

Radiofrequency ablation for metastatic spinal lesions

Systematic Review



Ludwig Boltzmann Institut
Health Technology Assessment

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

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List of abbreviations

AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.
CE Mark	Conformité Européene mark
CT	computed tomography
DRG	diagnosebezogene Fallgruppen (Diagnosis-Related Group)
FACT-BP	Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with bone pain
FACT-G7	Functional Assessment of Cancer Therapy-General 7
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	health-related quality of life
LKF	Leistungsorientierte Krankenanstaltenfinanzierung
min	minutes
mo	month
MODI	Modified Oswestry Disability Index
MRI	magnetic resonance imaging
NPRS	Numerical Pain Rating Scale
NR	not reported
NRCT	non-randomised controlled trial
NRS	Numeric Rating Scale
n.s.	not significant
RFA	radiofrequency ablation
SoC	standard of care
s.s.	statistically significant
US	ultrasound
VAS	Visual Analogue Scale
VBM	vertebral body metastases
WS	Wirbelsäule
yrs	year

Summary

Introduction

Health Problem

In the scope of this assessment, vertebral metastases are the condition of interest.

Many tumour patients develop painful vertebral metastases in the course of their disease that destroy the vertebrae. These metastases represent the most common cause of chronic pain, fractures, reduced mobility and spinal cord compression [1, 2]. Therefore, patients with untreated painful vertebral metastases may suffer from several complications, e.g., fractures, decreased health-related quality of life (HRQoL), decreased mobility, and a reduced performance status. Consequently, it can have negative effects on the functional capacity and can lead to depression and anxiety states [2-4]. The treatment of metastatic spinal lesions is usually palliative [5].

Description of Technology

Radiofrequency ablation (RFA) is an image-guided minimally invasive thermal ablation procedure for solid tumours [6, 7]. RFA for metastatic spinal lesions is performed using a transpedicular or parapedicular approach. During the procedure, the patient is positioned face down and sedated using conscious sedation or general anaesthesia [1, 8].

RFA uses imaging guidance to manually insert a needle electrode into the tumour tissue. To access the metastasis in the vertebral body a cannula and a navigable probe is used. Via a radiofrequency generator high frequency alternating current pulses are emitted into the tumour tissue [1, 9, 10]. The heat field generated by radiofrequency energy (50-90°C) causes the destruction of the malignant tissue and creates a cavity in the vertebral body [3]. These features allow the safe destruction of vertebral metastases near heat-sensitive structures such as the spinal cord [1, 11].

If the vertebral body implies a risk of fracture after RFA an additional preventive treatment with vertebroplasty (cementation of the vertebral body) can be performed [12].

Research question

Is radiofrequency ablation with/without vertebroplasty (or other add-on therapies) in comparison to the standard of care (SoC) or no treatment in patients with metastatic spinal lesions more effective and safe concerning pain, functional status, HRQoL and complications?

Methods

To answer the research questions on efficacy and safety-related outcomes, a systematic literature search in five databases was conducted. In addition, we performed a hand search and screened information provided by the manufacturer and the submitting hospital to identify further relevant studies. The study selection, data extraction, and assessing the methodological quality of the studies was performed by two independent researchers.

focus: metastases in the vertebrae

many tumour patients develop painful vertebral metastases that represent to be the most common cause of chronic pain, fractures, reduced mobility and spinal cord compression

RFA is a minimally invasive procedure performed using conscious sedation or general anaesthesia

a needle electrode is inserted into the tumour tissue using imaging guidance; the generated heat field causes the destruction of the malignant tissue; vertebral bodies at risk for fracture can additionally be stabilized with vertebroplasty

research question

systematic literature search

crucial outcomes for efficacy ...	<p>Domain effectiveness</p> <p>The following efficacy-related outcomes were used as evidence to derive a recommendation: pain relief, functional status and HRQoL.</p>
... and safety	<p>Domain safety</p> <p>The following safety-related outcomes were used as evidence to derive a recommendation: major complications and adverse events (procedure-related and not procedure-related).</p>
4 prospective and 5 retrospective single-arm studies	<p>Results</p> <p>Available evidence</p> <p>A total of 4 prospective and 5 retrospective single-arm studies were eligible for inclusion in the current report. A cut-off of more than 30 patients was defined as an inclusion criterion for retrospective studies.</p> <p>Overall, data on safety and efficacy was evaluated in 471 and 112 patients, respectively.</p>
4 prospective single-arm studies with 112 patients	<p>Clinical effectiveness</p> <p>To assess the effectiveness of radiofrequency ablation for metastatic spinal lesions we could not identify any comparative studies. The only studies that met our inclusion criteria were four prospective single arm, partly multicentre, studies with a total of 112 patients assessing the effectiveness of radiofrequency ablation combined with vertebroplasty.</p>
pain relief in 3 studies improvement in health-related quality of life (HRQoL) in 2 studies	<p>Three prospective studies reported overall significant outcomes on pain relief after treatment with RFA and vertebroplasty. Two studies assessed outcomes on HRQoL with significant improvements throughout the follow-up periods. One study recorded no recurrence of vertebral metastases during the follow-up.</p> <p>Since none of the studies included a control group, they could not provide any serious information on a possible survival prolongation.</p>
5 additional retrospective studies with 471 patients no major complications; a total of 105 (18%) adverse events occurred across the studies: RFA-related: pain and numbness * vertebroplasty-related: cement extravasation	<p>Safety</p> <p>In the absence of data from controlled studies, no comparisons can be made for the safety assessment of RFA. Overall, safety outcomes were evaluated in 4 prospective studies (112 patients) and in 5 retrospective studies (471 patients).</p> <p>None of the included studies reported major complications for the use of RFA. Overall, adverse events (procedure-related or not procedure-related) occurred in 105 patients who completed the follow-up, out of 583 included patients across the studies (18%).</p> <p>The most frequent procedure-related adverse events were increased pain and numbness (7.8%, 6/77 patients). The most frequent adverse event reported, which is not RFA-related, but vertebroplasty-related, was cement extravasation (18.7%, 67/358 patients).</p>

Upcoming evidence

Currently, there are three ongoing studies. One registry of the STAR[®] tumour ablation system (NCT02419703), one ongoing study on the combination of RFA and vertebroplasty (ChiCTR-INR-16010135) and one ongoing phase II study evaluating the efficacy of combining thermal ablation and stereotactic spine radiosurgery (NCT02713269).

3 ongoing studies

Reimbursement

At this point in time, the use of radiofrequency ablation for the treatment of spinal metastatic lesions is not reimbursed by the Austrian health care system.

no reimbursement of the intervention in Austria

Discussion

Overall, the strength of evidence on clinical effectiveness cannot be determined. For safety outcomes the strength of evidence is “very low”.

strength of evidence for clinical effectiveness not estimable; “very low” strength of evidence for safety outcomes

Considering the findings of the included studies in this review, it seems that image-guided RFA with or without vertebroplasty might be a feasible and safe technique for patients with painful metastatic spinal lesions. In particular, since there were no serious complications reported. No therapy means intolerable pain for the patient. If other treatments are contraindicated, RFA (in combination with vertebroplasty) may be an effective treatment for pain reduction on the basis of the included studies.

RFA (in combination with vertebroplasty) might be a feasible, safe and effective technique for patients with painful metastatic spinal lesions

A major concern of most of the identified prospective studies is the low number of included patients. Especially, to identify rare complications, low patient numbers are insufficient. Another essential issue are the short follow-up periods in the included studies. Yet, only one study had a follow-up of 60 months. Therefore, reliable data of long-term safety and efficacy outcomes are missing. However, data collection is extremely difficult, because long-term follow-up is challenging in patients with metastatic spinal lesions due to high morbidity and mortality rates.

small numbers of patients in prospective studies

Due to the palliative course of the disease and the limited life expectancy of patients with painful metastatic spinal lesions, an effective and safe therapy, such as RFA, to improve pain relief and HRQoL that can also be performed on an outpatient setting might be beneficial.

short follow-up periods (palliative)

Conclusion

The natural course of metastatic spinal lesions is fatal with intolerable pain. Thus, on ethical grounds, every therapy providing pain relief and causes no major complications may be justified. The current evidence indicates that the assessed technology RFA is, under certain conditions, effective and safe for the treatment of painful metastatic spinal lesions. The intervention should only be performed in specialized centres and, if possible, with registry acquisition for potential and rare adverse events.

RFA is recommended with restrictions → palliative pain treatment in specialized centres and, if possible, with registry acquisition for potential and rare adverse events

Due to the low quality of evidence of the included studies, we recommend radiofrequency ablation for metastatic spinal lesions with restrictions. The technology might be used for patients with metastatic spinal lesions as palliative pain treatment in whom alternative treatments do not achieve sufficient effect or are contraindicated.

A re-evaluation is recommended after 2021 because of relevant ongoing studies, including a registry study that may provide new evidence of the technology.

re-evaluation after 2021 recommended

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Fokus: Metastasen in der Wirbelsäule (WS)

viele TumorpatientInnen entwickeln WS-Metastasen, die die häufigste Ursache für chronische Schmerzen, Frakturen und Rückenmarkskompressionen darstellen

Der Fokus dieser systematischen Übersichtsarbeit liegt auf Wirbelsäulenmetastasen.

Viele TumorpatientInnen entwickeln im Laufe ihrer Erkrankung schmerzhafte Metastasen in der Wirbelsäule, die die Wirbel zerstören. Diese Metastasen stellen die häufigste Ursache für chronische Schmerzen, Frakturen, verminderte Beweglichkeit und Rückenmarkskompressionen bei TumorpatientInnen dar [1, 2]. Daher leiden PatientInnen mit unbehandelten schmerzhaften Wirbelsäulenmetastasen häufig an Frakturen, verminderter Lebensqualität und eingeschränkter Mobilität. Dies kann wiederum negative Auswirkungen auf die Funktionsfähigkeit haben und zu Depressionen und Angstzuständen führen [2-4]. Die Behandlung von Wirbelsäulenmetastasen ist meist palliativ, da der Tumor im Stadium der Metastasenbildung schon weit fortgeschritten ist und PatientInnen ein mittleres Überleben von lediglich 3-6 Monate haben [5].

Beschreibung der Technologie

RFA ist eine minimal-invasive Intervention, die unter Allgemein- oder Lokalanästhesie durchgeführt wird

eine navigierbare Nadelelektrode wird unter Bildüberwachung in das Tumorgewebe eingebracht

durch Wechselstrom wird malignes Gewebe zerstört

Vertebroplastie zur Stabilisierung von frakturgefährdeten Wirbelkörpern

Forschungsfrage

Radiofrequenzablation (RFA) ist ein minimal invasives thermisches Ablationsverfahren für solide Tumore [6, 7]. RFA wird bei Wirbelsäulenmetastasen mit einem transpedikulären oder parapedikulären Ansatz durchgeführt. Der Eingriff erfolgt in Bauchlage unter Allgemein- oder Lokalanästhesie [1, 8].

RFA verwendet bildgebende Verfahren, um eine Nadelelektrode manuell in das Tumorgewebe einzuführen. Eine Kanüle und eine navigierbare Sonde werden verwendet, um die Metastase im Wirbelkörper zu erreichen. Über einen Radiofrequenzgenerator werden hochfrequente Wechselstromimpulse in das Tumorgewebe abgegeben [1, 9, 10]. Das durch Radiofrequenzenergie (50-90°C) erzeugte Wärmefeld bewirkt die Zerstörung des malignen Gewebes und schafft einen Hohlraum im Wirbelkörper [3]. Dadurch wird die sichere Eliminierung von vertebrealen Metastasen nahe wärmeempfindlicher Strukturen wie dem Rückenmark ermöglicht [1, 11].

Zur Stabilisierung frakturgefährdeter Wirbelkörper kann als zusätzliche präventive Therapie im Anschluss an die RFA eine Vertebroplastie (Zementierung des Wirbelkörpers) durchgeführt werden [12].

Wissenschaftliche Fragestellung

Ist die RFA in Kombination mit oder ohne Vertebroplastie (oder anderen Zusatztherapien) im Vergleich zur Standardtherapie oder keiner Behandlung bei PatientInnen mit Wirbelsäulenmetastasen im Hinblick auf Schmerzen, Funktionsstatus, gesundheitsbezogener Lebensqualität und Komplikationen wirksamer und sicherer?

Methoden

Die Beantwortung der Forschungsfrage bezüglich Wirksamkeit und Sicherheit erfolgte anhand einer systematischen Literatursuche in folgenden Datenbanken:

- ✿ Medline via Ovid
- ✿ Embase
- ✿ The Cochrane Library
- ✿ CRD (DARE, NHS-EED, HTA)
- ✿ PubMed.

Zusätzlich wurde eine Handsuche durchgeführt und es erfolgte eine ergänzende Studienanfrage bei einzelnen Herstellern. Die Studienauswahl, Datenextraktion sowie die Bewertung der methodischen Qualität der Studien erfolgte unabhängig durch zwei Autorinnen. Insgesamt wurden neun Publikationen für eine Datensynthese eingeschlossen.

Die Daten, die für die Entscheidung herangezogenen Endpunkte, wurden aus den einzelnen Studien zusammengefasst und nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet.

Klinische Wirksamkeit

Zur Bewertung der Wirksamkeit wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

- ✿ Schmerzreduktion
- ✿ funktioneller Status und
- ✿ gesundheitsbezogene Lebensqualität (HRQoL).

Sicherheit

Zur Bewertung der Sicherheit wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

- ✿ schwerwiegende Komplikationen
- ✿ unerwünschte Ereignisse (verfahrensbezogen)
- ✿ unerwünschte Ereignisse (nicht-verfahrenbezogen).

Ergebnisse

Verfügbare Evidenz

Insgesamt konnten vier prospektive und fünf retrospektive einarmige Studien identifiziert werden, die den Einschlusskriterien entsprachen. Für retrospektive Studien wurde ein Cut-Off von mehr als 30 PatientInnen als Einschlusskriterium festgelegt.

Klinische Wirksamkeit

Zur Beurteilung der Wirksamkeit der RFA für die Behandlung von Metastasen in der Wirbelsäule konnten keine Vergleichsstudien identifiziert werden. Die einzigen Studien, die die Einschlusskriterien erfüllten, waren vier prospektive einarmige, teilweise multizentrische Studien mit insgesamt 112 PatientInnen, die die Wirksamkeit der RFA in Kombination mit Vertebroplastie beurteilten.

**systematische
Literatursuche**

**Handsuche,
Anfrage bei Herstellern**

**Studienbewertung
nach GRADE**

**entscheidende
Endpunkte für
Wirksamkeit ...**

... und Sicherheit

**4 prospektive und
5 retrospektive
Einzelarm-Studien**

**4 prospektive
Einzelarm-Studien mit
112 PatientInnen**

<p>Schmerzreduktion in 3 Studien; Verbesserung der Lebensqualität in 2 Studien</p>	<p>Drei der eingeschlossenen prospektiven Studien berichteten von signifikanten Ergebnissen bei der Schmerzreduktion nach der Behandlung mit RFA und Vertebroplastie. Zwei der Studien bewerteten die gesundheitsbezogene Lebensqualität. Diese zeigte eine erhebliche Verbesserung im Verlauf der Follow-up Zeiträume. Eine Studie verzeichnete kein Wiederauftreten von vertebrealen Metastasen, während die anderen eingeschlossenen Studien diesen Endpunkt nicht berichteten.</p>
<p>zusätzlich 5 retrospektive Studien mit 471 PatientInnen</p>	<p>Sicherheit</p> <p>In Abwesenheit von Daten aus kontrollierten Studien konnten auch für die Bewertung der Sicherheitsendpunkte keine Vergleiche von RFA mit anderen Therapieoptionen durchgeführt werden. Insgesamt wurden Ergebnisse zu den Sicherheitsendpunkten in vier prospektiven Studien (112 PatientInnen) und in fünf retrospektiven Studien (471 PatientInnen) berichtet.</p>
<p>keine schwerwiegenden Komplikationen</p> <p>insgesamt 105 (18 %) unerwünschte Ereignisse</p> <p>⊛ durch RFA häufig: Schmerzen und Taubheit</p> <p>⊛ aufgrund von Zusatz-Therapien häufig: Zementaustritt</p>	<p>Keine der eingeschlossenen Studien berichtete von schwerwiegenden Komplikationen bei einer Behandlung von Wirbelsäulenmetastasen mit RFA. Über die einzelnen Studien hinweg traten unerwünschte Ereignisse (verfahrensbezogene oder nicht-verfahrensbezogene) bei 105 von insgesamt 583 eingeschlossenen PatientInnen (18 %), die das jeweilige Follow-up durchlaufen sind, auf.</p> <p>Die am häufigsten berichteten verfahrensbezogenen unerwünschten Ereignisse waren vermehrte Schmerzen und Taubheitsgefühle (7,8 %, 6/77 PatientInnen). Die meisten unerwünschten Ereignisse, die nicht RFA-bezogen, aber durch die Vertebroplastie hervorgerufen wurden, waren Zementextravasationen. Dieses unerwünschte Ereignis wurde von 67 PatientInnen berichtet (18,7 %, 67/358 PatientInnen).</p>
<p>3 laufende Studien</p>	<p>Laufende Studien</p> <p>Aktuell sind drei laufende Studien registriert. Ein Studienregister des STAR® Tumor-Ablationssystems (NCT02419703), eine laufende Studie über die Kombination von RFA und Vertebroplastie (ChiCTR-INR-16010135) und eine Phase II Studie zur Bewertung der Wirksamkeit von thermischer Ablation in Kombination mit stereotaktischer Wirbelsäulen-Strahlentherapie (NCT02713269).</p>
<p>Intervention wird in Österreich derzeit nicht erstattet</p>	<p>Kostenerstattung</p> <p>In Österreich werden die Kosten der RFA zur Behandlung von Wirbelsäulenmetastasen derzeit nicht erstattet.</p>
<p>Stärke der Evidenz für klinische Wirksamkeit nicht bestimmbar; sehr geringe Stärke der Evidenz für Sicherheitsendpunkte</p> <p>RFA (in Kombination mit Vertebroplastie) ist umsetzbare,</p>	<p>Diskussion</p> <p>Das Ziel des vorliegenden Berichts war es, die klinische Wirksamkeit und Sicherheit der RFA (in Kombination mit Vertebroplastie) zu bewerten. Insgesamt kann die Stärke der Evidenz für die klinische Wirksamkeit nicht bestimmt werden, da keine kontrollierten Studien zur Beurteilung der Wirksamkeit identifiziert werden konnten. Für die Sicherheitsendpunkte wurde die Evidenzstärke als „sehr gering“ eingestuft.</p> <p>In Anbetracht der Ergebnisse der eingeschlossenen Studien scheint die bildgeführte RFA mit oder ohne anschließende Vertebroplastie eine durchführbare und sichere Technik für PatientInnen mit schmerzhaften Metastasen in der Wirbelsäule zu sein. Vor allem da keine schwerwiegenden Komplikationen in Verbindung mit RFA in den Studien aufgetreten sind. Sollten andere</p>

Behandlungen kontraindiziert sein und da keine Therapie für die betroffenen PatientInnen häufig zu unerträglichen Schmerzen führt, kann RFA (in Kombination mit Vertebroplastie), auf der Grundlage der eingeschlossenen Studien, eine wirksame Behandlung zur Schmerzreduktion sein.

Wesentlicher Kritikpunkt an der vorliegenden Evidenz ist die geringe Anzahl der PatientInnen in der Mehrzahl der eingeschlossenen prospektiven Studien. Zur Identifikation von seltenen unerwünschten Ereignissen könnte die kleine Fallzahl unzureichend sein. Ein weiterer essentieller Kritikpunkt sind die relativ kurzen Nachbeobachtungszeiträume in den einzelnen Studien. Lediglich eine Studie hatte einen Nachbeobachtungszeitraum von 60 Monaten. Daher fehlen zuverlässige Daten über die längerfristigen Sicherheits- und Wirksamkeitsergebnisse. Allerdings ist die Datenerhebung äußerst schwierig, da die Nachbeobachtung von PatientInnen mit Wirbelsäulenmetastasen aufgrund der hohen Morbidität und Mortalität eine große Herausforderung darstellt.

Aufgrund des palliativen Verlaufs der Erkrankung und der begrenzten Lebenserwartung von PatientInnen mit schmerzhaften Metastasen in der Wirbelsäule, könnte eine wirksame und sichere Therapie, wie RFA, zur Schmerzlinderung und Verbesserung der Lebensqualität, die auch auf ambulanter Basis durchgeführt werden kann, von Vorteil sein.

Entscheidende Limitationen des vorliegenden Berichts sind: Es konnten keine randomisierten kontrollierten Studien identifiziert werden und retrospektive Studien mit weniger als 30 PatientInnen wurden ausgeschlossen. Deshalb ist davon auszugehen, dass die Fehlerquellen aufgrund von Bias und Störfaktoren hoch sind. Zusätzlich basieren die Ergebnisse der Studien auf subjektiven Angaben (z. B. Schmerz), was ebenfalls zu einer möglichen Verzerrung der Ergebnisse führen kann.

Empfehlung

Die Prognose von Wirbelsäulenmetastasen ist äußerst schlecht. Sie sind mit unerträglichen Schmerzen verbunden und die betroffenen PatientInnen haben eine maximale Überlebensdauer von 6 Monaten. Aus ethischen Aspekten kann demnach jede Therapie ohne schwerwiegende Komplikationen, die eine Schmerzlinderung erreicht, gerechtfertigt sein. Die gegenwärtige Evidenz deutet darauf hin, dass RFA unter bestimmten Bedingungen wirksam und sicher für die Behandlung von schmerzhaften Wirbelsäulenmetastasen ist. Die Intervention sollte nur in spezialisierten Zentren erbracht und es sollte, soweit möglich, eine Registererhebung für potenzielle und seltene unerwünschte Ereignisse durchgeführt werden.

Aufgrund der geringen Qualität der Evidenz, wird RFA für Wirbelsäulenmetastasen nur mit Einschränkungen empfohlen. Die Technologie kann für PatientInnen mit metastasierten Wirbelsäulenläsionen, bei denen alternative Behandlungen nicht ausreichend oder kontraindiziert sind, als palliative Schmerzbehandlung durchgeführt werden.

Eine Re-Evaluierung wird ab 2021 empfohlen, da es derzeit laufende Studien und ein Studienregister gibt, die möglicherweise einen wichtigen Einfluss auf die Einschätzung des Effekts haben können.

sichere und effektive Intervention für PatientInnen mit schmerzhaften WS-Metastasen

häufig kleine Fallzahlen

relativ kurze Nachbeobachtungszeiträume (palliativ)

wirksame und sichere Therapie, könnte Vorteil für PatientInnen mit schmerzhaften WS-Metastasen sein

Limitationen:

- * nur pro- und retrospektive Einzelarm-Studien
→ Bias-Risiko hoch;
- * Studien basieren auf subjektiven Angaben
→ Verzerrung der Ergebnisse möglich

**Empfehlung unter bestimmten Bedingungen
→ palliative Schmerzbehandlung in spezialisierten Zentren (möglichst mit Registererfassung für unerwünschte Ereignisse)**

Re-Evaluierung nach 2021 empfohlen

1 Scope

1.1 PICO question

Is radiofrequency ablation with/without vertebroplasty (or other add-on therapies) in comparison to the standard of care (SoC) or no treatment in patients with metastatic spinal lesions more effective and safe concerning pain, functional status, health-related quality of life (HRQoL) and complications?

PIKO-Frage

1.2 Inclusion criteria

Inclusion criteria for relevant studies are summarized in Table 1-1.

**Einschlusskriterien
für relevante Studien**

Table 1-1: Inclusion criteria

Population	Patients with solitary fracture-related metastases of all entities in whom a curative tumor treatment (vertebral body extension and stabilization) is not indicated; patients in a palliative setting after maximal radiation dose or radiation-resistant lesions. ICD-10 code: C79.5 secondary malignant neoplasm of the bone and the bone marrow MeSH-terms: spinal neoplasms, catheter ablation
Intervention	Radiofrequency ablation (RFA) with/without vertebroplasty/other add-on therapies (e.g., radiation) All add-on therapies were included. MeSH term: Radiofrequency Catheter Ablation
Control	No treatment with RFA.
Outcomes	
Efficacy	<ul style="list-style-type: none"> ✳ pain (pain relief) ✳ functional status ✳ health-related quality of life (HRQoL) ✳ satisfaction with treatment ✳ recurrence of vertebral metastases (local relapse) ✳ mortality, improved survival
Safety	<ul style="list-style-type: none"> ✳ complications ✳ adverse events
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series Retrospective case-series (n > 30 patients)

2 Methods

2.1 Research questions

Description of the technology	
Element ID	Research question
B0001	What is radiofrequency ablation?
B0002	What is the claimed benefit of radiofrequency ablation?
B0003	What is the phase of development and implementation of radiofrequency ablation?
B0004	Who administers radiofrequency ablation and in what context and level of care is it provided?
B0008	What kind of special premises are needed to use radiofrequency ablation?
B0009	What supplies are needed to use radiofrequency ablation?
A0020	For which indications has radiofrequency ablation received marketing authorisation or CE marking?
A0021	What is the reimbursement status of radiofrequency ablation?

Health problem and Current Use	
Element ID	Research question
A0001	For which health conditions and for what purposes is radiofrequency ablation used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for vertebral metastases?
A0004	What is the natural course of vertebral metastases?
A0005	What are the symptoms and the burden of disease of vertebral metastases for the patient?
A0006	What are the consequences of vertebral metastases for the society?
A0024	How are vertebral metastases currently diagnosed according to published guidelines and in practice?
A0025	How are vertebral metastases currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is radiofrequency ablation of vertebral metastases utilised?

Clinical Effectiveness	
Element ID	Research question
D0005	How does radiofrequency ablation affect symptoms and findings (severity, frequency) of painful vertebral metastases?
D0006	How does radiofrequency ablation affect progression (or recurrence) of vertebral metastases?
D0012	What is the effect of radiofrequency ablation on generic health-related quality of life?
D0013	What is the effect of radiofrequency ablation on disease-specific quality of life?
D0011	What is the effect of radiofrequency ablation on patients' body functions?
D0016	How does the use of radiofrequency ablation affect activities of daily living?
D0017	Were patients satisfied with radiofrequency ablation?
D0001	What is the expected beneficial effect of radiofrequency ablation on mortality?

Safety	
Element ID	Research question
C0008	How safe is radiofrequency ablation in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying radiofrequency ablation?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of radiofrequency ablation?
C0007	Is radiofrequency ablation associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of radiofrequency ablation?

2.2 Sources

Description of the technology

Quellen:
systematische Suche,
Handsuche sowie
Informationen eines
Herstellers & des
einreichenden
Krankenhauses

- ✳ Handsearch in the POP and CRD databases for Health Technology Assessments, and in Google (for identifying manufacturers and product information)
- ✳ Background publications identified in database search: see Section 2.3
- ✳ Documentation provided by one manufacturer
- ✳ Questionnaire completed by the submitting hospital

Health problem and current use

- ✳ Handsearch in the UpToDate database, the POP, and CRD databases for Health Technology Assessments and in Google
- ✳ Background publications identified in database search: see Section 2.3
- ✳ Documentation provided by one manufacturer
- ✳ Questionnaire completed by the submitting hospital
- ✳ Handsearch for management guidelines in the National Comprehensive Cancer Network and the Onkopedia Database

2.3 Systematic literature search

The systematic literature search was conducted between 28th and 29th of December 2016 in the following databases:

- ✿ Medline via Ovid
- ✿ Embase
- ✿ The Cochrane Library
- ✿ CRD (DARE, NHS-EED, HTA)
- ✿ PubMed

The systematic search was limited to articles published in English or German. After deduplication, overall 293 citations were included. The specific search strategy employed can be found in the Appendix (Chapter “Literature search strategies”).

One manufacturer from the most common product (STARTM – *radiofrequency ablation system for vertebral metastasis*) submitted 6 publications of which 0 new citations were identified.

The submitting hospital sent 12 publications of which 3 new citations were identified.

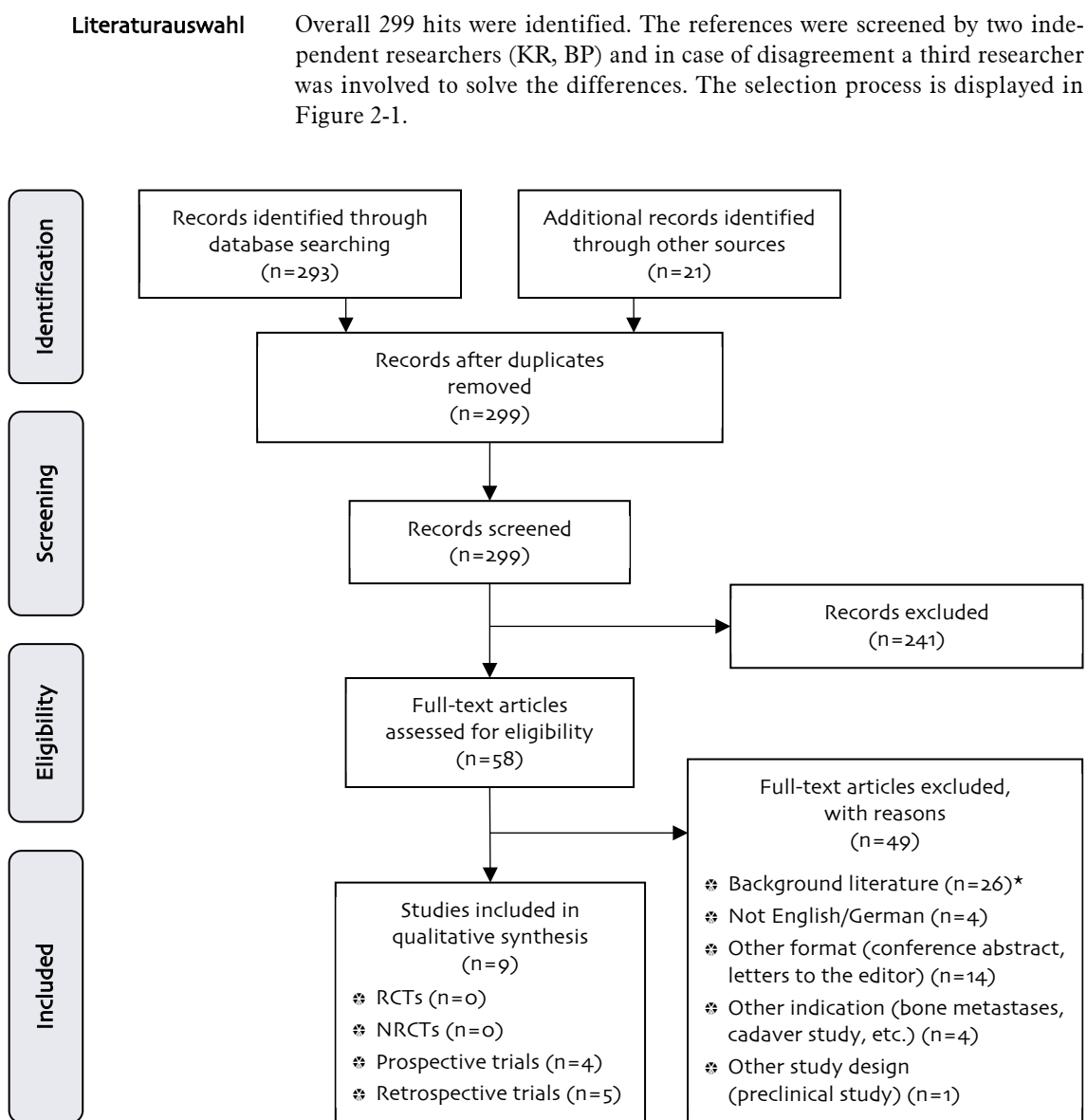
By hand-search, additional 2 records were found, resulting in overall 299 hits.

One Health Technology Assessment (HTA) from the *Comite d’Evaluation et de Diffusion des Innovations Technologiques* (CEDIT) that analysed a similar research question was identified by the systematic search [11]. Because the HTA is written in French, only the reference list was screened for additional relevant citations. In this reference list, we could identify another HTA, which provided background information on malignant spinal metastases and on technologies for identifying patients at high risk of vertebral fracture and spinal cord compression [7].

**systematische
Literatursuche in
5 Datenbanken**

**insgesamt 299
Publikationen
identifiziert**

2.4 Flow chart of study selection



* 5 publications presented sub-analytical results of 4 already included observational studies. Therefore, only the overall data of the primary studies are presented in the outcomes.

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

The data retrieved from the selected studies (see Chapter 2.4) were systematically extracted into a data-extraction-table (see Appendix Table A-1, Table A-2, Table A-3). No further data processing (e.g., indirect comparison) was applied. The studies were systematically assessed for quality and risk of bias by two independent researchers (KR, BP) using the IHE Risk of Bias checklist for case series [13] presented in the Appendix (see Table A-4).

**Datenextraktion
und Bewertung des
Bias-Risikos laut
IHE Checkliste**

2.6 Synthesis

Based on the data-extraction-table (see Appendix Table A-1, Table A-2, Table A-3), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [14]. The research questions were answered in plain text format with reference to GRADE evidence tables that are included in Table 7-1.

**Evidenzsynthese
mittels GRADE**

3 Description and technical characteristics of technology

Features of the technology and comparators

Boo01 – What is radiofrequency ablation?

The treatment of unresectable tumours and metastases in the area of the spine has made a substantial progress over the last decades. The treatment options mostly include cytoreductive therapies, i.e., radiation, hormonal ablation, and chemotherapy, but also of treatments that do not directly attack the tumour cells, but inhibit osteoclast activity. However, in some patients, all of these treatment options cannot provide sufficient symptom control [8, 15].

Radiofrequency ablation (RFA) is an image-guided minimally invasive thermal ablation procedure for solid tumours [6, 7]. In the last years, RFA has emerged as a feasible option in the palliative treatment of vertebral metastases because of short procedure times, its minimally invasive, and its capacity to be performed on an ambulatory basis [1, 8].

RFA for metastatic spinal lesions is performed using a transpedicular or parapedicular approach. The approach is either percutaneous, endoscopic, or surgical. During the procedure, the patient is positioned face down and sedated using conscious sedation or general anaesthesia [1, 8].

RFA uses imaging guidance to manually insert a needle electrode into the tumour tissue. The imaging guidance with ultrasound (US), fluoroscopy, computed tomography (CT), or magnetic resonance imaging (MRI) helps preventing injury to vascular structures. To access the metastasis in the vertebral body, a cannula and a navigable probe is used. Via a radiofrequency generator, high frequency alternating current pulses are emitted into the tumour tissue [1, 9, 10]. The heat field generated by radiofrequency energy (50-90°C) causes the destruction of the malignant tissue and creates a cavity in the vertebral body [3]. These features allow for the safe destruction of vertebral metastases near heat-sensitive structures such as the spinal cord [1, 11].

If the vertebral body implies a risk of fracture after RFA, an additional preventive treatment with vertebroplasty (cementation of the vertebral body) can be performed [12]. Vertebroplasty following RFA may be especially indicated in weight-bearing bones such as the vertebrae [16]. However, subsequent vertebroplasty carries a risk of spinal canal compromise and should only be performed with caution and by qualified physicians [15, 17].

RFA is not indicated if the metastasis is adjacent to neurological structures in order to avoid major complications such as neurological injury and to avoid fracture of large lesions in the vertebrae [18].

Several devices are in use for ablation of metastatic spinal lesions. The two most frequently used RFA-systems in the included studies are the *STAR Tumor Ablation System* and the *CAVITY SpineWand*:

**Fortschritte in
Behandlung von
WS-Metastasen**

**RFA ist eine
minimal-invasive
Intervention, die
unter Allgemein- oder
Lokalanästhesie
durchgeführt wird**

**eine navigierbare
Nadelelektrode wird
unter Bildüberwachung
in das Tumorgewebe
eingebracht;
ein Generator produziert
Wechselstrom, dadurch
erfolgt die Zerstörung
des malignen Gewebes
nahe hitzeempfindlichen
Strukturen**

**zur Stabilisierung von
frakturgefährdeten
Wirbelkörpern kann
anschließend an RFA
eine Vertebroplastie
durchgeführt werden**

**unterschiedliche
RFA-Techniken
verfügbar**

<p>Sonde mit bipolarer, erweiterbarer RF-Elektrode, die bis zu 90° gebogen werden kann um verschiedene Tumorbereiche zu erreichen</p>	<p>STAR® Tumor Ablation System</p> <p>This ablation probe has a bipolar extensible radiofrequency electrode at the top of the articulated distal segment. The segment can be curved up to 90° and, therefore, is able to access multiple areas of the tumour. The system comprises also a combination of two thermocouples, which enable real-time monitoring of temperature. This bipolar design reduces the risk of skin burn and does not require a grounding pad [9, 19].</p>
<p>Höhle wird mit Plasmaerzeugung bei niedriger Temperatur im Tumorgewebe erreicht; Ablation erfolgt mit vorgebogener, drehbarer Plasmasonde</p>	<p>CAVITY-SpineWand®</p> <p>The CAVITY-SpineWand® probe creates a cave in the tumour tissue by plasma generation (coblation-controlled ablation) at a low temperature (about 42°C) on the basis of plasma-mediated high-frequency energy. Coblation (radiofrequency-based plasma ablation) means a controlled ablation with a pre-bent plasma probe. The probe can be rotated so the ablation can take place in several directions. Coblation can be combined with additional procedures, in particular with vertebroplasty [8, 20, 21].</p>
<p>RFA hat verschiedene Vorteile gegenüber anderer Therapie:</p>	<p>Boo02 – What is the claimed benefit of radiofrequency ablation?</p> <p>Several advantages are discussed for RFA in comparison to other treatments: cell death of the metastasis can be achieved immediately, accurate control of the lesion size, monitoring of the lesion temperature, electrode placement with a percutaneous image-guided procedure, and RFA can be performed under local anaesthesia and conscious sedation [6].</p>
<p>kurze Behandlungsdauer, schonende Vorgehensweise, sofortige Schmerzreduktion & Stabilität/ Frakturprophylaxe</p>	<p>According to the information provided by the submitting hospital, RFA for metastatic spinal lesions may lead to immediate stabilization/prevention of fractures, immediate pain reduction, shortened length of hospital stay (1d), and shorter treatment duration. Therefore, an increased HRQoL and functionality may be recorded. Another advantage of this method is the minimally invasive approach (low potential for injuries of sensitive adjacent neural structures) as well as that interrupting chemotherapy is not necessary. Furthermore, the treatment represents an alternative to the therapy by radiation.</p>
<p>1992 erste Verwendung; aktuell noch nicht klinischer Standard</p>	<p>Boo03 – What is the phase of development and implementation of radiofrequency ablation?</p> <p>RFA was first described in 1992 as an auspicious technique for the treatment of osteoid osteomas [22, 23]. According to the information provided by the submitting hospital and the included studies, RFA is not a clinical standard for the treatment of metastatic spinal lesions.</p>

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers radiofrequency ablation and in what context and level of care is it provided?

B0008 – What kind of special premises are needed to use radiofrequency ablation?

B0009 – What supplies are needed for radiofrequency ablation?

According to the information received by the submitting hospital, neurosurgery departments of university hospitals with interdisciplinary tumour boards perform the intervention. The intervention is performed in general anaesthesia or conscious sedation and in prone position. RFA requires placing of the electrode under imaging guidance straight into the metastasis [4, 6].

A close interdisciplinary cooperation between the orthopaedic surgeons and spine surgeons with other specialists such as radiologists, radiotherapists, oncologists, histopathologists, pain therapists, physiotherapists etc. is of critical importance for the treatment of vertebral metastases [8, 20]. The appropriate therapy has to be carefully and individually planned on the basis of several criteria and parameters (clinical, radiological, histopathological, etc.) [9, 17, 18].

Constant follow-up examinations should be performed, clinical and radiological, in order to exclude local recurrence, relaxations, and fractures and to assess the condition, satisfaction, HRQoL, and pain relief. Postoperative local radiotherapy and chemotherapy may be performed to cope with the primary tumour and possible other metastases [8].

RFA can also be performed in an outpatient setting under conscious sedation because it is associated with short recovery [4].

Universitätsklinik für Neurochirurgie mit interdisziplinärem Tumorboard; Bauchlage, Intubationsnarkose, unter bildgebenden Verfahren

wichtig: interdisziplinäre Kooperation, sorgfältige Planung & konstante Folgeuntersuchungen

RFA kann auch im ambulanten Bereich erfolgen

Regulatory & reimbursement status

A0020 – For which indications has radiofrequency ablation received marketing authorisation or CE marking?

RFA for metastatic spinal lesions is a procedure and is therefore not subject to regulation by the Food and Drug Administration (FDA). However, the FDA regulates RFA devices and hence, there are various devices listed in the FDA 510(k) Premarket Notification database. The following products are an excerpt of devices that received FDA clearance (generators and lesion probe devices):

- ❖ OsteoCool® V-2 RF Ablation System for palliative treatment in spinal procedures by ablation of metastatic malignant lesions in a vertebral body (Baylis Medical Company Inc., approved 2015)
- ❖ STAR® Tumor Ablation System for palliative treatment in spinal procedures by ablation of metastatic malignant lesions in a vertebral body (SpineSTAR® ablation instrument and the MetaSTAR® generator) (DFine Inc., approved 2010/Merit Medical Systems, Inc.)
- ❖ ArthroCare® Cavity SpineWand® for resection, ablation, and coagulation of soft tissue and haemostasis of blood vessels in percutaneous, intraoperative, or spinal procedures including the creation of a cavity in malignant lesions in a vertebral body (ArthroCare Corporation, approved 2007)

FDA reguliert RFA Produkte (nicht indikationsspezifisch)

6 Systeme von der FDA zugelassen (evtl. weitere zugelassen)

- ❖ Cool-tip RF System (generator and accessories) for the use in percutaneous, laparoscopic, intraoperative coagulation and ablation of tissue such as partial or complete ablation of non-resectable liver lesions and osteoid osteoma tumors within bone (Valleylab, approved 2006)
- ❖ RITA® System (RF generator and electrosurgical devices) supplies energy for use in electrosurgery and is indicated for use in percutaneous, laparoscopic, or intraoperative coagulation and ablation of soft tissue, including the partial or complete ablation of non-resectable liver lesions and the palliation of pain associated with metastatic lesions involving bone in patients who have failed or are not candidates for standard pain therapy (RITA Medical Systems Inc., approved 2004)
- ❖ ArthroCare Orthopedic Electrosurgery System for resection, ablation, and coagulation of soft tissues and hemostasis of blood vessels in orthopaedic, arthroscopic, and spinal procedures (ArthroCare Corporation, approved 1999)

STAR® Tumor Ablation System ist CE-zertifiziert

The STAR® Tumor Ablation System has also received CE Marking according to the information received by the manufacturer. We were not able to identify a comprehensive list of other currently CE marked RFA systems and we refrained from a manual search for the CE marking of various RFA components.

Intervention wird in Österreich derzeit nicht erstattet

Aoo21 – What is the reimbursement status of radiofrequency ablation?

Currently, RFA for metastatic spinal lesions is not included in the Austrian DRG-system (Leistungsorientierte Krankenanstaltenfinanzierung/LKF). Therefore, the intervention itself is not reimbursed by the Austrian health care system. However, the intervention could be billed under another code, such as for erection and filling of the vertebral body by percutaneous puncture (e.g., RFA in combination with vertebroplasty) (Code LH020 – Aufrichtung und Füllung des Wirbelkörpers durch perkutane Punktion) [24].

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions and for what purposes is radiofrequency ablation used?

RFA is used for patients with vertebral and bone metastases of all entities and with fracture endangering, in whom a curative tumour therapy (e.g., radiation therapy) is not indicated or contraindications may occur [9]. The treatment with RFA should only be performed in patients with localised moderate pain (>4 VAS score) [2, 16].

Metastatic spinal lesions are often unstable and therefore, in most cases, cannot be treated with a conservative therapy (e.g., radiation) in most cases [21]. Additionally, patients who do not respond to a conventional treatment often have a contraindication to radiation therapy and may benefit from RFA [7]. Furthermore, this intervention can be performed in patients who cannot or will not undergo surgery.[15]. The intervention is not curative, but palliative [25].

Vertebral metastases are adjacent to nerves and there is a risk of nerve injury in the spinal cord that can be accompanied with curative treatments [26].

RFA is contraindicated for patients with asymptomatic vertebral compression fracture, effective medical therapy (e.g. analgesics), infections, coagulopathy, and tumour causing spinal cord compression [27].

A0002 – What is the disease or health condition in the scope of this assessment?

In the scope of this assessment, vertebral metastases are the condition of interest. Overall, bone metastases are a common manifestation of various types of solid cancers, e.g. those arising in the breast, lung and prostate [2, 3].

A0003 – What are the known risk factors for vertebral metastases?

The primary risk factor for vertebral metastases is the progress of the primary cancer. Risk factors for vertebral metastases depend on the primary cancer. Vertebral metastases are more often stemming from primary tumours in the lung, breast, and prostate than from other tumour types (e.g., melanoma). There are multiple additional risk factors: progression of the primary cancer, tumour spread, stage of disease etc. [7].

A0004 What is the natural course of vertebral metastases?

Many tumour patients develop painful vertebral metastases in the course of their disease, which destroy the vertebrae. These metastases represent the most common cause of chronic pain, fractures, reduced mobility and spinal cord compression [1, 2]. Therefore, patients with untreated painful vertebral metastases may suffer from several complications, e.g., fractures, decreased HRQoL, decreased mobility, and reduced performance status. Consequently, it can have negative effects on the functional capacity and can lead to depression and anxiety states [2-4]. The treatment of metastatic spinal lesions is usually palliative [5].

RFA für PatientInnen mit solitären spinalen Metastasen aller Entitäten, bei denen eine kurative Behandlung nicht indiziert ist

Intervention sollte in palliativem Setting erfolgen

Fokus: Metastasen in der Wirbelsäule

bedeutender Risikofaktor: Fortschreiten des primären Tumors

viele TumorpatientInnen entwickeln WS-Metastasen, die die häufigste Ursache für chronische Schmerzen, Frakturen und Rückenmarkskompressionen darstellen

**Knochen sehr häufig
von Metastasen
betroffen**

Besides the lung and liver, the bone is one of the most commonly affected organs by metastases [28]. Vertebral metastases are the most common bone metastases because of the high hematopoietic activity and vascularization of the vertebrae [15].

**Lebenserwartung
~3-6 Monate**

Patients with osseous metastatic disease have a limited life expectancy with an average median survival time of 3-6 months [6].

Effects of the disease or health condition on the individual and society

A0005 – What are the symptoms and the burden of disease of vertebral metastases for the patient?

**PatientInnen
haben verminderte
Lebensqualität aufgrund
unerträglicher
Schmerzen**

Patients in a progressed tumour stage can develop symptoms of paraplegia or massive pain because of a local spinal process. In many cases, those patients cannot be treated with surgery due to a reduced general condition and an adverse prognosis of the underlying disease [29]. Palliative care for patients with vertebral metastases can be challenging. Most patients have a very poor HRQoL because of intolerable pain. About 90% of the patients experience pain [9, 15, 30]. Another important factor is the risk of pathological fractures and spinal instability of the vertebral body, hypercalcemia, or spinal cord compression due to progression of metastatic spinal lesions [2, 28].

**pathologische Frakturen
sowie Instabilität der
Wirbelkörper**

A palliative approach, such as minimally invasive procedures, can be a useful treatment option [29].

A0006 – What are the consequences of vertebral metastases for the society?

**zunehmende Häufigkeit
aufgrund alternder
Bevölkerung**

Due to the aging population and the fact that higher age is the main risk factor for cancer, the incidence of cancer will increase over time [31]. In Austria, 38,908 newly diagnosed cancer patients were recorded in 2014. Of those, about 12% have already been diseased by remote metastases [32]. Bone metastases are very common in patients with metastasised cancer whereby the vertebrae is most frequently affected (~40%) [9].

Data on the actual number of patients affected by vertebral metastases could not be identified.

Current clinical management of the disease or health condition

A0024 – How are vertebral metastases currently diagnosed according to published guidelines and in practice?

**keine österreichischen,
dafür zahlreiche
internationale Leitlinien
zu diversen Krebser-
krankungen identifiziert
(z. B. AWMF)**

No Austrian guidelines for the diagnosis (and treatment) of vertebral metastases were identified. Depending on the primary tumour, several international guidelines can be found on the diagnosis and treatment of lung, prostate, or breast cancer. These guidelines mostly include a section for remote metastases, e.g., the guideline of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF) for “Interdisciplinary S3 guideline for the diagnosis, therapy and aftercare of breast cancer” (Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms). An intensified instrumental and laboratory diagnosis with chest X-ray, bone scintigraphy, CT, PET, or MRI as well as blood count determination, serum biochemistry, or tumour marker determination belong to the diagnosis of metastases and are only indicated in clinical abnormalities [33].

**bildgebende
Untersuchungen sind
essentiell für die
Diagnose von
Knochenmetastasen**

The diagnosis of the tumour or the vertebral metastases has to be confirmed clinically, radiologically, and histologically in each patient [8]. The diversity of clinical and radiological presentations may elucidate why there is no optimal treatment for vertebral metastases [10].

A0025 – How are vertebral metastases currently managed according to published guidelines and in practice?

Standard of care treatment options for vertebral metastases include localized therapies (radiation therapy and surgery), systemic therapies (chemotherapy, hormonal therapy, radiopharmaceuticals and bisphosphonates), and analgesics (opioids and nonsteroidal anti-inflammatory drugs). The mainstay of treatment is external beam radiotherapy, but 20-30% of patients do not experience accurate pain relief after radiotherapy [1, 3, 34]. A complete removal of vertebral metastases is not possible with these therapy approaches and furthermore, there is a considerable risk of injury of the healthy tissue. In addition, for many patients with a reduced general condition, major surgical procedures are contraindicated in the vertebrae [8].

In either case, in the curative as well as the palliative therapy, objectives of the operative treatment are a least possible traumatization of the soft tissues and bones, in addition to the pain reduction and the improvement of HRQoL by:

- ✧ using minimally invasive techniques,
- ✧ the reduction of blood loss,
- ✧ maintaining the stability of the vertebrae and spinal segments,
- ✧ the correction of deformities or the reduction of compression fractures,
- ✧ the decompression and dilatation of the spinal canal with as complete as possible removal of the tumour tissue,
- ✧ the avoidance of fractures in case of massive osteolysis of the vertebral body [8].

For stabilisation and prevention of fracture in weight-bearing bones, a vertebroplasty can be routinely performed into the ablated cavity [9].

Target population

A0007 – What is the target population in this assessment?

The target population in this assessment are, according to the information received by the submitting hospital, patients with solitary fracture-related metastases of all entities in whom a curative tumour treatment (vertebral body extension and stabilization) is not indicated in a palliative setting after maximal radiation dose or with radiation-resistant lesions.

It can be assumed that the target population for the intervention is small [11].

SoC:
Bestrahlung, Operation, systemische Therapien und Analgetika

Basisbehandlung:
externe Strahlentherapie

Ziel der Behandlung:
Schmerzreduktion, Verbesserung der Lebensqualität und eine geringe Traumatisierung des umliegenden Gewebes

PatientInnen bei denen kurative Behandlung nicht indiziert oder kontraindiziert ist

wahrscheinlich geringe Anzahl an PatientInnen

**KrebspatientInnen
entwickeln zu 30-90 %
Metastasen in der WS
(abhängig von
Primärtumor);
zum Zeitpunkt des
Todes leiden ~50 % der
KrebspatientInnen an
WS-Metastasen**

**Frequenz der RFA
von einreichender
Institution auf
~12/Jahr geschätzt;
für Gesamtösterreich
keine Schätzung**

A0023 – How many people belong to the target population?

Overall, the spine is most frequently affected by bone metastases accounting for 40% of all bone metastases. Patients with breast or prostate cancer develop metastases in the spine in about 70-90% of the cases, and patients with lung, kidney, or thyroid cancer about 30-40% [9]. Due to the high vascularization of adults' vertebrae, various patients develop metastases in the spine [1, 34]. At the time of death, about 80% of cancer patients are affected by bone metastases and of those, about 50% by vertebral metastases [3, 15].

A0011 – How much is radiofrequency ablation of vertebral metastases utilised?

According to the information provided by one Austrian hospital, the annual frequency in this hospital is estimated to be 12 RFA procedures of vertebral metastases. No total estimations were provided regarding the annual frequency in Austria.

5 Clinical effectiveness

5.1 Outcomes

Radiofrequency ablation for metastatic spinal lesions is primarily used to reduce the pain in the vertebrae of palliative patients to improve their HRQoL. Radiofrequency ablation devices are not used for a curative treatment of osseous cancers and metastases of the spine. Hence, the intervention does not influence patients' survival. Therefore, this outcome was not listed as crucial for the recommendation.

The following outcomes were defined as *crucial* to derive a recommendation:

- ✿ Pain relief
- ✿ Health-related quality of life (HRQoL)
- ✿ Functional status

Further outcomes were defined as *important, but not crucial* to derive a recommendation:

- ✿ Satisfaction with treatment
- ✿ Recurrence of vertebral metastases
- ✿ Mortality, improved survival

Changes in pain intensity and pain relief were measured in all but one of the included studies with the Visual Analogue Scale (VAS), the Numeric Rating Scale (NRS), or the Numerical Pain Rating Scale (NPRS). One study did not report any pain assessment tool [29].

The HRQoL was assessed by various tools: the included studies used the FACT-G7, FACT-BP [1], and the QoL Oswestry Index [22].

The functional status was measured in 2 studies using the Modified Oswestry Disability Index (MODI) [1].

The individual scores for pain, functional status, and HRQoL measurements will be further explained in the evidence tables (see Appendix Table A-1) where applicable.

5.2 Included studies

To assess the effectiveness of radiofrequency ablation for metastatic spinal lesions, we could not identify any comparative studies. The only studies that met our inclusion criteria were four prospective single arm, partly multicentric, studies [1, 22, 26, 29] with a total of 112 patients, which assessed the effectiveness of radiofrequency ablation combined with vertebroplasty.

The mean age of patients ranged from 61 to 67.8 years across trials. The female study participants were underrepresented in all but one study (100%; range 33.3-100%) [22]. The mean follow-up of the studies was 3, 4.5, and 20.4 months [1, 22, 26]. One study reported the outcomes only 24-48 hours post-treatment [29].

entscheidungsrelevante Endpunkte für die Wirksamkeit:

- ✿ Schmerzen
- ✿ Funktionalität
- ✿ Gesundheits-bezogene Lebensqualität

wichtige Endpunkte:

- ✿ PatientInnen-zufriedenheit
- ✿ Lokalrezidive
- ✿ Mortalität, verbesserte Überlebensrate

verwendete Messinstrumente in Evidenztabelle

4 prospektive Einzelarm-Studien mit 112 PatientInnen

hohes Alter, überwiegend männliche Patienten, Beobachtungszeitraum durchschnittlich bis zu 20,4 Monate

Einschlusskriterien:
schmerzhafte spinale
Metastasen,
keine Reaktion auf
bisherige Therapien
etc.

Inclusion criteria differed slightly between studies. Across studies, patients were eligible for inclusion if they had painful vertebral metastases and were unresponsive to previous treatments (e.g. analgesics, radiation, or chemotherapy). Other inclusion criteria were: absence of neurological deficits, pain increase during movement, intervertebral tumour spread, and risk of paraplegia and fracture. For detailed information see Appendix (Table A-1).

Patients with heart pacemakers or other electronic device implants, risk of bleeding, acute infections, or allergies to anaesthesia etc. were contraindicated for RFA treatment and hence usually excluded.

Ausschlusskriterien:
Schrittmacher,
Infektionen, Allergien

unterschiedliche
RFA-Systeme in Studien

Four different RFA systems were used in the studies: the STAR Tumour Ablations System (DFine Inc., USA) in [1], the CelonLab Power & Celon Aquaflo III (Celon AG Medical Instruments, Germany) in [29], the Celon Pro Surge & CelonPower System (Celon AG Medical Instruments, Germany) in [22], and the Cool-tip RF Ablation System (Valleylab, USA) in [26].

Loss to follow-up ranged from 0 [26] to 32% in [1], 2 studies did not report on loss to follow-up [22, 29].

Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table 7-1.

5.3 Results

Morbidity (Pain)

D0005 – How does radiofrequency ablation affect symptoms and findings (severity, frequency) of painful vertebral metastases?

Endpunkt Schmerz:

3 prospektive Studien
berichten von
signifikanter
Schmerzreduktion
sowohl direkt nach RFA-
Behandlung, als auch
1, 3 und 15-36 Monate
nach der Behandlung

Nachbeobachtungszeit-
räume unterscheiden
sich in allen 3 Studien

All four prospective studies reported outcomes on pain: two prospective studies reported pain reduction outcomes as changes in VAS scores [22, 26] and in one study as changes in NPRS scores [1]. Both scales range from 0 (no pain) to 10 (worst possible pain). The last prospective study only reports the percentage of patients with pain reduction without specification of the tool [29].

Three of those studies reported significant pain relief after the treatment with RFA, and in most cases with an additional treatment of vertebroplasty. The differences in pain relief can be explained by several factors including differences in tumour types or the number of painful sites previously radiated.

One study reported a statistically significant decrease in pain (decrease by 2.2, $p < 0.0001$) at one month (decrease by 3.3, $p < 0.0001$) as well as three months (decrease by 3.8, $p < 0.0001$) post treatment in comparison to baseline pain scores [1].

In the second study, pain was significantly decreased in all patients by 4.8 points ($p < 0.00005$) compared to baseline at one week post-intervention. 6 out of 10 patients received vertebroplasty after RFA, but no difference in pain was reported. In addition, in 90% of the included patients (9/10), pain relief sustained until the moment of death [26].

The third study performed RFA in the first group (n=8) and RFA in combination with vertebroplasty in the second group (n=8) of patients. No significant differences in pain relief were reported between the groups. This study reported a significant decrease in pain post-intervention in both groups (2.4 in group 1 (p<0.018) and 2.6 in group 2 (p<0.005)). After a follow-up of 15-36 months, the study stated an ongoing statistically significant decrease in pain in both groups compared to baseline (3.9 in group 1 (p<0.008) and 4.1 in group 2 (p<0.005)) [22].

The last prospective study only stated that a proportion of patients (19 cases; 52.8%) reported post-interventional pain reduction [29].

D0006 – How does radiofrequency ablation affect progression (or recurrence) of vertebral metastases?

To answer this research question, the outcome “recurrence of vertebral metastases (local relapse)” was used.

This outcome was reported in one prospective study with 16 patients and a mean follow-up of 20.4 months. In none of the patients who underwent RFA or RFA in combination with vertebroplasty a local relapse of the vertebral metastases was reported [22].

Health-related quality of life

D0012 – What is the effect of radiofrequency ablation on generic health-related quality of life?

D0013 – What is the effect of radiofrequency ablation on disease-specific quality of life?

HRQoL has been assessed in 2 prospective studies with different instruments.

One prospective study used cancer-specific health-related quality-of-life instruments, the Functional Assessment of Cancer Therapy-General 7 (FACT-G7) and Functional Assessment of Cancer Therapy Quality-of-Life Measurement in Patients with Bone Pain (FACT-BP)¹ to assess the HRQoL. This study observed statistically significant improvement in both scores compared to baseline throughout the follow-up of 1 month (improvement of 4.8 in FACT-G7 and 14.7 in FACT-BP) and 3 months (improvement of 5.2 in FACT-G7 and 16.3 in FACT-BP) [1].

Another prospective study used the Oswestry Disability Questionnaire² for assessing HRQoL. This study performed RFA in the first group (n=8) and RFA in combination with vertebroplasty in the second group (n=8). No significant differences in HRQoL were reported between groups. After 3-6 months

keine signifikanten Unterschiede zwischen RFA und RFA in Kombination mit Vertebroplastie; 1 weitere Studie berichtet lediglich von einer Schmerzreduktion in 19 Fällen post-interventionell;

Endpunkt Lokalrezidive:

in einer prospektiven Studie (~20,4 Monate Nachbeobachtung) sind keine Lokalrezidive aufgetreten

Endpunkt Lebensqualität

Signifikante Verbesserung der Lebensqualität nach 1 und 3 Monaten (1 Studie)

1 weitere Studie: signifikante Verbesserung mit RFA (3-6 Monate)

¹ The FACT-G7 is abbreviated to seven evaluable questions and it is considered a rapid version of the FACT-G that has 27 questions. FACT-BP is specifically designed for use in cancer patients with bone pain and it contains 15 evaluable questions. Each questionnaire provides a calculation to generate a composite score. Higher scores are interpreted as greater patient quality of life and lower scores are interpreted as lower patient quality of life. FACT-G7 has a scale 0-28 and FACT-BP 0-60.

² The Oswestry Disability Index (ODI) is a validated scale comprised of ten questions designed to assess pain intensity and activities of daily living. The ODI ratings and corresponding categories are 0-20 (minimal disability), 20-40 (moderate disability), 40-60 (severe disability), 60-80 (crippled) and 80-100% (bed bound).

sowie mit RFA & Vertebroplastie (15-36 Monate); keine signifikanten Gruppenunterschiede

in the first group and after 15-36 months in the second group, the score significantly improved by 31% compared to baseline. The improvement in HRQoL right after the treatment was reported the same for both groups (significant improvement of 30% compared to baseline). Thus, it is a categorical improvement in HRQoL from “crippled” to moderate disability, but no further improvement occurred during follow-up [22].

The remaining 2 studies did not report this outcome.

Functional status

Doo11 – What is the effect of radiofrequency ablation on patients’ body functions?

keine Evidenz

None of the studies reported results on patients’ body functions.

Doo16 – How does the use of radiofrequency ablation affect activities of daily living?

Endpunkt Funktionalität: signifikante Verbesserung nach 1 und 3 Monaten im Vergleich zum Ausgangswert, jedoch basierend auf 1 Studie

One of the included prospective studies provided Modified Oswestry Disability Index (MODI)³ data on back-related disability with statistical significant improvement in short term (1 month: 40%) and midterm (3 months: 37%) post-treatment compared to baseline (52.9%). That represents an improvement in functional status from severe to moderate disability [1]. The remaining 3 studies did not report on this outcome [22, 26, 29].

Because functionality and HRQoL are both related with pain, there are unclear interfaces between the MODI and ODI scores.

Patient satisfaction

Doo17 – Were patients satisfied with radiofrequency ablation?

keine Evidenz

None of the included studies reported results on patient satisfaction.

Mortality

Dooo1 – What is the expected beneficial effect of radiofrequency ablation on mortality?

Endpunkt Mortalität, verbesserte Überlebensrate:

RFA zielt nicht auf Verbesserung der Überlebensrate ab, da palliative Therapie

Mortality (improved survival) is an important outcome that is, however, not crucial for assessing the clinical effectiveness of RFA because it is a palliative treatment that does not aim for life-prolonging effects.

Only two studies reported outcomes on mortality: one study reported 5 deceased patients (10%) during the follow-up period of 3 months [1]. Another study followed the total of 10 patients until their death, median of 4.5 months (100%) [26]. Since none of the studies included a control group, they could not provide any serious information on a possible survival prolongation.

³ The Modified Oswestry Disability Index (MODI) is a validated scale comprised of ten questions designed to assess pain intensity and activities of daily living. The MODI ratings and corresponding categories are 0–20 (minimal disability), 21–40 (moderate disability), 41–60 (severe disability), 61–80 (crippled) and 81–100% (bed bound).

6 Safety

6.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

- ✿ Complications:
 - ✿ Major complications
 - ✿ Adverse events (procedure-related)
 - ✿ Adverse events (not procedure-related)

According to the Society of Interventional Radiology classifications C-E, a major complication is an event that resulted in substantial morbidity or disability, an increase in the level of care, admission to the hospital, or substantial prolongation of the hospital stay [26].

Procedure-related Adverse Events are complications that are associated with the intervention. Possible procedure-related complications are events associated with anaesthesia, infections, damages to nerves or blood vessels, bleeding, or the occurrence of blood clots (e.g. thrombosis).

An Adverse Event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons whether or not related to the investigational medical device. This includes events related to the investigational device or related to the procedures involved (any procedure in the clinical investigation plan).⁴

**entscheidungsrelevanter
Endpunkt für die
Sicherheit:
Komplikationen**

6.2 Included Studies

There are no comparative studies to assess the safety of radiofrequency ablation. In order to assess safety-related outcomes, we accepted all published evidence, except for retrospective studies. We only included studies with more than 30 patients.

We identified four prospective single arm studies that assessed the safety of RFA in a total of 112 patients besides the clinical effectiveness [1, 22, 26, 29]. Patient and study characteristics are displayed in Chapter 5.2.

In addition, we identified five retrospective single arm studies that assessed the safety of radiofrequency ablation in a total of 471 patients [4, 8, 12, 15, 25].

keine Vergleichsstudien

**4 prospektive Studien
bereits inkludiert
(siehe 5.2)**

**5 retrospektive
Einzelarm-Studien
mit insgesamt
471 PatientInnen**

⁴ http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf

hohes Alter,
überwiegend weibliche
Patientinnen,
Beobachtungszeitraum
durchschnittlich bis zu
60 Monate

The mean age of patients ranged from 62.7-69.6 years across these studies. The percentage of female participants was more than 57% in all but one study (39%) [25] with a maximum of up to 62.4% [8]. One study did not report the baseline characteristics for age and gender [15]. All studies included patients with painful vertebral metastases, intravertebral tumour spread, disease progression and fractures with instability.

The follow-up of the studies was 2-4 weeks [12], 1 month [4], ≥ 6 months [15, 25], and up to 60 months [8]. Loss to follow-up ranged from 3.1 [8] to 61% [25]. The high loss to follow-up rate in [25] is probably attributable to the follow-up of 278-617 days and a more severe progression of the primary cancer at study entry (see Appendix Table A-1, Table A-2, Table A-3).

2 Studien basieren
möglicherweise auf
überschneidender
PatientInnen-Gruppe →
evtl. unscharfe
Ergebnisdarstellung

For two of the included retrospective studies, it can be assumed, but it is not clearly stated, that observed patient populations overlap (some of the 72 patients included in [4] are assumed to be summarized in the 92 patients of [15]). We decided to report outcomes of these studies separately, but consequently, data may be imprecise.

Study characteristics and results of included studies are displayed in Table A-1, Table A-2 and Table A-3 and in the evidence profile in Table 7-1.

6.3 Results

Patient safety

C0008 – How safe is radiofrequency ablation in comparison to the comparator(s)?

There is no direct comparator to RFA therapy.

None of the included studies reported major complications with the use of RFA.

Overall, adverse events (procedure-related or not procedure-related) occurred in 105 patients who completed the follow-up, out of 583 included patients across the studies (18%).

Adverse events (procedure-related)

The most frequent adverse events reported were increased pain and numbness (7.8%, 6/77 patients) [25, 29], and post-procedure radicular symptoms and pain (4.6%, 5/109 patients) [4, 12]. Other occurred procedure-related adverse events were epidural extravasation (5.4%, 2/37 patients) [12], transient nerve injury (10%, 1/10) [26], unilateral monoradiculopathy (2.4%, 1/41), and “heavy legs” with paraesthesia (2.4%, 1/41) [25].

Four of the included studies did not report any procedure-related adverse events [1, 8, 15, 22].

Endpunkt
Komplikationen:
keine schwerwiegenden
Komplikationen durch
RFA aufgetreten

insgesamt 105 (18 %)
unerwünschte
Ereignisse aufgetreten

häufigste
Nebenwirkungen von
RFA: Schmerzen und
Taubheit, sowie
Radikulärsyndrome

Adverse events (not procedure-related)

The most frequent adverse event reported, which is not RFA-related, but vertebroplasty-related, was cement extravasation (18.7%, 67/358 patients) [8, 12, 15]. Progression of primary cancer was reported in 8/57 patients (14%) [22, 25], fracture (without vertebroplasty) occurred in 2/92 patients (2.2%) [15], nerve root block in 3/36 patients (8.3%) [29], pain outside the target vertebrae due to progression of the primary or other metastatic disease in 3/50 patients (6%), ruptured disk adjacent to the index vertebra in 1/50 patients (2%), neuropathic pain in 1/50 patients (2%), and syncope in 1/50 patients (2%) [1]. Recurrent pain after 2 months occurred in 1/10 patients (10%) and newly developed pain after 2 months in 2/10 patients (20%) [26].

Only one study did not report any procedure-unrelated adverse events [4].

häufigstes unerwünschtes Ereignis aufgrund von Zusatz-Therapien: Zementaustritt

weitere unerwünschte Ereignisse: Fortschreiten des Tumors, Frakturen und Nervenwurzelblockaden

C0002 – Are the harms related to dosage or frequency of applying radiofrequency ablation?

No evidence was found to answer the research question.

keine Evidenz

C0004 – How does the frequency or severity of harms change over time or in different settings?

No evidence was found to answer the research question.

keine Evidenz

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of radiofrequency ablation?

No evidence was found to answer the research question.

keine Evidenz

C0007 – Is radiofrequency ablation associated with user-dependent harms?

No evidence was found to answer the research question.

keine Evidenz

Investments and tools required**B0010 – What kind of data/records and/or registry is needed to monitor the use of radiofrequency ablation?**

No evidence was found to answer the research question.

keine Evidenz

7 Quality of evidence

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [14] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [14].

GRADE uses four categories to rank the strength of evidence:

- ✧ **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- ✧ **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- ✧ **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- ✧ **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in Table 7-1.

The strength of evidence on clinical effectiveness of RFA for metastatic spinal lesions could not be assessed due to the lack of trials with a comparative treatment arm (study design).

Overall, the strength of evidence for the safety of RFA for metastatic spinal lesions is very low.

Qualität der Evidenz nach GRADE

GRADE Tabelle nächste Seite

Gesamtstärke der Evidenz für klinische Wirksamkeit nicht bestimmbar

Gesamtstärke der Evidenz für Sicherheitsendpunkte sehr niedrig

Table 7-1: Evidence profile: efficacy and safety of radiofrequency ablation for metastatic spinal lesions

No of studies/ patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
Pain relief							
No data ⁵							
Functional status							
No data ⁵							
Health related quality of life (HRQoL)							
No data ⁵							
Safety							
Overall complications							
4/112	Prospective single arm studies	20/112 (17.9%); Range: 19.4-40%	Serious limitations (-1) ⁶	o	Direct	Imprecise data (-1) ⁷	Very low
5/471 ⁸	Retrospective single arm studies	58/471 (12.3%); Range: 4.3-21.9%	Serious limitations (-1) ⁶	o	Direct	Imprecise data (-1) ⁹	Very low
Major complications (procedure-related) *							
4/112	Prospective single arm studies	o	Serious limitations (-1) ⁶	o	Direct	Imprecise data (-1) ⁷	Very low
5/471 ⁸	Retrospective single arm studies	o	Serious limitations (-1) ⁶	o	Direct	Imprecise data (-1) ⁹	Very low
Adverse events (procedure-related)							
4/112	Prospective single arm studies	5/112 (4.5%); Range: 10-11.1%	Serious limitations (-1) ⁶	o	Direct	Imprecise data (-1) ⁷	Very low
5/471 ⁸	Retrospective single arm studies	11/471 (2.3%); Range: 0-9.8%	Serious limitations (-1) ⁶	o	Direct	Imprecise data (-1) ⁹	Very low
Adverse events (not procedure-related)							
4/112	Prospective single arm studies	15/112 (13.4%); Range: 8.3-30%	Serious limitations (-1) ⁶	o	Direct	Imprecise data (-1) ⁷	Very low
5/471 ⁸	Retrospective single arm studies	74/471 (15.7%); Range: 4.3-73%	Serious limitations (-1) ⁶	o	Direct	Imprecise data (-1) ⁹	Very low

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

* None of the included studies reported any serious adverse events related to the procedure.

⁵ Due to the lack of a controlled group, no data on efficacy outcomes can be compared and synthesized.

⁶ No control group.

⁷ Small numbers of patients in included studies.

⁸ 72 patients of [4] may already be included in another retrospective study [15].

⁹ Overlap of patients in two studies.

8 Discussion

Vertebral metastatic lesions are difficult-to-treat entities that most frequently affect patients who are suffering from breast, lung, or prostate cancer. Vertebral metastases are most commonly associated with (progressive) pain and severely reduced HRQoL of affected patients. Untreated or progressing bone lesions can lead to pathological fractures and spinal instability, hypercalcemia or spinal cord compression. For a variety of patients, RFA is performed as a palliative therapy, especially for multimorbid elderly patients. Hence, RFA is performed in patients with metastatic spinal lesions primarily as a palliative pain therapy [1, 2, 8]. Currently, available evidence focusses on the feasibility and safety of radiofrequency ablation as a palliative pain treatment.

The aim of this report was to assess the clinical effectiveness and safety of RFA (with/without vertebroplasty or other add-on therapies) compared to another or no treatment.

Interpretation of the findings

We identified 9 single-arm studies (4 prospective and 5 retrospective studies) for assessing the clinical effectiveness and safety of radiofrequency ablation for metastatic spinal lesions. A total of 583 patients were enrolled in the included studies.

Our systematic search was not limited to a specific study design or time period. Retrospective studies had to include more than 30 patients diseased by vertebral metastases. Across all studies, a variety of ablation systems were used, the most commonly used was the *STAR[®] Tumor Ablation System*. All of the identified studies included patients with vertebral metastases suffering from severe pain.

In terms of clinical effectiveness, we could not identify any controlled trials to assess the efficacy of RFA due to the lack of trials with a comparative treatment arm (study design; no robust evidence). Nevertheless, four prospective studies provided outcomes on the clinical effectiveness of RFA. Eligible patients of these studies had painful vertebral metastases and were unresponsive to previous treatments (e.g. analgesics, radiation, or chemotherapy). Other inclusion criteria were absence of neurological deficits, pain increase during movement, intervertebral tumour spread, and risk of paraplegia or fracture. Because the inclusion criteria differed slightly between studies, the determination of the best time for initiation of the treatment is difficult.

Scores that measured pain (measured in all studies), HRQoL (reported in 2 studies), and functional status (reported only in 1 study) were improved with the treatment of RFA (and vertebroplasty). All these changes were statistically significant in studies reporting on these outcomes. None of the studies reported changes on patient satisfaction with the treatment.

In one study, no recurrence of vertebral metastases was reported during a mean follow-up period of 20.4 months [22]. However, other studies did not report on this outcome. Data on mortality during the follow-up periods was assessed in two studies. Because RFA is a palliative treatment life-prolonging effects are not the primary aim of this technology and were not assessed in the studies.

**WS-Metastasen
schwierig zu behandeln
& assoziiert mit
Schmerzen und
Verminderung der
Lebensqualität**

**RFA meist als palliative
Schmerzbehandlung
durchgeführt**

**9 Einzelarm-Studien
eingeschlossen
(4 prospektiv &
5 retrospektiv)
mit insgesamt
583 PatientInnen**

**keine robuste Evidenz
für klinische
Wirksamkeit;
4 prospektive Studien:
statistisch signifikante
Verbesserungen in
Schmerzen,
Lebensqualität und
funktionellem Status
mit RFA (und
Vertebroplastie)**

**keine Evidenz
zu allgemeiner
Verbesserung oder
Therapiezufriedenheit**

**RFA wirkt sich nicht
auf Verbesserung der
Überlebensrate aus,
da palliative Therapie**

alle 9 Studien berichten von unerwünschten Ereignissen

In terms of safety, all of the 9 included studies reported complications, however, no major complications occurred in any of the studies. Hence, major complications may be rare and may only be determined in studies with larger patient samples or study registries.

keine schwerwiegenden Komplikationen

The overall complication rates were similar in all but two studies [12, 26]. This might be related to different follow-up periods and the stage of the disease. Procedure-related adverse events occurred in 5.6-16.6% of the patients across studies. The rates of adverse events that were not RFA-related (but vertebroplasty-related) ranged from 4.3-73% across all studies (most frequently reported adverse event was cement extravasation). These may be associated with the treatment near the spinal cord and are, therefore, of a particular concern.

Vertebroplastie häufig im Anschluss an RFA → Zementaustritt häufigstes unerwünschtes Ereignis

All of the included studies performed vertebroplasty treatment following RFA in most of the patients; if the destroyed tumour caused instability of the bone structure and a risk of fracture. Hence, vertebroplasty seems to offer a supportive treatment option following RFA in patients with vertebral metastases at the risk for fracture. Nevertheless, vertebroplasty might also be a confounder of the post-interventional pain evaluation.

Chemotherapie, Bestrahlung etc. kann ohne Unterbrechung fortgesetzt werden

According to included studies, adjuvant therapies, such as radiation or chemotherapy, are not postponed due to RFA and can be performed continuously as a therapy for primary cancers [4, 8].

Quality of Evidence

Stärke der Evidenz für klinische Wirksamkeit nicht bestimmbar; sehr geringe Stärke der Evidenz für Sicherheitsendpunkte

Overall, the strength of evidence on clinical effectiveness cannot be determined. The strength of evidence is “very low” for safety outcomes. The strength of evidence was mainly downgraded due to missing data of control groups and overlap of patients in two studies. Most of the effectiveness outcomes were patient reported, hence subject to a high risk of bias.

relativ kleine Fallzahlen in prospektiven Studien

A major concern of most of the identified prospective studies is the low number of included patients. For instance, one study included only 10 patients. In order to identify rare complications, low patient numbers are insufficient.

relativ kurze Nachbeobachtungszeiträume (palliativ)

Two studies had a very short follow-up period of 2-4 weeks. Yet, only one study had a follow-up of 60 months. Therefore, reliable data of long-term safety and efficacy outcomes are missing. However, data collection is extremely difficult because long-term follow-up is challenging in patients with metastatic spinal lesions due to high morbidity and mortality rates.

Mehrfachberichte von PatientInnen in 2 Studien möglich

Two studies were conducted in multiple centres [1, 15]. Four studies [4, 8, 12, 15] were most likely reporting on the same cohort as studies that we consequently excluded due to that fact [5, 20, 21, 34, 35]. It is probable that [4] included patients from [15], but only those patients with a VAS pain score of >4. This may distort the effect of RFA treatment.

zahlreiche Subanalysen zu Studien (ausgeschlossen); unklare Einschlusskriterien, nicht-konsequente Rekrutierung

Eligibility criteria were unclear in 3 studies [8, 12, 15] and non-consecutive patient recruitment was performed in 3 retrospective studies [4, 15, 25]. Three studies were included at first, but excluded after data extraction because too few patients with vertebral metastases were included [3, 6, 23]. Two of the studies were sponsored by manufacturers [1, 12], whereby the other studies did not report direct study sponsoring.

The utilised RFA systems and interventions differed slightly between the individual studies. For instance, patients were treated with additional therapies before or following RFA such as radiation therapy or analgesics. It is possible that these therapies and the different RFA systems have had an impact on the recorded outcomes of the studies (such as pain and HRQoL).

Nevertheless, the included studies in this review show that image-guided RFA with or without vertebroplasty might be a feasible and safe technique for patients with painful metastatic spinal lesions. Particularly so because there were no serious complications reported. No therapy means intolerable pain for the patient. If other treatments are contraindicated, RFA (in combination with vertebroplasty) may be an effective treatment for pain reduction on the basis of the included studies.

Due to the palliative course of the disease and the limited life expectancy of patients with painful metastatic spinal lesions, an effective and safe therapy, such as RFA, to improve pain relief and HRQoL that can also be performed on an outpatient setting might be beneficial.

Upcoming evidence

We identified 3 ongoing studies: one study is a phase II clinical trial evaluating the efficacy of thermal ablation in combination with spinal stereotactic radiosurgery with the primary outcome of the rate of local tumour control (estimated completion date August 2022) (NCT02713269).

Another one of the ongoing studies is listed as “STAR Tumour Ablation Registry” (observational study) with the estimated completion date in August 2018 and with pain relief as the primary outcome (NCT02419703).

We also identified one ongoing randomized parallel controlled trial, which analyses the effect of analgesia and tumour local control rate with the application of radiofrequency ablation combined with vertebroplasty compared to vertebroplasty only for vertebral metastases (ChiCTR-INR-16010135). This trial might show effects with a higher quality of evidence on pain and complications.

Furthermore, we found two “ongoing” interventional studies that were terminated because of difficulties with enrolling patients (NCT02225223 (n=36) & NCT02081053 (n=30)). Their primary completion date was October and November 2016, but no data was published.

Limitations

First of all, no RCT's or controlled trials were found in our literature search. Therefore, we decided to include prospective and retrospective observational studies and case-series for assessing the clinical effectiveness and safety of RFA. We only considered retrospective case-series with a patient cut-off of at least 30 patients treated for vertebral metastases. Thus, we excluded case-series with less than 30 patients. Presumably, there were numerous retrospective studies with less than 30 patients that were not included. It may be possible that we excluded studies that may have reported results of e.g., different complications or other products. Since we included single-arm prospective and retrospective studies, the sources of error due to confounding and bias are high.

**Interventionen in Studien wichen leicht voneinander ab
→ könnte Einfluss auf Ergebnisse haben**

eingeschlossene Studien zeigen, dass RFA (in Kombination mit Vertebroplastie) eine sichere Intervention für PatientInnen mit schmerzhaften WS-Metastasen ist

bei Kontraindikation mit anderen Therapien scheint RFA effektive Schmerzbehandlung zu sein

3 laufende Studien, eine davon ist als Registerstudie gelistet

mögliche Limitationen:
* keine RCT's verfügbar, deshalb pro- und retrospektive Studien eingeschlossen;
* nur Einzelarm-Studien
→ Bias-Risiko hoch

- ✦ Einsatz von Schmerzmitteln wurde nicht in Extraktionen erfasst → möglicher Confounder;
- ✦ Studien basieren auf subjektiven Angaben

RFA könnte eine sichere und wirksame Schmerzbehandlung für PatientInnen mit WS-Metastasen sein

diverse Therapien verfügbar; weitere Evaluierung wichtig, um Empfehlung aufrecht zu erhalten

weitere Studien bzw. Studienregister sind notwendig, um jene PatientInnen zu erreichen, die am meisten von der Intervention profitieren

Another limitation of this systematic review is that pain medication usage was not collected in the extraction table, but also not reported in all of the included studies and might be a possible confounder for the decrease in pain.

An additional limitation is that all the studies rely on subjective reported outcomes. For example, subjective pain scores may be confounded by analgesic medication. In addition, most of the RFA treatments were followed by vertebroplasty that is likely to be a possible confounder on post-interventional pain assessment.

Conclusion

In patients with metastatic spinal lesions who are unresponsive to conventional therapies, such as radiation or chemotherapy, who have contraindications to such therapies, or who are vulnerable for tumour progression, RFA (most commonly used in combination with vertebroplasty) may be a safe and effective therapy to palliate pain.

Further evaluation of RFA (in combination with vertebroplasty) for longer-term clinical efficacy and complication rates, in particular compared with traditional therapies, e.g., radiation, may be useful. The recommendation for the intervention cannot be maintained otherwise.

Because there are various operation techniques (e.g., differences in RFA-techniques, vertebroplasty following RFA etc.), further studies should be conducted to help determine the exact patient group that would benefit most from the intervention. Study registries may serve this purpose well.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlungsschema

Table 9-1: Evidence based recommendations

	The inclusion in the catalogue of benefits is recommended .
X	The inclusion in the catalogue of benefits is recommended with restrictions .
	The inclusion in the catalogue of benefits is currently not recommended .
	The inclusion in the catalogue of benefits is not recommended .

Reasoning:

The natural course of metastatic spinal lesions is fatal with intolerable pain. Thus, on ethical grounds, every therapy providing pain relief and causes no major complications may be justified. The current evidence indicates that the assessed technology RFA is, under certain conditions, effective and safe for the treatment of painful metastatic spinal lesions. The intervention should only be performed in specialized centres and, as possible, with registry acquisition for potential and rare adverse events.

Due to the low quality of evidence of the included studies, we recommend radiofrequency ablation for metastatic spinal lesions with restrictions. The technology might be used for patients with metastatic spinal lesions as palliative pain treatment in whom alternative treatments do not achieve sufficient effect or are contraindicated.

A re-evaluation is recommended after 2021 because of relevant ongoing studies, including a registry study that may provide new evidence of the technology (see Appendix Table A-6).

Empfehlung unter bestimmten Bedingungen → palliative Schmerzbehandlung in spezialisierten Zentren (möglichst mit Registererfassung für unerwünschte Ereignisse)

Re-Evaluierung nach 2021 empfohlen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: RFA: Results from prospective studies

Author, year	Bagla, 2016 [1]	Gazis, 2014 [29]	Nakatsuka, 2009 [26]	Proschek, 2009 [22]
Country	USA	Germany	Japan	Germany
Sponsor	DFINE Inc.	NR	NR	NR
Intervention/Product	RFA <i>STAR Tumor Ablation System (DFine Inc., USA)</i> Co-Intervention: vertebroplasty (47 pts)	RFA <i>CelonLab Power and Celon Aquaflow III (Celon AG Medical Instruments, Germany)</i>	RFA <i>Cool-tip RF Ablation System (Valleylab, USA)</i> Co-Intervention: vertebroplasty (n=6)	RFA (group 1) RFA & vertebroplasty (group 2) <i>Celon Pro Surge & CelonPOWER System (Celon AG Medical Instruments, Germany)</i> Co-Intervention: vertebroplasty (n=8/Group 2)
Study design	Multicentre single-arm prospective study (8 sites, USA)	Single-centre prospective cohort study (Retrospective analysis)	Single-centre prospective study	Single-centre prospective pilot-study
Setting (e.g. outpatient, university hospital etc.)	Hospital	University hospital	University hospital	University hospital (treated on an outpatient basis)
Number of pts	50	36	10	16 (8 vs. 8)
Inclusion criteria	<ul style="list-style-type: none"> ✳ ≥18 years; ✳ Painful vertebral body metastasis (VBM) in at least one thoracolumbar vertebra with the pain concordant to the metastatic lesion on cross-sectional imaging; ✳ Considered candidates for spinal tumor ablation by the operating physician; 	<ul style="list-style-type: none"> ✳ Severe local tumor pain insufficiently responsive to opiates and other analgesics; ✳ Disease progression despite previous surgery, maximal chemotherapy, maximal radiation and hormone therapy, lack of or highly invasive surgical option; ✳ Intervertebral tumor spread; ✳ Risk of paraplegia/fracture because of tumor progression; ✳ Locomotor disability because of local tumor process, and osteolytic/mixed metastases with palliative intention; 	<ul style="list-style-type: none"> ✳ Painful spinal tumor refractory to previous medical treatment with radiation therapy and/or chemotherapy; ✳ Distance of 1 cm or less between the spinal tumor invaded the posterior cortex of the vertebral body or pedicle and spinal cord; 	<ul style="list-style-type: none"> ✳ Pain (refractory to previous treatment), improvement of quality of life as well as imminent fracture or instability of the bone due to rapid tumor growth; ✳ Absence of neurological deficits; ✳ Increase of pain during movement or excessive stress;

Author, year	Bagla, 2016 [1]	Gazis, 2014 [29]	Nakatsuka, 2009 [26]	Proschek, 2009 [22]
Exclusion criteria	<ul style="list-style-type: none"> ✱ VBM in cervical vertebrae and posterior tumor extension with cord compression; ✱ Contraindication with heart pacemakers, or other electronic device implants; ✱ Contraindicated in vertebral body levels C1-7; 	<ul style="list-style-type: none"> ✱ Presence of intradural and intramedullary tumors; ✱ Risk of bleeding (acetylsalicylic acid, anticoagulants); ✱ Acute general infections, local infections in the target zone; ✱ Allergies against periinterventional applied drugs; 	<ul style="list-style-type: none"> ✱ Zubrod performance status of 4; ✱ Symptomatic spinal cord compression; ✱ Platelet count of less than 50,000/μL or an international normalized ratio greater than 1.5; 	<ul style="list-style-type: none"> ✱ Vertebral fractures; ✱ Radicular neurological symptoms; ✱ Coagulation disturbances; ✱ Rheumatic diseases; ✱ Allergy to local anesthesia; <ul style="list-style-type: none"> ✱ Pregnancy; ✱ Infections (e.g. spondylitis, spondylodiscitis);
Mean age of patients, yrs (SD)	61, range 23-83 (13)	67.8, range 40-84	61, range 52-78 (13)	59.5, range 52-69
Sex, female vs. male (% female)	24 vs. 26 (48)*	12 vs. 24 (33.3)*	4 vs. 6 (40)	16 vs. 0 (100)
Total vertebra treated metastatic bodies/lesions (mean per patient)	69 (1.4)	39	10	16 pts
Mean duration of intervention, min (range)	Ablation time/VB: 6.7 min	22.6 min (12-43)	8.3 (5-12)	NR
Follow-up (months)	3	NR	4.5, range 2.7-7.1 (SD 1.3)	20.4, range 8-36
Follow-up time periods	Pre- & post-treatment; 3 days 1 week 1 mo 3 mo	24-48 hours post-treatment	1 week every 4 weeks until death	NR
Loss to follow-up, n (%)	16 (32%), at 3 mo	NR	0	NR
Pre-interventional procedure (e.g. MRI, CT), (n)	Physical examination; review of the patients' imaging	MRI (36)	Routine physical examination, laboratory tests, CT and MRI	CT scans, MRI and X-ray
Post-interventional procedure (n)	No additional therapy (42 pts, 84%) Radiation therapy (2 pts, 4%) NR (6 pts, 12%)	MRI (36)	-	-
Outcomes				
Efficacy				
Pain (increase of pain relief)	NPRS ¹⁰	NR	VAS ¹¹	VAS ¹¹ No significant group differences.
✱ Pre-interventional	5.9	NR	7.5 (SD 2.7)	Group 1: 7.9, range 6-10 Group 2: 7.6, range 7-10

¹⁰ Pain was measured on a Numerical Pain Rating Scale (NPRS). NPRS ranges from 0 (no pain) to 10 (worst possible pain).

¹¹ Pain was measured on a Visual Analogue Scale (VAS). VAS ranges from 0 (no pain) to 10 (worst possible pain).

Author, year	Bagla, 2016 [1]	Gazis, 2014 [29]	Nakatsuka, 2009 [26]	Proschek, 2009 [22]
✳ Post-interventional	3.7 (decrease of 2.2), s.s.	Pain reduction in 19 cases (52.8%) No change in 13 cases (36.1%)	NR	Group 1: 5.5, range 3-8 (decrease of 2.4), s.s. Group 2: 5, range 3-7 (decrease of 2.6), s.s.
✳ Short term (<6 weeks)	1 mo (n=40): 2.6 (decrease of 3.3), s.s.	NR	1 week: 2.7 (SD 2) (decrease of 4.8), s.s.	NR
✳ Mid term (>6 weeks - ≤6 months)	3 mo (n=34): 2.1 (decrease of 3.8), s.s.	NR	In 90% of pts pain relief lasted during survival period (9/10)	NR
✳ Longer term (>6 months)	-	NR	-	15-36 mo post: Group 1: 4, range 2-6 (decrease of 3.9), s.s. Group 2: 3.5, range 1-5 (decrease of 4.1), s.s.
Functional status	Back-related disability (MODI) ¹²	NR	NR	NR
✳ Pre-interventional	52.9%	NR	NR	NR
✳ Post-interventional	NR	NR	NR	NR
✳ Short term (≤6 weeks)	1 mo (n=40): 40.0% (change to baseline: 12.9%), s.s.	NR	NR	NR
✳ Mid term (>6 weeks up to ≤6 months)	3 mo (n=34): 37.0% (change to baseline: 15.9%), s.s.	NR	NR	NR
✳ Longer term (>6 months)	-	NR	NR	NR
Health-related quality of life (HRQoL)	FACT-G ⁴ FACT-BP ¹³	NR	NR	QoL Oswestry Index No significant group differences.
✳ Pre-interventional	FACT-G7 11.0 FACT-BP 22.6	NR	NR	Group 1: 64%, range 38-84% Group 2: 66%, range 39-86%
✳ Post-interventional	NR	NR	NR	Group 1: 34%, range 28-38% (improvement 30%) Group 2: 36%, range 31-39% (improvement 30%)

¹² The Modified Oswestry Disability Index (MODI) ratings and corresponding categories are 0–20 (minimal disability), 21–40 (moderate disability), 41–60 (severe disability), 61–80 (crippled) and 81–100% (bed bound).

¹³ The FACT-G7 is abbreviated to seven evaluable questions and considered a rapid version of the FACT-G which has 27 questions. FACT-BP is specifically designed for use in cancer patients with bone pain and contains 15 evaluable questions. Higher scores are interpreted as greater patient quality of life, and lower scores are interpreted as lower patient quality of life. FACT-G7 has a scale from 0 to 28 and FACT-BP 0–60.

Author, year	Bagla, 2016 [1]	Gazis, 2014 [29]	Nakatsuka, 2009 [26]	Proschek, 2009 [22]
✱ Short term (≤6 weeks)	FACT-G7 1 mo (n=40): 15.8 (change to baseline: 4.8), s.s. FACT-BP 1 mo (n=40): 37.3 (change to baseline: 14.7), s.s.	NR	NR	NR
✱ Mid term (>6 weeks up to ≤6 months)	FACT-G7 3 mo (n=34): 16.2 (change to baseline: 5.2), s.s. FACT-BP 3 mo (n=34): 38.9 (change to baseline: 16.3), s.s.	NR	NR	3-6 mo post: Group 1: 33%, range 23-38% (improvement 31%) Group 2: NR
✱ Longer term (>6 months)	-	NR	NR	15-36 mo post: Group 1: NR Group 2: 35%, range 26-38% (improvement 31%)
Satisfaction with treatment	NR	NR	NR	NR
Recurrence of vertebral metastases, n (%), (local relapse)	NR	NR	NR	0
Mortality, n (%)	5 (10)	NR	10 (100) ^b	NR
Safety				
Overall complications, n (%)	6 (12)*	7 (19.4)*	4 (40)*	3 (18.7)*
✱ Major complications (n) ^a	-	-	-	-
✱ Adverse events (not procedure related), n (%)	6 (12) ✱ Pain outside the target vertebrae due to progression of the primary or other metastatic disease (3), ✱ ruptured disk (1) adjacent to the index vertebra, ✱ neuropathic pain (1) and syncope (1)	3 (8.3) ✱ Nerve root block (3)	3 (30) ✱ Recurrent pain after 2 mo (1), ✱ newly developed pain after 2 mo (2)	3 (18.7) ✱ Progress of primary tumor (3)
✱ Adverse events (procedure related), n (%)	-	4 (11.1) ✱ Worsening of pain (4)	1 (10) ✱ Transient nerve injury (1)	-

Abbreviations: FACT-G7 Functional Assessment of Cancer Therapy-General 7; FACT-BP Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with bone pain; MODI Modified Oswestry Disability Index; NPRS Numerical Pain Rating Scale; NR not reported; n.s. not significant; RFA radiofrequency ablation; s.s. statistically significant; VAS visual analogue scale; VBM vertebral body metastases; yrs years;

^a The definition of a major complication was an event that resulted in substantial morbidity or disability, an increase in the level of care, admission to the hospital, or substantial prolongation of the hospital stay (Society of Interventional Radiology classifications C-E).

^b All patients died due to the follow-up until death. * own calculations

Table A-2: RFA: Results from retrospective studies

Author, year	Anchala, 2014[15] ^a	Gevargez, 2008 [25] ¹⁴	Wallace, 2015 [4] ^b
Country	USA	Germany	USA
Sponsor	NR ¹⁵	NR	NR ⁹
Intervention/Product	RFA <i>STAR Tumor Ablation System</i> (DFine Inc., USA) Co-intervention: vertebroplasty (88)	RFA <i>Radionics System & RITA Medical System</i> (Radionics Inc., USA & RITA Medical System Inc., USA) Co-Intervention: vertebroplasty (n=22)	RFA <i>STAR Tumor Ablation System</i> (DFine Inc., USA) Co-intervention: vertebroplasty (95% of ablations)
Study design	Multicentre retrospective study	Single-centre retrospective study	Single-centre retrospective study
Setting (e.g. outpatient, university hospital etc.)	University hospital	University hospital	University hospital
Number of pts	92	41	72
Inclusion criteria	NR	<ul style="list-style-type: none"> ✱ Severe local tumor pain insufficiently responsive to opiates and other analgesics; ✱ Disease progression despite previous surgery, maximal chemotherapy, maximal radiation, and hormone therapy; ✱ Lack of or highlyinvasive surgical option; ✱ Lack of other therapeutic options; ✱ Metastases in bone or spine; ✱ Intravertebral tumor spread; ✱ Risk of paraplegia or fracture because of tumor progression; ✱ Osteolytic and mixed metastases; 	<ul style="list-style-type: none"> ✱ Pain limiting quality-of-life and uncontrolled with opioid analgesics (≥ 4 NRS); ✱ Tumor within 1 cm of the spinal cord or nerves was no contraindication for RFA;
Exclusion criteria	NR	<ul style="list-style-type: none"> ✱ Progressive metastases (involving more than three organs) with reduced life expectancy; ✱ Poor general condition; ✱ Intradural and intramedullary tumors; ✱ Risk of bleeding (acetylsalicylic acid, anticoagulants); ✱ Osteoblastic metastases; 	<ul style="list-style-type: none"> ✱ Osteoblastic metastases, associated with pathologic compression fracture with spinal instability, or causing metastatic spinal cord compression;

¹⁴ The number of patients is different at each time point of the assessment due to a number of incomplete questionnaires.

¹⁵ Conflict of Interest: DFine Inc. (speaker panel, consultant, lab instructor).

Author, year	Anchala, 2014[15] ^a	Gevargez, 2008 [25] ¹⁴	Wallace, 2015 [4] ^b
Mean age of patients, yrs (SD)	NR	62.7, range 46-82 (SD 9)	68.4 (18.8)
Sex, female vs. male (% female)	NR	16 vs. 25 (39)	44 vs. 28 (61)
Total vertebra treated metastatic bodies/lesions (mean per patient)	128	RFA/pts: 1.8, range 1-6 (SD 1.1)	110
Mean duration of intervention, min (range)	At largest centre: 55-653 sec (average 361 sec)	NR	8 min 32 sec (4 min 49 sec)
Follow-up (months)	6	>6 (278-617 days)	1
Follow-up time periods	1 week 1 mo 6 mo	6 weeks 6 mo >6 mo	1 week 4 weeks
Loss to follow-up, n (%)	9 at 1 month (9.8)	25 (61)	8 (11.1)
Pre-interventional procedure (e.g. MRI, CT)	MRI	neurological examination, hematology/clinical chemistry, MRT and CT	MRI, PET-CT, CT
Post-interventional procedure (n)	MRI	-	NR
Outcomes			
Efficacy			
Pain (Increase of pain relief)	VAS ¹⁶	VAS ¹⁶	NRS ¹⁷
* Pre-treatment	7.51 (SD 2.46), (n=92)	NR	8 (SD 1.9), (n=64)
* Post-interventional	NR	NR	NR
* Short term (<6 weeks)	1 week (n=56): 1.73 (SD 2.28), s.s. 1 mo (n=83): 2.25 (SD 2.44), s.s.	6 weeks: relative reduction 36.2% (n=26), s.s.	1 week (n=64): 3.9 (SD 3), s.s. 4 weeks (n=58): 2.9 (3), s.s.
* Mid term (>6 weeks - ≤6 months)	6 mo (n=9): 1.75 (SD 2.62), s.s.	6 mo: relative reduction 50% (n=19), s.s.	-
* Longer term (>6 months)	-	>6 mo: relative reduction 50% (n=14), s.s.	-
Functional status	NR	Overall functional activity PDI scores ¹⁸	NR
* Post-interventional	NR	-	NR
* Short term (≤6 weeks)	NR	6 weeks: relative improvement 8% (n=24)	NR
* Mid term (>6 weeks up to ≤6 months)	NR	6 mo: relative improvement 4% (n=21)	NR

¹⁶ Pain was measured on a Visual Analogue Scale (VAS). VAS ranges from 0 (no pain) to 10 (worst possible pain).

¹⁷ Numerical rating scale (NRS) ranges from 0 (no pain) to 10 (worst possible pain).

¹⁸ The Pain Disability Index (PDI) is a 10-Item scale: 0 = no interference, 10 = total interference.

Author, year	Anchala, 2014 [15] ^a	Gevargez, 2008 [25] ¹⁴	Wallace, 2015 [4] ^b
⊛ Longer term (>6 months)	NR	>6 mo: relative improvement 10% (n=15)	NR
Health-related quality of life (HRQoL)	NR	Karnofsky index ¹⁹ "No changes in short, mid and longer term."	NR
Satisfaction with treatment	NR	NR	NR
Recurrence of vertebral metastases, n (%) (local relapse)	NR	NR	NR
Mortality, n (%)	NR	NR	6 (9.4)
Safety			
Overall complications, n (%)	4 (4.3)*	9 (22)*	4 (5.6)*
⊛ Major complications (n) ^c	-	-	-
⊛ Adverse events (not procedure related), n (%)	4 (4.3) ⊛ Fracture without cement augmentation (2), ⊛ cement extravasation (2)	5 (12.2) ⊛ Tumor progression (5)	-
⊛ Adverse events (procedure related), n (%)	-	4 (9.8) ⊛ Increased pain and numbness (2), ⊛ unilateral monoradiculopathy (1), ⊛ "heavy legs" with paresthesia (1)	4 (5.6) ⊛ Post-procedure radicular pain (4)

Abbreviations: NRS Numerical Rating Scale; NR not reported; n.s. not significant; PDI Pain Disability Index; RFA radiofrequency ablation; s.s. statistically significant; VAS visual analogue scale; VBM vertebral body metastases; yrs years;

^a For sub analysis see references Hillen 2014 [34] and Greenwood 2015 [5].

^b This study is also a sub analysis of Anchala 2014 [15]; (34 patients are already included in Anchala 2014). For further sub analysis see reference Wallace 2016 [35].

^c The definition of a major complication was an event that resulted in substantial morbidity or disability, an increase in the level of care, admission to the hospital, or substantial prolongation of the hospital stay (Society of Interventional Radiology classifications C-E).

* own calculations

¹⁹ There were no changes of the median percentage changes in the Karnofsky index at any time point indicating an overall stable general condition of the patients.

Table A-3: RFA: Results from retrospective studies (continued)

Author, year	Dabravolski, 2015 [8] ^a	Georgy, 2009 [12] ^b
Country	Germany	USA
Sponsor	NR	ArthroCare Corporation
Intervention/Product	RFA <i>CAVITY SpineWand (ArthroCare Corporation, USA)</i> Co-Intervention: vertebroplasty (229 pts); Dorsal percutaneous instrumentation (59 pts) Combination with chemotherapy & radiation (229 pts);	RFA <i>CAVITY SpineWand (ArthroCare Corporation, USA)</i> Co-Intervention: vertebroplasty (37 pts)
Study design	Single-centre retrospective study ²⁰	Single-centre retrospective study ²⁰ (consecutively treated & retrospectively reviewed)
Setting (e.g. outpatient, university hospital etc.)	University hospital	NR
Number of pts	250 (total) 229 pts with spinal metastases	37
Inclusion criteria	✱ Tumors and spinal metastases with destruction/osteolysis; ✱ Fractures with instability and pain syndrome;	NR
Exclusion criteria	NR	NR
Mean age of patients, yrs (SD)	65.5, range 31-92	69.6, range 34-89*
Sex, female vs. male (% female)	156 vs. 94 (62.4)	21 vs. 16 (57)
Total vertebra treated metastatic bodies/lesions (mean per patient)	812 (229 pts)	44
Mean duration of intervention, min (range)	NR (only as combination: cavity & vertebro-/kyphoplasty: 30-60 min (n=172))	NR
Follow-up (months)	60	2-4 weeks
Follow-up time periods	2 days 2 weeks 3 mo 6 mo 12 mo 24 mo 36 mo 48 mo 60 mo	Pre-treatment 2-4 weeks post-treatment
Loss to follow-up, n (%)	7 (3.1)	9 (24%)*, VAS of 2-4 weeks
Pre-interventional procedure (e.g. MRI, CT)	MRI, X-ray, PET-CT, CT, whole body scintigraphy	MRI (36), Bone scan (1)
Post-interventional procedure (n)	Every 6 mo: MRI, PET-CT, CT	CT examination (37)

²⁰ Judged as retrospective studies.

Author, year	Dabravolski, 2015 [8] ^a	Georgy, 2009 [12] ^b
Outcomes		
Efficacy		
Pain (increase of pain relief)	VAS ²¹	VAS ²¹
✱ Pre-treatment	7-10	NR
✱ Post-interventional	0-3 (decrease by 6-8 points), s.s.	NR
✱ Short term (<6 weeks)	NR	2-4 weeks: 25 pts (89.5%) reported pain relief
✱ Mid term (>6 weeks - ≤6 months)	NR	-
✱ Longer term (>6 months)	NR	-
Functional status	Improvement in mobilisation	NR
Health-related quality of life (HRQoL)	Improvement in QoL	NR
Satisfaction with treatment	Improvement in overall satisfaction	NR
Recurrence of vertebral metastases, n (%), (local relapse)	30 (13.1)	NR
✱ Post-interventional	-	NR
✱ Short term (≤6 weeks)	-	NR
✱ Mid term (>6 weeks up to ≤6 months)	6 mo: 4 (1.7%)	NR
✱ Longer term (>6 months)	1 yr: 8 (3.5%) 2 yrs: 12 (5.2%) 3 yrs: 6 (2.6%) 4 yrs: - 5 yrs: -	NR
Mortality, n (%)	188 (75.2)	NR
Safety		
Overall complications, n (%)	38 (16.6)*	30 (81.1)*
✱ Major complications (n) ^c	-	NR
✱ Adverse events (not procedure related), n (%)	38 (16.6) ✱ Cement extravasation (38)	27 (73) ✱ Cement extravasation (27)*
✱ Adverse events (procedure related), n (%)	-	3 (8.1) ✱ Epidural extravasation (2), ✱ radicular symptoms (1)

Abbreviations: NR not reported; n.s. not significant; RFA radiofrequency ablation; s.s. statistically significant; VAS visual analogue scale; VBM vertebral body metastases; yrs years;

^a For sub analysis see reference Dabravolski 2014 [20].

^b For sub analysis see reference Georgy 2007 [21].

^c The definition of a major complication was an event that resulted in substantial morbidity or disability, an increase in the level of care, admission to the hospital, or substantial prolongation of the hospital stay (Society of Interventional Radiology classifications C-E).

* own calculations

²¹ Pain was measured on a Visual Analogue Scale (VAS). VAS ranges from 0 (no pain) to 10 (worst possible pain).

Risk of bias tables

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [36] and in the Guidelines of EUnetHTA [37, 38].

Table A-4: Risk of bias – study level (case series)²²

Study reference/ID	Anchala, 2014 [15]	Bagla, 2016 [1]	Dabravolski, 2015 [8]	Gazis, 2014 [29]	Georgy, 2009 [12]	Gevargez, 2008 [25]	Nakatsuka, 2009 [26]	Proschek, 2009 [22]	Wallace, 2015 [4]
Study objective									
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	No	Yes	Yes	Yes	Partial	Yes	Partial
Study population									
2. Are the characteristics of the participants included in the study described?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	Yes	Unclear	No	No	No	No	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	No	Yes	Partial	Yes	No	Yes	Yes	Yes	Yes
5. Were participants recruited consecutively?	No	Unclear ²³	Unclear ²⁴	Unclear ²⁵	Yes	Unclear ²⁶	Yes	Unclear	Unclear ²⁷
6. Did participants enter the study at similar point in the disease?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intervention and co-intervention									
7. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	Partial	Partial	Yes	Yes ²⁸	Yes	Partial	No	Yes	Partial

²² IHE Risk of Bias checklist, see [13]

²³ Patients were enrolled in an institutional review board approved study at eight sites in the USA between August 2013 and September 2014.

²⁴ Patients were enrolled between March 2008 and February 2014 with tumours and mainly spinal metastases.

²⁵ After providing written informed consent, 36 patients were treated for 39 lesions in the institution between November 2006 and April 2009.

²⁶ Patients with primary or secondary tumour involvement of the spine were treated between March 2000 and August 2002.

²⁷ Patients were selected and consecutively treated with RFA between April 2012 and July 2014.

²⁸ No additional intervention was performed.

Study reference/ID	Anchala, 2014 [15]	Bagla, 2016 [1]	Dabravolski, 2015 [8]	Gazis, 2014 [29]	Georgy, 2009 [12]	Gevargez, 2008 [25]	Nakatsuka, 2009 [26]	Proschek, 2009 [22]	Wallace, 2015 [4]
Outcome measures									
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Partial	Partial	Partial	Yes	Partial	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Partial	Yes	Yes	No	Yes	Yes	Partial
Statistical Analysis									
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Results and Conclusions									
13. Was the length of follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Was the loss to follow-up reported?	Yes	Yes	Yes	No	Unclear	Yes	Yes	No	Yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Partial	No	No	No	No	No	Partial	Partial	Partial
16. Are adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Partial	Partial
Competing interest and source of support									
18. Are both competing interest and source of support for the study reported?	Partial	Yes	No	No	Yes	No	No	No	No
Overall Risk of bias	High	Moderate	High	High	Moderate	Moderate	High	Moderate	High

Applicability table

Table A-5: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	All studies included patients with painful vertebral metastases. The studies included a total of 583 patients. The mean age of included patients ranged 61-69.6 years. The inclusion criteria and the population in the studies seem to be in accordance with the intended patient population for the technology.
Intervention	Patients in the included studies were treated with different RFA-systems and the intervention was mainly performed in university hospitals and treated in an outpatient setting. In all studies, it was stated that most of the patients received vertebroplasty after RFA.
Comparators	There were no comparators. To date, there are no published studies in which RFA (in combination with vertebroplasty or other add-on therapies) are compared to other or no treatment.
Outcomes	The most frequently reported crucial outcomes were changes in pain and adverse events (procedure-related and not procedure-related). Other important outcomes, such as health-related quality of life, functional status and satisfaction with treatment were only reported in some of the included studies. The outcomes on clinical effectiveness have shown subjective benefits from the treatment with RFA (in combination with vertebroplasty). For the safety assessment, no major complications were reported across studies. However, the presented data in the studies is limited, especially due to small sample sizes in prospective studies and short follow-up times (due to the palliative setting). Possible multiple-reporting of study participants in different studies may also lead to imprecise data.
Setting	The intervention was performed under image-guiding and general anaesthesia. Two of the studies were multi-centre studies carried out in the US. The other seven studies were single-centre studies conducted in the US (2), Japan (1), and Europe (4). All of the European studies were based in Germany. The studies were published between 2008 and 2016. The intervention was performed in University hospitals across studies, but in some it was reported that the intervention might also be performed in an outpatient setting because of its minimal-invasive procedure and short recovery time. The settings of the studies reflect the clinical setting in which the technology is intended to be used in an appropriate way. No applicability issues are expected from the geographical setting.

List of ongoing trials

Table A-6: List of ongoing trials (radiofrequency ablation and metastatic spinal lesions)

Source	Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
ClinicalTrials.gov	NCT02713269 A Phase II Clinical Trial Evaluating the Efficacy of Combining Thermal Ablation and Spine Stereotactic Radiosurgery for Patients With Spine Metastases With Moderate to Severe Epidural Involvement	Patients ≥ 18 years old; Histologic diagnosis of solid malignant tumor epidural spinal cord compression 1C, 2, or 3; vertebral body site located from T2-T12; < 3 contiguous or discontinuous vertebral levels involved with metastasis in the spine; motor strength ≥ 4 out of 5 in extremity or extremities affected by the level of the spinal cord compression; ECOG performance status ≤ 2 or Karnofsky performance status (KPS) ≥ 50 ; life expectancy > 3 months; inoperable disease because of patient refusal, neurosurgical evaluation, or other medical reasons	Thermal Ablation Procedure, Stereotactic Spine Radiosurgery (SSRS)	-	Rate of local tumor control	August 2022	M.D. Anderson Cancer Center, Medtronic
ClinicalTrials.gov	NCT02419703 The STAR™ Tumor Ablation Registry	Male or female patients ≥ 22 years old; painful spinal metastatic lesions in thoracolumbar vertebrae (T1-L5) that will be treated with t-RFA using the STAR™ Tumor Ablation System; signed informed consent	Device: STAR™ Tumor Ablation System (Targeted-radiofrequency ablation (t-RFA) of painful metastatic tumor in the vertebral body)	-	Pain relief	December 2018	DFINE Inc., Merit Medical Systems, Inc.
ClinicalTrials.gov	NCT02225223 Evaluation of Targeted Radiofrequency Ablation and Vertebral Augmentation Prior to or Following Radiation Therapy to Treat Painful Metastatic Vertebral Body Tumor(s) [The STARRT Study] ²⁹	Male or female patients ≥ 18 years old; one to two painful vertebrae (T1-L5) with evidence of osteolytic or mixed lytic and blastic metastatic lesion by cross sectional imaging and pathologic fracture; Brief Pain Inventory (BPI) worst pain score of ≥ 4 ; life expectancy of ≥ 2 months	Device: STAR™ Tumor Ablation System (Targeted-radiofrequency ablation (t-RFA)) Device: StabiliT® Vertebral Augmentation System (Radiofrequency-targeted vertebral augmentation (RF-TVA))	-	Pain relief	October 2016	DFINE Inc., Merit Medical Systems, Inc.

²⁹ This study has been terminated. (Difficulty Enrolling).

<https://clinicaltrials.gov/ct2/show/record/NCT02225223?term=radiofrequency+ablation+AND+metastatic+spinal+lesions&rank=1>

Source	Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
ClinicalTrials.gov	NCT02081053 A Prospective, Multicenter Clinical Study to Evaluate the Clinical Outcomes of Targeted Radiofrequency Ablation and Vertebral Augmentation to Treat Painful Metastatic Vertebral Body Tumor(s) ³⁰	One to 2 painful vertebrae (T1-L5) with evidence of osteolytic metastatic lesion with known primary histology with pathologic fracture(s) at index vertebra by MRI; pain score ≥ 4 on the numerical rating pain scale; Life expectancy of ≥ 6 months	Device: STAR™ Tumor Ablation System and StabiliT® Vertebral Augmentation System (Radiofrequency targeted radiofrequency ablation (t-RFA) and targeted vertebral augmentation (RF-TVA))	-	Pain relief	November 2016	DFINE Inc., Merit Medical Systems, Inc.
WHO-ITCRP	ChiCTR-INR-16010135 The Medium-and Long-Term Clinical Research of Radiofrequency Ablation Combined With Percutaneous Vertebroplasty in Spine Metastases	Male or female patients; meet the diagnostic criteria; moderate pain(VAS>3); aged over 18 years; vertebral bone cortical continuity was intact; expected survival is more than 3 months; informed consent	Radiofrequency Ablation Combined With Percutaneous Vertebroplasty	Percutaneous Vertebroplasty	Pain	September 2021	National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

³⁰ This study has been terminated. (Difficulty Enrolling).

<https://clinicaltrials.gov/ct2/show/record/NCT02081053?term=radiofrequency+ablation+AND+metastatic+spinal+lesions&rank=2>

Literature search strategies

Search strategy for Cochrane

Search Name: RFA for Spinal Metastases	
Search Date: 28.12.2016	
ID	Search
#1	radiofrequency near (ablati* or therap* or treatment* or intervention* or program* or procedure*) (Word variations have been searched)
#2	radio-frequency near (ablati* or therap* or treatment* or intervention* or program* or procedure*) (Word variations have been searched)
#3	MeSH descriptor: [Catheter Ablation] explode all trees
#4	#1 OR #2 OR #3
#5	MeSH descriptor: [Spinal Neoplasms] explode all trees
#6	(neoplasm* or tumor* or tumour* or cancer* or carcinoma*) near (spine* or spinal or vertebra*) (Word variations have been searched)
#7	#5 OR #6
#8	MeSH descriptor: [Neoplasm Metastasis] explode all trees
#9	metasta* (Word variations have been searched)
#10	#8 OR #9
#11	#7 AND #10
#12	(spine* or spinal or vertebra*) near metasta* (Word variations have been searched)
#13	#11 OR #12
#14	#4 AND #13
Total: 5 Hits	

Search strategy for CRD (DARE, NHS-EED, HTA)

#### RFA for Spinal Metastases	
Search Date: 28.12.2016	
1	(radiofrequency NEAR (ablati* OR therap* OR treatment* OR intervention* OR program* OR procedure*))
2	(radio-frequency NEAR (ablati* OR therap* OR treatment* OR intervention* OR program* OR procedure*))
3	MeSH DESCRIPTOR Catheter Ablation EXPLODE ALL TREES
4	#1 OR #2 OR #3
5	MeSH DESCRIPTOR Spinal Neoplasms EXPLODE ALL TREES
6	((neoplasm* OR tumor* OR tumour* OR cancer* OR carcinoma*) NEAR (spine* OR spinal OR vertebra*))
7	#5 OR #6
8	MeSH DESCRIPTOR Neoplasm Metastasis EXPLODE ALL TREES
9	(metasta*)
10	#8 OR #9
11	#7 AND #10
12	((spine* or spinal or vertebra*) NEAR metasta*)
13	#5 OR #6 OR #11 OR #12
14	#4 AND #13
Total: 1 Hit	

Search strategy for Embase

No.	Query results	Results	Date
#14	(radiofrequency NEAR/5 (ablati* OR therap* OR treatment* OR intervention* OR program* OR procedure*)):ti,ab OR ('radio-frequency' NEAR/5 (ablati* OR therap* OR treatment* OR intervention* OR program* OR procedure*)):ti,ab OR 'catheter ablation'/exp AND ('spine tumor'/exp OR (spine* OR spinal OR vertebra*) NEAR/5 (neoplasm* OR tumor* OR tumour* OR cancer* OR carcinoma*) AND ('metastasis'/exp OR metasta*) OR (spine* OR spinal OR vertebra*) NEAR/5 metasta*)	170	28 Dec 2016
#13	'spine tumor'/exp OR (spine* OR spinal OR vertebra*) NEAR/5 (neoplasm* OR tumor* OR tumour* OR cancer* OR carcinoma*) AND ('metastasis'/exp OR metasta*) OR (spine* OR spinal OR vertebra*) NEAR/5 metasta*	14,381	28 Dec 2016
#12	(spine* OR spinal OR vertebra*) NEAR/5 metasta*	10,559	28 Dec 2016
#11	'spine tumor'/exp OR (spine* OR spinal OR vertebra*) NEAR/5 (neoplasm* OR tumor* OR tumour* OR cancer* OR carcinoma*) AND ('metastasis'/exp OR metasta*)	11,186	28 Dec 2016
#10	'metastasis'/exp OR metasta*	682,426	28 Dec 2016
#9	metasta*	679,081	28 Dec 2016
#8	'metastasis'/exp	494,038	28 Dec 2016
#7	'spine tumor'/exp OR (spine* OR spinal OR vertebra*) NEAR/5 (neoplasm* OR tumor* OR tumour* OR cancer* OR carcinoma*)	33,890	28 Dec 2016
#6	(spine* OR spinal OR vertebra*) NEAR/5 (neoplasm* OR tumor* OR tumour* OR cancer* OR carcinoma*)	32,084	28 Dec 2016
#5	'spine tumor'/exp	7,604	28 Dec 2016
#4	(radiofrequency NEAR/5 (ablati* OR therap* OR treatment* OR intervention* OR program* OR procedure*)):ti,ab OR ('radio-frequency' NEAR/5 (ablati* OR therap* OR treatment* OR intervention* OR program* OR procedure*)):ti,ab OR 'catheter ablation'/exp	44,184	28 Dec 2016
#3	'catheter ablation'/exp	26,304	28 Dec 2016
#2	('radio-frequency' NEAR/5 (ablati* OR therap* OR treatment* OR intervention* OR program* OR procedure*)):ti,ab	1,688	28 Dec 2016
#1	(radiofrequency NEAR/5 (ablati* OR therap* OR treatment* OR intervention* OR program* OR procedure*)):ti,ab	25,486	28 Dec 2016

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) Epub Ahead of Print <December 27, 2016>, Ovid MEDLINE(R) <1946 to December Week 1 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 27, 2016>, Ovid MEDLINE(R) Daily Update <December 07, 2016>	
Search Date: 28.12.2016	
Search Strategy:	
1	((radiofrequency adj3 (ablati* or therap* or treatment* or intervention* or program* or procedure*))).mp. (17673)
2	((radio-frequency adj3 (ablati* or therap* or treatment* or intervention* or program* or procedure*))).mp. (1067)
3	exp Catheter Ablation/(28685)
4	1 or 2 or 3 (34735)
5	exp Spinal Neoplasms/(14195)
6	((neoplasm* or tumo?r* or cancer* or carcinoma*) adj3 (spine* or spinal or vertebra*))).mp. (27604)
7	5 or 6 (27604)
8	exp Neoplasm Metastasis/(198561)
9	metasta*.mp. (523323)
10	8 or 9 (530739)
11	7 and 10 (7392)
12	((spine* or spinal or vertebra*) adj5 metasta*).mp. (6194)
13	11 or 12 (9441)
14	4 and 13 (81)
15	remove duplicates from 14 (75)

Search strategy for PubMed

Search Name: RFA for Metastases of the Spine
Search Date: 29.12.2016
((radiofrequency ablation OR radiofrequency therapy OR radiofrequency treatment OR radiofrequency intervention OR radiofrequency program OR radiofrequency procedure OR RFA OR Catheter Ablation)) AND (((Spinal Neoplasms OR Spinal Tumors OR Spinal Cancer OR Spinal Carcinoma OR Spine Neoplasms OR Spine Tumors OR Spine Cancer OR Spine Carcinoma OR Vertebral Neoplasms OR Vertebral Tumors OR Vertebral Cancer OR Vertebral Carcinoma) AND (Neoplasm Metastasis[MesH] OR metastasis OR metastases OR metastatic))) OR (Spinal metastasis OR Spinal metastases OR Spinal metastatic OR Spine metastasis OR Spine metastases OR Spine metastatic OR Vertebral metastasis OR Vertebral metastases OR Vertebral metastatic)
Total: 193 Hits



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