Review Article

Management of metastatic vertebral lesions by interventional techniques: Systematic review of outcomes

ABSTRACT

Vertebral metastases represent an important cause of cancer-related morbidity and mortality. Among all available treatments, interventional percutaneous techniques have recently emerged as potential strategies for the management of oncologic patients with vertebral lesions. Minimally invasive image-guided therapies include "ablative" and "consolidative" ones. According to the number of metastases and the patient's performance status, ablative techniques can be performed with a curative or a palliative purpose since necrosis induced by critic changes of intralesional temperature determines both tumor debulking and destruction of pain receptors. On the other hand, consolidative treatments are based on the injection of polymethylmethacrylate cement to improve structural vertebral integrity and obtain pain alleviation and prevention of skeletal-related events. This article reviews the current recommendations supporting the role of interventional radiology in the management of vertebral metastases, focusing on the last updates in literature.

Keywords: Ablative therapy, consolidative therapy, minimally invasive technique, oligometastasis, palliative and curative intent, vertebral lesions

BACKGROUND

Bone is the third most common site of metastases after liver and lungs for all kinds of tumors.[1] The primary tumors that most frequently metastasize to the vertebrae include breast, prostate, and lung cancer.[2] In the course of their disease, about 50% of patients with vertebral metastases will develop pain, which is the most common symptom among all the potential complications associated with vertebral metastasis, such as pathological fractures, spinal compression, and hypercalcemia. All these events result in a significant deterioration in the quality of life as well as a reduction in survival.[3] External-beam radiation is currently the standard of care for the management of painful vertebral metastases. This technique achieves pain relief through several biological effects, such as tumor burden and osteolysis reduction.[4] In addiction to radiotherapy, a systemic approach including chemotherapy, hormonal therapy, bisphosphonates, and analgesics is also adopted in case of widespread metastatic disease. However, many patients do not obtain adequate benefits from the use of conventional therapies. In the past decades, different minimally invasive image-guided techniques have been explored as new strategies for the management of patients with vertebral metastases, especially in those who are refractory to radiation therapy and systemic palliation. Among these alternative strategies, which are mainly in the hands of interventional radiologists, image-guided percutaneous therapies can be distinguished into "ablative" or "consolidative." Ablative techniques are based on the use of specific devices that induce tumor necrosis by dramatically increasing or decreasing intralesional temperature.[5] These include radiofrequency ablation (RFA), cryoablation (CA), microwave ablation (MWA),

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Reddy Ravikanth
Department of Radiology, St. John's Hospital, Kattappana, Kerala, India

Address for correspondence: Dr. Reddy Ravikanth, Department of Radiology, St. John's Hospital, Kattappana - 685 515, Kerala, India.
E-mail: ravikanthreddy06@gmail.com

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and high-intensity focused ultrasound (HIFU) and can be performed for either a curative or palliative intent. On the other hand, consolidative treatments such as cementoplasty or osteoplasty achieve vertebral defect reinforcement through percutaneous injection of polymethylmethacrylate (PMMA) cement to alleviate pain and prevent pathological fractures.[6]

Despite the fact that these techniques are minimally invasive, several procedure-related adverse events can occur. According to the Society of Interventional Radiology (SIR) standards-of-practice classification, complications are distinguished into minor and major.[7] Major complications are events that lead to substantial morbidity and disability and often require hospitalization; they include all those cases in which blood transfusions or interventional drainage procedures are needed. In literature, a very low rate of major complications is reported, with the high percentage reported by Liberman *et al*. which find major complications in 3 of 43 treated patients. All other complications are considered minor, including asymptomatic minimal bleeding or fluid accumulation visible on computed tomography (CT) and postablation syndrome (fever, fatigue, and malaise induced by the release of inflammatory factors from necrotic tissues). In this review, evidence supporting the role of interventional radiology in the management of vertebral metastases has been presented [Tables 1 and 2].

CURATIVE TREATMENT

Patients with distant metastases are considered noncompletely curable. However, recently published data suggest that a small percentage of oncologic patients with a low number of metastases at the time of diagnosis, treated with a curative purpose, may remain disease-free for years without developing additional metastatic lesions. The oligometastatic disease has increasingly gained support within the oncology community, which has defined a distinct clinical entity,[8] such that in patients with oligometastatic disease, local treatments can still be performed to completely destroy the tumoral tissue with a curative intent. In regard to vertebral metastases, surgical resection is less common than hepatic or pulmonary metastasectomy due to its high morbidity levels, while stereotactic body radiotherapy (SBRT) is considered less invasive and seems to be a promising and valid alternative according to the literature evidence.[9] In their prospective study, Milano *et al*. analyzed the long-term overall survival (OS) and cancer control outcomes of 121 patients with five or fewer clinically detectable metastases, showing good long-term survival (>4 years) outcomes after SBRT for limited metastases, particularly in patients with breast cancer (1 of 2) rather than patients with cancer from other primary sites (1 of 6). Furthermore, the variables of "vertebral metastases" and "one versus >one metastasis" were associated with a fourfold and threefold reduced hazard of death. Similarly, as mentioned above, curative treatment can be achieved with several percutaneous thermal ablation techniques.[10] Unfortunately, the evidence supporting the application of these methods originates from single-center experiences and is therefore limited due to the lack of randomized controlled trials.[6] This work reports that the therapeutic option should be reserved to the selected patients presenting limited vertebral disease (<3 potentially treatable vertebral metastases, each sized <3 cm), especially if they are young, affected by slow-evolving disease or without extravertebral disease.

Although there are no well-defined inclusion criteria, an aggressive locoregional approach should be reserved to patients with limited vertebral disease. In most studies, it is considered limited disease when there are a number of 1–5 metastases localized in noncritical body structures. Importantly, other characteristics influencing the prognosis such as age, tumor histology, and performance status should also be evaluated during patient selection. Curative image-guided ablation is therefore often reserved to young patients, affected by slow-evolving disease and/or without extravertebral metastases, especially if they are not surgical candidates.[11] It is also important to point out that according to the quality improvement guidelines for vertebral tumor management, ablation of malignant vertebral lesions should be established through a multidisciplinary evaluation. A curative approach should be attempted in slow-growing tumors with metastases measuring <3 cm in <3 proven locations.[12]

Table 1: Results of curative treatment

Curative reference	Design	Tumor histology	Site	Ablation modality	Patients/tumors	Treated tumors
Deschamps *et al*.	Retrospective	Mixed	Bone	RFA, CA	89/122	122
Wallance *et al*.	Retrospective	Mixed	Bone	RFA + CP	NR/55	55
Mcmenomy *et al*.	Retrospective	Mixed	Bone	CA	40/52	19
Littrup *et al*.	Prospective	Mixed	Bone	CA	126/251	34
Aubry *et al*.	Prospective	NR	Bone	MWA	NR/16	16
Napoli *et al*.	Prospective	Mixed	Bone	HIFU	18/18	18

Presentation of the study characteristics for each review, with summary of the study design and final results. *NR – Not recorded; RFA – Radio-frequency ablation; CA – Cryoablation, MWA – Microwave ablation, HIFU – High-intensity focused ultrasound; CP - Cementoplasty

Table 2: Results of palliative treatment

Palliative reference	Design	Tumor histology	Site	Ablation modality	Patients/tumors	Treated tumors	Pain reduction rate
Goetz *et al*.	Prospective	Mixed	Bone	RFA	43/43	43	95% (41)
Dupuy *et al*.	Prospective	Mixed	Bone	RFA	55/55	55	NR
Wallace *et al*.	Retrospective	Mixed	Bone	RFA + CP	72/110	110	78% (45/58)
Callstrom *et al*.	Prospective	Mixed	Bone	CA	61/69	69	69% (42)
Tomasian *et al*.	Retrospective	Mixed	Bone	CA	14/31	31	100% (14)
McArthur *et al*.	Retrospective	Mixed	Bone	CA	16/16	16	100%/3 m (16)
Kastler *et al*.	Retrospective	Mixed	Bone	MWA	17/20	20	100% (20)
Pusceddu *et al*.	Retrospective	Mixed	Bone	MWA + CP	35/37	37	100%/1 m (35)
Wei *et al*	Retrospective	NSCLC	Bone (extraspinal)	MWA + CP	26/33	33	96% (25/26)
Gainfelice *et al*.	Retrospective	Mixed	Bone (extraspinal)	HIFU	11/12	12	100% (11)
Hurwitz *et al*.	Randomized control trial	Mixed	Bone	HIFU	147/147	112 (35 control)	64% (72) versus placebo 20% (7)
Napoli *et al*.	Prospective	Mixed	Bone	HIFU	18/18	18	89% (16)
Anselmetti *et al*.	Prospective	NR	Bone	CP	4547/644	644	88% (of all parients)
Berenson *et al*.	Randomized control trial	Mixed	Bone	CP	134/247	138 (109 control)	NR
Cazzato *et al*.	Systematic Review	Mixed	Bone (extraspinal)	CP	196/223	223	95.60%

Presentation of the study characteristics for each review, with summary of the study design and final results. *NR – Not recorded; RFA – Radiofrequency ablation; CA – Cryoablation, MWA – Microwave ablation, HIFU – High-intensity focused ultrasound; NSCLC - Nonsmall-cell lung cancer; CP - Cementoplasty

RADIOFREQUENCY ABLATION

RFA generates heat by application of high-energy frequency current through an electrode placed in the treatment site under CT guidance. Frictional processes at the tip of the probe create heat (Joule effect), determining the destruction of adjacent tumor tissue. Bone provides a natural barrier for thermal energy; thus, RFA is ideal for the treatment of lesions surrounded by the bone. Depending on tumor size and location, one or more RF electrodes can be used. An additional probe performs continuous monitoring of the tissue temperature.

There are only a few studies assessing the curative aim of RFA in oncologic patients with vertebral metastases. For example, in the work of Deschamps *et al*.,[13] 122 vertebral lesions from several primary cancers were treated: 74 metastases with RFA and 48 metastases with CA. The aim was to reach a result as complete as possible in oligometastatic patients (Group 1) and to prevent skeletal related events (SREs), including pain, fractures, and nerve or spinal cord compression, in patients with long-life expectancy (Group 2). The 1-year control rate was 67% and only seven patients experienced SREs during the follow-up period. Furthermore, an oligometastatic condition associated with metachronous and small-sized metastases correlated with a reduction in the risk of treatment failure.

RFA is often associated with stabilization by cementoplasty, especially for vertebral lesions – which are easily subjected to compression stresses.[12] In the previously mentioned study, 38 lesions required additional cementoplasty. More recently, Wallace *et al*. retrospectively reviewed their clinical experience aimed to evaluate the local control rate of vertebral metastases in patients treated with a combination of RFA and cementoplasty.[14] Patients who underwent radiotherapy were excluded, as well as those with entirely osteoblastic metastases. All the reviewed examinations were performed during the 1-year follow-up. Criteria assessing local tumor control failure included increased osteolysis or paravertebral tumor extension on CT, new or persistent enhancement of soft tissue extending into the epidural space, neural foramina or paravertebral space on magnetic resonance imaging (MRI), and persistent fluorodeoxyglucose uptake on positron-emission tomography/CT. Fifty-five tumors were treated, with estimated local control rates of 89% (41/46) at 3 months, 74% (26/35) at 6 months, and 70% (21/30) at 1 year. In terms of systemic disease progression, the rates were 86% (32/37) at 3 months, 71% (22/31) at 6 months, and 67% (18/27) at 1 year. Neither acute nor delayed postprocedural complications were documented during the median clinical follow-up of 34 weeks (according to the SIR classification). In 8 of 9 cases who did not achieve local tumor control after RFA and vertebral augmentation, the residual tissue was present in the posterior vertebral body and/or epidural space; this occurred due to the difficulty to treat these areas in a protective attempt to avoid damage to the adjacent nerve roots. In the ninth case, a lesion of the anterolateral vertebral body was treated through a unipedicular approach and tumor recurrence occurred in the contralateral hemivertebral body.

CRYOABLATION

CA works through percutaneous probes that have two chambers, filled with compressed argon and helium. According to the Joule–Thomson effect, when the gases expand in the space surrounding the probe tip, a change in temperature occurs depending on the inversion temperature of the gases; the aim is to cool and thaw tissues, resulting in cell death. The volume of frozen tissue can be directly seen as a low-density ice ball on CT; temperature on the surface of the ice ball is not lethal (0°C); thus, the boundary should extend at least 5 mm beyond the target lesion to guarantee a complete ablation of the lesion itself. Furthermore, CA has an intrinsic analgesic effect on tissues, so it is well tolerated.

As far as indications and procedural technical recommendations are concerned, for curative CA, they are similar to those for RFA. Additional consolidation with cementoplasty is often necessary too.[12] In a single-institution retrospective study, McMenomy *et al*.[15] assessed the curative aim of CA in 40 patients with 1–5 musculoskeletal metastases from different primary cancers for a total of 52 metastasis. Nineteen of these were vertebral metastasis and 13/19 (68%) showed local control after treatment. Over the whole population, OS rates were 91% at 1-year and 84% at 2-year follow-up, with a median OS of 47 months. One- and two-year disease-free survival (DFS) rates were 22% and 7%, respectively (median DFS = 7 months). Only two major complications were reported during the 40 procedures (5%). As a part of their study, Littrup *et al*.[16] prospectively collected data on CA procedures of 34 vertebral metastases (mean tumor size: 4.6 cm) in 21 patients with oligometastatic disease (1–6 lesions). A further 217 soft-tissue lesions were treated, classified according to the body region in retroperitoneal, superficial, intraperitoneal, and head and neck. Any increase in ablation size or distinct development of asymmetric and/or nodular enhancement was considered as local treatment failure and then distinguished between local tumor progression and recurrence to differentiate incomplete tumor ablation from adjacent disease recurrence. At a mean 11-month follow-up, total recurrence rate was 10% (26/251). Three recurrences (1.2%) occurred within the ablation zone and therefore considered as local progression. Average time to recurrence was 4.9 months. In terms of vertebral metastases, the average follow-up period was 14.5 months, with a recurrence rate of 3% (1/34); this recurrence was marked as satellite and did not result from an incomplete treatment. A total of five major complications (2.3%) were referable to the procedure, two of which occurred during vertebral lesion treatment. These include pericardial effusion during chest wall ablation and prolonged peripheral nerve palsy following ablation of a sacral lesion.

MICROWAVE ABLATION

During MWA, a high-frequency electromagnetic field is produced at the tip of the antenna inserted into the tumor. The water dipoles in the adjacent tissue continuously realign with the oscillating microwave field, and their consequent rotation generates frictional heat. MWA is independent of changes in tissue impedence, and the negative cooling effect of blood flow in the near vessels (heat sink effect) is little. Consequently, MWA has emerged as an alternative to RFA because of its ability to achieve faster results with larger ablation zones. However, MWA is a newer technique and it is characterized by a higher learning curve due to the heterogeneity of clinical systems (antenna design, wavelengths, and power output of generators). Thus, clinical data and experience are minimal. Literature data on the curative potential of MWA in patients with vertebral metastasis are still limited but encouraging. Aubry *et al*.[17] found that CT-guided MWA in patients with oligometastatic vertebral disease had good short-term anticancer effects. In their study, a total amount of 16 lesions were treated: 6 osteolytic metastases, 5 osteoblastic metastases, and 5 soft-tissue sarcomas. The results were assessed through contrast-enhanced MRI at 1, 3, 6 and 12 months after the procedure, and treatment success was defined as ≥80% necrosis. At 1- and 3-month follow-up, the success rate was about 80%; at 6 and 12 months following MWA, it was 76.9% and 63.6%, respectively. No major complications were described during the procedures.

HIGH-INTENSITY FOCUSED ULTRASOUND

MR-HIFU-guided is a recently emerged technique that focuses acoustic energy on a small target volume under MR guidance to perform thermal ablation. Real-time monitoring of the temperature increase in the adjacent soft tissue and of the corresponding thermal damage allows immediate optimization of treatment delivery. In addition to temperature increase in the target volume, the introduced ultrasonic pulse (sonication) causes mechanical effects, namely gas formation (cavitation effect). Consequently, brief pauses between individual sonications are necessary to avoid uncontrolled reflections and deformation of the ultrasound beam.

Much experience with MR-HIFU has been gained with the treatment of some soft-tissue tumors, such as symptomatic uterine fibroids.[18] Cortical bone is characterized by a high absorption of ultrasound and low-thermal conductivity; thus, the maximum energy deposition occurs in the region of periosteal localized pain fibers. This is a very important advantage in the treatment of painful vertebral lesions. However, little information is available on HIFU as a curative option for vertebral metastases. In a recent prospective study, Napoli *et al*. assessed palliation of painful vertebral metastases achieved with MR-HIFU while also confirming its potential for local tumor control.[19] Targeted lesions were located in the ilium (10/18; 55.6%), the scapula (3/18; 16.7%), the transverse process of the T7 vertebra (1/18; 5.6%), and the extremities (4/18; 22.2%). An increase of bone density with restoration of cortical borders was observed in 5 of the 18 treated patients. In terms of local control, complete and partial responses (according to the MD Anderson Criteria) were obtained in two and four patients, respectively, during a 3-month follow-up. Contrast-enhanced images were used to quantify the nonperfused volume (NPV), as defined by the percentage of cancer tissue volume enhancing before the treatment and not enhancing after the treatment: NPV remained substantially stable during the follow-up, and no statistically significant difference was found between responders and nonresponders.

PALLIATIVE TREATMENT

The main goal of palliative treatment is not the ablation of the tumor, but rather, its aim should be to obtain pain relief and improvement in patients' quality of life. However, despite the availability of several traditional approaches, not all patients benefit equally from the same treatment option. The effect of ablation to achieve immediate pain reduction is based on thermal destruction of pain receptors, debulking of vertebral lesions, and reduction of tumor-related pain mediators such as tumor necrosis factor. In this regard, pain palliation is achieved through ablation of the boundary surface between normal vertebra and neoplastic tissue, which is the most aggressive part of the tumor.[6]

Patient selection for successful locoregional treatment of vertebral metastases is very important. There are no well-defined criteria to submit patients to palliative ablation, yet there is a recommendation for patients with pain, evaluated as >4 points in a 10-point visual analogue scale (VAS), with one or two predominant pain locations. Less eligible candidates are oncologic patients with disseminated vertebral disease, as well as those with osteoblastic metastases.[20] Another important aim of palliative treatment in vertebral metastatic patients is the prevention of SREs, first of which are pathologic fractures. Osteolytic metastases located in weight-bearing regions, such as the vertebral body, acetabulum, or condyles, can be treated with a combination of local ablation and consolidative treatment like cementoplasty.[21]

RADIOFREQUENCY ABLATION

Over the past two decades, at least 25 studies involving >400 patients have appeared in the literature regarding the role of RFA in pain palliation.[22] Among these, two multicenter trials, assessing the efficacy of RFA as a palliative approach in patients with painful vertebral metastases, have produced significant results.

The first study[23] by Goetz *et al*. considered 43 patients with painful refractory vertebral metastases between 1 and 18 cm in size, who either failed or were poor candidates for standard treatments. The patients were included if they had one or two painful sites and a score of at least 4 on the VAS over a 24-h period. An improvement following the treatment of at least 2 points from the worst pain was considered successful. During the follow-up period at 4, 12, and 24 weeks, 41 patients (95%) experienced pain relief, as well as a reduction in the consumption of analgesics at 8 and 12 weeks. Adverse events were seen in three patients, which include cutaneous burn, transient bowel and bladder incontinence after the treatment of a sacral lesion, and acetabulum fracture.

The second study involved six centers belonging to the American College of Radiology Imaging Network (ACRIN).[24] Fifty-five patients with a single painful (score >50 on a 1–100-point scale) vertebral metastasis underwent RFA. These lesions measured between 2 and 8 cm in size (average 5.2 cm) and were located in the pelvis, chest wall, spine, and extremities. Patients with hematological diseases, lesions of 9 cm or greater, impending pathological fractures, or with spinal canal infiltration were excluded from the study. The patients who previously underwent chemotherapy or external-beam radiation were admitted if the therapy was suspended at least 2 weeks or 1 month, respectively, before ablation. The mean pain score before ablation was 54 (range 51–91) of 100. The pain relief was achieved in all cases during the follow-up period, with an average reduction in pain intensity of 26.9 points at 1 month and 14.2 points at 3 months. Moreover, there was an improvement in patients' clinical status, with an increase of 19.9 and 14.9 points from pre-RFA score at 1- and 3-month follow-up, respectively. Major complications were reported in 3 of 55 (5.4%) patients, which consisted of refractory pain and neural damage. These two multicenter clinical trials have demonstrated the efficacy and safety of RFA for the palliation of painful vertebral metastases, though differences in pain relief results have also emerged, which may be due to several factors, for example, patient selection criteria or technical aspects linked to the procedures (i.e. different types of RF electrodes used).

In fact, the variability of patient eligibility criteria and the procedural differences between these two studies may explain the relatively decreased pain relief achieved in the ACRIN study. For example, 74% of patients in the Goetz *et al*. trial underwent previous radiation therapy to the tumor site, compared to the 24% of population in the ACRIN study. On the other hand, no statistically significant difference in pain relief was found between patients who previously received external-beam radiation therapy and those who underwent ablation alone, although a combination of the two techniques showed a higher efficacy in the palliation of chest wall masses. Moreover, procedural pain management and control in the Goetz *et al*. trial was accomplished with either general anaesthesia or conscious sedation, while in the ACRIN trial, conscious sedation was used for the majority of cases. It is possible that this difference could have influenced the volume of tissue destruction due to the painfulness limiting the procedure. Finally, differences in the types of treated tumors could account for the differential results of the two studies; although the most common primary tumors were the same in both the studies (lung, colon, and renal carcinomas), in the Goetz *et al*. trial, there was a higher proportion of other tumors, some of which with more favourable biology (desmoid, paraganglioma, meningioma, thyroid, prostate, and breast).

More recently, Wallace *et al*.[25] retrospectively reviewed their experience with RFA applied to achieve pain relief in 72 patients suffering spinal bone metastases from several primary cancers, with a total amount of 110 vertebral lesions. Cement was also instilled into the vertebral body for structural support in 105 cases (95%). Patients with osteoblastic metastases, as well as those with lesions causing spinal instability or spinal cord compression, were excluded. For each patient, preprocedural worst pain score was assessed on the day of ablation, and then 1 and 4 weeks after treatment, using a 10-point scale (Numeric Rating Scale). A reduction of 2 or more points was considered as partial relief, while complete relief was defined when a postprocedural score ≤1.89% of the treated patients (64/72) had at least moderate pain (≥4 out of 10) prior to the procedure, with a mean score of 8.0. All patients achieved pain palliation after the procedure, including those who did not receive previous or concurrent external beam radiation therapy or corticosteroids injections. The mean pain scores were 3.9 after 1 week and 2.9 after 4 weeks, which translated into complete relief rates of 23% and 45%, respectively. The 4-week follow-up pain score corresponded to a decrease in the use of pain medication in 31% of the patients, as well as an increase in activity in 50% of the patients. According to the SIR guidelines, no major complications related to RFA were reported. Three of the five lesions that were ablated but not augmented fractured within 12 months.

CRYOABLATION

CA of musculoskeletal metastases has produced similar rates of pain palliation compared with RFA;[26] yet it presents several advantages over RFA, including intrinsic direct analgesic properties, preservation of tissue collagenous architecture, and potential treatment of larger tumors due to the excellent imaging-guided monitoring.[27] In the largest available study supporting the therapeutic aim of CA, Callstrom *et al*.[28] treated 61 patients with one or two painful vertebral metastases and a pretreatment pain score of 4 or higher on a 10-point scale. Lesions in close proximity to neural structures or those causing impending fractures were excluded. A total of 69 tumors ranging from 1 to 11 cm (average 4.8 cm) in size were cryoablated. Response was assessed through the brief pain inventory-short form; prior to CA, the mean score for worst pain in a 24-h period was 7.1/10, which then decreased to 5.1/10 after 1 week, 4/10 after 4 weeks, and 1.4/10 after 24 weeks. A reduction in the use of analgesics was obtained in 83% of the patients. Only one patient experienced a major complication (osteomyelitis at the site of ablation), thus confirming the safety of CA.

A recent case series including 14 oncologic patients with a total number of 31 vertebral metastases from different tumors and a significant pain score (≥4 out of 10) showed statistically significant improvement in pain and reduction of analgesic usage at 1-week, 1-month, and 3-month follow-up.[29] Local tumor control was also achieved in 30/31 ablations (96.7%) during a median follow-up of 10 months (range: 1–24 months). Moreover, this was the first study assessing the efficacy of CA in the palliation and local control of osteoblastic painful metastases; only one single case report was excluded.[30] No major complications were reported, while two patients had postprocedural radicular pain that required corticosteroid injections. In a retrospective single-center review by McArthur *et al*.,[31] 16 patients with a single vertebral metastasis from different tumors underwent CA. All reported improvement in pain within 1 week following the procedure and at 3-month follow-up. In two cases, there was a near-to-complete pain relief, with a 10/10 preprocedural pain score dropping to 1–2/10 at 3 months, while one patient reported only mild pain improvement at 3 months, with a 2-point reduction in pain levels. Over the total of patients, 93.8% had tumor arrest or shrinkage on follow-up CT. Posttreatment CT examinations demonstrated marginal enhancement at the ablation site in 62.5% of cases, although only one patient had interval growth. A single case of neuroapraxia was reported, which resolved within 48 h.

MICROWAVE ABLATION

MWA of vertebral lesions has emerged as an alternative to RFA in some cases. Since MWA does not rely on the flow of current but rather on the induction of an electromagnetic field, it is independent of changes in tissue electrical impedance, thus allowing achieving faster results with larger ablation zones.[20] However, it is a rather new technology, so there are fewer studies compared to other techniques, and therefore, clinical data are still limited. In a retrospective study, Kastler *et al*.[32] suggested that MWA may be advantageous for palliation of sclerotic vertebral metastases. MWA was performed on 17 patients with 20 painful spinal metastatic tumors from different primary cancers, measuring from 12 to 70 mm in size. Concurrent cementoplasty was performed in nine cases. A significant reduction in pain was achieved, shown by a preprocedural VAS score of 7.4/10 that dropped to postprocedural scores of 1.9, 2.2, and 2.3 at 1-month, 3-month, and 6-month time points, respectively. Eleven patients suspended pain medications, while the remaining six replaced opioid agents with nonsteroidal anti-inflammatory drugs. No major complications were reported.

In a further study, 35 patients were treated with MWA plus cementoplasty, achieving a mean reduction in VAS scores of 90% at 1- and 6-month follow-up (0.7 and 0.6, respectively, vs. 6.8 at baseline).[33] All patients were discharged in stable conditions and without complications 24 h after the procedure. More recently, Wei *et al*.[34] confirmed that MWA in combination with osteoplasty could represent an efficacious and safe treatment for extraspinal skeletal metastases. In their study, researchers treated 26 lung-cancer metastatic patients with refractory vertebral pain localized to one or two regions, life expectancy ≥3 months, and a tumor size no larger than 6 cm. A total of 33 lesions localized in the iliums (11), acetabulums (9), ischiums (8), femurs (2), clavicle (1), sacrum (1), and tibia (1) were ablated and treated with cementoplasty. The effectiveness was evaluated by a 10-point VAS: the mean preprocedural score was 7.4, which then decreased to 1.5 after 1 month, 0.9 after 3 months, and 1.2 after 6 months. A significant reduction in the average use of mean opioids was also shown in the results. Due to the occurrence of additional vertebral metastases, two patients experienced pain increase after 5 months; MWA was performed again, in combination with osteoplasty, which then resulted in complete pain relief. According to the International Working Group on Imaging-Guided Tumor Ablation, two major complications (7.7%) were reported (a local infection and a pathologic fracture), while the minor complication rate was 23.1% (6/26).

HIGH-INTENSITY FOCUSED ULTRASOUND

Preliminary clinical experience with MRI-guided HIFU for palliative treatment of pain was described in 11 patients with extraspinal vertebral metastases (osteolytic, osteoblastic, and mixed) by Gianfelice *et al*.[35] The mean preprocedural VAS score was 6.0, and all patients reported progressive improvement of pain at 1- and 3-month follow-up, with VAS scores dropping to 1.3 and 0.5, respectively. Seven patients no longer needed treatment for pain, and the remaining four patients reduced their intake of analgesics by at least 50%. In five cases, there was an increase of bone density at the site of treated osteolytic metastases, suggesting a potential consolidative role of HIFU. No adverse events were reported. The first phase III trial studying HIFU on patients with painful vertebral metastases was presented by Hurwitz *et al*.[36] Targeted tumors were device accessible located in the ribs, extremities (excluding joints), pelvis, shoulders, or posterior aspects of spinal vertebra below L2. A group of 147 oncologic patients were randomly assigned, in a 3:1 ratio, to MR-HIFU sonication treatment or placebo. At 3-month follow-up, a response rate of 64.3% was found in the HIFU arm, compared with 20.0% in the placebo-treated group. Fast pain response was achieved through HIFU since pain relief was observed within 3 days from the procedure in about two-third of the responders. The most common minor complication was pain during treatment (32%), while major adverse events were observed in 3% of the treated patients, which included pathological fractures, neuropathy, and skin burn. In their prospective study, Napoli *et al*.[19] treated 18 consecutive patients with MR-HIFU, showing a higher response rate at 3 months following the procedure. The overall pain response rate was 89%, with complete pain relief in 72% of the patients. Recently, through an international consensus statement, a number of recognised experts in focused ultrasound reviewed all the available data in literature, confirming the effectiveness and safeness of HIFU in the treatment of painful vertebral metastases, especially for those lesions that were refractory to conventional therapeutic modalities (for example, external-beam radiation treatment).[37] To date, treatment of vertebral metastases with HIFU is not performed due to the proximity to the spinal cord and its potential thermal damage.

CEMENTOPLASTY OR VERTEBROPLASTY

Cementoplasty or vertebroplasty when it involves the spine consists of percutaneous injection of PMMA cement into the vertebra, most commonly used for benign vertebral body compression fractures.[21] This treatment is increasingly performed to improve the structural integrity of lytic lesions in weight-bearing bones, both in the axial and appendicular skeleton to stabilize them and minimize the risk of pathologic fractures. Once injected, PMMA polymerizes through an exothermic reaction, causing local temperature to rise. As a result, cementoplasty determines not only micro- and macrofracture consolidation but also pain relief through the destruction of nociception terminals [Figure 1]. However, the cytotoxic effects of PMMA polymerization are limited, and for such reason, if procedures are performed with a curative purpose, cementoplasty should always be preceded by an ablative treatment.[6] As far as timing is concerned, cementoplasty can be performed immediately after RFA or MWA, whereas for CA, the operator must wait for the ice ball to melt before proceeding so that polymerization of the PMMA is not affected.[38] Consolidative treatments are most often performed on axial loading locations, including spine and acetabular regions, which are the areas mainly subjected to compressive forces. In these cases, cement injection could be sufficient to achieve bone consolidation. Conversely, in the appendicular skeleton, torsional forces are also involved, especially for long bone diaphysis, implying that further strategies of consolidation such as endomedullary nailing or external fixation should be adopted along with cementoplasty. The risk of impending fractures for bone metastases of the limbs may be quantified through Mirels' score.[39]

Consolidative treatments should be offered to patients at high risk, with a score of 9 or higher. In a large prospective multicenter trial by the European VErtebroplasty RESearch Team, 4547 patients with vertebral compressive fractures due to several pathologies (osteoporosis, trauma, and metastases) underwent vertebroplasty.[40] Pain entity was evaluated through a 10-point VAS, at baseline, 48 h, and 12 months following the procedure, and a reduction of 2 or more points was considered successful. A significant pain relief was observed in 88% of the patients within 48 h from the procedure. In the vertebral metastases group, including 644 patients, the average pretreatment VAS score of 8.3 dropped to 2.4 at 48-h follow-up, while no significant change was noted at 12-month follow-up (mean VAS score 2.9). No major complications were reported, whereas minor complications were observed in 32.9% of the cases, first of which was venous leakage (20.5% of the cases). The Cancer Patient Fracture Evaluation study[41] prospectively enrolled 134 oncologic patients with 1–3 vertebral compressive fractures, moderate pain (≥4 of 10), and Roland-Morris disability Questionnaire (RDQ) score >10. They were randomly assigned to kyphoplasty ($n = 70$) or nonsurgical conservative management ($n = 64$). A significant RDQ improvement was obtained in the first group, while the improvement was minimal in the nonsurgical arm, as demonstrated by an average decrease of 8.3 versus 0.1 points, respectively. This result was impressive to the point that strong ethical reasons allowed for crossover from the nonsurgical group to the kyphoplasty one. However, although the greater beneficial effects of kyphoplasty over conservative treatment were evidently demonstrated, statistical significance tended to vanish with time, probably due to the relatively low number of patients remaining in the conservative treatment group. As far as adverse events are concerned, two patients from the kyphoplasty group were involved: one patient had an intraoperative non-Q-wave myocardial infarction and one had a new fracture in the adjacent level of treatment. Several authors assessed the efficacy of balloon kyphoplasty (BKP) compared to simple vertebroplasty (SVP) for pain palliation of vertebral metastases. Recently, Bae *et al*.[42] reviewed over 10 years of their experience in the stabilization of metastatic vertebral compression fractures. Three hundred forty-two patients who underwent SVP (238) or BKP (104) for painful metastatic compression fractures from solid cancer were included. For the BKP group, the mean preoperative VAS score was 5.8, which was then reduced on average by 2.7 points after the procedure. Effective improvement in VAS score (≥3 points) was achieved in 206 patients (60%). Although the pretreatment degree of compression was significantly higher in the kyphoplasty arm (47%) compared to the SVP arm (30%), no differences were observed in terms of VAS score improvement between the two groups. In conclusion, kyphoplasty showed better results in terms of pain reduction. In regard to cementoplasty for pain palliation of extravertebral metastases, the evidence originating from prospective and retrospective case series is scientifically less strong.

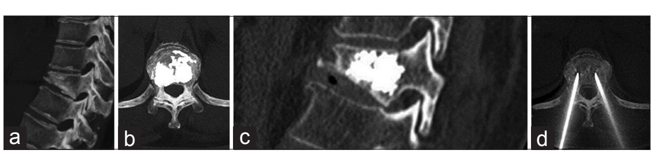

Figure 1: A 67-year-old woman with breast cancer and a solitary D11 vertebral body metastasis. Reformatted computed tomography images before (a) and after treatment (b and c). Coxial percutaneous biopsy and vertebroplasty with bilateral transpedicular access using 13G needles performed in the same session (d)

A systematic review of the current evidence by Cazzato *et al*.[43] demonstrated the safeness and effectiveness of percutaneous long bone cementoplasty (PLBC) for palliation of malignant lesions. Overall, 13 papers were included, with a total of 382 patients treated. Among these, 196 patients with 223 metastatic lesions (average 45 mm in size) underwent PLBC. The work obtained from 10 of the 13 articles using the 10-point VAS to assess pain provided data suitable for statistical analysis. In this subgroup, consisting of 115 patients, a pain control rate of 95.6% was achieved (68.2% high improvement and 27.4% mild improvement), showing an extremely significant correlation between PLBC and pain relief. In a further subgroup of patients considered from 7 papers, researchers also evaluated functional improvement, which was achieved in 77.9% of cases. PLBC showed a low rate of complications: 16 patients (8%) experienced a secondary fracture, whereas other complications (hematomas, infections, and PMMA leakage) were reported in 5 cases (2%).

Moreover, PLBC can be combined with other interventional and noninterventional procedures. In his review, Cazzato reports that previous external-beam radiation therapy was performed in 39% of cases, while percutaneous thermal ablation was combined with cementoplasty treatment in 6% of patients. Besides the Mirels' score,[39] another way to quantify the risk of impending femoral fractures was proposed by Deschamps *et al*.[44] Patients with cortical involvement >30 mm or a previous fracture of the lesser trochanter should receive some form of bone stabilization. Therefore, it was shown that in combination with PLBC, 32 of the 196 patients received minimally invasive endomedullary stabilization,[43] which resulted more suitable than any surgical technique, given the generally poor prognosis reserved to these patients.

CONCLUSION

With the increase of OS rate of oncologic patients and the improvement in sophistication and accuracy of imaging techniques, the number of patients detected with vertebral metastases is growing. In this scenario, minimally invasive image-guided procedures have become an important tool in the palliative and potentially curative management of these patients. The role of interventional radiology in the curative treatment of malignant vertebral lesions is limited to the few patients with oligometastatic vertebral disease and good life expectancy. These techniques are in fact more frequently performed with a palliative aim, in the attempt to achieve pain relief and prevent skeletal-related events. Aside from the objective advantage of being minimally invasive, interventional radiology strategies can also be safely combined with standard treatments, including chemotherapy and external-beam radiation therapy. There is great interest for prospective randomized clinical trials to establish well-defined therapeutic plans and standardize the choice of treatment among the minimally invasive procedures available today, which were performed by interventional radiologists on a regular basis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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