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Combined Vertebral Augmentation and Radiofrequency Ablation in the Management of Spinal Metastases: an Update

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Opinion statement

Spinal metastases are the most commonly encountered tumour of the spine, occurring in up to 40% of patients with cancer. Each year, approximately 5% of cancer patients will develop spinal metastases. This number is expected to increase as the life expectancy of cancer patients increases. Patients with spinal metastases experience severe and frequently debilitating pain, which often decreases their remaining quality of life. With a median survival of less than 1 year, the goals of treatment in spinal metastases are reducing pain, improving or maintaining level of function and providing mechanical stability. Currently, conventional treatment strategies involve a combination of analgesics, bisphosphonates, radiotherapy and/or relatively extensive surgery. Despite these measures, pain management in patients with spinal metastases is often suboptimal. In the last two decades, minimally invasive percutaneous interventional radiology techniques such as vertebral augmentation and radiofrequency ablation (RFA) have shown progressive success in reducing pain and improving function in many patients with symptomatic spinal metastases. Both vertebral augmentation and RFA are increasingly being recognised as excellent alternative to medical and surgical management in carefully selected patients with spinal metastases, namely those with severe refractory pain limiting daily activities and stable pathological vertebral compression fractures. In addition, for more complicated lesions such as spinal metastasis with soft tissue extension, combined treatments such as vertebral augmentation in conjunction with RFA may be helpful. While combined RFA and vertebral augmentation have theoretical benefits, comparative trials have not been performed to establish superiority of combined therapy. We believe that a multidisciplinary approach as well as careful pre-procedure evaluation and imaging will be necessary for effective and safe management of spinal metastases. RFA and vertebral augmentation should be considered during early stages of the disease so as to maintain the remaining quality of life in this patient population group.

Introduction

Spinal metastases are the most commonly encountered tumour of the spine, occurring in up to 40% of patients with cancer [1]. Each year, approximately 5% of cancer patients will develop spinal metastases, most commonly from a primary lesion in the breast (21%), lung (14%), prostate (8%) or kidney (5%) [2–4]. These patients are often in the advanced stages of their disease with a median survival of less than a year [2, 5]. These metastases may be osteoblastic, osteolytic or mixed depending on the primary tumour.

Spinal metastases, which cause progressive and relentless pain, are debilitating and have a significant impact on quality of life. Nearly 80% of patients experience severe pain before a sufficient treatment plan is initiated [2, 6]. Furthermore, additional complications include vertebral fractures, nerve root and spinal cord compression. Up to 10–20% of patients present with spinal cord compression, most often due to posterior extension of vertebral body tumour [1, 7, 8•]. Therefore, the primary goals of treatment in spinal metastases are mainly palliation and preservation of neurological function.

Treatment of spinal metastases is complex due to marked patient frailty. Conventional pain management techniques involve a combination of analgesics, bisphosphonates and radiotherapy [2, 3, 5, 9, 10]. Despite these measures, pain management in patients with spinal metastases is often suboptimal. While surgical options have shown to significantly improve pain and stabilise vertebral compression fractures, many

oncological patients are frequently reluctant to pursue extensive surgery.

Radiofrequency ablation (RFA) and vertebral augmentation are minimally invasive image-guided procedures that have shown to provide satisfactory outcomes in terms of pain management and bone stabilisation for patients with spinal metastases [3, 11, 12, 13•, 14–16].

This review summarises the current literature on percutaneous vertebral augmentation and RFA on painful spinal metastases, in particular their clinical significance, safety profile, indications and techniques, and appraises the clinical utility of combined vertebroplasty and RFA for pain relief in patients with spinal metastasis.

Conventional treatment regimen

Current standard of care usually involves a multidisciplinary approach with clinicians often opting for a combination of non-operative measures including analgesics, bisphosphonates and radiotherapy. While bisphosphate therapy has shown some benefit in relieving metastatic bone pain and delaying complications of metastatic disease, they can cause adverse effects on the gastrointestinal, renal and haematopoietic system such as oesophagitis and osteonecrosis of the jaw [17]. Frequently, narcotic analgesics are the first-line treatment option offered to these patients. However, these medications are often insufficient to control pain and have major side effects, such as excessive drowsiness, nausea and constipation, which may limit their use.

Various reports estimate response rates (partial or complete pain relief) of 50–90% from palliative radiotherapy [6, 18]. However, the therapeutic effect of radiation therapy may be delayed for 10–14 days after the start of treatment with maximal benefit usually occurring 12–20 weeks after completion of treatment [6]. Furthermore, pain relief is frequently temporary, with recurrence of pain reported in up to 57% of patients at a median of 15 weeks after completion of radiotherapy [19]. Due to limitations in normal tissue tolerance and potential toxicity such as osteonecrosis, gastrointestinal complaints (nausea or diarrhoea) and radiation-induced myelopathy which ranges from transient paralysis to progressive nerve damage, additional radiotherapy for recurrent pain at a previously irradiated metastatic site is limited [6, 10]. In addition, a recent meta-analysis of seven studies reported that approximately 40% of patients with painful bone metastasis often do not benefit from re-irradiation [20]. Radiation insensitivity has been suggested although the underlying aetiology is unclear [21].

Surgical management of spinal metastases is generally reserved for patients with unstable pathological fractures or potentially unstable metastatic deposits and those at risk of significant neurological compromise [3]. Current techniques include surgical decompression and debulking with laminectomy and/or vertebrectomy and reconstruction with pedicle screws and cages [1, 4]. These techniques are often reserved for patients with at least 6 months of life expectancy [22]. However, the high post operative morbidity and mortality make this approach a less favourable alternative in patients with metastatic disease where palliation and quality of life are paramount. In a review of the surgical literature, the average complication rate was approximately 20–40%, with a sizeable number of patients experiencing surgical wound infection as well as medical complications such as pneumonia and urinary tract infection [1, 22, 23].

Despite advances in surgical techniques, the response rates for spinal metastases are often varied and limited. A single-centre prospective case series of 113 patients undergoing various surgical procedures demonstrated minimal increase in quality of life post surgery, with a mean EuroQol five dimensions (EQ-5D) score improving from 0.44 pre-surgery to 0.59 at 3-month post surgery ($p < 0.001$) [22]. In a smaller study of 80 patients, Sundaresan et al. reported that 76% of participants had complete pain recovery, with 98% becoming ambulatory following spinal surgery compared to 60% pre-surgery [23].

Vertebral augmentation

Vertebroplasty, a form of percutaneous vertebral body augmentation, is often performed in patients with refractory painful metastases in which conservative therapy has failed. It involves percutaneous instillation of polymethylmethacrylate (PMMA), a medical grade bone cement, into a diseased bone under radiological guidance using fluoroscopy or CT [4]. Approaches are either via a unipedicular or bipedicular approach, depending on operator preference and technical parameters. PMMA cement is instilled until the anterior two thirds of the vertebral body is filled and until cement is equally distributed on both sides [2, 3]. Of note, percutaneous balloon kyphoplasty, a modification of vertebroplasty, has been introduced to overcome some of the limitations of vertebroplasty. In kyphoplasty, a balloon-like device is inflated within a collapsed vertebra to restore height and reduce deformity, creating a cavity into which PMMA is then injected. The balloon is removed prior to cement injection.

While the risk of cement extravasation is theoretically reduced as the balloon establishes a void within the bone into which cement can be administered under relatively low pressure, there is no good evidence that kyphoplasty is superior to vertebroplasty for tumour-related vertebral compression fractures [3, 24–26]. However, in osteoporotic-related vertebral compression fractures, a randomised controlled trial in 77 patients showed the number of levels with leaks ($p = 0.0132$) and the total number of leaks per level ($p = 0.0012$) to be significantly reduced in kyphoplasty compared to verebroplasty group [27••]. Both techniques are recommended by the National Institute of Health and Care Excellence (NICE), Health Quality Ontario, American College of Radiology (ACR), Society of NeuroInterventional Surgery (SNIS) and Society of Interventional Radiology (SIR) in the management of symptomatic spinal metastasis and cancer-related fractures refractory to medical therapy [5, 28–30]. Often performed as a day-case procedure under sedation, vertebral augmentation has been shown to be a safe and efficacious procedure for prompt pain relief, bone strengthening and stabilisation of pathological or insufficiency fractures [2–4].

In the CAFE multicentre randomised control trial of 134 patients with cancer-related vertebral compression fractures, patients undergoing balloon kyphoplasty experienced substantial improvement in pain control as early as 1 week post procedure compared to conventional non-operative measures (mean numeric rated scale (NRS) at 1 week 3.5 vs 7.0, $p < 0.0001$) [31]. An increase in level of function was also observed in the kyphoplasty group at 1 month with a change of 8.3 in mean Roland-Morris disability questionnaire

(RDQ) score ($p < 0.0001$) compared to 0.1 in the control group ($p = 0.83$).

Various studies (Table 1) report pain relief following vertebroplasty for spinal metastases in 70–94% of patients [32–35]. A multicentre prospective observation study of 33 patients improved pain scores in 70% (95% CI 54–83%) of its participants, with a median therapeutic efficacy apparent on day 1 (mean 2.4) [32]. In another series, 35 of 37 patients (94%) with osteolytic spinal metastases treated with vertebroplasty reported less pain within 1 week of receiving treatment [36]. The reduction in spinal pain was maintained in 73% of patients at 6 months and 65% patients at 1 year.

A recent systemic review of 14 reports (639 patients) from 2002 to 2012 on vertebroplasty for metastatic cancer-related vertebral compression fractures reported statistically and clinically significant reduction of pain intensity, with mean visual analogue scale (VAS) improving from > 7 pre-treatment to < 4 post treatment in all studies [5]. The reports included in the systematic review involved a diverse group of primary cancers including breast, prostate, lung and renal, with a range of 2 to 128 patients included in each study.

Similarly, another systemic review of 30 reports from 1996 to 2010 on vertebroplasty in spinal metastases and multiple myeloma in 987 subjects demonstrated that patients receiving vertebroplasty had a 47–89% reduction in pain levels at 6 months with up to 2% developing serious complications, mostly neuropathy-related [37]. The majority of the reports included were observational studies with a follow-up period ranging from 1 week to 60 months. In addition to pain relief, McDonald and colleagues have suggested that the prompt and effective pain management in vertebroplasty can considerably improve level of function in patients, with a median improvement of 5.3 points (95% CI 4.2–6.4) on pain-related disability measures (RDQ) 1 week post procedure [38].

While vertebroplasty has been widely used in the treatment of osteolytic metastases, there is growing evidence that painful osteoblastic metastatic spinal lesions can also be safely managed [34, 35, 39]. In a single-centre retrospective analysis of 39 consecutive patients with 51 osteoblastic spinal metastases, Tian and colleagues reported 100% technical success rates and substantial pain relief after vertebroplasty with mean VAS scores of 7.4 ± 1.1 pre-procedure declining to 1.7 ± 0.7 at 18 months post procedure ($p < 0.001$) [34]. In a larger study of 52 patients with painful pure osteoblastic and mixed spinal metastases, Calmels et al. reported 86% analgesia efficacy at 1-month follow-up. In particular, 67% had a VAS score of 0–2 and 19% experienced a VAS score of 2.5–4.5 [39].

While there may be more difficulty in bone puncture and resistance to PMMA injection due to the thickened bone trabeculae in osteoblastic metastases, these technical problems can be effectively managed. Overall, several factors are at play in providing pain relief in vertebroplasty:

1. The injection of acrylic cement reduces the activity of pain-sensitive periosteal nerves by means of internal trabecular stabilisation [12].
2. PMMA confers structural support in the vertebrae and thus prevents further compression [11, 12, 33].
3. Direct chemical toxicity and thermal necrosis by an exothermic reaction to the nerve endings by PMMA have also been postulated [10, 34].

Complications from vertebroplasty are often minor and infrequent, with major complication rates of < 1–2% [28, 37, 40]. The majority of complications

Table 1. Clinical outcomes in studies evaluating the safety and effectiveness of vertebroplasty in spinal metastases

Author, year	Report type	Patients (*n*), age (mean, range)	Pain intensity/relief	Complications
Weill, 1996 [36]	Single-site retrospective	*N* = 37, 61.4 years (33–86 years)	24/33 had clear improvement (reduction of analgesia dose by > 50%), 7/33 had moderate improvement (decrease in analgesia dose < 50%), 2 had no improvement. Improvement was stable in 73% at 6 months	38% (20/52) had cement leaks, majority were asymptomatic except 5 which led to transient pain (*n* = 2), vena dave intrusion without symptoms (*n* = 1), difficulty swallowing (*n* = 2)
Barragan-Campos, 2006 [41]	Single-site retrospective	*N* = 117, 58.2 years (26.6–88.2 years)	Nil	423 cement leakages from 304 treated vertebrae during 159 vertebroplasty procedures Of these leakages, only 6.8% (8 patients) experienced complications. 5.1% had local complications including radicular pain and hematoma and 1.7% had systemic complications in terms of pulmonary embolism
Calmels, 2007 [39]	Single-site retrospective	*N* = 52, 54 years (27–84 years)	Analgesic efficacy (residual VAS pain score of 0–2 for 'excellent' and 2.5–4.5 for 'good') 86% at 1 month (67% excellent and 19% good), 92% at 6 months (71% excellent, 21% good)	50.5% cement leaks, majority asymptomatic except for 5 cases (8.5%) which resulted in radiculalgias (*n* = 4), cauda equina syndrome (*n* = 1), symptomatic pulmonary embolism (*n* = 2)
Kobayashi, 2009 [32]	Multicentre prospective observational	*N* = 32, 62 years (37–87 years)	Mean VAS pre-treatment 6.2 ± 2.1, 1 week post 2.4 ± 2.3, 4 weeks post 1.8 ± 2.3 Response rate 1 week post procedure 70% (95% CI 54–83%), with significantly effective (VAS 0–2 or decrease ≥ 5) in 20 cases (61%), moderately effective (VAS 2–4) in 3 (9%). Mean time to response 2.4 days	No major adverse events reported. 1 patient experienced minor bleeding from puncture site controlled with local compression
Lee, 2009 [33]	Single-site retrospective	*N* = 19, 70 years (44–89 years)	84% (16/19) reported immediate (24–48 h post procedure) and long-term benefit in pain and mobility with 78.9% (15/19) having a step down in analgesic requirement	5.3% (1/13) had cement extravasation around the site of the procedure leading to transient pain managed with simple analgesia
McDonald, 2009 [38]	Single-site retrospective	*N* = 841, mean age 71–75 years	Baseline RDQ (at rest): 3.9 ± 0.65 RDQ (activity): 8.5 ± 0.35 Post intervention RDQ (at rest) decreased at 48 h ($p < 0.01$). At 1 week, RDQ had a median improvement of 2.7 points (25%, 95% CI 1.7 to − 3.7) and remained improved at 6 months ($p < 0.01$) and at 1 year ($p = 0.03$). RDQ (activity) at 1 week had a median improvement of 5.3 points (48%, 95% CI − 4.2 to − 6.4) Subjective global pain improvement rating at 24 h (at rest/activity): Complete resolution 22 (45%)/11 (22%); significant resolution 18 (37%)/33 (67%); no change 8 (16%)/4 (8%); increased pain 1 (2%)/1 (2%)	Nil
Chen, 2011 [35]	Case series	*N* = 4, range 47–67 years	Mean VAS pre-treatment 8.5 ± 0.6, 1 day post 1.5 ± 0.6, 1 month post 1.8 ± 0.5	1 patient had asymptomatic cement leak
Tian, 2016 [34]	Single-site retrospective	*N* = 39, 60.1 years (range 39–78 years)	Mean VAS scores declined significantly from 7.4 ± 1.1 pre-procedure to 2.5 ± 0.9 by day 3 after the procedure and were 2.1 ± 1.1 at 1 month, 2.0 ± 1.1 at 3 months, 1.9 ± 1.1 at 6 months, 1.8 ± 0.9 at 12 months and 1.7 ± 0.7 at 18 months after the procedure ($p < 0.001$)	38.5% (15/39) had asymptomatic cement leakages

VAS visual analogue scale (out of 10), *RDQ* Roland-Morris disability questionnaire score

result from cement extravasation from outside of the vertebral canal [3, 5]. While rates of cement extravasation vary widely in the literature ranging from 20 to 50% [5, 34, 35, 41], most cement leaks are asymptomatic and clinically insignificant. Nevertheless, there is a potential for severe complications such as spinal cord injury to occur in the event of intracanalicular extravasation [33].

Other complications include cement pulmonary embolism, fat emboli, transient radiculopathy and acute hypotension [3, 5]. Based on a systemic review, Chew and colleagues suggest that a cement volume greater than 4 ml is associated with an increased number of complications [37].

Radiofrequency ablation

Dupuy et al. first reported that RFA may provide pain relief in two patients with metastatic haemangiopericytoma and osteoid osteoma, respectively [42]. RFA utilises a high-frequency alternating current that is passed from a needle electrode into the surrounding tissue, resulting in heating and eventual coagulative tissue necrosis [3]. It can be performed under conscious sedation with local anaesthesia in patients who are otherwise poor surgical candidates [9]. The operator has the ability to deliver thermal energy to the lesion by precise placement of ablation electrode(s) or antenna(e) under imaging guidance.

While Dupuy et al. demonstrated that temperature levels in the spinal canal do not reach cytotoxic levels, the use of RFA is traditionally limited in posterior vertebral body lesions due to the close proximity to spinal cord and nerve roots in posterior vertebral body lesions [3, 8•, 10, 42]. However, newer techniques including RFA bipolar tumour ablation systems (e.g. STAR; Merit Medical Systems, Utah) have shown promise. Anchala and colleagues have shown that metastatic posterior vertebrae lesions can potentially be managed easily using this system [43].

Several trials (Table 2) have shown excellent palliation of painful bone metastases using RFA [15, 21, 42, 44]. A prospective, single-arm, multicentre study supported by the American College of Radiology Imaging Network found that RFA significantly reduces pain intensity and severity in patients with unremitting pain from bone metastasis [45]. In this trial, 55 patients had reduced pain severity at 1 month (OR 14.0, $p < 0.0001$) and 3 months (OR 8.0, $p < 0.001$) after RFA procedure based on Memorial Pain Assessment Card (MPAC) scores. The study also found significantly improved mood levels post RFA, with MPAC scores of 19.9/100 at 1 month ($p < 0.0001$) and 14.9/100 ($p = 0.005$) at 3 months follow-up. Another similar multicentre prospective single-arm study by Goetz et al. described a substantial reduction in pain scores and improvement in quality of life following RFA of painful metastases involving the bone [44]. Out of 43 patients, 41 patients (95%) experienced a > 2 brief pain inventory (BPI) point decrease in the worst pain following RFA with 41% (17/41, $p < 0.0001$) achieving pain relief 1 week post procedure. Gronemeyer et al. described 10 patients with unresectable metastatic spinal lesions treated with RFA—90% reported reduced pain across a follow-up period from 3 to 11 months, with an average reduction of 74% in pain intensity [15].

Several factors underlying the pathophysiology and therapeutic effect of tumour radiofrequency ablation have been proposed [11, 14, 46]:

Table 2. Clinical outcomes in studies evaluating the effectiveness of radiofrequency ablation in bony metastases

Author, year	Report type	Patients (*n*), age (median, range)	Tumour size (mean ± SD)	Location of lesions (*n*)	Pain intensity/relief	Analgesic use
Callstrom, 2002 [21]	Single-site prospective observational study	*N* = 12, 65 years (56–75 years)	Range1–11 cm	Pelvis = 5, sacrum = 2, spine = 1, chest wall = 2, extremity = 2	Average worst BPI pre-treatment 8.0, 1 week post treatment 4.6 ($p < 0.012$), 4 weeks 3.1 ($p = 0.001$), 6 weeks 3.1 ($p = 0.002$), 8 weeks 2.4 ($p < 0.004$) Mean score for interference of pain in ADL 6.6 pre-treatment, 4.2 at 1 week ($p = 0.023$), 2.7 at 4 weeks ($p = 0.002$), 2.2 at 6 weeks ($p = 0.001$) and 1.8 at 8 weeks ($p < 0.004$)	8/10 patients reported reduced use of analgesics at some time post RFA
Gronemeyer, 2002 [15]	Single-site retrospective	*N* = 10, mean age 64.4 years (57–76 years)	Range1.5–9 cm	Spine = 21	Average % relative pain reduction 74% (range 30–100%) at follow-up (range 2–11 months)	Nil
Goetz, 2004 [44]	Multicentre prospective observational study	*N* = 43, 64 years (28–88 years)	6.3 cm, range 1.4–18 cm	Pelvis = 12, sacrum = 12, rib = 6, vertebrae = 4, other = 9	Average BPI pre-procedure 7.9, 4 weeks post 4.5 ($p < 0.0001$), 12 weeks 3.0 ($p < 0.0001$), 24 weeks 1.4 ($p = 0.0005$)	Mean opioid requirements at baseline 99.0, week 1105.7, week 4 95.5, week 8 40.4 ($p = 0.01$), week 12 45.4 ($p = 0.01$), week 24 93 ($p = 0.5$)
Dupuy, 2010 [45]	Multicentre prospective observational study	*N* = 66, 62 years (34–85 years)	5.2 ± 0.2 cm	Pelvis = 22, chest wall = 20, spine = 8, extremity = 5	Pain relief pre-RFA to 1-month follow-up 26.3 (95% CI 17.7–34.9), pre-RFA to 3-month follow-up 16.38 (95% CI 3.4–29.4) Odds of lower pain severity at 1-month follow-up 14.0 (95% CI 2.3–25.7), at 3-month follow-up 8.0 (95% CI 0.9–15.2) than pre-RFA	Nil
Anchala, 2014 [43]	Multicentre retrospective study	*N* = 92	Nil	Spinal = 128	Average VAS pre-procedure 7.51, 1 week 1.73 ($p < 0.0001$), 1 month 2.25 ($p < 0.0001$), 6 months 1.75 ($p = 0.009$)	54% reduction in pain medications post treatment, 30% no change, 16% increase in analgesics

BPI brief pain inventory short form, *VAS* visual analogue scale (out of 10), *ADL* activities of daily living

1. Reduction of transmission of pain signals to the periosteum mediated by heat destruction of pain-sensitive fibres in the immediate- to early-phase post RFA
2. Mechanical stabilisation from the destruction of a bulging lesion
3. The destruction of tumor cells that produce cytokines including TNF alpha, substance P and interleukins responsible for stimulation of sensitive nerve fibres
4. Destruction of osteoclasts

RFA for spinal metastases is usually well tolerated and the observed toxicity rate is often low. Previous case series report low rates of major complications in RFA, ranging between 5.4% and 6.5% in two large series [44, 45]. The most frequently encountered minor complications are puncture site hematomas, transient hyperthermia and transient pain exacerbation [3, 46]. Major complications include skin burns, which range from mild erythema to third-degree burns, and neurovascular injury which may encompass foot drop, transient bowel and bladder incontinence and neuropathic pain. [17, 19].

Neurovascular and soft tissue injuries during RFA of spinal metastasis may be limited if the nidus of the ablation zone is at least 1 cm from vital structures [14, 21, 47]. Dupuy et al. also reported that neural injury may be reduced in cases where there is preserved cancellous or cortical bone between the lesions [42]. The presence of cortical bone serves as an insulator and cancellous bone has reduced heat transmission compared to soft tissues [42]. The risk of ablation-induced injury to nerves or viscera may also be reduced by injecting carbon dioxide into fascial planes to create more separation between sensitive structures and ablation probe [7].

Combination of vertebroplasty and RFA: current evidence

In the last decade, several authors have begun to investigate the role of combined RFA with vertebroplasty for spinal metastasis. Some reports have emerged in the literature suggesting that combined RFA and vertebroplasty is a safe and efficacious procedure for not only pain management but also local tumour control in spinal metastasis. In addition, the Metastatic Spine Working Group recommends the application of combined vertebral augmentation and RFA in the management of spinal metastases for pain alleviation and vertebral stabilisation [48]. They have suggested an algorithm where clinicians should consider combined RFA and vertebral augmentation, in particular, in cancer patients with good performance status, life expectancy of greater than 6 months and few visceral metastases who have either of the following: (1) asymptomatic spinal metastases, (2) uncomplicated painful spinal metastases or (3) stable pathological vertebral compression fractures.

While RFA and vertebroplasty are independently effective in pain palliation in spinal metastasis, some studies (Table 3) suggest that the combination of RFA and vertebroplasty may have a synergistic effect on pain management [7, 11, 12, 13•, 14, 16, 46, 49, 50]. The majority of these studies are single-arm observational studies and there is a lack of level 1 evidence supporting increased efficacy in pain management following combined RFA and vertebroplasty in the current literature. In a retrospective single-arm study of 22 adult patients

Table 3. Clinical outcomes in studies evaluating the safety and effectiveness of combined radiofrequency ablation and vertebroplasty in bony metastases

Author, year	Report type	Patients (*n*), age (mean ± SD, range)	Location of lesions (*n*)	Pain intensity/relief	Complications
Schaefer, 2003 [16]	Single case study	*N* = 1, 80 years	Lumbar spine	At 3 months FU, patient was pain-free without medications and had no limitations in activities of daily living	Small asymptomatic ventral cement leakage
Halpin, 2005 [14]	Single case study	*N* = 1, 45 years	Thoracic spine	Excellent pain control with all analgesics discontinued at 2 months FU	No complications observed
Toyota, 2005 [49]	Single-site prospective single-arm observational	*N* = 17, 64.2 years (54–81 years)	Spine = 6, pelvis = 10, sacrum = 2, extremities = 2, maxilla = 1, mandibular = 1	100% pain relief within several days. Mean VAS reduced from 63 to 24 post procedure ($p < 0.001$). Analgesic reduction achieved in 41% (7/17 patients). Mean duration of pain relief 7.3 months (median 6 months) in all patients	No major complications occurred. Minor complications include hematoma ($n = 2$) and transient local pain in most cases
Hoffman, 2008 [50]	Single-site single-arm retrospective	*N* = 22, median age 64 years (41–86 years)	Spine = 16, sacrum = 2, pelvis = 6, extremities = 3	100% pain relief within 24 h; mean pre-treatment VAS 8.5, 24 h post 5.5 ($p < 0.01$), 3 months FU 3.5 ($p < 0.01$). Amount or strength of analgesics reduced in 15 patients, unchanged in 5, increased in 2 (due to tumour progression elsewhere)	No major complications occurred
Munk, 2009 [11]	Single-site single-arm retrospective	*N* = 19, 58.9 years (42–82 years)	Spine = 11, acetabulae = 9, pelvis = 4, humerus = 1	100% pain relief; mean pre-treatment VAS 7.9, 6 weeks post procedure VAS 4.2. Mean difference in VAS score 4.08 (95% CI 3.92–4.87, $p < 0.0001$). Analgesic reduction and improvement in mobility occurred in 18 of 19 patients	Minor complications occurred in 7 of 15 patients, of which majority were self-limiting but 1 experienced transient thermal nerve injury manifesting as motor-sensory disturbance
Lane, 2011 [12]	Single-site single-arm retrospective	*N* = 36, 57.6 years (34–81 years)	Spine = 34, pelvis = 15, sacrum =3 , humerus = 1	Mean pre-treatment VAS 7.2, 24 h post procedure VAS 3.4 ($p < 0.01$)	Cement extravasation occurred in 47% (17/36) with majority being asymptomatic with the exception of 3 in terms of transient paraesthesia, transient neuropathic pain and asymptomatic pulmonary embolism
Clarencon, 2013 [46]	Single-site retrospective	*N* = 24, 61 years (42–82 years). 12 had both vertebroplasty and RFA	Spine = 7, pelvis = 11, femur = 5, scapula = 1	Mean pre-treatment VAS 6.4 (± 2.7), 1 month FU 1.9 (± 2.4), 6 months FU 2.3 (± 2.9) Pain significantly reduced at 6 months FU (mean VAS reduction 4.1; $p < 0.00001$). 74% had functional improvement	12.5% (3/24) major complications rate with 2 skin burns and 1 case of myelopathy
Madaelil, 2016 [7]	Single-site single-arm retrospective	*N* = 11, 58 years (37–79 years) 11 had both RFA and vertebroplasty	Sacral = 16	Median pre-treatment NRS 8 (IQR 6–9.25), 1 month post procedure 3 (IQR 1.75–6.3) ($p = 0.004$)	No acute or long-term complications documented during the overall medial follow-up of 4.7 months (range 0.9 to 28.7 months)
Reyes, 2017 [13•]	Multicentre retrospective single-arm	*N* = 49, 64.3 ± 12.6 years	Spine = 72	Mean pre-treatment VAS 7.9 ± 2.5, 2–4 weeks post procedure VAS 3.5 ± 2.6 ($p < 0.0001$). Mean ODI improved from 34.9 ± 18.3 to 21.6 ± 13.8 2–4 weeks post procedure ($p < 0.0001$)	No procedure-related complications and clinically significant cases of cement extravasation occurred

FU follow-up, *VAS* visual analogue scale, *NRS* numerical rating scale, *IQR* interquartile range, *ODI* Oswestry Disability Index (out of 100)

with 28 painful osteolytic bone metastasis, of which 18 were found in the spine, Hoffman et al. reported 100% pain relief within 24 hour post tandem RFA and vertebroplasty [50]. There was a significant reduction in VAS pain scores from 8.5/10 pre-procedure to 3.5/10 at 3 months ($p < 0.01$) with no major complications. In a similar retrospective paired comparison study of 53 combined RFA and vertebroplasty procedures in 36 patients, of which 34 were conducted on spinal metastases, all patients had improved pain scores within 24 h post procedure without significant complications with mean VAS scores decreasing from 7.2/10 pre-procedure to 3.4/10 post procedure ($p < 0.01$) [12].

Of note, in a recent larger multicentre retrospective study of 49 patients with 72 painful vertebral metastasis, Reyes et al. reported significant improvement in pain relief and level of function with combined RFA and vertebroplasty [13•]. While mean VAS decreased from 7.9/10 pre-procedure to 3.5/10 2–4 weeks post procedure ($p < 0.0001$), the Oswestry Disability Index (ODI) scores improved from 34.9/100 to 21.6/100 post procedure ($p < 0.0001$). In addition, using a combination of RFA and kyphoplasty in 38 thoracolumbar vertebral metastases, Zheng and colleagues demonstrated 100% pain relief post procedure with a mean VAS score of 7.69 pre-procedure and 2.96 at 6 months post procedure ($p < 0.01$). Importantly, no treatment-related complications occurred during the procedure and follow-up [47].

In contrast, Clarencon and colleagues did not find an additional benefit in performing vertebroplasty with RFA for pain relief in patients with painful neoplastic bone lesions [46]. Out of 24 patients with painful bone metastasis, 12 had a combination of RFA and vertebroplasty, although it is uncertain how many of these are spinal metastases. Together with age, sex and metastasis type, additional vertebroplasty did not show any influence on pain relief post procedure in a multivariate analysis. However, the study may be limited by its retrospective nature, small population size and lack of adjustments for other potential confounders such as pre-procedure analgesic use and concurrent radiotherapy/chemotherapy. In addition to that, there is a paucity of information regarding the temporal relationship between RFA and vertebroplasty as well as tumour size which may perhaps reduce the validity of the study.

In a separate randomised controlled trial of 36 consecutive patients with spinal osteolytic lesions secondary to multiple myeloma, Orgera et al. reported similar pain scores post procedure in both vertebroplasty alone and combined RFA and vertebroplasty groups (mean VAS scores at baseline 9.3 vs 9.1, at 24 h 3.0 vs 3.4 ($p = 0.33$), at 6 weeks post procedure 2.3 vs 2.0 ($p = 0.29$)) [51]. Both groups also had similar analgesic use and functional levels at all time points without any major complications following procedure. While it appears that additional RFA may not provide added benefit in pain management of patients with multiple myeloma and vertebral deposits in the medium term, a larger study is required.

Several reasons have been postulated for the safety and efficacy of combined RFA and vertebroplasty in the palliative management of spinal metastasis. RFA alone has been shown to provide significant and prompt pain relief in spinal metastases. However, unlike vertebroplasty, it does not provide mechanical stability to the vertebrae weakened by neoplastic infiltration [14, 33]. Similarly, vertebroplasty may be limited in larger lesions with a substantial soft tissue component due to unpredictable cement distribution [49]. Incomplete cement migration to the bone-tumour interface may correlate with a poorer clinical

response [11]. By destroying tumour tissue at the site of vertebroplasty, RFA may improve the cement distribution of the vertebral lesion during vertebroplasty and thereby increase the duration of stability provided by vertebroplasty [12, 14, 52].

Moreover, in vertebroplasty, the injection of PMMA into metastatic spinal lesions invariably results in displacement of tumour cells, some of each may enter the venous system and potentially lead to more distant metastasis [53]. In principle, utilising RFA prior to vertebroplasty causes thrombosis of the paravertebral and vertebral venous plexus, thereby reducing the risk of embolization-related complications from vertebroplasty [16]. In addition, the creation of a cavity into which PMMA is then injected under low pressure can reduce the rate of cement leakage [54].

In addition to pain relief, there has been increasing notion that combined RFA and vertebroplasty may contribute to local tumour control. Radiographic local control failure, judged by CT and/or MRI and/or 18-fluorodeoxyglucose (FDG) PET-CT and/or SPECT-CT findings, is defined by either one of the following: (1) increased osteolysis or paravertebral tumour extension on CT; (2) new or persistently enhancing soft tissue extending into the epidural space, neural foramina or paravertebral space on MRI; and (3) persistent FDG uptake noted on PET-CT or whole-body I-131 SPECT-CT [7, 8•].

In a retrospective single-centre observational study of 55 spinal metastases post combined RFA and vertebroplasty over a median follow-up period of 34 weeks, Wallace and colleagues reported 89% (41/46) and 70% (21/30) radiographic local control rate at 3 months and 1 year post procedure, respectively, despite systemic metastatic disease progression [8•]. No complications were reported during the length of the study and no patients had clinical evidence of metastatic spinal cord compression at the treated levels. However, the significant number of patients without follow-up imaging (25/55) may be a form of selection bias, thus limiting the validity of the study. In a small case series by Madaelil et al., 75% (3/4) of patients with sacral metastases achieved radiographic local tumour control after a median period of 7.6 months [7]. Out of these 4 patients, 3 had received combined RFA and vertebroplasty and 1 had RFA alone. These preliminary results from combined RFA and vertebroplasty are promising.

Alternative tumour ablation strategies and vertebroplasty

In addition to RFA and vertebroplasty, percutaneous cryoablation, which refers to the application of extreme cold to destroy diseased tissue, has also been used in the management of spinal metastases. A key advantage of cryoablation over other methods is the ability to carefully monitor the ablation margin because of the visibility of the ice-ball as a well-marginated, low-attenuation region on CT, or low-signal region on MRI, with the outer edge of the ice-ball corresponding to 0 °C [9]. Cryoablation is also able to penetrate deeply into the bone, which, unlike RFA or microwave energy, may allow more complete treatment of painful bony metastases, especially in osteoblastic lesions where high impedance is a limiting factor [10, 54]. Moreover, patients do not experience increased pain post procedure in contrast to transient increased pain following RFA [9, 55].

Tomasian et al. reported significant improvement in pain palliation, reduced analgesic use and local tumour control after cryoablation in a single-centre

retrospective analysis of 14 patients with 31 vertebral metastases [55]. In detail, median NRS scores were 8 ± 1 pre-procedure and 3 ± 1.3 months post procedure ($p < 0.001$) with substantial reduction in median morphine-equivalent dosages at 1 week, 1 month and 3 months post procedure (95 ± 55, 85 ± 50 and 80 ± 45 mg/day, respectively; $p < 0.001$ for all). Local tumour control, as judged by no radiographic evidence of progression at treated sites, was achieved in 96.7% (30/31) of tumours (median follow-up 10 months, range 1–24 months).

Moreover, combined cryoablation and vertebroplasty may potentially offer better pain reduction and improvement in quality of life than vertebroplasty alone in the management of spinal metastasis. In a double-arm retrospective analysis of 46 patients with single vertebral metastasis, where 23 patients received cyroablation and vertebroplasty (CVT) and 23 receiving vertebroplasty alone, patients who were treated with CVT were found to have better pain control at each follow-up (mean VAS score at 3 months 2.2 ± 0.9 vs 3.8 ± 1.4; 6 months 2.1 ± 1.1 vs 4.2 ± 1.1; all $p < 0.001$) and higher quality of life (QOL) (mean ODI score at 3 months 25.6 ± 4.34 vs 45.2 ± 6.62; 6 months 26.55 ± 4.12 vs 40.65 ± 7.19; all $p < 0.001$) than vertebroplasty alone [54]. Nevertheless, it should be noted that while both groups shared similar baseline characteristics in terms of age, gender, baseline pain and QOL scores, patients in the vertebroplasty alone group received less PMMA during the procedure and other potential confounders such as analgesic regimen and previous radiotherapy/chemotherapy were not accounted for.

Microwave ablation (MWA) has also been discussed, but less well described, in the management of spinal metastases. Unlike RFA, MWA is less influenced by variable tissue impedance and perfusion-mediated tissue cooling, potentially reaching higher intratumoural temperatures as well as creating a more uniform ablation zone with shorter ablation timing [9]. In a retrospective study of 17 patients with 20 spinal metastases treated with MWA, and with 9 cases having adjunct vertebroplasty, Kastler et al. reported improvement in pain control immediately post procedure (baseline mean VAS 7.4 ± 1.2 vs day 0 1.3 ± 1.8, $p < 0.001$) and during follow-up (day 7 1.6 ± 1.7, $p < 0.001$; 3-month 2.2 ± 1.5, $p < 0.001$; 6-month 2.3 ± 1.4, $p < 0.01$) [56]. No complications were reported following procedures. However, it should be noted that while adjunct vertebroplasty is potentially a confounding factor, no statistical analysis was carried out between patients who had adjunct vertebroplasty and those without.

Patient and lesion selection

When selecting patients for percutaneous RFA or vertebroplasty or indeed, both procedures, a multidisciplinary approach is essential with input from an interventional radiologist, spinal surgeon and oncologist [48]. Appropriate imaging should be performed pre-procedure, including CT and MRI with fluid-sensitive sequences and contrast-enhanced sequences where available [4].

MRI allows assessment of the degree of marrow involvement, epidural and paraspinal extension, spinal cord compression, presence of other lesions and vascularity. CT provides assessment of cortex and allows evaluation of the vertebral body anatomy and assessment of the posterior cortex and pedicles for treatment planning.

Indeed, each technique has its advantages and drawbacks. The management of patients with spinal metastases requires careful consideration of various

factors—tumour histology, patient performance status and prognosis, understanding of the disease process, appreciation of the extent of spinal destruction and the goal of treatment (curative or palliative). In particular, Gangi suggests that in painful spinal metastasis with extension to surrounding soft tissues and risk of pathological fractures, combined RFA and vertebroplasty should be considered [57].

In patients with spinal metastases, percutaneous RFA and vertebroplasty are recommended for the following clinical scenarios (Fig. 1) [2, 3, 5, 8•, 12, 16, 28, 46, 50, 58]:

- Painful spinal metastases not controlled with conventional analgesic therapy with significant limitation to activities of daily living
- Palliation of symptomatic metastases with at least moderate pain (VAS of at least > 4)
- Localising pain to one or two sites with corresponding metastatic disease on cross-sectional imaging

Absolute contraindications are [2, 3, 5, 8•, 12, 16, 46, 50, 58]:

- Local or systemic infection
- Uncorrectable coagulopathy: platelet count < 50,000 μ/L and/or INR > 1.3
- Tumours causing spinal cord compression or spinal instability
- Allergy to bone cement
- Asymptomatic patients or pain that is responding to medical management
- Patients with severe cardiorespiratory disease

Relative contraindications depend on operator experience and include [2, 3]:

- Lack of orthopaedic and neurosurgical support
- Complete or greater than 70% vertebral collapse (difficult for vertebral access)
- Vertebral fractures with posterior column involvement (higher risk of cement extravasation)
- Metastases with close proximity to important neurovascular structures

Technique of RFA and vertebroplasty

Depending on the location of the tumour, either CT or fluoroscopic guidance is used. The procedures can be performed under local anaesthesia, local anaesthesia and conscious sedation and epidural/spinal or general anaesthesia. During the intervention, vital signs are to be monitored frequently. Strict asepsis is to be maintained. Prophylactic antibiotic cover is administered, usually intravenous cephazolin or clindamycin, if there is a documented penicillin allergy.

An 11G bone biopsy needle is inserted close to the lesion under imaging guidance after local anaesthetic (1% lidocaine) is given. Then, the RFA electrode is inserted coaxially into the needle with the mid-portion of the active length of the electrode positioned at the estimated epicentre of the targeted lesion. Depending on lesion size, the length of the active tip of the electrode differs. The temperature reached at the tip of the needle can range from 60 to 100 °C,

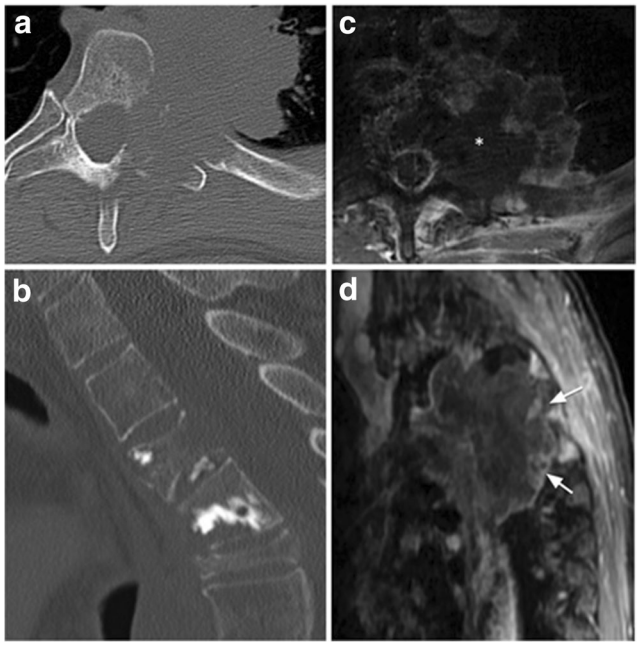

Fig. 1. Combined RFA and VP for severe back pain due to locally invasive and metastatic non-small cell lung carcinoma involving the left posterior chest wall and T4-6 thoracic vertebrae. **a** Axial CT chest demonstrates a large mass centred in the posterior segment of the left upper lobe with erosion and infiltration of the left posterior chest and left posterior elements of T4. The patient was treated with combined RFA and vertebroplasty. **b** Sagittal CT reconstruction showing vertebroplasty cement at T4 and T5 levels. T6 was not treated due to a vertebra plana morphology. **c** Axial and **d** sagittal T1-weighted fat-saturated post contrast MRI following RFA demonstrating absence of central enhancement within the infiltrating left posterior chest mass (asterisk) consistent with treatment response. Some residual peripheral enhancing tumour (arrow) at the edge of the ablation zone is also present.

with a mean duration of heating of 5 min (range 3–7 min) [11, 46].

Following completion of RFA, the radiofrequency probe is replaced with a 10–15G vertebroplasty cannula which is positioned in place using a sterile surgical hammer. Depending on the location of the spinal metastases, the needle trajectory may differ. According to CIRSE guidelines [40], for lesions in the cervical spine, an anterolateral or posterior transpedicular approach is suggested. For thoracic and lumbar level lesions, a unilateral transpedicular approach is preferred.

Cement is usually prepared once the needle is in position. Injection can be performed either using a dedicated injection set or a 2 ml luer lock syringe. Unlike free-hand injection, cement injection kits, which enable aspiration and direct injection in continuous flow, are a safer option and offer less radiation exposure risk to the operator [40]. Cement injection is performed under continuous lateral fluoroscopic control in order to detect epidural leakage and intermittent anteroposterior screening to exclude lateral leaks and assess cement distribution. The risk of cement leakage is higher at the initial phase where the cement is more liquid.

When cement leakage is detected, the injection should be stopped [40]. Pausing for about 30–60 s will enable the cement to set and seal the leak. Should the leaking continue, despite change in needle position or bevel direction, injection should be stopped [41]. Guidelines to stop cement injection include when the anterior two thirds of the vertebral body is filled and cement is homogenously distributed in between lateral borders of the vertebral body and

endplate [32, 40]. A CT scan should be performed, if available, following the procedure to check cement distribution and detect any cement leakage. Appropriate post procedure care should include repeated assessment of pain, vital signs and deterioration of neurology requiring potential intervention.

Conclusions

Vertebral augmentation and RFA are excellent alternatives to conventional medical and surgical options for patients with vertebral compression fractures associated with spinal metastasis. In carefully selected patient groups, vertebral augmentation and RFA alone have shown to provide effective pain relief and improve the remaining quality of life in patients with spinal metastases without causing significant complications. Importantly, for effective and safe treatment of vertebral compression fractures secondary to advanced spinal metastasis, a multidisciplinary approach and appropriate patient and tumour selection with necessary anatomic considerations are essential.

The combination of RFA and vertebral augmentation, in theory, may have a possible synergistic effect on pain management as well as local tumour control. Large observational studies by Lane and colleagues as well as Munk et al. have suggested that combined RFA and vertebral augmentation appears to be a safe and effective approach in the management of painful metastatic bone lesions. After combined RFA and vertebral augmentation, not only may pain levels be significantly reduced with a mean VAS score reductions of 4/10 but refractory pain may be also managed as early as 24 h post procedure. Nevertheless, the potentially higher operative costs of combined RFA and vertebral augmentation compared to conventional pain management strategies might mean that additional studies are required before it can be offered as a mainstay treatment option.

However, to our knowledge, there has yet to be a study comparing RFA or vertebral augmentation alone with combined RFA and vertebral augmentation in spinal metastases. Most of the published studies to date are single-arm retrospective observational studies with short- to medium-term follow-up. No randomised controlled trials have been conducted.

Further prospective studies of combined RFA and vertebral augmentation with multicentre involvement and ideally randomisation and blinding to different treatment arms as well as longer follow-up will be required. Ideally, studies should focus on pain management, functional status and local tumour control as study end points.

Compliance with Ethical Standards

Conflict of Interest

Ning Mao Kam, Julian Maingard, Hong Kuan Kok, Dinesh Ranatunga, Duncan Brooks, William C. Torreggiani, Peter L. Munk, Michael J. Lee, Ronil V. Chandra and Hamed Asadi declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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