryoablation was evaluated using a VAS (0 to 10). At final follow-up, patients were asked how satisfied they were with the cryoablation treatment (scale 0 to 100 where 0 is not satisfied at all and 100 is absolutely satisfied) and whether they would be willing to have the treatment again, if needed.

Study population issues: Mean duration of pain before treatment was 8.4 months (range 2 to 24 months). The mean time interval between amputation and cryoablation was 100 months (range 11 to 336 months). Of the 7 patients, 2 had upper leg amputations and 5 had lower leg amputations.

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## Key efficacy findings

Number of patients analysed: 7 (8 neuromas, 9 cryoablation procedures)

- Technical success=100%
- Mean pain score (VAS, 0 to 10)
  - Before treatment=8.3 (range 5 to 10)
  - 1 day after treatment=4 (range 1 to 7); p=0.008 compared with baseline
  - 1 week after treatment=2.1 (range 0 to 6); p=0.004 compared with baseline
  - At last follow up=3 (range 0 to 7); p=0.004 compared with baseline
- Mean satisfaction with treatment at last follow up=69 (range 10 to 100)
- Willing to have repeat treatment if needed=85.7% (6/7) of patients

The single patient that was not satisfied with treatment outcome (satisfaction score 10/100) had a 30% reduction of pain after cryoablation and indicated that he would not be willing to have reablation.

There was no correlation of pain decrease with patient age, duration of pain before ablation or time interval between amputation and ablation.

## Key safety findings

There were no major complications.

In 1 patient, local redness of the skin was visible 1 day after ablation, which resolved spontaneously without any specific treatment.

## Study 4 Prologo JD (2017)

### Study details

<b>Study type</b>	Case series
<b>Country</b>	US
<b>Recruitment period</b>	2015 to 2016
<b>Study population and number</b>	n=21 (13 with a neuroma) Patients with refractory phantom limb pain
<b>Age and sex</b>	Mean 56.9 years (range 34 to 91 years); 57% (12/21) female
<b>Patient selection criteria</b>	<p>All patients reported phantom pains or unwanted sensations related to a previously amputated upper or lower limb that were refractory to conventional treatment for at least 6 months. To have cryoablation, each patient was required to have documented symptomatic relief from an image-guided perineural injection of bupivacaine and betamethasone.</p> <p>Exclusion criteria: active infection, underlying congenital segmentation or other spinal anomalies that result in differential nerve root pressures, severe spinal stenosis, pregnant or planning to become pregnant, immunosuppression, history or laboratory results indicative of any significant cardiac, endocrine, hematologic, hepatic, immunologic, infectious, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neoplastic, or other disorder that in the opinion of the principal investigator would preclude safe performance of cryoablation, uncorrectable coagulopathies, concurrent participation in another investigational trial involving systemic administration of agents or within the previous 30 days, previous surgical intervention, after amputation, that may have altered the target nerve.</p>
<b>Technique</b>	<p>A 2-step method was used, with a diagnostic nerve block injection followed by cryoablation that occurred on separate occasions. For the nerve block, a 22-gauge spinal needle was advanced under CT or ultrasound guidance to the target nerve or neuroma. Needle position was confirmed with fluoroscopic CT.</p> <p>All ablation procedures were done under conscious sedation. Using technique and targeting analogous to the diagnostic injections, an Ice-Sphere cryoablation needle (Galil Medical Inc., US) was advanced under imaging guidance to the previously identified nerve or neuroma. When position was confirmed, the probe temperature was decreased to <math>-40^{\circ}\text{C}</math> over 10 minutes using the Galil Visual-ICE system. Images were obtained and reviewed 8 minutes into the freeze. A passive thaw cycle was then done for 5 minutes, followed by a second 10-minute freeze and subsequent final 5-minute passive thaw.</p>
<b>Follow up</b>	Mean 194 days
<b>Conflict of interest/source of funding</b>	None

### Analysis

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Follow up issues: Patients were routinely followed up 7 and 45 days after the procedure. A final, long-term follow-up assessment was done after the 45-day visit. One patient died during the period between visit 3 and the long-term follow-up assessment and was considered lost to follow-up.

Study design issues: Prospective single-arm pilot study. The main aim was to derive parameters to design a larger, randomised, parallel-armed, controlled trial. Ratings of perceived pain intensity were captured using a VAS from 0 (no pain) to 100 (worst possible pain). Functional status was evaluated with a modified Roland Morris Disability Questionnaire (RMDQ). This consists of 24 statements describing activity limitations resulting from back pain to which patients answer with either “yes,” equal to 1 point, or “no,” corresponding to zero, for a total of 24 possible points. A minimum score of zero corresponds to no disability, whereas a maximum score of 24 corresponds to maximum disability. For the purposes of this study, the RMDQ was adapted to focus on phantom limb pain. At the long-term follow-up assessment, patients were asked to rate their pain and to report whether they would have the cryoablation procedure again.

Study population issues: Of the 21 patients, 17 (81%) had a lower extremity amputation (10 above knee and 7 below knee) and 4 (19%) had an upper extremity amputation (2 complete forequarter, 1 above elbow and 1 below elbow). A neuroma was identified in 13 (62%) patients. The mean time since amputation was 10 years. The mean pain intensity before the procedure was 6.2 and the mean functional status score was 11.3.

## Key efficacy findings

Number of patients analysed: 21

- Technical success=100%
- Mean pain score (VAS, 0 to 10)
  - Before treatment=6.2 (95% CI 5.2 to 7.3)
  - 7 days after treatment=5.4 (95% CI 4.2 to 6.6), p=not significant compared with baseline
  - 45 days after treatment=2.3 (95% CI 1.6 to 3.0), p<0.0001 compared with baseline
  - At last follow up=2.0 (95% CI 0.9 to 3.0), p<0.0001 compared with baseline
- Mean functional score (range 0 to 24)
  - Before treatment=11.3 (95% CI 8.8 to 13.9)
  - 7 days after treatment=9.4 (95% CI 7.3 to 11.5), p=not significant compared with baseline
  - 45 days after treatment=3.3 (95% CI 2.2 to 4.4), p<0.001 compared with baseline
- When patients were asked if they would have the procedure again at the long-term follow-up assessment, 4 patients (19%) volunteered to have a second cryoablation, and 14 (67%) responded affirmatively.

## Repeat procedures

All 4 of the repeat ablations were technically successful. The mean long-term follow-up assessment after the second ablation was 165 days. Pain intensity scores were statistically significantly decreased by a mean of 4.25 points (p=0.0013) compared with baseline of the first procedure. Of the 4 patients who had a repeat procedure, only 1 responded that they would have the procedure again.

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### **Explanatory variables identified through modelling**

- Statistically significant predictors were found for pain intensity ratings. Patients with upper limb amputations had greater mean pain intensity scores compared with patients with lower limb amputations, and patients with residual limb pain had lower baseline and lower overall improvements over time in pain intensity ratings compared with patients without residual limb pain.
- No explanatory variables were found to influence functional status ratings either at each follow-up visit or over time.

### **Key safety findings**

- During the initial days after the procedure, 6 patients (29%) had pain that needed additional anti-inflammatory prescription medication.
- There were no reports of adverse events throughout the follow-up periods after either the cryoablation procedure or diagnostic nerve block.
- One patient died, which was concluded to be unrelated to treatment or the patient's participation in the study.

## Study 5 Yoon J (2016)

### Study details

<b>Study type</b>	Case series
<b>Country</b>	US
<b>Recruitment period</b>	2011 to 2013
<b>Study population and number</b>	n=22 (3 plantar neuromas, 3 ilioinguinal, 4 posterior tibial, 7 saphenous, 1 gluteal, 1 sural, 1 geniculate, and 2 digital nerves were treated) Patients with refractory peripheral neuropathic pain
<b>Age and sex</b>	Mean age 49.5 years; 41% female
<b>Patient selection criteria</b>	Patients had peripheral neuropathy that failed to respond to first- and second-line therapy. Before referral for neurolysis, all patients had a complete evaluation by a pain physician that included motor testing. All patients showed a response to nerve blocks. Exclusion criteria included an inability to participate in the pain assessments at any of the scheduled follow-up intervals.
<b>Technique</b>	Device: PerCryo 17R (Endocare/Healthtronics, US) was used with ultrasound imaging. All procedures were done under deep sedation. The site of pain was localised by palpation and then the nerve proximal to the area of pain was localised using ultrasound. The ablation probe was advanced to the location of the nerve. When the nerve was localized, 2 to 3 ml of bupivacaine was injected into the nerve. For superficial nerves less than 1 to 2 cm from the skin surface, hydrodissection was used to elevate the skin from the probe tip to prevent skin injury. The ice ball formed as a sphere as much as 1.5 cm proximal to the tip of the probe, and saline solution was injected around this peripheral aspect of the ice ball to ensure at least 1 cm of separation from the ice ball to the skin surface to prevent thermal injury. The cryoablation was performed at 30% of maximum power with a single freeze cycle of 3 minutes. The probe tip reached a minimum temperature of about -135°C to -160°C. A single active thaw cycle was done until the probe temperature reached 5°C to 10°C. At the end of the procedure, ketorolac was given intravenously if the patient had no contraindication to it.
<b>Follow up</b>	12 months
<b>Conflict of interest/source of funding</b>	1 author has received grants from EDDA Technologies (US) and Endo Pharmaceuticals (US) outside the present work and has a patent pending for Scannerside (US). None of the other authors identified a conflict of interest.

### Analysis

Follow up issues: No losses to follow up were described.

Study design issues: Prospective case series, evaluating the safety and efficacy of cryoneurolysis in patients with refractory peripheral neuropathic pain. Pain levels were recorded on a VAS from 0 to 10, with 0 indicating no pain and 10 being the worst pain imaginable. Assessment of pain and concomitant medications at the

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primary endpoints was done by telephone by an independent staff member who was not involved in the treatment of the patients. If a patient's pain score returned to baseline levels or was treated again with cryoablation, or if the treatment was ineffective, the highest recorded pain score was continued for all future time points, based on an intent-to-treat assumption. Therefore, after a patient's repeat treatment, their new postprocedural pain scores were not included in the analysis; only their highest pain score was included.

Study population issues: nerves were treated at several different sites.

## Key efficacy findings

Number of patients analysed: 22

- Mean pain score (VAS, 0 to 10)
  - Before treatment=8.3 (SD 1.9)
  - 1 month after treatment=2.3 (SD 2.5), p=0.0001
  - 3 months after treatment=3.2 (SD 2.5), p=0.0002
  - 6 months after treatment=4.7 (SD 2.7), p=0.002
  - 12 months after treatment=5.1 (SD 3.7), p=0.03
- Mean time to pain recurrence=9.3 months
- Number of patients who had repeat cryoablation by follow up period
  - 1 month=1
  - 3 months=2
  - 6 months=3
  - 12 months=6
  - 13 to 18 months=5

1 patient chose to have a neurectomy 9 months after the cryoablation procedure.

## Key safety findings

The report stated that there were no complications.

## Study 6 Calixte N (2019)

### Study details

<b>Study type</b>	Case series
<b>Country</b>	US
<b>Recruitment period</b>	2012 to 2016
<b>Study population and number</b>	n=221 Patients with persistent pain after having microsurgical denervation of the spermatic cord who had transient pain relief after a spermatic cord block
<b>Age and sex</b>	median 43 years (range 16 to 77 years); 100% male
<b>Patient selection criteria</b>	All patients had persistent pain after having microsurgical denervation of the spermatic cord and had transient pain relief after a spermatic cord block. Before microsurgical denervation all patients had a detailed physical examination to identify the precise location of the persistent pain. Scrotal ultrasound was done at least once to exclude structural abnormality including tumour, torsion, varicocele, hydrocele, spermatocele, inguinal hernia, and epididymo-orchitis. CT of the abdomen was done when there was a history of back pain or trauma, or any other reason for concerns regarding possible intrabdominal pathology as a cause of referred pain. Persistence of significant pain for more than 3 months after microsurgical denervation was a selection criterion for ultrasound-guided targeted cryoablation.
<b>Technique</b>	The cryoprobe (Endocare 1.7mm PerCryo) was placed medial and then lateral to the spermatic cord at the level of external inguinal ring. These 2 areas contain nerve branches of the ilioinguinal, genitofemoral, and inferior hypogastric nerves. Two freeze cycles of 90 seconds each with a passive thaw cycle in between were used for the treatment. A 1.5 cm ice ball was created medial and lateral to the spermatic cord under real-time ultrasound (with doppler flow guidance) up to the edge of the cord, but not extending into the cord.  After the first 20 patients, a spacer agent was injected in the area between the medial side of the spermatic cord and the penile corporal bodies to prevent inadvertent injury to the penile nerves.
<b>Follow up</b>	Median 36 months (range 24 to 60 months)
<b>Conflict of interest/source of funding</b>	None

### Analysis

Study design issues: Retrospective case series. The level of pain was assessed before and after the procedure using 2 assessment tools: the subjective visual analogue scale and a quantitative, objective, standardised, and externally validated pain assessment tool (PIQ-6). The data collected was analysed using analysis of variance (ANOVA) for pairwise comparisons (paired samples) of each patient's reported pain levels

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as indicated by the PIQ-6 before the procedure, and at the 1 month, 6 month, 1 year, 2 year, 3 year, 4 year, and 5 year follow up periods.

Study population issues: Most patients had tried conservative treatment options such as antibiotics, anti-inflammatories, physical therapy, and acupuncture. The median duration of pain before the procedure was 6 years (range 1 to 52 years). Pain was attributed to a variety of causes, including epididymitis, varicocele, vasectomy, inguinal hernia repair, sports injury, orchiopexy for undescended testicle, and spinal surgery.

## Key efficacy findings

Number of patients analysed: 221 (279 procedures)

### Subjective VAS pain scale outcomes:

- 75% of patients reported a greater than 50% reduction in pain. Of the 75% reporting a reduction, 11% of patients reported complete resolution of pain. There were no statistically significant differences in outcome based on aetiology.

### Objective Pain Index Questionnaire (PIQ-6) outcomes:

- Proportion of procedures with pain reduction by follow-up period:
  - 1 month=53% (n=279)
  - 3 months=55% (n=279)
  - 6 months=60% (n=279)
  - 1 year=63% (n=279)
  - 2 years=65% (n=275)
  - 3 years=64% (n=232)
  - 4 years=59% (n=128)
  - 5 years=64% (n=53)
- Pairwise comparisons (n=279): there was a statistically significant decrease in pain between baseline and 1 month follow up ( $p \leq 0.000$ ), as well as between baseline and 3 month follow up ( $p \leq 0.000$ ), 6 month follow up ( $p \leq 0.000$ ), 1 year follow up ( $p \leq 0.000$ ), 2 year follow up ( $p \leq 0.000$ ), 3 year follow up ( $p \leq 0.000$ ), 4 year follow up ( $p \leq 0.000$ ), and 5 year follow up ( $p \leq 0.000$ ).

## Key safety findings

- Wound infection=0.9% (2/221); treated with antibiotics
- Penile pain=1.8% (4/221); all 4 patients were in the initial 20 patients to be treated. All subsequent procedures were done with a spacer and there were no further incidences of penile pain.

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## Validity and generalisability of the studies

- No randomised controlled trials or non-randomised comparative studies were identified.
- Four of the studies were retrospective.
- The studies included different indications and a proportion of patients did not have a neuroma identified as the cause of their pain.
- One study only included patients with Morton's neuroma (Cazzato 2016) and 1 only included patients with a stump neuroma after limb amputation (von Falck 2022).
- In 1 study, 25% of patients were lost to follow up (Cazzato 2016).
- The studies included different cryotherapy devices and different imaging modalities were used.
- The use of concomitant pain management therapy may be a confounding variable in these studies.
- The 5 studies included data from the US, France and Germany.

## Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

## Related NICE guidance

Below is a list of NICE guidance related to this procedure.

### Interventional procedures

- Radiofrequency ablation for symptomatic interdigital (Morton's) neuroma. NICE interventional procedures guidance 539 (2015). Available from <http://www.nice.org.uk/guidance/IPG539>

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- Percutaneous electrical nerve stimulation for refractory neuropathic pain. NICE interventional procedures guidance 450 (2013). Available from <http://www.nice.org.uk/guidance/IPG450>

### Technology appraisals

- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal 159 (2008). Available from <http://www.nice.org.uk/guidance/TA159>

### NICE guidelines

- Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. NICE guideline 193 (2021). Available from <http://www.nice.org.uk/guidance/NG193>
- Neuropathic pain in adults: pharmacological management in non-specialist settings. NICE clinical guideline 173 (2013, updated 2020)]. Available from <http://www.nice.org.uk/guidance/CG173>

## Additional information considered by IPAC

### Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, when comments are considered voluminous, or publication would be unlawful or inappropriate.

Three professional expert questionnaires for percutaneous image-guided cryoablation of peripheral neuroma for chronic pain were submitted and can be found on the [NICE website](#).

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## **Patient commentators' opinions**

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

## **Company engagement**

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

## **Issues for consideration by IPAC**

- Evidence that used cryoablation without image guidance has been excluded.

## References

1. Cazzato RL, Garnon J, Ramamurthy N et al. (2016) Percutaneous MR-guided cryoablation of Morton's neuroma: rationale and technical details after the first 20 patients. *Cardiovascular and Interventional Radiology* 39: 1491–8
2. Friedman T, Richman D, Adler R (2012) Sonographically guided cryoneurolysis: preliminary experience and clinical outcomes. *Journal of Ultrasound in Medicine* 31: 2025–34
3. von Falck C, Orgel M, Wacker F et al. (2022) Icing the pain-ultrasound-guided cryoablation of symptomatic post-amputation stump neuroma. *Cardiovascular and Interventional Radiology* 45: 223–7
4. Prologo JD, Gilliland CA, Miller M et al. (2017) Percutaneous image-guided cryoablation for the treatment of phantom limb pain in amputees: a pilot study. *Journal of Vascular and Interventional Radiology* 28: 24–34
5. Yoon JHE, Grechushkin V, Chaudhry A et al. (2016) Cryoneurolysis in patients with refractory chronic peripheral neuropathic pain. *Journal of Vascular and Interventional Radiology* 27: 239–43
6. Calixte N, Kartal IG, Tojuola B, et al. (2019) Salvage ultrasound-guided targeted cryoablation of the perispermatic cord for persistent chronic scrotal content pain after microsurgical denervation of the spermatic cord. *Urology* 130: 181–185

## Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	08/08/2022	1946 to August 05, 2022
MEDLINE In-Process (Ovid)	08/08/2022	1946 to August 05, 2022
MEDLINE Epubs ahead of print (Ovid)	08/08/2022	August 05, 2022
EMBASE (Ovid)	08/08/2022	1974 to August 05, 2022
EMBASE Conference (Ovid)	08/08/2022	1974 to August 05, 2022
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	08/08/2022	Issue 8 of 12, August 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	08/08/2022	Issue 7 of 12, July 2022
International HTA database (INAHTA)	08/08/2022	-

### Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

### Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

- 1 Neuroma/ or morton neuroma/ or exp Neurilemmoma/
- 2 (neuroma\* or neuronal tissue\* or neurile?moma\* or neurole?moma\* or neurinoma\* or schwann\*).tw.
- 3 ((morton\* or plantar\* or interdigital\* or inter-digital\* or inter-metatarsal\* or intermetatarsal\*) adj4 (disease\* or disorder\* or syndrome\* or neuroma\* or entrap\* or neuralgi\* or neuritis\* or metatarsalgi\* or neuropath\* or neurectom\*)).tw.
- 4 exp Peripheral Nervous System Neoplasms/

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- 5 ((benign or non-cancer\* or noncancer\*) adj4 (nerve\* or nervous\* or neuronal or peripher\*) adj4 (tumo?r\* or growth\* or tissue\* or lump\* or mass\* or lesion\* or neoplasm\*)).tw.
- 6 Neuralgia/ or Neuritis/ or Peripheral Nerve Injuries/ or Peripheral Nerves/
- 7 (peripher\* adj4 (nerve\* or neuropath\* or neuritis or neuralgia\* or neuraxitis or polyneuritis or pain\* or injur\* or damage\*)).tw.
- 8 nerve\* cell\* tumo?r\*.tw.
- 9 nerve compression syndromes/
- 10 (nerve\* adj4 (pinch\* or compress\* or entrap\* or crush\*)).tw.
- 11 (neuropath\* adj4 (entrap\* or compress\*)).tw.
- 12 or/1-11
- 13 Cryosurgery/
- 14 Ablation Techniques/
- 15 Freezing/
- 16 ((cryo\* or freez\* or cold) adj4 (therap\* or surg\* or ablat\* or method\* or technique\* or procedure\* or treatment\* or destruct\*)).tw.
- 17 (cryosurg\* or cryoanalgesia or cryoneurolysis or cryoneuroablation or cryoablat\* or cryogenic neuroablation or cryogenic denervation or cryotherapy\*).tw.
- 18 ((freez\* adj2 thaw\*) or freez\* thaw\*).tw.
- 19 or/13-18
- 20 12 and 19
- 21 (Visual ICE Cryoablation System\* or iovera system\* or iovera or Cryocare CS or Westco Neurostat-III cryoneedle\* or CryoSystem\*).tw.
- 22 20 or 21
- 23 animals/ not humans/
- 24 22 not 23

## Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the [summary of the key evidence](#). It is by no means an exhaustive list of potentially relevant studies.

### Additional papers identified

Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Bittman RW, Behbahani K, Gonzalez F et al. (2019) Interventional cryoneurolysis: what is the same, what is different, what is new? Seminars in Interventional Radiology 36: 374–80	Review	The integration of interventional radiology to the longstanding clinical concept of applying cold temperatures to nerves has illuminated several new procedural options and potential applications for the therapy.	Relevant cited papers have been included in the key evidence.
Bittman RW, Peters GL, Newsome JM et al. (2018) Percutaneous image-guided cryoneurolysis. AJR. American Journal of Roentgenology vol. 210: 454–65	Review	Percutaneous image-guided cryoneurolysis is safe and effective for the management of several well-described syndromes involving neuropathic pain. Additional rigorous prospective study is warranted to further define the efficacy and specific role of these interventions.	Relevant cited papers have been included in the key evidence or appendix.
Djebbar S, Rossi IM, Adler RS (2016) Ultrasound-guided cryoanalgesia of peripheral nerve lesions. Seminars in Musculoskeletal Radiology 20: 461–71	Review	Ultrasound enables a continuous monitoring of adjacent soft tissue structures while the cryoprobe is active, minimising collateral damage. Cryoablation of painful peripheral	Descriptive review with some outcome data on patients with a variety of nerve lesions.

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		nerve lesions is a safe alternative to other ablative techniques to achieve long-term analgesia.	
Fiala M, Azariah A, Woo J et al. (2022) Treating phantom limb pain: cryoablation of the posterior tibial nerve. <i>Radiology Case Reports</i> 17: 3168–3171	Case report n=1	Ultrasound-guided cryotherapy successfully reduced phantom limb pain.	Case report
Filippiadis D, Efthymiou E, Tsochatzis A et al. (2021) Percutaneous cryoanalgesia for pain palliation: Current status and future trends. <i>Diagnostic and Interventional Imaging</i> 102: 273–8	Review	Percutaneous cryoanalgesia under imaging guidance can be considered demonstrably effective at treating pain of both neo-plastic and non-neoplastic substrate. Imaging guidance and ability to visualise ice ball adds to safety and efficacy.	Relevant cited papers have been included in the key evidence or appendix.
Matthews BG, Hurn SE, Harding MP et al. (2019) The effectiveness of non-surgical interventions for common plantar digital compressive neuropathy (Morton's neuroma): a systematic review and meta-analysis. <i>Journal of Foot and Ankle Research</i> 12: 12	Systematic review (8 interventions) n=1,974 (25 studies)	Corticosteroid injections and manipulation or mobilisation are the 2 interventions with the strongest evidence for pain reduction, however high-quality evidence for a gold standard intervention was not found. Although the evidence base is expanding, further high quality RCTs are needed. Two case series of cryoneurolysis showed a weighted success rate of 75% (95% CI 54 to 92%) but studies were described as low quality.	Only 2 studies on cryoablation were included, both of which are described in the key evidence.

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Ramsook RR, Spinner D (2017) Ultrasound-guided cryoablation of a traumatic hip disarticulation neuroma. Pain practice: the official journal of World Institute of Pain 17: 941–4	Case report n=1	Ultrasound-guided cryoablation of a traumatic hip disarticulation neuroma resulted in complete pain relief and improved functionality and independence.	Case report
Rhame, Ellen E; Debonet, Alexander F; Simopoulos, Thomas T (2011) Ultrasonographic guidance and characterization of cryoanalgesic lesions in treating a case of refractory sural neuroma. Case Reports in Anesthesiology 2011: 691478-691478	Case report n=1	Cryoanalgesia in conjunction with ultrasound guidance was used successfully to manage recurrent pain of a neuroma following surgical excision and burial of nerve endings. Ultrasound provided visualisation of the cryolesions, as well as the relationships of the ice ball to the surrounding tissue.	Case report
Sconfienza LM, Adriaensen M, Albano D et al. (2022) Clinical indications for image-guided interventional procedures in the musculoskeletal system: a Delphi-based consensus paper from the European Society of Musculoskeletal Radiology (ESSR)-part VI, foot and ankle. European Radiology 32: 1384–94	Delphi-based consensus paper	Image-guided thermal ablation of Morton's neuroma is safe with promising initial results and might reduce the need for surgery in the short term. Although ethanol injections, radiofrequency, and cryoablation seem to be safe alternatives for treating Morton's neuroma, the clinical value of these interventions still needs further clarification.	Only 2 papers are included on image-guided cryoablation, both of which are included in the key evidence (Cazzato 2016 and Friedman 2012).
Thomson L, Aujla RS, Divall P et al. (2020) Non-surgical treatments for Morton's neuroma: A systematic review. Foot and Ankle Surgery 26: 736–43	Systematic review 22 studies	Following review, the authors would recommend the use of corticosteroid injections to treat Morton's neuromas.	Only 1 study on cryoablation was included, which did not

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		The authors feel that radiofrequency ablation and cryoablation would benefit from further well designed randomised controlled trials.	use image guidance.
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