Radiofrequency ablation of bone metastases induces long-lasting palliation in patients with untreatable cancer

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ABSTRACT

Introduction: In oncological patients, life quality can be greatly impaired by the presence of painful bone metastases, as standard forms of treatment often achieve inadequate palliation. The aim of our study was to evaluate the clinical efficacy of radiofrequency ablation (RFA) with respect to pain relief in patients with refractory bone metastases or who are ineligible to conventional treatments.

Methods: 12 patients with 13 painful osteolytic skeletal metastases, and who were unresponsive to analgesic drug therapy, underwent one (seven lesions) or two (five lesions) RFA sessions under computed tomography (CT) guidance. The RFA procedure was completed in all patients without complications. One patient also received cementoplasty after the RFA procedure. To obtain semiquantitative pain scores, the brief pain inventory (BPI) was administered before treatment and during follow-up. The local effects of RFA were monitored for at least one year in eight of 12 patients with CT and/or magnetic resonance imaging.

Results: Immediate pain relief after treatment was experienced by nine of 12 patients, but in two cases, pain recurred within the first week. Long-lasting palliation was obtained in seven of 12 patients. BPI mean scores for worst and average daily pain decreased from 7.7 and 5.0, respectively, at baseline, to 3.1 and 1.8, respectively, at one year. Imaging follow-up showed large areas of necrosis in nine of 12 lesions.

Conclusion: In our preliminary experience, RFA showed good and long-lasting efficacy for pain control in bone metastases. A possible role of RFA as a coadjuvant palliative treatment in these cases is suggested.

Keywords: bone metastases, imaging-guided intervention, pain palliation, radiofrequency ablation, thermoablation

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INTRODUCTION

Bone metastases represent an important factor for impaired life quality in patients with advanced cancer. Radiation therapy is currently considered the treatment of choice for local pain control,[1] but with specific limitations, such as poor responsivity of some neoplastic histotypes, need of preserving adjacent, radiosensitive tissues, and contraindication of retreating recurrent lesions in previously-irradiated sites.[2] Among the other therapeutic options, surgery and chemotherapy can be useful only in selected cases, due to the frequent occurrence of advanced local and systemic disease and/or poor physical status. When these options are not feasible or effective, the remaining approach is systemic administration of major analgesic drugs, often at high dosage and with undesirable collateral effects.

The search for a valid therapeutic alternative for these patients has prompted the use of percutaneous ablation procedures, which already proved efficacious in clinical trials on malignant neoplasms located in other organs, such as the liver and lung,[3] and also for pain control in benign skeletal tumours such as osteoid osteoma.[4] Among these techniques, radiofrequency ablation (RFA) offers great accuracy in predicting the final size and shape of the necrotic area, particularly in small lesions, due to the possibility of constant monitoring parameters such as tissue temperature, impedance, and energy deployment.[5] The aim of our study was to assess the feasibility of RFA, performed with palliative intent, in patients with refractory bone metastases or ineligible to conventional pain therapies, and the evaluation of its clinical efficacy in terms of pain relief, as measured by a widespread semiquantitative pain rating scale, such as the brief pain inventory (BPI).[6]

METHODS

12 patients (seven men and five women, mean age 65 [range 51–75] years) with 13 painful osteolytic skeletal metastases unresponsive to analgesic drug therapy, gave their informed consent to enter the study, which was approved by the local ethical committee. In order to correctly plan the treatment, all patients had recent (< 2 weeks) contrast-enhanced computed tomography

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Table I. Characteristics of patients treated with radiofrequency ablation.

Patient	Age (years)	Gender	Site	Tumour type	Size (cm)	RFA procedure		Follow-up
						Treatment	Retreatment	
1	65	M	Vertebrae	Lung adenoCA	4	Valleylab	-	Dropped out at one month
2	70	M	Sacrum	Colorectal CA	5	Valleylab	RITA	18 months
3	51	F	Humerus	Breast CA	2	Valleylab	-	Two years
4	60	M	Femur	HepatoCA	5	RITA	Valleylab	One year
5	65	M	Iliac wing	Renal CA	2	Valleylab	-	Exitus at six months
6	61	M	Sacrum	Colorectal CA	5	Valleylab (+ cementoplasty)	-	One year
7	69	F	Femur	Colorectal CA	2	Valleylab	-	One year
8	68	F	Scapula	Breast CA	5	RITA	RITA	One year (unresponsive)
9	75	M	Humerus	Colorectal CA	5	RITA	RITA	Dropped out at six months (unresponsive)
10	65	F	Femur	Breast CA	2	Valleylab	-	Two years
11	72	F	Iliac wing	Renal CA	4	RITA	Valleylab	Exitus at one year (unresponsive)
12	60	M	Rib	HepatoCA	2	Valleylab	-	One year

(CECT) documentation of the lesion selected for RFA, showing mostly solid lesions in all cases. Immediately prior to the RF procedure, they also compiled the BPI, a short and effective questionnaire for quantitation of pain intensity and interference with everyday life. The patient data, treated metastatic sites, tumour types, lesion size, RF procedure(s) and follow-up findings are reported in Table I. Exclusion criteria were: lesions greater than 5 cm or located closer than 1 cm to the spinal cord, aorta or inferior vena cava, bowel or bladder, and presence of severe coagulation disorders.

Premedication and sedation were obtained with intravenous (IV) administration of midazolam (0.04 mg/kg), tramadol (50 mg), and atropine (0.5 mg/kg). A local anaesthetic cocktail, composed of carbocain (5–10 ml) and naropin (4–5 ml, at 10%), was injected in the periosteal area of the bone to be treated some 15 minutes before the procedure. After the introduction of the targeting RF-electrode under CT-guidance, analgesia was obtained using IV remifentanil (0.06–0.1 mg/kg/min). During the treatment, patients underwent continuous pulse oximetry and electrocardiography. Initial signs of respiratory depression, which occurred in approximately 30% of the procedures, prompted the use of further assistance with a facial mask. Arterial blood pressure was checked every seven minutes.

In six lesions with maximum diameter < 3 cm, RFA was performed with single positioning of a 17-gauge Cool-tip needle, internally cooled by 0°C saline infusion, ending with a single (four cases) or cluster (two cases) electrode, and a 200-watt RF generator (Cosman Coagulator-1; Valleylab®, Burlington, MA, USA) (Fig. 1). This approach was also used in 3/7 lesions with maximum diameter > 3 cm. The remaining four lesions (size > 3 cm) were treated with a single positioning of a 15-gauge multitined expandable electrode connected to a 1500X StarBurst RF generator (RITA Medical System Inc®, Mountain View, CA, USA) (Fig. 2). With both systems, the target tissue temperature was 80–90°C. Once the target temperature was achieved, the RF energy deployment was continued for 9–12 minutes in all cases. Grounding was obtained using dispersive pads placed on the patient's upper thighs.

Immediately after the RFA, to reinforce the bone in one patient with a sacral metastasis at risk of fracture, cementoplasty was performed, using 5 ml of polymethylmethacrylate (PMMA, CementoFixx®, Optimed, Germany) injected through the same channel created by the RFA electrode (Fig. 3). In five lesions (all > 3 cm) treated with Cool-tip (one case) or expandable Hot-tip (four cases) electrodes, unsatisfactory pain palliation (Tables I and II) prompted retreatment, within 30 days from the initial RF procedure. The approach used for each retreatment was chosen individually, according to the imaging features (particularly shape and size) of the residual lesions. Clinical follow-up was performed by administration of BPI at one, seven, 30, 180 and 365 days after the procedure. Imaging follow-up was performed by CECT and/or magnetic resonance (MR) imaging at three, six, and 12 months.

RESULTS

The RF ablation procedure was completed according to protocol in all patients without major complications. Subtotal analgesia was reported in 6/18 RFA procedures, leading to some discomfort when treating the tumour-

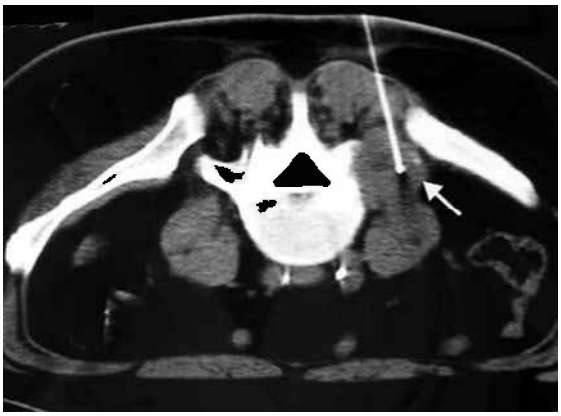


Fig. 1 A 65-year-old man with lung adenocarcinoma metastasis involving the L5 right transverse process. Axial CT image, acquired with the patient prone, shows a 3-cm exposed Cool-tip electrode (Valleylab®) placed into the lesion (arrow), passing through right paravertebral muscles.

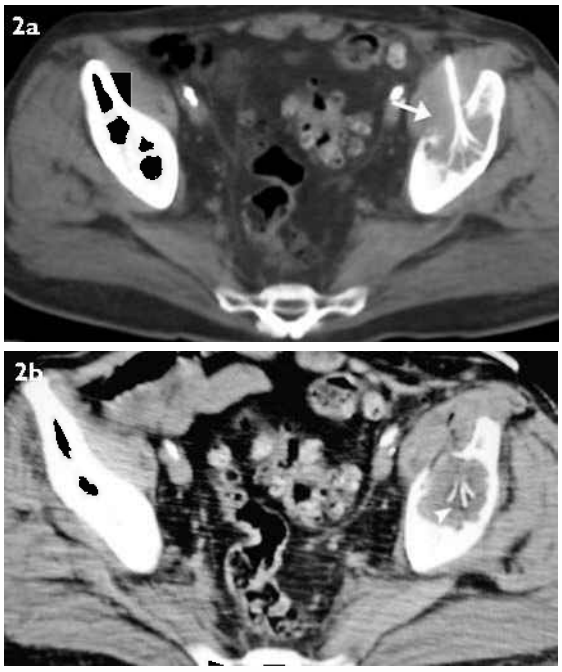


Fig. 2 A 72-year-old woman with renal cell carcinoma metastasis involving the left iliac wing. (a) Axial CT image shows insertion of the expandable electrode (RITA Medical System Inc®) into the lesion (arrow). (b) Axial CT image done at the end of the ablation, shows initial coagulative necrosis, which is indicated by the development of microbubbles within the lesion (arrowhead).

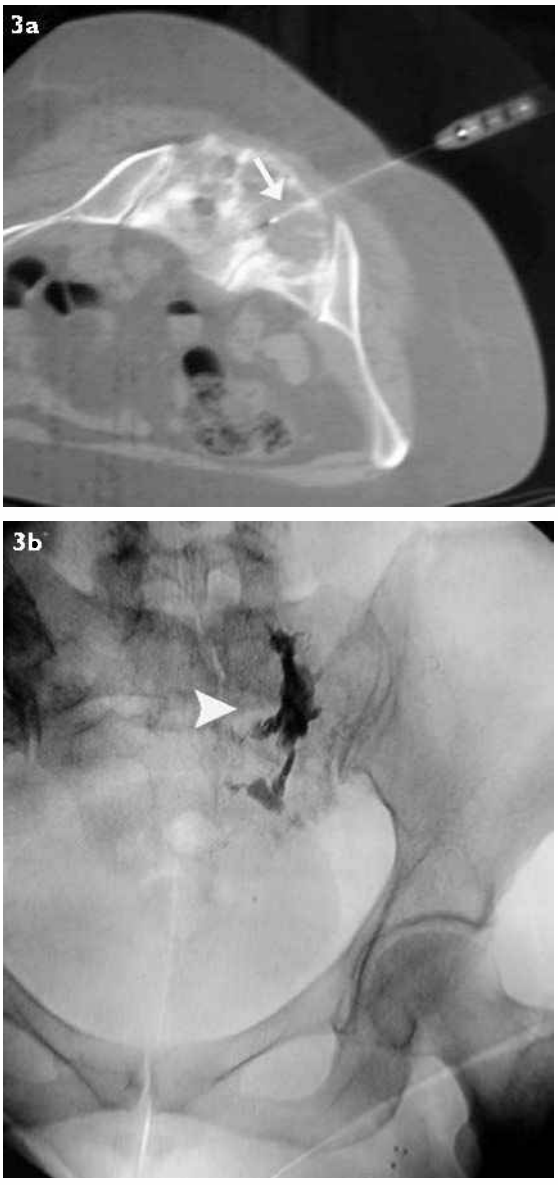


Fig. 3 A 61-year-old man with rectal adenocarcinoma metastasis involving the sacrum. (a) Axial CT image, acquired with the patient semi-prone, shows RFA treatment performed with a 3-cm exposed Cool-tip electrode (Valleylab®) (arrow). (b) Radiograph done at the end of the combined RFA-cementoplasty treatment shows bone cement visible within the right sacrum (arrowhead).

bone interface, but not preventing the completion of the treatment. The individual BPI scores (worst and average daily pain evaluated at any assessment) during the follow-up of the 12 patients are shown in Table II. Baseline BPI mean scores for worst and average pain were 7.7 and 5.0, respectively. The decreasing trend of BPI scores during follow-up is reported in Fig. 4. Overall, a marked decrease in BPI pain scores was observed at one-month, six-month and one-year follow-up assessments, with worst and average mean scores decreasing from 3.9 to 3.6 and to 3.1, and from 2.4 to 2.0 and to 1.8, respectively (Table II). After treatment, 9/12 patients experienced immediate pain relief, while at seven days, palliation was considered satisfactory in 7/12 cases, and then lasted throughout the follow-up (Table II). The two patients with pain recurrence within one week from the RFA were successfully retreated within one month (Table I), and reported a long-lasting palliation (Table II, Fig. 5). On the contrary, three patients unresponsive to the first RFA did not experience significant pain relief, even after retreatment. As shown in Table II, two patients (cases 3 and 10) could be followed-up to 24 months after RFA, with persisting adequate pain control.

Table II. Individual BPI scores (worst and average pain at any assessment and mean value) during the follow-up.

Patient	Baseline		Day 1		Week 1		Month 1		Month 6		Month 12	
	W	A	W	A	W	A	W	A	W	A	W	A
1	8	5	3	2	3	2	dropped out					
2	7	4	3	1	6	4	4*	2*	3	1	3	1
3	9	6	3	1	3	1	3	1	3	1	3	1
4	8	5	3	2	5	3	3*	2*	3	2	3	2
5	8	5	4	2	3	2	3	2	exitus			
6	6	4	2	1	2	1	2	1	2	1	2	1
7	7	5	2	1	2	1	2	1	2	1	2	1
8	7	5	7	4	6	4	6*	4*	6	4	6	4
9	9	6	8	5	8	5	8*	5*	dropped out			
10	8	5	4	3	4	2	3	2	3	2	3	2
11	8	5	7	5	7	5	7*	5*	8	5	exitus	
12	7	5	3	2	3	2	2	1	2	1	3	2
Mean value	7.7	5.0	4.1	2.4	4.3	2.7	3.9	2.4	3.6	2.0	3.1	1.8

W: worst pain; A: average pain
*Retreatment

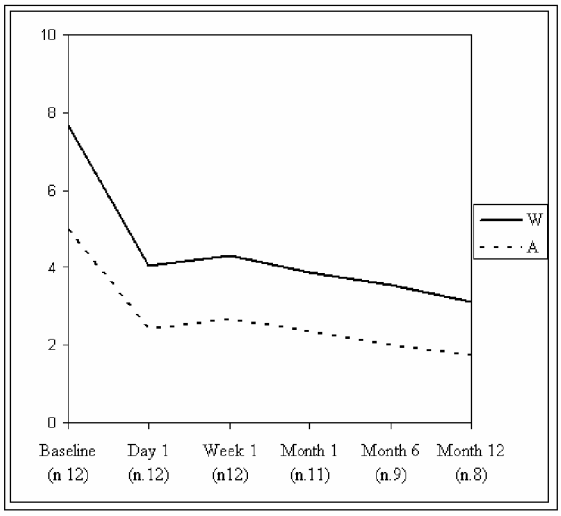


Fig. 4 Graph shows the BPI worst and average mean scores during follow-up.
W: worst pain; A: average pain; n: number of patients with BPI scores at any follow-up assessment

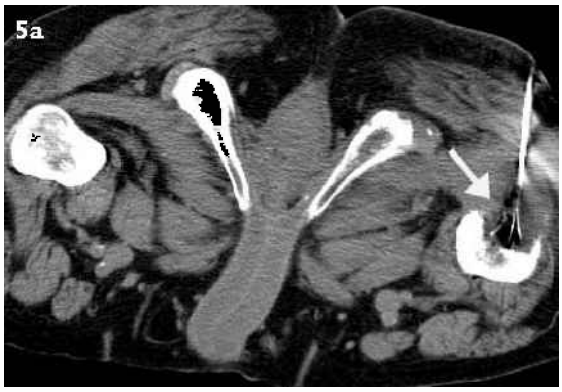
Another patient (case 2), who underwent early retreatment, still experienced pain relief 18 months after the first RFA procedure.

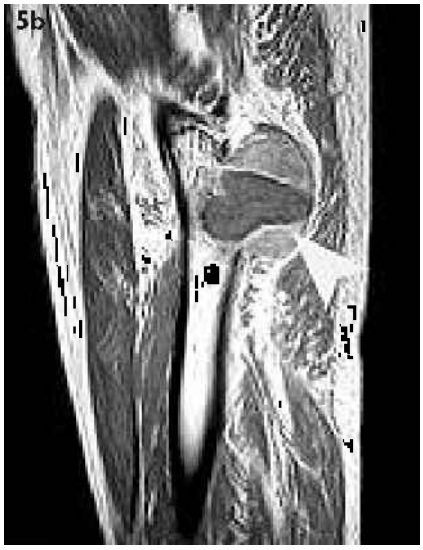
In the nine lesions of patients reporting satisfactory pain palliation, CECT and/or MR imaging follow-up showed large areas of necrosis involving the tumour-bone interface, even if not covering the whole osteolytic lesion. In the two cases that were successfully retreated, MR imaging after the first procedure showed incomplete ablation of the tumour-bone interface. The sacral metastasis from rectal adenocarcinoma, which was further treated with cementoplasty immediately after RFA procedure, appeared stable at imaging follow-up. An example of the imaging findings in a lesion associated with long-lasting pain palliation (case four, Table I) is shown in Fig. 5. Other three lesions (size > 3 cm; location: humerus, scapula and iliac wing), which had to be retreated within one month (Table I) and with poor results at clinical evaluation, did not show satisfactory ablation of the tumour-bone interface on the imaging follow-up available. The remaining patient, with a vertebral metastasis from lung adenocarcinoma, was lost to follow-up after one month and could not be further evaluated (Table I).

DISCUSSION

The primary aim of this study was to evaluate the palliative effect of percutaneous RFA of bone metastases over time. In our cohort, 9/12 patients, refractory to conventional analgesic treatments, were rapidly rendered almost pain-free, and this relief was maintained for one year in 7/8 assessable patients. Also, the feasibility, safety and efficacy of the RF procedure, even in patients with advanced cancer, are confirmed in the present report.

Relatively few studies have investigated the long-term palliative effects of RFA on bone metastases; this paucity of data represents a formidable therapeutic challenge in patients with advanced cancer. Poggi et al treated five patients with six painful bone metastases.[7] One patient with a rib metastasis from breast cancer had complete pain relief within 48 hours after the ablation, and maintained it for 88 weeks. Three other patients reached at least a 50% pain reduction, which lasted on average, 12 weeks. A recent multicentre clinical RFA trial, with reduction of the worst pain scores as the primary end-point, enrolled 62 patients with > 4/10 worst pain scores at the BPI and no more than two sites of disease. A clinically-significant pain relief (at least a two-unit drop in pain scores) was achieved in 95% of cases, with worst pain scores decreasing from 7.7 (baseline) to 4.9, 3.5 and 2.4 at four, 12 and 24 weeks, respectively. Patients also experienced significant reductions in average pain scores and pain interference with daily activities.[2]





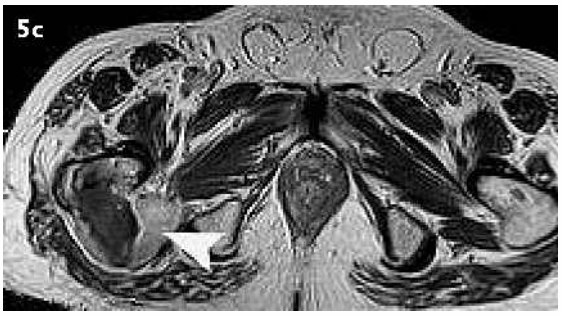


Fig. 5 A 60-year-old man with hepatocarcinoma metastasis involving the right femur neck. (a) Axial CT image, acquired with the patient prone, shows the first treatment performed using an expandable electrode (RITA Medical System Inc®) (arrow). Contrast-enhanced (b) sagittal and (c) axial T1-weighted MR images, obtained 12 months after the first RFA (11 months after retreatment), show large but incomplete necrosis of the lesion, involving the tumour-bone interface (arrowhead). Clinically, satisfactory pain control was reported by the patient (case 4, Table 1).

In this trial, lesions > 5 cm in diameter were ablated, by placing the RF electrodes on the margin of the metastases, in order to completely treat the tumour-bone interface; this was the area thought to be responsible for pain. In fact, for effective and long-lasting pain palliation, local control of neoplastic growth is sufficient.[2] An actual reduction in lesion size or even a radical result after RFA is, in fact, only sometimes observed (as also occurred in our study), and usually occurs only in smaller metastases.[8] The mechanisms by which bone metastases may induce pain include: increased pressure and microfractures within the bone, stretching of periosteum and nerve root infiltration, increased pain transmission by cytokine release.[9] Pain relief from RFA is probably derived from the destruction of local sensitive fibres and from lesion debulking, with bone decompression and decreased production of chemical mediators.[10]

Other forms of treatment have been performed in patients with bone metastases, such as alcoholisation, laser coagulation, cryoablation and embolisation. Alcoholisation is one of the first effective minimally-invasive treatments to be widely used, especially in hepatic lesions, but is limited by the poor reproducibility of the size and shape of the ablation area.[11] Laser coagulation and cryoablation are new, accurate percutaneous procedures that have been tested for the palliative treatment of bone metastases with encouraging results.[12,13] As for clinical efficacy, these techniques seem comparable with RFA, although their optimisation may still benefit from technical improvement and large clinical trials.[5,8,11] For the preoperative, palliative or curative treatment of bone metastases, especially if large and hypervascularised, angiographical embolisation may also be used, alone or in association with other treatment types, including RFA.[14,15]

RFA can be successfully associated with other percutaneous treatment modalities, such as cementoplasty.[16-20] Theoretically, cementoplasty may increase the palliative effect of the RFA treatment by reinforcing and stabilising the ablated area. However, the added therapeutic value of combining the two techniques versus one alone remains to be demonstrated, with the possible exception of some sites, such as spine and acetabulum, in which a structural support is usually required. Grönemeyer et al used RFA in the treatment of unresectable painful spinal metastases in ten patients with 21 lesions; four patients also underwent cementoplasty.[16] At the last follow-up (2–11 months), pain reduction was achieved in 9/10 cases and scored 74% on average (range 30%–100%) at a visual analogue scale (VAS) evaluation.

Nakatsuka et al treated 17 patients with 23 bone metastases.[19] In all 13 cases with painful lesions, significant relief was reported within one week, with a decrease in the VAS score from 8.4 to 1.1. Pain recurred in five patients, after a period ranging from 3 to 12 months, but only in two patients, it originated from on a local tumour recurrence. Toyota et al also obtained a satisfactory pain relief in painful bone metastases by combining RFA and cementoplasty.[20] In all 17 cases, initial pain relief was reported. In eight patients, the drop in mean VAS scores (from 63 to 24) lasted 7.3 months on average, with only

three patients experiencing pain recurrence, between two weeks and three months after treatment.

In our experience, RFA produced a rapid, significant and enduring pain control in bone metastases, still evident at one-year follow-up in most cases, and elicited marked improvement in the quality of life of these patients. The association of RFA with cementoplasty in one patient with a lesion at risk of fracture also proved safe and effective. Consequently, it is possible to suggest a role of RFA, alone or in combination with other (percutaneous) techniques, as a coadjuvant palliative treatment in patients with bone metastases and who do not benefit from standard therapy.

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