NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of radiofrequency ablation for palliation of painful spinal metastases

Cancer from elsewhere in the body can spread to the spine (spinal metastases), causing severe pain, weakness in the vertebrae (bones of the spine) leading to instability or fractures, and spinal cord compression. In this procedure a needle-like probe containing an electrode is inserted into the spinal metastases. It produces an electrical current that heats the cancer cells and destroys them (radiofrequency ablation). The aim is to shrink the spinal metastases to relieve pain and other symptoms (palliation). To reduce the risk of future fractures, usually bone cement is injected into the resultant cavity after the radiofrequency treatment.

Contents

Abbreviations

Word or phrase	Abbreviation
Functional assessment of cancer therapy-general 7	FACT-G7
Functional assessment of cancer therapy quality-of life measurement in patients with bone pain	FACT-BP
Health related quality of life	HRQoL
Oswestry disability index	ODI
Radiofrequency ablation	RFA
Numeric pain rating scale	NPRS
Visual Analog Scale	VAS
Not measured	NM
Not reported	NR
World Health Organisation	WHO

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 September 2020.

Procedure name

- Radiofrequency ablation for palliation of painful spinal metastases

Professional societies

- British Society of Interventional Radiology
- Faculty of Clinical Oncology, Royal College of Radiologists
- British Association of Spinal Surgeons (BASS)
- Society of British Neurological Surgeons (SBNS)
- Faculty of Pain Medicine, The Royal College of Anaesthetists.

Description of the procedure

Indications and current treatment

Spinal metastases can affect quality of life by causing severe pain, functional impairment, vertebral fractures, nerve root impingement, spinal cord compression and hypercalcaemia.

Treatment for spinal metastases is mainly palliative. It aims to reduce pain, improve and maintain function, provide mechanical stability, and prevent further local tumour progression. Current treatment options include a combination of medical therapies (such as analgesics, systemic therapies including osteoclastic inhibitors such as bisphosphonates and denosumab, chemotherapy or hormone therapy), orthotic support, radiation therapy, cryoablation, microwave ablation, vertebroplasty or kyphoplasty (for stabilisation of vertebral fractures). Open surgery may be suitable for some patients with spinal cord compression and vertebral fractures.

What the procedure involves

Radiofrequency ablation is a procedure for palliative treatment of spinal metastases. It is done in an outpatient setting using a transpedicular or parapedicular approach under general anaesthesia or conscious sedation. The approach is either percutaneous, endoscopic or surgical.

Under imaging guidance (fluoroscopy, CT or MRI) a radiofrequency probe is inserted into the spinal tumour. The radiofrequency probe is attached to a radiofrequency generator, which creates high frequency alternating current

pulses that heat and destroy the tumour. This creates a cavity in the vertebral body. To prevent subsequent fractures in the treated vertebrae, percutaneous vertebroplasty or balloon kyphoplasty is usually done at the same time as the procedure.

Radiofrequency ablation is not usually done if the spinal metastases are near neurological structures because of the risk of neurological injury.

Efficacy summary

Pain reduction

In a systematic review of 9 studies (4 prospective and 5 retrospective) on radiofrequency ablation (RFA) as a palliative treatment in 583 patients with painful metastatic spinal lesions, all studies reported that patients experienced a reduction in pain. Pain was measured using instruments such as visual analogue scale (VAS) and numeric pain rating scale (NPRS), where higher scores represented worst pain. In the 4 prospective studies, 1 study (Bagla 2016) reported a statistically significant decrease in pain from baseline NPRS score of 5.9 to 2.6 at 1 month and 2.1 at 3 months (a decrease of 3.3 and 3.8 points, respectively; $p<0.001$). Similar results (decrease in baseline VAS mean score from 7.5 to 2.7, $p<0.005$ after 1 week) were reported in another study (Nakatsuka 2009). Local pain relief was reported in 87% (13/15) of patients at 2 to 4 weeks (Georgy 2009) and sustained in 90% (9/10) of patients during 6 months follow-up (Nakatsuka 2009). In another study (Proschek 2009), pain at baseline (mean VAS score 7.6 in RFA group [n=8] and 7.9 in RFA plus vertebroplasty group[n=8]) decreased to 4.0 ($p<0.005$) in the RFA group and 3.5 ($p<0.005$) in RFA plus vertebroplasty group, respectively, at 15 to 36 months follow-up (Rosian 2018).

A systematic review of 8 studies (4 prospective and 4 retrospective) of RFA treatment in 261 patients with painful spinal metastases reported statistically significant pain relief compared with baseline (mean baseline VAS scores ranged between 5.9 and 8; mean baseline NRS scores ranged between 5.9 and 8). Five studies reported more than 4 points of pain reduction (mean score ranged from 4 to 5.7) and 2 studies reported more than 2 points of pain reduction (mean score 3.3 and 3.8) between baseline and last follow up ([range 1 week to 6 months). Two studies reported results separately for the group having RFA plus cement augmentation compared with the group having RFA alone. One study (Nakatsuka 2009) reported that at 1-week follow up, VAS decreased from baseline 4.3 to 1.7 ($p=0.0004$) in the RFA alone group (n=4) and from 6.6 to 1.7 ($p=0.003$) in the RFA plus cement augmentation group (n=6). Similarly, in another study (Proschek 2009) between 15 to 36 months of follow up, VAS decreased from

7.9 to 4 (p=0.008) in the RFA alone group (n=8), and from 7.6 to 3.5 (p=0.005) in the RFA plus cement augmentation group (n=8) (Cazzato 2018).

A systematic review of 8 retrospective studies on combined RFA and vertebral stabilisation techniques for palliative treatment of vertebral metastases reported decrease in pain VAS scores from baseline. RFA followed by percutaneous kyphoplasty (in 3 studies) resulted in decreased pain scores from baseline and between 1 week to 6 months of follow up (VAS scores at baseline ranged from 7.2 to 7.9 and at last follow up ranged from 2.96 to 3.82). RFA followed by vertebroplasty (in 4 studies) resulted in decreased pain scores from baseline and between 3 days to 15 months of follow up (VAS scores at baseline ranged from 6.3 to 8.5 and at last follow up ranged from 2.4 to 3.5) (Greif 2019).

A retrospective analysis of 64 patients comparing RFA plus vertebral augmentation (n=34) with kyphoplasty alone (n=30) reported an overall decrease in pain scores for all treatment groups from baseline and between 7 to 14 days (RFA with SpineStar system 6.9 to 3.3; RFA with OsteoCool system 6 to 3.28; kyphoplasty alone 6.3 to 3.69). However, difference of square means analysis showed no statistical difference in pain scores at each time interval between the two RFA systems, and there was no statistical difference in pain scores when each RFA system was compared with kyphoplasty alone (Jain 2020).

A retrospective analysis of 26 patients (with 28 spinal metastases) who had RFA alone (n=17) or RFA plus radiotherapy (n=10) reported that there was a significant decrease in the pain scores in both the groups (RFA alone group VAS score decreased from baseline 4.2 to 2.7 at 3 weeks and 2.1 at 12 weeks, p<0.0001; RFA plus radiotherapy group VAS score decreased from baseline 4.5 to 2.7 at 3 weeks and 1.6 at 12 weeks, p<0.0001). However, there was no significant difference in pain scores between the 2 groups at these follow-up periods (p=0.96) (Prezzano 2019).

In a retrospective analysis of 169 patients with spinal metastases comparing combined percutaneous vertebroplasty with radiofrequency ablation, 125I seed implantation, zoledronic acid or radiotherapy, there was no statistically significant difference in VAS, ODI scores and WHO pain relief during the follow-up periods (24 hours, 1 month or 6 months, all p>0.05). Patients who had PVP plus 125I seed implantation (n=49) reported significantly decreased VAS scores from a baseline of 8.16 to 2.39 at 6-month follow up (p<0.005) and WHO pain relief was reported in only 67% patients (6 months after treatment). Patients who had PVP plus radiotherapy (n=31) reported decreased VAS scores (from baseline 7.91 to 4.63 at 6 months, p<0.005) and had better pain relief, with the highest WHO pain relief reported by 84% of patients. The PVP plus Zoledronic acid group (n=38) reported decreased VAS scores (from baseline 8.02 to 3.99 at 6 months, p<0.05) but only 66% of patients had WHO pain relief at 6 months. The PVP plus RFA

group (n=51) also reported decreased VAS scores from baseline 8 to 4.3 at 6 months, ($p<0.05$) (Lu 2019).

Progression or recurrence of vertebral metastases

In the systematic review of 9 studies, one study (Proschek 2009) reported that none of the patients had a local relapse after treatment with RFA alone or RFA in combination with vertebroplasty (Rosian 2018).

In the systematic review of 8 studies (Cazzato 2018), 3 studies reported local tumour control and progression outcomes. One study (Anchala 2004) reported stable disease in 77% of patients at an average 82 days follow-up and local progression was noted in 23% of patients at an average 82-day follow up. Another study (Greenwood 2015) reported locally stable disease in 92% (12/13) of patients at 3 months and 100% at 6-month follow up. In another study (Yang 2017), 67% of patients did not have tumour progression at 2-year follow up.

The retrospective analysis of 26 patients (with 28 spinal metastases) who had RFA alone (n=17) or RFA plus radiotherapy (n=10) reported that at a median follow-up of 8.2 months, local failure (recurrence or progression within the treated vertebral level) was noted in 47% (8/17) of metastases treated with RFA alone compared with 9% (1/11) of metastases treated with RFA plus radiotherapy ($p=0.049$). Time to local failure was 44 weeks in patients who had RFA alone but was not yet reached in those treated with RFA plus radiotherapy ($p=0.016$). There was no difference in distant failure (any disease progression outside of the treated vertebral level) between the 2 groups ($p=0.70$). Time to distant failure was not statistically significantly different between the 2 groups (RFA alone: 11.3 weeks versus RFA plus radiotherapy: 36.3 weeks, $p=0.15$) (Prezzano 2019).

Health-related quality of life (HRQoL)

In the systematic review of 9 studies, HRQoL was assessed in 2 studies using different measures (functional assessment of cancer therapy-general 7 [FACT-G7] and the functional assessment of cancer therapy quality-of-life measurement in patients with bone pain [FACT-BP] and Oswestry disability questionnaire [ODI]). In 1 prospective study of 50 patients treated with RFA plus cement augmentation (Bagla 2016), significant improvement in mean scores for disability and cancer-specific health-related quality of life from baseline to 3 months were reported (ODI improved from 52.9 to 37.0, $p<0.01$; FACT-G7 improved from mean 11 to 16.2, $p = 0.0001$; FACT-BP improved from 22.6 to 38.9, $p<0.0001$). In a study of 16 patients (Proschek 2019), 8 who had RFA alone and 8 who had RFA plus vertebroplasty, improved quality of life was reported (mean ODI scores improved from 64% at baseline to 33%, $p=0.06$ at 3 to 6 months follow-up in RFA group; and from 66% at baseline to 35%, $p=0.071$ at

15 to 36 months follow-up in RFA plus vertebroplasty group) (Rosian 2018, Cazzato 2018).

In the retrospective analysis of 169 patients, the PVP plus RFA group (n=51) reported lowest ODI scores (decreased from baseline score 71 to 36 at 6 months, $p<0.05$) whereas the PVP plus Zoledronic acid group (n=38) reported highest ODI scores (from baseline score 68 to 49 at 6 months, $p<0.05$) (Lu 2019).

Medication use

The retrospective analysis of 64 patients comparing RFA plus vertebral augmentation (n=34) with kyphoplasty alone (n=30) reported that the 2 RFA groups and the kyphoplasty-alone group had similar opioid usage during the first month after the procedure ($p=0.82$) (Jain 2020).

Survival

The retrospective analysis of 26 patients (with 28 spinal metastases) who had RFA alone (n=17) or RFA plus radiotherapy (n=10) reported that median survival in the RFA-alone group was 31.9 weeks, compared with 55.3 weeks for the RFA plus radiotherapy group ($p=0.0045$) (Prezzano 2019).

Safety summary

RFA-related adverse events

Procedure-related adverse events occurred in 3% (16/583) of patients (range 0 to 11%) in the systematic review of 9 studies. All 9 studies reported complications. Increased pain and numbness (n=6) and post-procedure radicular symptoms and pain (n=5) were the most frequently described procedure-related adverse events. No procedure-related adverse events were reported in 4 of the studies (Rosian 2018).

Immediate onset of lower extremity paralysis, diminished sensation and bowel and bladder dysfunction after the RFA procedure was reported in 1 patient. Radiology reports indicated suspicion for thermal injury to the ventral nerve roots at L1. Authors state that this might have been caused by inaccurate placement of the RFA probe or more extensive zones of thermal ablation. The patient had prolonged inpatient rehabilitation and sensation in the lower extremities was noted at 1 year follow-up, but severe neurogenic bladder and bowel dysfunction continued. Electromyography study showed severe membrane instability with no active motor units in L1, L2, L3, L4, and L5, consistent with a conus medullaris or cauda equina injury (Huntoon 2020).

Pain and numbness

Increased pain and numbness were reported in 1% (6/583) of patients in the systematic review of 9 studies with 583 patients (Rosian 2018).

Contralateral lower limb pain and numbness during the procedure was reported in 16% (4/25) of patients in a case series (Yang 2017) included in the systematic review of 8 studies. These symptoms spontaneously resolved with temperature decrease after RFA (grade 1 complication) in 2 patients and the other 2 patients needed steroids. One of them experienced heaviness in the legs 1 day after RFA without any subsequent consequence at 1-week follow-up (grade 1 to 3a complications) (Cazzato 2018).

Post-procedure radicular symptoms and pain

Post-procedure radicular symptoms and pain were reported in 1% (5/583) of patients in the systematic review of 9 studies with 583 patients (Rosian 2018).

Post-procedure radicular pain needing selective nerve block (grade 3a complication) was reported in 1 patient in a case series included in the systematic review of 8 studies (Cazzato 2018).

Postoperative radicular pain was reported in 4 patients in a study (Wallace 2015) included in the systematic review of 8 studies on combined RFA and vertebral stabilisation techniques for patients with palliative treatment of vertebral metastases (Greif 2019).

Neural damage

Transient neural damage related to the high temperature rise during RFA treatment was reported in 1 patient (Nakatsuka 2009) in a systematic review of 8 studies. This resolved 2 days after the procedure with intravenous administration of steroids (Cazzato 2018).

Vertebroplasty-related adverse events

The rate of vertebroplasty-related adverse events ranged from 4% to 73% in the systematic review of 9 studies with 583 patients (Rosian 2018). Cement extravasation after vertebroplasty was the most frequently reported adverse event, occurring in 15% (76/437) of patients. It is not clear if these events resulted in any clinically relevant episodes (Rosian 2018).

Bone cement leakage outside the vertebral body occurred in 71% (26/37) of patients at 31 levels in a case series (Gregory 2009) included in the systematic review of 8 studies (Cazzato 2018).

Extravasation after RFA followed by kyphoplasty was reported in 19 patients and anterior leaks were reported in 2 patients in a case series (Lane 2011) included in the systematic review of 8 studies on combined RFA and vertebral stabilisation techniques for patients with palliative treatment of vertebral metastases (Greif 2019). Cement leakage (in 7 and 8 patients) was reported in 2 studies (Munk 2009, Madaelil 2016) included in the same systematic review (Greif 2019).

Haematoma

Haematoma at the site of treatment was reported in 6 patients from 3 studies (Burgard 2014, Toyota 2005, Hoffman 2008) included in the systematic review of 8 studies on combined RFA and vertebral stabilisation techniques for patients with palliative treatment of vertebral metastases (Greif 2019).

Mortality

Deaths (5 and 10) were reported in 2 studies in the systematic review of 9 studies (Rosian 2018).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts listed the following anecdotal adverse events: Cement extravasation into spinal canal or vasculature with pulmonary embolism, thermal burns of spinal cord or nerve root, spinal cord or nerve compression and lung infarction. They considered that the following were theoretical adverse events: visceral damage as a result of inaccurate positioning of needle or RFA probe, adverse effects of anaesthesia and effect on pacemaker function.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to radiofrequency ablation for palliation of painful spinal metastases. The following databases were searched, covering the period from their start to 25.09.2020: 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 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. Where 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 where no clinical outcomes were reported, or where 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 painful spinal metastases.
Intervention/test	Radiofrequency ablation for palliation.
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 1,369 patients from 3 systematic reviews, 3 retrospective cohort studies and 1 case report. There is an overlap of studies included in the systematic reviews.

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 radiofrequency ablation for palliation of painful spinal metastases

Study 1 Rosian K (2018)

Study details

Study type	Systematic review
Country	Austria
Study period	Databases searched (Ovid MEDLINE, Embase, the Cochrane Library, CRD and PubMed; until December 2016. Manual search for additional records done.
Study population and number	n= 9 studies (4 prospective and 5 retrospective studies) with 583 patients with painful vertebral metastases.
Age and sex	Mean age across studies ranged from 61 to 69.6 years. Sex not reported.
Patient selection criteria	Inclusion criteria: patients with solitary fracture-related vertebral metastases unresponsive to previous curative or symptomatic treatments; RFA with or without vertebroplasty or other add-on therapies (e.g., radiation); randomised controlled trials, nonrandomised controlled trials, prospective and retrospective case series (with more than 30 patients); published in English or German. Exclusion criteria: multiple publications including sub-group analysis published by the same investigator in a previous article were excluded from the final analysis.
Technique	Patients were treated with radiofrequency ablation (RFA) and 72% (437/583) had an additional vertebroplasty treatment. Vertebroplasty was performed if there was a risk of fracture and instability of the bone structure due to tumour removal. Variety of ablation systems were used in the studies; most commonly used were the STAR® Tumor Ablation System (temperature used for ablation 50degrees) and the CAVITY SpineWand (cold energy temperature 42 degrees)
Follow-up	mean follow-up periods varied across studies (range of 24–48 hours [1 study], 2-4 weeks [2 studies] to 60 months)
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Loss to follow-up ranged from 0 to 61%. One study of patients with a severe progression of cancer and a long follow-up period reported high losses to follow-up.
Study design issues: systematic review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Sample size was low in included studies and study characteristics were heterogenous in most. The review methodology was based on the HTA Core Model and

data were analysed according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE). The strength of evidence was found to be “very low” for safety outcomes and could not be assessed for efficacy outcomes due to lack of comparative studies. Data extraction, study quality and risk of bias was done by 2 reviewers using the Institute of Health Economics (IHE) risk of bias checklist for case series. Studies were categorised as having a moderate (n=4) to high risk of bias (n=5). Any disagreements were resolved by a third researcher.

Study population issues: overlap of patients in 2 studies. Adjuvant therapies were given in 2 studies.
Other issues: authors state that comparison of the effectiveness of RFA alone to RFA in combination with vertebroplasty was not done in this review due to low number of patients.

There is an overlap of studies between the 3 systematic reviews (Rosian 2018, Cazzato 2018, Greif 2019).

Key efficacy findings

Number of patients analysed: 583

Pain reduction (n=4 studies)

Assessed using different instruments: Visual Analog Scale [VAS] and Numeric pain rating scale [NPRS]). Higher scores represented worst pain.

Study	Measures	Baseline	1 month	3 months
Bagla 2016 (n=50)	NPRS (0-100)	Mean score 5.9	2.6 (p<0.0001) (n=40)	2.1 (p<0.0001) (n=33)
Nakatsuka 2009 (n=10)	VAS (0-10)	Mean score 7.5 ± 2.7	**1 week** 2.7 ± 2 (P=.00005)*	
Proschek 2009 (n=16)	VAS (0-10)	RFA group Mean score 7.6 RFA+ cement Mean score 7.9	**After treatment** RFA group [n=8] 5.5 (p=0.018) RFA+ cement (n=8) 5.0	**15-36 months** RFA group [n=8] 4.0 (p<0.008) RFA+ cement (n=8) 3.5 (p<0.005)
Georgy 2007 (n=15)	VAS (0–10-point scale)	Pain scores range 6 to 10	Range 0-5	Pain relief in 87% (13/15) **at 2-4 weeks**

*in all patients who had RFA alone (n=4) or RFA+ cement (n=6). Local pain relief lasted in 90% (9/10) of patients during survival period.

Progression or recurrence of vertebral metastases

One study (Proschek 2009) reported that none of the patients had a local relapse after treatment with RFA or RFA in combination with vertebroplasty.

Health related quality of life (HRQoL, n=2 studies)
Assessed across studies using different measures: Functional Assessment of Cancer Therapy-General 7 (FACT-G7) and the Functional Assessment of Cancer Therapy Quality-of Life Measurement in Patients with Bone Pain (FACT-BP) and Oswestry Disability Questionnaire (ODI)

Studies	**HRQoL measures**	**Baseline**	**1 month**	**3 months**
Bagla 2016 (n=50)	FACT-G7 (0-28)	Mean score 11	15.8 (p<0.0001)	16.2 (p<0.0001)
	FACT-BP (0-60)	Mean score 22.6	37.3 (p<0.0001)	38.9 (p<0.0001)
	Modified Oswestry Disability Index (0-100)	Mean score 52.9%	40% (p<0.01)	37% (p<0.01)
Proschek 2009 (n=16)	Oswestry Disability Questionnaire score	**Baseline**	**3-6 months**	**15-36 months**
		RFA group 64% (range 38-84%) RFA plus vertebroplasty group 66% points (range 39-86%)	33%, range 23-38%; p=0.06 (RFA group)	35%, range 26-38%; p=0.071 (RFA plus vertebroplasty group)

Key safety findings

	% (n)
Major complications (procedure related)	0
Overall complications	30.2 (78/583) Ranged from 4.3 to 40%
Adverse events (procedure-related or non-procedure-related)	18 (105/583) ranged from 5.6% to 11.1% in each study.
Procedure related adverse events	2.74 (16/583) range 0 to 11%
Non-procedure related adverse events	15.2 (89/583) range 4.3 to 73%
Increased pain and numbness	1 (6/583)
Post-procedure radicular symptoms and pain	0.8 (5/583)
Rate of adverse events not RFA-related (but vertebroplasty-related)	ranged from 4.3% to 73.0%
Cement extravasation after vertebroplasty	15.3% (67/437)
Mortality (reported in 2 studies)	5 to 10 deaths

Procedure-related adverse events were not reported in 4 studies. 1 study did not report any adverse events.

Study 2 Cazzato (2018)

Study details

Study type	Systematic review
Country	France
Study period	Databases searched (Ovid MEDLINE, Embase, the Cochrane CENTRAL and PubMed; until March 2017. conference abstracts were also searched.
Study population and number	n= 8 studies (4 prospective and 4 retrospective studies) with 261 patients with painful spinal metastases (340 vertebral lesions) Lesions were located mainly in lumbar or thoracic area. Metastases origin from breast, lung, and renal cancers. previous treatments (n=4) chemotherapy, radiation therapy, surgery, or a combination.
Age and sex	Mean age across studies ranged from 59 to 69.6 years. Sex not reported.
Patient selection criteria	Inclusion criteria: randomised controlled or non-randomised studies with a prospective or retrospective design; adults with spinal metastasis; treated with RFA alone or in combination/ comparison with other treatments; studies reporting patients' pain before and after RFA; and English-language studies. Exclusion criteria: multiple publications were excluded.
Technique	Patients were treated with radiofrequency ablation (RFA) and 239 had cement augmentation (during RFA in 40-60%, or in 95.8% of treated vertebrae in the same treatment session). 4 patients underwent cement augmentation after a few days or months. Variety of ablation systems were used in the studies (STAR Tumor Ablation System, the CAVITY SpineWand, RITA, Celon power cool tip RF) Lumbar ones were the most commonly treated. Mean ablation time ranged between 6 and 9.75 min. across four studies. Ablation zone ranged from 1-8cm. Bipolar RFA was applied in 4 out of the 8 studies.
Follow-up	mean follow-up periods varied across studies (ranged from 2-4 weeks [2 studies] to mean 20 months)
Conflict of interest/source of funding	Authors are proctors for Medtronic and Galil Medical.

Analysis

Study design issues: systematic review was done following the guidelines of the Cochrane Collaboration for systematic reviews of interventions. Studies were small case series with different treatment strategies. 2 reviewers selected studies and extracted data; any disagreements were resolved by consensus. Study quality and risk of bias was not assessed due to heterogeneity in study designs and authors also thought there was no single suitable critical appraisal tool for all studies.

Study population issues: sample size ranged between 10 and 92 patients across studies. Overlap of patients in 2 studies.

Other issues: There is an overlap of studies between the 3 systematic reviews (Rosian 2018, Cazzato 2018, Grief 2019).

Key efficacy findings

Number of patients analysed: 261

Pain assessment

Assessed using different instruments: Visual Analog Scale [VAS] and Numeric pain rating scale [NPRS]). Higher scores represented worst pain.

Study	Intervention	Pain scale	Baseline	Post-operative	Mean difference (P value)	Mean pain reduction %	Pain relief %
Bagla 2016 (n=50)	RFA	NRS (0-100)	5.9	3.7 (discharge)	2.2 (<0.0001)	37	-
				2.6 (1 month, n=40)	3.3 (<0.0001)	56	-
				2.1 (3 months, n=34)	3.8 (<0.0001)	64	-
Gronemeyer 2002 (n=10)	RFA	VAS (0-10)	5.9	2.6 (mean 5.8 months	3.3	56	-
Nakatsuka 2009 (n=10)	RFA (all patients)	VAS	7.5	2.7 (1 week)	4.8 (0.00005)	64	-
	RFA alone (n=4)		4.3	1.7 (1 week)	2.6 (0.0004)	60	
	RFA + cement augmentation (n=6)		6.6	1.7 (1 week)	4.9 (0.003)	74	-
Proschek 2009 (n=16)	RFA alone (n=8)	VAS	7.9	4 (15-36 months)	3.9 (0.008)	49	-
	RFA +cement augmentation (n=8)		7.6	3.5 (15-36 months	4 (0.005)	52	-
Greenwood 2015 (n=21)	RFA	NRS	8	2.9 (4 weeks)	5.1 (<0.0003)	63	-

Anchala 2004 (n=92)	RFA	VAS	7.5	2.2 (1 month, n=83)	5.26 (<0.0001)	70	-
				1.7 (6 months, n=9)	5.7 (0.009)	76	-
Georgy 2009 (n=37)	RFA	VAS	8	4 (2-4 weeks)	4	50	89.5
Yang 2017 (n=25)	RFA	VAS					100 Mean 7.8 months

Pain medication

Pain medication intake following RFA was reported by two studies. In 1 study (Greenwood 2015) reported that 62% of patients reduced their intake,19% increased intake and 19% kept it stable compared with baseline. Another study (Anchala 2004) reported that 54% of patients reduced their intake,16% increased it and 30% kept it stable at the 4-week follow-up.

Local tumour control (n=3 studies)

	Stable disease	**Progression**
Anchala 2004	76.9% (70/92) at average 92 days after RFA.	23.1% (22/92) at average 82 days
Greenwood 2015	92.3 (12/13) at 3 months 100% (at 6 months)	-
Yang 2017	66.67% (at 2 years)	-

Health related quality of life (HRQoL, n=2 studies)

Assessed across studies using different measures: Functional Assessment of Cancer Therapy-General 7 (FACT-G7) and the Functional Assessment of Cancer Therapy Quality-of Life Measurement in Patients with Bone Pain (FACT-BP) and Oswestry Disability Questionnaire (ODI)

Studies	**HRQoL measures**	**Baseline**	**1 month**	**3 months**
Bagla 2016 (n=50)	FACT-G7 (0-28)	Mean score 11	15.8 (p<0.0001)	16.2 (p<0.0001)
	FACT-BP (0-60)	Mean score 22.6	37.3 (p<0.0001)	38.9 (p<0.0001)
	Modified Oswestry Disability Index (0-100)	Mean score 52.9%	40% (p<0.01)	37% (p<0.01)
		Baseline	**3-6 months**	**15-36 months**

Proschek 2009 (n=16)	Oswestry Disability Questionnaire score	RFA group 64% (range 38-84%) RFA plus vertebroplasty group 66% points (range 39-86%)	33%, range 23-38%; p=0.06 (RFA group)	35%, range 26-38%; p=0.071 (in both RFA alone and RFA plus vertebroplasty groups)

Key safety findings

	% (n)
Grade IV-V complications	0
Transient neural damage (grade II) related to high temperature rise during RFA (resolved 2 days after the procedure with intravenous administration of steroids).	n=1 (Nakatsuka 2009)
Contralateral lower limb pain and numbness during RFA -grade I (2 spontaneously resolved with temperature decrease and 2 needed steroids, but one developed heaviness in legs 1 day after treatment which resolved at 1 week (grade II-IIIa)	16% (4/25) (Yang 2017)
Bone cement leakage outside the vertebral body (Gregory 2009)	70.5% (26/37) 31 levels
Radicular pain due to cement leakage needing selective nerve block (grade IIIa)	(1/26)

Study 3 Greif (2019)

Study details

Study type	Systematic review
Country	USA
Study period	PubMed was searched and bibliographies of selected articles were examined for additional studies. Search dates not reported.
Study population and number	n= 8 retrospective studies with 265 patients with palliative treatment of vertebral metastasis. Combined tumour treatment with vertebral stabilisation techniques 1. RFA followed by percutaneous kyphoplasty [PKP] (n=4 studies, 110 patients, 142 vertebrae), 2. RFA followed by vertebroplasty (n=4 studies, 155 patients, 172 vertebrae)
Age and sex	not reported.
Patient selection criteria	Inclusion criteria: randomised controlled trials and retrospective studies in English using a multidisciplinary approach of tumour treatment and vertebral stabilisation. Exclusion criteria: nonhuman studies, case reports, narrative reviews, clinical reports without technical outcomes, and studies involving patients with osteoporotic, traumatic, or metastatic vertebral compression fractures were excluded.
Technique	RFA followed by PKP (n=4 studies, 110 patients, 142 vertebrae) Mean RFA procedure time ranged from 9 to 47 minutes. Mean ablation temperature 95˚C Mean cement used ranged from 6.1 to 7.9ml. RFA followed by vertebroplasty (n=4 studies, 155 patients, 172 vertebrae) Mean RFA time ranged from 4.1 to 8.6 minutes. Mean ablation temperature ranged 71.8°C to 95°C. Mean cement used ranged from 2.9 to 9.1 ml
Follow-up	mean follow-up periods varied across studies (3 days to 15 months).
Conflict of interest/source of funding	No conflicts of interest.

Analysis

Follow-up issues: majority of the studies had a limited follow-up.
Study design issues: systematic review was done PRISMA (preferred reporting Items for systematic reviews and meta-analyses) guidelines for retrospective studies. There is a lack of standard protocol, outcomes assessed among studies within combined treatments, including different ranges of follow-up times. Quality assessment of studies was not done.

Other issues: outcomes from studies related to radiotherapy combination techniques: radiotherapy followed by PKP (n =1), radiotherapy followed by vertebroplasty (n = 3), PKP followed by radiotherapy (n = 4), and vertebroplasty followed by radiotherapy (n =2) were not reported in this overview as it is outside the remit. There is an overlap of studies between the 3 systematic reviews (Rosian 2018, Cazzato 2018, Greif 2019).

Key efficacy findings

Number of patients analysed: 265

Pain assessment

RFA followed by percutaneous kyphoplasty (PKP) (4 studies)

Study	Preoperative pain	Postoperative pain	Last follow-up	Change in VAS
Zheng 2014 (n=26)	7.69 ±1.12	6.62 ±1.02	2.96± 0.92 (6 months)	4.73
Lane 2011 (n=36)	7.2±1.69	NM	3.4±1.6 (1 week)	3.8
Munk 2009 (n=19)	7.9±1	NM	3.82±3.82 (6 weeks)	4.08
Burgard 2014 (n=29)	NM	NM	NM	NM

RFA followed by vertebroplasty (4 studies)

Study	Preoperative pain	Postoperative pain	Last follow-up	Change in VAS
Wallace 2015 (n=105)	8.0	3.9	2.9 (4 weeks)	5.1
Toyota 2005 (n=17)	6.3	NM	2.4 (3 days)	3.9
Madaelil 2016 (n=11)	8	NM	3 (1 month)	5
Hoffman 2008 (n=22)	8.5	5.5	3.5 (15 months)	5

Key safety findings

RFA followed by percutaneous kyphoplasty (PKP) (4 studies)

	n
Extravasation	19 (Lane 2011)
Anterior leaks	2 (Lane 2011)
Cement leakage	7 (Munk 2009)
Local hematoma	2 (Burgard 2014)
Pain	2 (Burgard 2014)
Oxygen saturation decrease	1 (Burgard 2014)
Increased paresis	1 (Burgard 2014)

RFA followed by vertebroplasty (4 studies)

	N
Postoperative radicular pain	4 (Wallace 2015)
Hematoma	4 (2 in Toyota 2005, 2 in Hoffman 2008)
Cement leaks	8 (Madaelil 216)

Study 4 Jain S (2020)

Study details

Study type	Retrospective cohort study
Country	USA (one centre)
Recruitment period	2011-2017
Study population and number	n= 64 patients with painful spinal metastases RFA (Spine star) with vertebral augmentation (n=22) RFA (OsteoCool) with vertebral augmentation (n=12) Kyphoplasty alone (n=30)
Age and sex	Mean age 62.6 years; male 56% (36/64)
Patient selection criteria	Inclusion criteria: patients greater than 18 years old having metastatic vertebral compression fracture involving the thoracolumbar spine. Exclusion criteria consisted of non-pathologic osteoporotic compression fractures, metastasis in cervical spine, or previous radiofrequency ablation (RFA) treatment. patients with coagulopathy greater than 1.4 and platelet count less than 50,000, or an active infection either systemically or locally.
Technique	Patients were treated with radiofrequency ablation (RFA) using 2 ablation systems (STAR Tumor Ablation System, the CAVITY SpineWand). RFA was performed at 70 °C for 5–15 min with subsequent cement injection. Kyphoplasty alone was done in 30 cases.
Follow-up	2 weeks
Conflict of interest/source of funding	Authors declare that they have no conflict of interest.

Analysis

Follow-up issues: very short follow-up period limited to 2 weeks.
Study design issues: small retrospective analysis of medical records, pain scores (using VAS score) immediately and between 7-14 days and opioid use after 1 month were assessed and compared between RFA systems and kyphoplasty alone.

Study population issues: The demographic characteristics between the treatment arms were similar. Mean age of diagnosis 62 years, diseases leading to vertebral metastases were multiple myeloma (20.3%) and lung adenocarcinoma (12.5%). The most common previous treatment modality was chemotherapy and radiotherapy.

Key efficacy findings

Number of patients analysed: 64 (RFA systems 34 versus kyphoplasty alone 30)

Pain scores (assessed on a VAS 0 to 10) and opioid use

	RFA SpineStar	RFA OsteoCool	Kyphoplasty alone
Pre-operative pain score	6.9	6	6.3
Post-operative pain score	2.7	1.7	2.3
Between 7-14 days pain score	3.3	3.28	3.69
Opioid use	50% (11/22)	41.7 (5/12)	30% (9/30)

Difference of square means analysis between kyphoplasty and the two RFA systems (SpineStar and OsteoCool)

	T value (SE)	P value
Postoperative day 0		
Kyphoplasty versus OsteoCool	0.49 (1.08)	0.99
Kyphoplasty versus SpineStar	1.63 (0.49)	0.79
OsteoCool versus SpineStar	0.86 (1.12)	0.99
Day 1-14		
Kyphoplasty versus OsteoCool	0.17 (1.12)	1
Kyphoplasty versus SpineStar	1.76 (1.02)	0.72
OsteoCool versus SpineStar	1.67 (1.12)	0.76
30 days and above		
Kyphoplasty versus OsteoCool	1.07 (1.33)	0.98
Kyphoplasty versus SpineStar	2.76 (1.17)	0.14
OsteoCool versus SpineStar	1.23 (1.48)	0.95

Chi-squared analysis reveals no statistical difference in opioid usage among the 3 groups (p = 0.82).

Study 5 Prezzano KM (2019)

Study details

Study type	Retrospective cohort study
Country	USA (one centre)
Recruitment period	2016-2017
Study population and number	n= 26 patients with 28 painful spinal metastases (in thoracic/lumbar spine) treated with RFA alone (n=17 [17 lesions]) versus combined RFA with radiation therapy (RT, n=10 [11 lesions])
Age and sex	Median age 63 years [no significant difference between 2 groups p=0.57); male
Patient selection criteria	Inclusion criteria: all patients who underwent RFA for painful spinal metastases, regardless of metastatic disease burden. Exclusion criteria: patients treated with RT alone.
Technique	RFA (n=11 lesions) OsteoCool ablation device was used at more than 60 C. Vertebral augmentation was performed after RFA using balloon-assisted techniques with the Kyphon system. Polymethyl methacrylate was injected. At a median of 11 months post-RFA, 3 lesions were treated with radiotherapy for local progression. Radiotherapy (n=11 lesions) majority of the patients were treated using 3-dimensional conformal radiotherapy (3D-CRT, with a median dose of 30 Gy in 3 Gy daily fractions). Some were treated using volumetric-arc therapy, or stereotactic body radiotherapy (SBRT) (in 2 cases at 28 days post-RFA, both having 35 Gy in 5 fractions). 10 lesions were treated at a median of 28 days and 1 lesion was treated 1 day prior to RFA.
Follow-up	12 weeks
Conflict of interest/source of funding	Authors declare that they have no conflict of interest.

Analysis

Study design issues: small retrospective analysis. Patients were treated with varying treatment schedules (the dose, radiotherapy techniques used, and the treatment timing (i.e., during or after RFA). Some patients were treated with concurrent systemic therapy. Local failure, distant failure, and overall survival were compared and Kaplan-Meier statistics were calculated.

Study population issues: There was uneven allocation of primary tumour histologies between the 2 groups (more patients with lung primaries were treated with RFA alone and more patients with breast primaries were treated with combination RFA plus RT). The majority of patients had narcotic analgesics (of varying doses) at initial treatment and were similar between groups (p=0.70).

Key efficacy findings

Number of patients analysed: 27 (28 lesions)

IP overview: Radiofrequency ablation for palliation of painful spinal metastases

Pain scores (assessed on a VAS 0 to 10)

	Baseline (mean±SD)	**3 weeks** (mean±SD)	**12 weeks** (mean±SD)
RFA	4.2	2.7±2.9 (p<0.0001)	2.1
RFA plus radiotherapy	4.5±3.07	2.7±2.9 (p<0.0001	1.6±2.6 (p<0.0001)

There is no significant difference in pain scores between groups (p=0.96).

Local failure, distant failure, and survival (median follow-up 8.2 months) (Kaplan-Meier statistics)

	RFA alone	**RFA plus RT**	**P value**
Local failure^ %	47 (8/17)	9 (1/11)*	0.049
Time to local failure (weeks)	44	Not reached	0.016
Distant failure	NR	NR	0.70
Time to distant failure (weeks)	11.3	36.3	0.15
Survival (median, weeks)	31.9	55.3	0.0045

* in a patient treated with 30 Gy in 10 fractions, 6 days after RFA.
Of the 3 lesions treated with RT for local progression after RFA alone, there was no local failure.
^ All local failure occurred in the setting of prior or simultaneous distant failure.

Study 6 Lu CW (2019)

Study details

Study type	Retrospective cohort study
Country	China
Recruitment period	2010-2013
Study population and number	n= 169 patients with painful spinal metastases (in thoracic/lumbar spine) treated with Group A: percutaneous vertebroplasty (PVP) combined with ^{125}I seed implantation (n=49) Group B: PVP combined with RFA (n=51) Group C PVP combined with Zoledronic acid (n=38) and Group D: PVP combined with radiotherapy (n=31).
Age and sex	Median age 56.9 years. (95/169) male
Patient selection criteria	not reported
Technique	Group A: underwent PVP combined with ^{125}I seed implantation (n=49) Based on patient condition the dose and distribution of ^{125}I seed implantation was done and further evaluated using the dosimetry protocol. Then, bone cement was injected into the patient's diseased vertebra. Group B: underwent PVP combined with RFA (n=51) radiofrequency ablation (RFA) was performed and bone cement in a semi-solidified state was injected. Group C: underwent PVP combined with Zoledronic acid (n=38) PVP procedure was under local anaesthesia, then bone cement was slowly injected into the vertebral body until reaching the edge. The patients were then treated with intravenous drip of 4 mg Zoledronic acid for 15 minutes and once every 3–4 weeks. Group D: underwent PVP combined with radiotherapy (n=31) PVP was done under local anaesthesia and then bone cement was separately injected into the thoracic and lumbar region, respectively. Three or 4 days after PVP, patients had radiotherapy, with the diseased vertebra as the central point of radiotherapy, 10 times in 2 weeks and total radiation dose of 30 Gy. All patients were supervised for 24 hours after operation. CT was performed to investigate the distribution of bone cement in the diseased vertebra, and antibiotics were given to prevent postoperative infection.
Follow-up	6 months
Conflict of interest/source of funding	Authors state that they have no conflict of interest to declare.

Analysis

Follow-up issues: complete clinical follow-up.

Study design issues: retrospective analysis was done, all patients diagnosed with spinal metastases were randomly assigned to 4 groups to have 4 different combinations treatments. Pain and function scores were assessed using measures such as VAS (score 0-10, higher values representing worse scores) , ODI (score of 0-10) , and WHO pain relief (scored as complete, partial, mild or pain relief). These were collected through telephone after 24 hours, 1 month, and at 6 months follow-up.

Study population issues: All patients underwent routine examinations before operation.

Key efficacy findings

Number of patients analysed: 169

Pain and function scores

	VAS	ODI	WHO pain relief
PVP combined with 125 I seed implantation			
Baseline	8.16±1.06	68.19±0.89	-
24 hours	3.91±1.01^	49.92±1.01^*	73.47%+
1 month	3.15±1.16^	48.26±0.99^	71.43%
6 months	2.39±0.89^	47.99±0.89^	67.35%
PVP combined with RFA			
Baseline	8.07±0.79	71.04±0.83	-
24 hours	4.61±0.75^#	37.03±0.76^	76.47%+
1 month	4.38±0.61^	36.84±0.91^	74.51%
6 months	4.34±0.31^	36.61±1.04^	72.55%
PVP combined with zoledronic acid			
Baseline	8.02±0.93	67.85±0.88	-
24 hours	4.43±1.19^#	49.21±0.87^*	73.68%+
1 month	4.27±0.76^	48.94±0.44^	71.05%
6 months	3.99±0.41^	48.87±0.54^	65.79%
PVP combined with radiotherapy			
Baseline	7.91±0.92	70.22±0.92	-
24 hours	4.72±0.21^#	41.01±0.37^*	90.32%
1 month	4.66±0.31^	40.83±0.43^	87.10%
6 months	4.63±0.10^	40.74±0.54^	83.87%

^P<0.05 compared with baseline values.
#P<0.05 when the VAS of 4 different combination treatments was compared.

+P<0.05 when the WHO pain relief of 4 different combination treatments was compared.

*P<0.05 when the ODI of 4 different combination treatments was compared.

Safety

Adverse events

PVP combined with RFA

Rate of bone cement extravasation was 16% (8/51). 2 cases into paravertebral soft tissues, 3 into paravertebral veins, 2 into spinal epidural, and 1 into upper intervertebral disc through bone breaks.

Study 7 Huntoon K (2020)

Study details

Study type	Case report
Country	USA
Recruitment period	Not reported
Study population and number	N=1 patient with spinal metastases.
Age	61-year-old woman
Patient selection criteria	
Technique	RFA and kyphoplasty using polymethylmethacrylate for spinal metastases using a bipolar cooled RFA system to treat lesions at L1 and L3.
Follow-up	1 year
Conflict of interest/source of funding	Not reported

Key efficacy findings

- Number of patients analysed: 1

Key safety findings

Immediate onset of lower extremity paralysis, diminished sensation and bowel and bladder dysfunction after the procedure was reported. Patient was unable to move legs. No evidence of new fractures or evidence of polymethylmethacrylate extravasation into the spinal canal or spine foramina was noted. Imaging findings did not reveal any pathologic changes in the spinal cord at any level (no focal stenosis or spinal cord compression/injury). Radiology reports indicated suspicion for thermal injury to the ventral nerve roots at L1. Authors state that this might have occurred due to inaccurate placement of the RFA probe or more extensive zones of thermal ablation.
She underwent a prolonged inpatient rehabilitation stay and was discharged with follow up. At 4 months follow-up, neurological examination revealed a power strength of 4 of 5 plantar flexion bilaterally, but otherwise 0 of 5 in her legs. At 1 year follow-up, she has sensation in the lower extremities, but continued to have severe neurogenic bladder and bowel dysfunction. electromyography study showed severe membrane instability with no active motor units in L1, L2, L3, L4, and L5, consistent with a conus medullaris/cauda equina injury.

Validity and generalisability of the studies

- There are no RCTs comparing the effect of RFA alone with RFA in combination with vertebroplasty (or other treatments) for painful vertebral metastases. Evidence included in systematic reviews was mainly from small prospective and retrospective studies.
- RFA systems with different ablation methods (bipolar RF electrodes) and temperatures, protocols were used in studies.
- The majority of the patients (40 –100%) or treated vertebrae (94 to 96%) had vertebral augmentation following RFA making it difficult to differentiate the benefits of RFA alone.
- Most of the outcomes were variable patient reported outcomes and are subject to high risk of bias.
- Follow-up periods varied across studies and was less than 6 months in many studies.
- Limited studies show that RFA is likely to provide effective short to mid-term (1 week to 6 months) pain relief. There is a lack of long-term safety and efficacy data.

Existing assessments of this procedure

A recently published guideline on percutaneous vertebral augmentation recommends treatment with vertebroplasty following different tumour treatments (like RFA) in patients with painful vertebrae due to metastases to achieve pain relief and the consolidation of vertebra (Tsoumakidou G 2017).

NICE guideline on ‘metastatic spinal cord compression in adults: risk assessment, diagnosis and management’ in section 1.5.1.8 recommends to ‘consider vertebroplasty or kyphoplasty for patients who have vertebral metastases and no evidence of metastatic spinal cord compression or spinal instability if they have: mechanical pain resistant to conventional analgesia, or vertebral body collapse’ (NICE clinical guideline CG75, 2008).

Related NICE guidance

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

Interventional procedures

- Percutaneous insertion of craniocaudal expandable implants for vertebral compression fracture. Interventional procedures guidance IPG568 (November 2016) Available from https://www.nice.org.uk/guidance/ipg568
- Percutaneous cementoplasty for palliative treatment of bony malignancies. Interventional procedures guidance IPG179 (June 2006) Available from https://www.nice.org.uk/guidance/ipg179
- Balloon kyphoplasty for vertebral compression fractures. Interventional procedures guidance IPG166 (April 2006) Available from https://www.nice.org.uk/guidance/ipg166
- Percutaneous vertebroplasty. Interventional procedures guidance IPG12 (September 2003) Available from https://www.nice.org.uk/guidance/ipg12

Technology appraisals

- Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours. NICE technology appraisal TA265 (October 2012). Available from http://www.nice.org.uk/guidance/TA265XXX

NICE guidelines

- Metastatic spinal cord compression in adults: risk assessment, diagnosis, and management. Clinical guideline CG75 (November 2008). Available from http://www.nice.org.uk/guidance/CG75

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, where comments are considered voluminous, or publication would be unlawful or inappropriate. 2

Professional expert questionnaires for radiofrequency ablation for palliation of painful spinal metastases were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

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

Issues for consideration by IPAC

NCT02419703 The STAR™ Tumor Ablation Registry

A prospective observational study of 65 patients with painful spinal metastases in the thoracolumbar spine (T1-L5) following targeted radiofrequency ablation (t-RFA) treatment with the STAR™ Tumor Ablation System, follow up 12 months, outcome measures are pain relief and quality of life improvement; location USA, study completion date March 2017; status: study was terminated due to difficulty enrolling.

References

1. Rosian K, Hawlik K and Piso B (2018). Efficacy assessment of radiofrequency ablation as a palliative pain treatment in patients with painful metastatic spinal lesions: A systematic review. Pain Physician 2018; 21: E467-E476.
2. Cazzato RL, Garnon J, Caudrelier J et al (2018). Percutaneous radiofrequency ablation of painful spinal metastasis: a systematic literature assessment of analgesia and safety. International Journal of Hyperthermia. 34:8, 1272-1281.
3. Greif DN, Ghasem A, Butler A et al (2019). Multidisciplinary management of spinal metastasis and vertebral instability: a systematic review. World neurosurgery, Vol 128, e944-e955.
4. Jain S, Kinch L, Rana M et al (2020). Comparison of post-operative pain scores and opioid use between kyphoplasty and radiofrequency ablation (RFA) systems combined with cement augmentation. Skeletal Radiology (2020) 49:1789–1794
5. Prezzano KM, Prasad D, Hermann GM et al (2019). Radiofrequency ablation and radiation therapy improve local control in spinal metastases compared to radiofrequency ablation alone. American Journal of Hospice & Palliative Medicine, Vol. 36(5) 417-422
6. Lu WC, Shao J, Wu YG et al (2019). Which combination treatment Is better for spinal metastasis: percutaneous vertebroplasty with radiofrequency ablation, 125I Seed, Zoledronic Acid, or Radiotherapy? American journal of therapeutics. 26 (1), E38-E44.
7. Huntoon K, Mostafa E, Moheyldin A et al (2020). Lower extremity paralysis after radiofrequency ablation of vertebral metastases. World neurosurgery. 133: 178-184.
8. Tsoumakidou G, Too CW, Koch G et al (2017). CIRSE guidelines on percutaneous vertebral augmentation. Cardiovasc Intervent Radiol; 40:331-342.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	25/09/2020	Issue 9 of 12, September 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	25/09/2020	Issue 9 of 12, September 2020
International HTA database	25/09/2020	-
MEDLINE (Ovid)	25/09/2020	1946 to September 21, 2020
MEDLINE In-Process (Ovid) & MEDLINE ePubs ahead of print (Ovid)	25/09/2020	1946 to September 21, 2020
EMBASE (Ovid)	25/09/2020	1946 to September 21, 2020
BLIC	25/09/2020	n/a

Trial sources searched December 2019

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

Websites searched December 2019

- 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.

Number	Search term
1	Catheter Ablation/
2	(Catheter* adj4 Ablat*).tw.
3	((needle* or electrode* or heat*) adj4 ablat*).tw.
4	exp Radiofrequency Ablation/
5	(Radiofrequen* adj4 (ablat* or therap* or treatment* or intervent* or program* or procedure*)).tw.
6	(Radio-frequen* adj4 (ablat* or therap* or treatment* or intervent* or program* or procedure*)).tw.
7	(rf adj4 ablat*).tw.
8	RFA.tw.
9	target* radiofreq* ablat*.tw.
10	t-rfa.tw.
11	(radio* adj4 frequen* adj4 ablat*).tw.
12	or/1-11
13	exp Spinal Neoplasms/
14	((spine* or spina* or vertebra* or lumbar*) adj4 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or dysplasia* or disease* or lesion* or metasta*)).tw.
15	exp Spinal Cord Neoplasms/
16	((spine* or spina* or vertebra* or lumbar*) adj4 cord* adj4 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or dysplasia* or disease* or lesion* or metasta*)).tw.
17	(thoracolumb* adj4 (spine* or spina* or vertebra* or lumbar*)).tw.
18	osseous metastatic disease.tw.
19	Bone Neoplasms/
20	((bone* or osseous*) adj4 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or dysplasia* or disease* or lesion* or metasta* or osteoma*)).tw.
21	(vertebral adj4 tumor*).tw.

22	(Radio adj4 resistan* adj4 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or dysplasia* or disease* or lesion* or metasta* or osteoma*)).tw.
23	or/13-22
24	exp Neoplasm Metastasis/
25	metastas*.tw.
26	(secondar* adj4 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or dysplasis* or disease* or lesion* or metasta*)).tw.
27	or/24-26
28	23 and 27
29	CAVITY spineWand.tw.
30	cool-tip RF ablation system.tw.
31	osteoCool RF spinal tumor ablation.tw.
32	STAR tumor ablation.tw.
33	Radioion* system.tw.
34	RITA medical system.tw.
35	celonpro power system.tw.
36	celon* power system.tw.
37	or/29-36
38	12 and 28
39	37 or 38
40	Animals/ not Humans/
41	39 not 40

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
Anchala PR, Irving WD, Hillen TJ et al (2014). Treatment of metastatic spinal lesions with a navigational bipolar radiofrequency ablation device: A multicenter retrospective study. Pain Physician; 17:317-327.	Retrospective study N=92 patients with 128 spinal metastatic osseous lesions radiofrequency ablation (RFA) STAR tumour ablation system used (96 procedures were done). Cement augmentation was done when needed. Follow-up 6 months	RFA was successful in all. Significant (p< 0.01) decreases in the VAS scores noted at follow-up. 54% patients experienced a decrease and 30% had no change in their pain medications.	Study included in systematic review added to table 2.
Bagla S, Sayed D, Smirniotopoulos J et al (2016). Multicenter prospective clinical series evaluating radiofrequency ablation in the treatment of painful spine metastases. Cardiovasc Intervent Radiol; 39:1289-1297.	Prospective study N=50 patients with vertebral body metastases. Radiofrequency ablation (RFA) STAR tumour ablation system used (69 treatments). Cement augmentation was done in 96%. Follow-up 3 months	Significant improvement in scores for pain, disability, and cancer-specific health-related quality of life from baseline was seen. NRPS improved from 5.9 to 2.1 (p<0.0001). ODI improved from 52.9 to 37.0 (p<0.08). FACT-G7 improved from 10.9 to 16.2 (p	Study included in systematic review added to table 2.

		= 0.0001). FACT-BP improved from 22.6 to 38.9 (p<0.001). No complications related to the procedure were reported.	
Dupuy De, Hong R, Oliver B et al (2000). Radiofrequency ablation of spinal tumors: temperature distribution in the spinal canal. Technical Innovation. AJR:175, 1263-66.	Review	This innovative new approach provides not only pain palliation but also local tumour control, thus avoiding additional therapy such as radiation or surgery.	Review
Dabravolski D, Lahm A, Eser J, Merk H (2015). Tumours and metastases of the spine: Cavity/coblation surgery and vertebroplasty/kyphoplasty. Orthopade; 44:806-819.	Retrospective study N=250 patients with spinal tumours or metastases Radiofrequency ablation done with CAVITY SpineWand followed by kyphoplasty. Follow-up 60 months	Significant pain reduction, satisfaction, early mobilization, and improvement in quality of life were demonstrated in all patients. Lower complication rates reported.	Study included in systematic review added to table 2.
Gazis AN, Beuing O, Franke J et al (2014). Bipolar radiofrequency ablation of spinal tumors: Predictability, safety, and outcome. Spine J; 14:604-608.	Prospective study N=36 patients with advanced spine tumor (39 lesions) had radiofrequency ablation. CelonLab Power and Celon Aquaflow III Follow-up not reported.	The extent of the ablation zones was predictable to the millimetre because it did not cross planned dorsal and ventral boundaries. No complications were observed.	Study included in systematic review added to table 2.
Gazis A, Beuing O, Jollenbeck B et al (2012). Bipolar radiofrequency ablation of spinal neoplasms in late stage cancer disease. A report	Case series N=3 patients with metastases of the spine had bipolar radiofrequency ablation.	Ablation of tumours adjacent to neural structures is feasible. Spinal cord damage can be	Larger studies with longer follow-up included in table 2.

of three cases. SPINE 37, 1, pp E64–E68.		avoided by planning.	
Georgy BA, Wong W. Plasma-mediated radiofrequency ablation assisted percutaneous cement injection for treating advanced malignant vertebral compression fractures. AJNR Am J Neuroradiology 2007; 28:700-705.	Prospective series N=15 patients with metastatic lesions epidural extension and/or cortical disruption had radiofrequency ablation and cement augmentation.	Extraosseous extension of cement was observed in 4 cases but was clinically inconsequential. No thermal or neuronal insult was observed. 87% (13/15) of patients reported decreased pain.	Larger studies with longer follow-up included in table 2.
Georgy BA. Bone cement deposition patterns with plasma-mediated radiofrequency ablation and cement augmentation for advanced metastatic spine lesions. AJNR Am J Neuroradiology 2009; 30:1197-1202.	Retrospective study N=37 patients with advanced metastatic lesions (at 44 levels) had plasma mediated RFA and cement augmentation. Cavity SpineWand was used. Follow-up 2-4 weeks	Procedure allowed greater cement-deposition control, successfully stabilising the anterior two thirds of the vertebral body. This combined technique was useful in cases with posteriorly located lesions. The incidence of cement extravasation was high but clinically insignificant.	Study included in systematic review added to table 2.
Gronemeyer DH, Schirp S, Gevargez A. (2002). Image-guided radiofrequency ablation of spinal tumors: preliminary experience with an expandable array electrode. Cancer J 8:33–9.	Case series N=10 (21 vertebral lesions) spine metastases were treated with radiofrequency ablation. Vertebroplasty done in 4 cases. Follow-up average 5.8 months.	90% of patients reported pain relief, disability reduced by 27%, neurological function preserved in 9, general health stabilised in 6 and improved in 3.	Study included in systematic review added to table 2.
Greenwood TJ, Wallace A, Friedman MV et al (2005). Combined ablation and radiation therapy of spinal	Retrospective study N= 21 patients with 36 spine metastases were treated with	Mean worst pain score (8.0) significantly decreased at both one week (4.3, p<	Combined treatment (RFA plus radiotherapy)

metastases: a novel multimodality treatment approach. Pain Physician; 18:573-581	radiotherapy and either RFA or cryoablation.	.02) and 4 weeks (2.9, p<.0003). Radicular pain occurred in 1 patient. Post-procedural imaging at 6 months showed stable disease in 12/13 treatments at 3 months and 10/10 at 6 months.	
Halpin RJ, Bendok BR, Sato K et al (2005). Combination treatment of vertebral metastases using image-guided percutaneous radiofrequency ablation and vertebroplasty: a case report. Surgical neurology. 63 (5), 469-474.	Case report n-1 case of vertebral metastases treated with a combination of percutaneous radiofrequency ablation (RFA) and vertebroplasty.	No complications. pain relief was immediate.	Larger studies with longer follow-up included in table 2.
Holbert JA, Nguyen DA (2018). Percutaneous Radiofrequency Ablation for painful spinal metastases resulting in resolution of epidural disease: a case report. Cureus 10(5): e2579.	Case report N=1 case of metastatic prostate cancer with epidural extension treated with percutaneous image-guided radiofrequency ablation and vertebral augmentation	This case showed that epidural disease can be treated with radiofrequency ablation and vertebral augmentation.	Larger studies with longer follow-up included in table 2.
Kai G, Chuan L and Fang L (2015). Minimally invasive treatments of spinal metastases: Vertebroplasty, radiofrequency ablation and radiation therapy. Chinese Journal of Tissue Engineering Research. DOI: 10.3969/j.issn.2095-4344.2015.16.029	Review of 3 kinds of minimally invasive treatments for spinal metastases.	Vertebral cement augmentation efficiency is 80-90%. Radiofrequency ablation and radiation can kill the tumour but cannot rebuild the vertebral stability. Therefore, the combination of different technologies can	Review

		improve the therapeutic effect on spinal tumours. Above all, there is not a perfect minimally invasive treatment for spinal metastases	
Kam NM, Maingard JM, Kok HK et al (2017). Combined vertebral augmentation and radiofrequency ablation in the management of spinal metastases: an update. Curr. Treat. Options in Oncol. 18: 74.		Radiofrequency ablation have shown success in reducing pain and improving function in patients with symptomatic spinal metastases. Both vertebral augmentation and RFA are recognised as excellent alternative in patients with spinal metastases.	Opinion statement.
Li M, Zhang N and Zhang X et al (2020). Effects of surgery and radiofrequency ablation in the treatment of spinal metastases and analysis of the influencing factors of prognosis. Experimental and Therapeutic Medicine 19: 1072-1078.	Retrospective comparative study N= 132 patients with spinal metastases (65 had surgery alone and 65 had RFA assisted surgery). Follow-up 36 months	Operation time and blood loss, rate of complications and 3-year recurrence rate in the RFA assisted surgery group was significantly lower than in surgery alone group ($p<0.05$). The VAS and KPS scores significantly improved in RFA surgery group compared with those in the control group ($p<0.05$). The 3-year survival rate was significantly higher than that in the surgery group ($p<0.05$).	Combined treatment Surgery plus RFA

Madaelil TP, Wallace AN, Jennings JW (2016). Radiofrequency ablation alone or in combination with cementoplasty for local control and pain palliation of sacral metastases: preliminary results in 11 patients. Skeletal Radiol; 45:1213-1219.	Retrospective study N=11 RFA procedures done to treat 16 sacral metastases. Cementoplasty was done in 63% (7/11) cases. Follow-up 4.7 months.	The median pain score decreased from 8 at baseline to 3 at 1 month following RFA (p= 0.004). No acute or long-term complications were noted.	Study included in systematic review added to table 2.
Masala S, Roselli M, Massari M et al (2004). Radiofrequency heat ablation and vertebroplasty in the treatment of neoplastic vertebral body fractures. Anticancer Research 24: 3129-3134	Case series N=3 patients with metastatic vertebral collapse.	Procedure success 100%. swift pain relief and reduction in symptoms, associated with an evident augmentation in the weight-bearing resistance.	Larger studies with longer follow-up included in table 2.
Mayer T, Cazzato RL, Marini P De et al (2020). Spinal metastases treated with bipolar radiofrequency ablation with increased (> 70 ◦C) target temperature: Pain management and local tumor control. Diagnostic and Interventional Imaging 102, 27–34	Retrospective study N=31 patients with 37 metastases who were treated with b-RFA with mean temperature 88 C and vertebroplasty.	Technical success was 100% (37/37). One major complication unrelated to b-RFA was reported. Pain management in 80% (16/20) at a mean follow-up of 3.4 months or 100% (6/6) with oligometastatic/oligo-progressive disease at a mean follow-up of 5 months. In patients receiving b-RFA to prevent complications, 60% (6/10) had favourable outcome at a mean follow-up of 3 months.	Larger studies included in table 2.
Nakatsuka A, Yamakado K, Takaki H et al (2009). Percutaneous radiofrequency ablation of	Prospective study N=10 patients with spinal tumors treated with cool-tip	Procedure success was 100%. Clinical success was achieved within 1	Study included in systematic review

painful spinal tumors adjacent to the spinal cord with real-time monitoring of spinal canal temperature: A prospective study. Cardiovasc Intervent Radiol; 32:70-75.	RF ablation system. Follow-up 4.5 months	week in all patients (100).	added to table 2.
Proschek D, Kurth A, Proschek P, et al. (2009). Prospective pilot study of combined bipolar radiofrequency ablation and application of bone cement in bone metastases. Anticancer Res 29:2787–92.	Prospective study N=16 patients with painful spinal bone metastases treated with RFA alone (n=8) or RFA with bone cement (n=8). Celon prosurge & celon power RFA system was used Follow-up 20.4 months	In both groups (RFA alone and RFA with bone cement), pain was reduced significantly (mean reduction of pain 51.7%, p=0.0065). Quality of life was improved up to 61%. No side-effects and complications. Complete ablation of the bone tumour in all. No local tumour progression was seen.	Study included in systematic review added to table 2.
Sandri A, Carbognin G, Regis D et al (2010). Combined radiofrequency and kyphoplasty in painful osteolytic metastases to vertebral bodies. Radiol med; 115:261–271	Case series N=11 patients with painful osteolytic vertebral body metastases unresponsive to conservative treatments had combined radiofrequency ablation and kyphoplasty.	No complication occurred but an asymptomatic cement leakage noted in 1. Pain significantly decreased: the mean VAS pain score before treatment was 8 vs. 1.8 and 1.9 at 72 h and 6 weeks. Analgesic reduction was achieved in all.	Larger studies with longer follow-up added to table 2.
Schafer O, Lohrmann C, Markmiller M et al (2003). Combined treatment of a spinal metastasis with radiofrequency heat ablation and vertebroplasty. Technical	Case report N=1 case of spinal metastases treated with radiofrequency ablation and vertebroplasty. Follow-up 3 months	A stable vertebral body with no further tumour growth reported. The patient was pain-free and had no limitations in his activity.	Larger studies with longer follow-up added to table 2.

Innovation. AJR; 180:1075–1077			
Sayed D, Jacobs D, Sowder T et al (2019). Spinal Radiofrequency Ablation Combined with Cement Augmentation for Painful Spinal Vertebral Metastasis: A Single-Center Prospective Study. Pain Physician; 22:E441-E449	Prospective study N=30 patients undergoing RFA with cement vertebral augmentation for a painful thoracic or lumbar vertebral metastases.	Average NRS-11 scores decreased from a baseline of 5.77 to 4.65 (3 days; p = 0.16), 3.33 (one week; p<0.01), 2.64 (one month; p<0.01), and 2.61 (3 months; p<0.01). FACT-G7 increased from a baseline average of 13.0 to 14.7 (3 days; p=0.13), 14.69 (one week; p=0.15), 14.04 (one month; p=0.35), and 15.11 (3 months; p=0.07). No major adverse events were reported.	Larger studies included in table 2.
Tomasian A, Hillen TJ, Chang RO et al (2018). Simultaneous bipedicular radiofrequency ablation combined with vertebral augmentation for local tumor control of spinal metastases. AJNR Am J Neuroradiology 39:1768 – 73	Retrospective study N=27 patients (33 tumors) with vertebral metastases treated with simultaneous bipedicular radiofrequency ablation combined with vertebral augmentation. Posterior vertebral body or pedicle involvement or both present in 94% (31/33) of cases.	Local tumour control was achieved in 96% (25/26) of tumours median follow up of 16 weeks. No complications were reported, and no patients had clinical evidence of metastatic spinal cord compression at the treated levels.	Larger studies included in table 2.
Wallace AN, Greenwood TJ, Jennings JW (2015). Radiofrequency ablation and vertebral augmentation for palliation of painful spinal	Retrospective study N=72 patient with 110 spinal metastases. RFA and vertebral augmentation in	Patients reported clinically significant decreased pain scores at both 1-week (mean, 3.9 ± 3.0; p<0.0001) and 4-week (mean, 2.9	Study included in systematic review added to table 2.

metastases. J Neurooncol; 124:111-118.	95% (105/110) ablations. Star tumour ablation system was used. Follow-up 1 month	± 3.0; p<0.0001) follow-up. No major complications related to RFA and no cement extravasation reported.	
Wallace AN, Tomasian A, Vaswani D et al (2016). Radiographic local control of spinal metastases with percutaneous radiofrequency ablation and vertebral augmentation. AJNR Am J Neuroradiology; 37:759-765.	Retrospective review (sub-group analysis) N=55 tumours reporting rate of radiographic local control in patients with spinal metastases treated with RFA and vertebral augmentation. Star tumour ablation system was used. Follow-up 1 year in 93% (51/55) patients. (median 34 weeks)	Radiographic local tumour control rates were 89% (41/46) at 3 months, 74% (26/35) at 6 months, and 70% (21/30) at 1 year. No complications were reported, and no patients had metastatic spinal cord compression at treated levels.	Subgroup analysis of above study (included in systematic review added to table 2).
Yang PL, He XJ, Li HP, et al. (2017). Image-guided minimally invasive percutaneous treatment of spinal metastasis. Exp Ther Med 13:705–9.	Retrospective case series N=25 (32 vertebral lesions) RFA plus cement augmentation Follow-up mean 7.8 months.	Biomechanical stability of the spine increased, pain within 6 weeks reduced, while the daily activities and quality of life improved. Mean progression-free survival of tumours was 330±54 days, and no complications occurred.	Study included in systematic review added to table 2.
Yuntong M, Wallace AN, Madaelil TP et al (2016). Treatment of osseous metastases using the Spinal Tumor Ablation with Radiofrequency	Review of epidemiology, pathophysiology, natural history, and traditional management of	Although evidence supporting the efficacy of RFA for the treatment of bone metastases is limited to case	Review

(STAR) system. e: Expert review of medical devices. VOL. 13, NO. 12, 1137–1145	metastatic bone disease and Spinal Tumor Ablation with Radiofrequency (STAR) System for treatment of osseous metastases.	series, it is a reasonable therapy when other options have been exhausted, especially given the safety and minimal morbidity of the procedure. The STAR Tumor Ablation System has expanded the anatomic scope of bone metastases that can be safely and effectively treated with percutaneous ablation.	