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ORIGINAL STUDY

Preoperative radiofrequency ablation in painful osteolytic long bone metastases

Alexander Di Francesco, Stefano Flamini, Luigi Zugaro, Carmine Zoccali

From San Salvatore Hospital, L'Aquila, Italy

This study aimed to determine whether Radio - frequency Ablation (RFA) followed by prophylactic internal fixation produces better palliation in terms of pain and reduces the need for blood transfusion more than radiotherapy and surgical stabilization (RT-SS).

Patients with solitary long bone metastases and a pain score of 5 or more on the VAS scale were selected. Fifteen patients were treated with RFA and surgical stabilization (RFA-SS) and were compared with a matched group (15 subjects) treated by radiotherapy and surgical stabilization (RT-SS). A complete response in terms of pain relief at 12 weeks was documented in 20% (3/15) and 53.3% (8/15) of the subjects treated by RT-SS or RFA-SS, respectively (p = 0.027). The overall response rate at 12 weeks was 93.3% (14 patients) in the group treated by RFA-SS and 59.9% (9 patients) in the group treated by RT-SS (p = 0.048). Although recurrent pain was documented more frequently after RT-SS (26.6%) than after RFA-SS (6.7%) the difference did not reach statistical significance. The morbidity related to RT-SS did not significantly differ when the treatment was associated with RFA. We observed a reduction in blood transfusion, as 3 patients in the RT-SS group required a blood transfusion, versus none in the RFA-SS group. Our results suggest that RFA-SS is safe and is more effective than RT-SS ; furthermore, RFA may become an option for patients with metastases of the long bones to prevent tumour dissemination and reduce intraoperative blood loss. The findings described here should serve as a framework around which to design future clinical trials.

Keywords : skeletal metastases ; radiofrequency ablation ; morbidity ; palliative care ; surgical stabilization.

INTRODUCTION

The true incidence of long bone metastases is the subject of much debate, and is not known with precision. The probability of bone metastasis originating from a primary site can be assessed only by knowing the prevalence of the primary tumour and its predilection for bone (*2*). Once metastases occur, patient survival is low with a median survival time of a few months after chemotherapy or radiotherapy (*2*). Long bone metastases are a major clinical concern and cause severe pain, fractures, hypercalcaemia with a significant degradation of quality of life (*12*). For all these reasons, pain relief is an important clinical challenge and represents the primary goal of any therapy aiming to manage skeletal metastases (*10,12*).

■ Alexander Di Francesco, MD, Trauma Surgeon.
■ Stefano Flamini, MD, Trauma Surgeon.
Department of Orthopaedic Surgery, San Salvatore Hospital, via Vetoio, N° 1, 67100 L'Aquila, Italy.
■ Luigi Zugaro, MD, Radiologist.
Department of Radiology, San Salvatore Hospital, via Vetoio, N° 1, 67100 L'Aquila, Italy.
■ Carmine Zoccali, MD, Oncologist.
Reina Elena National Cancer Institute, Oncological Orthopaedics, Rome, Italy.
Correspondence : Alexander Di Francesco, MD, Via G. Di Vincenzo 23/B, 67100 L'Aquila, Italy.
E-mail : alexdifranco@tiscali.it

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Despite its limitations, radiotherapy and surgical stabilization (SS) is a standard of care for localised pain caused by long bone metastases (*2,12*). Radiofrequency ablation (RFA) has proved to be a useful therapeutic option for the management of bone tumours. Its efficacy lies not only in relieving pain in a shorter time but also in controlling the tumour (*13,15*). This technique was initially developed for patients with malignant primary or metastatic liver tumours (*8*). Considering that the life expectancy of most patients with bone metastases is limited, the aim of any treatment must be to provide the earliest possible pain relief. RFA of tumour lesions less than 3 cm in diameter results in considerable necrosis but this phenomenon decreases drastically for diameters greater than 3 cm. Literature reveals that few data exist on the association of RFA and SS for the management of bone lesions (*15*). This article reports that the combined treatment using RFA followed by SS is technically feasible and well tolerated with a satisfactory profile of adverse events (*15*). However a comparison between this combined approach RFA-SS and RT-SS has never been carried out. Thus, the primary objective of this feasibility study was to determine whether the combined treatment using RFA with SS produces better palliation of skeletal metastases in terms of complete and overall response and blood transfusion than RT-SS in patients with painful long bone metastases.

MATERIALS AND METHODS

Study population

Patients with radiologically and histologically confirmed solitary painful osteolytic long bone metastases were selected. The worst pain intensity was assessed using the validated visual analogue scale (VAS). The choice of this parameter (worst pain) was because of its greatest correlation with functional interference (*6,15,16*). The pain score of 5 or more on a scale of 1-10 (or a score of less than five with the use of narcotic medications) with pain localised to the site of the bone metastases and the Karnofsky performance status (KPS) score greater than 70 were other eligibility criteria. Patients receiving systemic therapy were included in the final analysis. Patients with (1) two or more separate sites of painful bone metastases, (2) a painful area previously treated with radiation therapy, (3) abnormal fracture of the treatment site, (4) radiographic evidence of spinal cord or cauda equina compression and (5) cardiac pacemaker were not treated. From October 2008 to June 2010, 15 patients were treated by RFA-SS after providing informed consent. The combined treatment was as follows : RFA followed by SS 10-15 days later. The group of patients undergoing the combined procedure was retrospectively compared with a group of subjects (15 subjects) treated from August 2003 to December 2006 with RT-SS and matched for age, KPS, primary tumours and VAS scale. Required information before treatments included history and physical examination, Karnofsky performance status and completed VAS scale. Analgesic consumption was recorded and all narcotic analgesics were converted to an oral morphine equivalent dose. Non-narcotic analgesics were classified as 0 for an oral morphine-equivalent dose. Another aim of this study has been to compare the blood transfusion requirements in the two group. This retrospective study was approved by the local Ethical Committee.

Surgical stabilization

Surgery was performed in all cases by a surgeon trained in traumatology. Low-molecular weight heparin was given to prevent deep vein thrombosis. Heparin was administered from the day before the operation, or before if the patient was bedridden, until the patient regained adequate upper and lower limb motion.

Antibiotic prophylaxis with cefotaxime was started upon the induction of anaesthesia, at a dosage of 1000 mg every 12 hours, and continued for one day. The patient was discharged after 7-10 days from surgery unless any complications occurred.

All the operations were performed under general anaesthesia ; table I shows the type of bone metastases in each group. We used intra-medullary nailing for shaft metastases (CITTIEFFE®) and the Less invasive stabilization system (LISS® SYNTHES) for tibial and femoral proximal metastases (*7*) (Fig. 1).

Radiofrequency ablation

Procedures were carried out with patients under conscious sedation. This was achieved with alfentanil, midazolam and continuous infusion of propofol. During the procedure, all patients received oxygen and monitoring

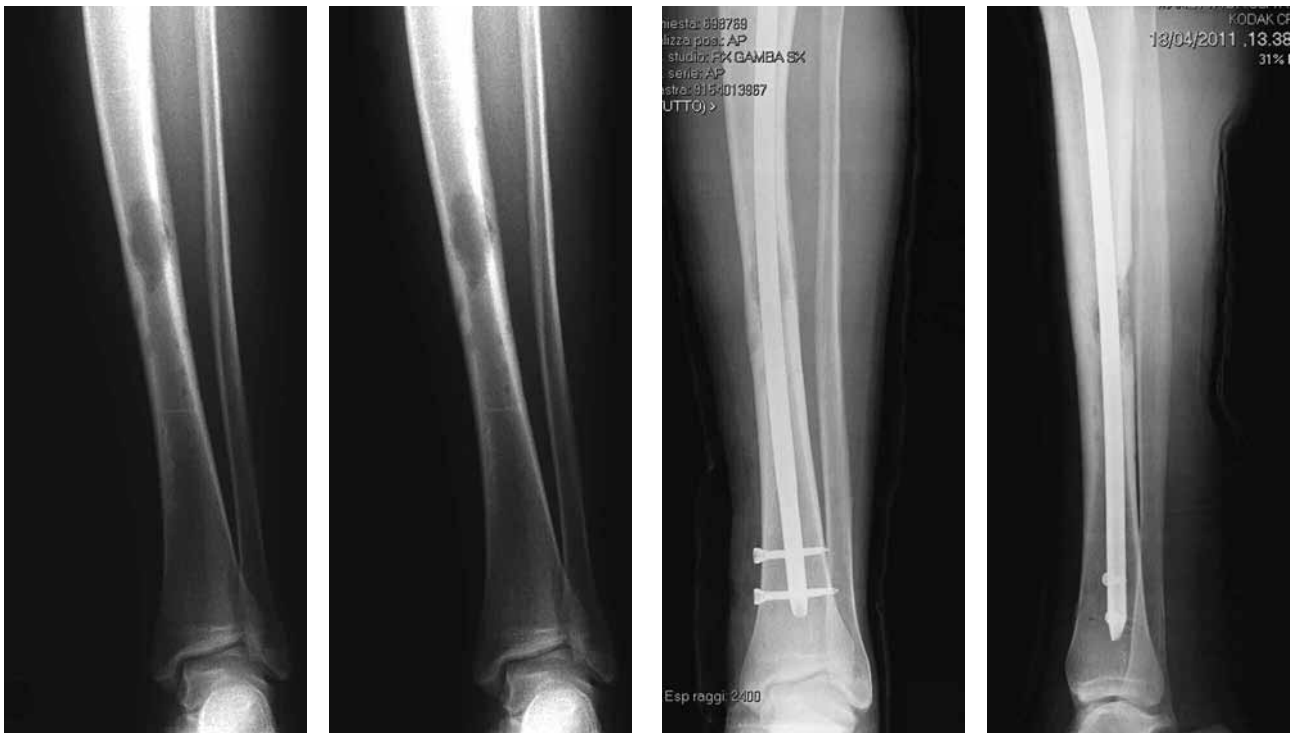

Fig. 1. — Tibial metastates treated by intramedullary nailing

of heart rate, blood pressure, electrocardiographic trace, oxygen saturation and respiratory rate. Local anaesthesia (1% carbocaine) was applied to the skin at the access site. Following sterile preparation a LeVeen needle electrode (Boston Scientific Corporation, Natick, MA, USA) was introduced under CT guidance into the metastases. After unfolding the electrode tines into the metastases, the needle was connected with a radiofrequency generator (RF 3,000 ; Boston Scientific Corporation, Natick, MA, USA). The procedure was conducted according to the protocols supplied by the equipment manufacturers (Boston Scientific Corporation, Natick, MA, USA). Briefly, the energy developed was increased 10 W every 3 min up to 90W until tissue impedance increased and further current flow was prevented (roll-off). A target intratumoral temperature higher than 60°C was considered as an indicator of adequate thermocoagulation. A single ablation was performed for lesions measuring less than 3 cm in the longest diameter. For larger lesions (3-7 cm) a cluster RFA electrode technique was used (3 needles spaced 5 mm apart). At the end of each procedure, contrast-enhanced CT was performed to ensure that the extent of ablation was confined to target tissue and that there was no substantial damage in the tissue surrounding the target.

Radiation therapy

Computed tomography (CT)-based simulations were routinely performed. A three-dimensional conformal technique was used. The nominal prescribed dose was 20 Gy delivered in 5 fractions of 4 Gy over 1 week using 6 MV photons for both fields. Planning target volume (PTV) was defined as the tumour volume with a surrounding margin varied for the different bone localisations. For long bones the PTV included the radiographic abnormality with a margin of at least 2 cm proximally and distally *(3,5,11)*. For bone lesions localised at the spinal cord, the PTV included one vertebra above and below the involved vertebra(s) *(3)*. The total dose was prescribed to the isocenter, with the 95% isodose surrounding the PTVs. defined as the tumour volume with a surrounding margin varied for the different bone localisations. For long bones the PTV included the radiographic abnormality with a margin of at least 2 cm proximally and distally *(3,5,11)*. For bone lesions localised at the

spinal cord, the PTV included one vertebra above and below the involved vertebra(s) (3). The total dose was prescribed to the isocenter, with the 95% isodose surrounding the PTVs.

Blood transfusion

We observed a reduction in blood transfusion, as 3 patients with a femoral metastasis in the RT-SS group required a 400 mL blood transfusion, whereas no blood transfusion was necessary within the RFA-SS group.

The difference was not statistically significant owing to the small number of patients.

Follow-up

Patients were assessed at baseline, every week for the first month and every month thereafter for six months. Each follow-up visit included a full physical examination, a visual analogue pain score questionnaire (VAS) and a medication level questionnaire, providing data on direct and indirect changes in pain levels.

Statistical methods

The primary null hypothesis of this feasibility study was that, for patients with painful solitary long bone metastasis, pain relief achieved following RFA-SS should be higher than that achieved following RT-SS. The current study was powered to determine an increase of 20% or greater in the complete response at 12 weeks after RFA-RT. Literature data indicate that when the response outcomes were redefined in accordance with the international consensus criteria, about 11-21% of intention-to-treat patients achieved complete responses after RT-SS (14). Thus we set the rate of complete response after RT-SS at 14% (P0 = 14%). Using a one-sided test and a 5% type I error with a number of matched controls per case of 2 :1, 15 subjects in the experimental group (RFA-SS) and 15 in the control group (SS) would provide greater than 80% power to detect an increase of 20% (P1 = 34%) in the complete response. All tests were two sided except where specified and were determined by Monte Carlo significance. An alpha value threshold of 0.05 was used. An intention-to-treat (ITT) strategy was used for the analysis of primary endpoints. A per-protocol analysis was used for the analysis of toxicity. Continuous variables were not normally distributed (Shapiro-Wilk test) and were presented as medians and confidence intervals at 95% (CI95%). The Mann-Whitney U test was used to test a significant difference between two groups. Dichotomous variables were summarized by absolute and/or relative frequencies. Chi-squared test or Fisher's exact test were used to test a significant difference between two groups.

For multiple comparisons the alpha value threshold was adjusted by using the Bonferroni correction. The odds that a patient treated with RFA-SS will achieve complete or overall response as a function of time before a patient treated by RT-SS have been determined by the use of the Cox proportional hazard model. All statistical analyses were performed using the SPSS® statistical analysis software package, version 10.0.

RESULTS

A total of 30 patients with histologically and radiologically confirmed long bone metastases were included in the study. Table I lists the clinical and demographic characteristics of treated patients. A significant difference between the two groups was documented with regard to the sex of patients and the median size of bone lesions. In the RT-SS group many more subjects were male whereas the median size of skeletal metastases was significantly greater in the group treated with RFA with SS. After Bonferroni correction no difference in metastases locations was documented between the two groups (Table I). The other pretreatment variables were balanced between the two groups. The overall number of patients available for follow-up was 27 (93.3%) at 8 weeks, 25 (84.4%) at 12 weeks, and 20 (66.6%) at 24 weeks. The main contributors to the loss of follow-up were death and hospitalisation.

Pain outcome

At baseline the median value of the pain score was 6.5 (95% CI 5.9 to 7.2) and 6.3 (95% CI 5.6 to 8) in the RT-SS and RFA-SS group, respectively (p = 0.36) (Table I). A complete response at 12 weeks was documented in 16.6% (5/30) and 53.3% (8/15) of the subjects treated by RT-SS or RFA-SS, respectively (p = 0.027) (Table II). Partial response was documented in 40.0% of 15 patients treated with RFA-SS and in 43.3% of 15 patients treated by RT-SS. The overall response rate at 12 weeks was 93.3% (14 patients) in the group treated with

Table I. — KPS = Karnofsky Performance Status ; a Mann-Whitney U test for independent samples ; Medians and 95% CI ; b Chi-Squared test with Bonferroni correction ; § the alpha value threshold of 0.01 was considered significant after Bonferroni correction ; c Fisher's Exact test

Characteristic	RT-SS	RFA-SS	p-value
Age (years)	68.0 (65.6 to 71.8)	67.0 (65.1 to 70.3)	0.220a
VAS Scale	* 6.5 (5.9 to 7.2)	6.3 (5.6 to 8.0)	0.36a
Sex, No (%)			
Male	10 (66.6)	3 (20)	0.004c
Female	5 (33.4)	12 (80)	
KPS, No			
91-100	8 (53.3)	6 (40.0)	0.598b
70-89	7 (46.7)	9 (60.0)	
Tumour Size, cm (longest diameter)	5.0 (4.5 to 5.1)	6.0 (5.4 to 6.4)	0.002a
Primary Tumours, No (%)			
Lung Cancer	1 (6.7)	1 (6.7)	
Prostate Cancer	4(26.7)	3 (20)	
Kidney Cancer	1 (6.7)	1 (6.7)	§0.935b
Colorectal Cancer	4 (26.7)	3 (20)	
Breast Cancer	5 (33.3)	7 (46.7)	
Metastasis Location No (%)			
Femur	8	7	
Tibia diaphysis	3	3	
Humerus	1	2	
Proximal tibia	2	2	
Distal femur	1	1	
Systemic Treatments			
Systemic Radioisotope Therapy	0 (0)	0 (0)	1.0c
Bisphosphonates	4 (26.7)	3 (20)	0.726c
Narcotic Analgesics	14 (90)	12 (80)	0.642b
Non-Narcotic Analgesics	1 (6.7)	3 (20)	0.384c
Hormonal Therapy	4 (26.7)	5 (33.3)	0.495c
Chemotherapy	15 (100)	15 (100)	1.0b
Immunotherapy	1 (6.7)	1 (6.7)	1.0c

RFA-SS and 59.9% (9 patients) in the group treated with RT-SS ($p = 0.048$). The Cox proportional hazard model indicated that patients treated with RFA in association with SS achieved complete (HR = 7.0 ; CI 95% 1.96 to 24.8) and overall response (HR = 10.11 ; CI 95% 3.71 to 27.55) before patients treated with RT-SS (Fig. 1). The analysis of the interval to response indicated that subjects treated by RFA-SS achieved an overall response faster than patients treated by RT-SS alone. The interval to response after RT was of 9 weeks (CI 95% 7.0 to 12.0), versus 3 weeks [CI 95% 1.6 to 6.4] in the patients treated by RFA-SS, a significant difference ($p < 0.0001$). Thirteen patients (90%) in the RFA- SS group and 12 (80%) in the RT-SS group received oral narcotic analgesics before treatment.

Table II. — Complete and overall response following treatments
(a) Chi-Squared test and (b) Fisher's Exact test

Response typeNo (%)	Week 8	Week 12	Week 24
Complete response			
RT-SS	2/15(13.4)	3/15 (16.6)	1/15 (6.7)
RFA-SS	7/15 (46.6)	8/15 (53.3)	7/15 (46.6)
p value	0.009 b	0.027 a	0.003 b
Partial response			
RT-SS	4/15 (26.7)	13/30(46.7)	5/15 (33.3)
RFA-SS	4/15 (26.7)	6/15 (40.0)	6/15 (40.0)
p value	1.0 b	1.0 b	0.912
Stable pain or progression			
RT-SS	9/15 (60)	6/15 (40.0)	9/15 (60.0)
RFA-SS	4/15 (26.7)	1/15 (6.7)	2/15 (13.4)
p value	0.0428	0.034	0.004

Table III. — Narcotic analgesic use at 12 weeks after treatments
(a) Chi-Squared test

Drug	RT-SS (N = 15)	RFA-SS (N = 15)	p value
None No, %	4 (26.9)	9 (60.0%)	0.036 a
Narcotic analgesic No, %	11 (79.7)	6 (40.0)	

No significant difference between the two groups was measured at baseline (p = 0.642) (Table I). At 12 weeks 25.3% of patients (3/15) in the RT-SS group and 60.0% of patients (9/15) in the RFA- SS group did not require narcotic medications (p = 0.036) (Table III).

Morbidity

Treatment safety was monitored by recording the incidence of any major or minor complication. Patients tolerated the combined treatment well with a very low incidence of adverse events. There were no major complications except a transient nerve injury (1/15 ; 6.7%) and one infection at the access site (1/15 ; 6.7%). In the patient with nerve injury, transient leg paralysis occurred 2 days after RFA-SS with improvement within 15 days after steroid administration. There were no minor complications and no death in relation to the combined treatment (Table IV).

DISCUSSION

Long bone metastases are the most important source of morbidity in cancer (*2,4,15*) owing to pathological fracture and consolidated evidence suggests that radiotherapy and surgical stabilization may be the standard care for the management of this condition.

Radiofrequency ablation (RFA) is currently considered to be the procedure of choice in the treatment of osteoid osteomas (*6*). A number of reports have been published on RFA as palliative treatment for bone metastases, documenting good effectiveness in terms of pain relief and complications (*8,13*). According to these studies RFA-SS can provide palliation for patients with painful long bone metastases configuring this treatment as an alternative to RT and surgical stabilization (*8*). The principal aim of this study is to demonstrate that RFA is a possible alternative to RT, before surgical stabilization of the long bone metastases. It is difficult to decide

Table IV. — RT related Toxicity at 12 weeks after treatments (a = Chi-Squared test or b = Fisher's Exact test with Bonferroni correction). GU = Genitourinary ; GI = gastrointestinal ; RT = radiotherapy ; RFA = radiofrequency ablation ; SS = surgical stabilisation

RT-SS (n = 13)					RFA-SS (n = 14)				
Toxicity No (%)	G1	G2	G3	G4	G1	G2	G3	G4	
Skin	2 (8.36)	1 (4.2)	0 (0)	0 (0)	2 (14.3)	1 (7.1)	0 (0)	0 (0)	b0.65
Lung	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.1)	0 (0)	0 (0)	1.0
GI	3 (12.5)	2 (8.3)	0 (0)	0 (0)	1 (7.1)	1 (7.1)	0 (0)	0 (0)	b0.93
GU	2 (8.3)	1 (4.2)	0 (0)	0 (0)	2 (14.3)	0 (0)	0 (0)	0 (0)	b0.60
Haematological	3 (12.5)	1 (4.2)	0 (0)	0 (0)	2 (14.3)	0 (0)	0 (0)	0 (0)	b0.74
Other	2 (8.3)	0 (0)	0 (0)	0 (0)	1 (7.1)	0 (0)	0 (0)	0 (0)	b0.52

which parameters must be considered to demonstrate whether RT is better than RFA, before surgical stabilization. One of these could be a reduction in blood transfusion requirements. In this study, RFA was found to be associated with some reduction in blood transfusion, but the difference did not reach statistical significance owing to the limited number of patients. For this reason the assessment of pain was chosen as a valid parameter for this study. Additionally, a number of studies on RFA suffer from lack of uniformity in their response criteria (*8,13*) which makes comparisons of results difficult. Thus, there is a need for studies aimed at comparing the results of different treatments with more standard criteria and to address the role and the timing of other local and systemic treatments in the management of bone metastases. A significant improvement in complete and overall response was documented after RFA-SS treatment. The CR rates at 12 weeks were 16.5% (3 of 15) and 53.3% (8 of 15) for RT-SS and RFA-SS, respectively. In terms of overall response, the crude rate significantly differed between the two groups. This was 93.3% (14 of 15 patients) in the RFA-SS group and 59.9% (9 of 15 patients) in the RT-SS group. The Cox Proportional Hazard Model indicated that patients treated by RFA-SS achieved complete (HR = 7.0 ; 95% CI 1.96 to 24.8) and overall response (HR = 10.11 ; 95% CI 3.71 to 27.55) before patients treated by RT-SS. On the contrary, no significant difference was documented in terms of partial response (PR) between the two groups. PR was achieved in 43.3% of patients treated by RT-SS and in 40.0% of those treated by RFA-SS. The significant improvement in the complete response and the overall response in the RFA-SS group was associated with a significant decrease in the percentage of patients requiring narcotic analgesics. The interval to response was shorter after RFA-SS, ranging from 1.69 to 6.4 weeks, versus 7.0 to 12.0 weeks in patients treated with RT-SS. In the RFA-SS group only one patient experienced progression after the treatment, with no further increase at 24 weeks. Our study has some limitations such as the small number of patients and the retrospective design. The generalisation and the applicability of our results to the general population with osteolytic long bone metastases must be demonstrated. Finally, based on the aforementioned biases, we are aware that the methodology of our study is far from being the best way of carrying out a comparative assessment of the two techniques associated with surgical stabilization. Therefore, although the results illustrated here suggest that RFA followed by SS can be safe and may reduce the need for blood transfusion and besides reduce significantly the level of pain experienced by cancer patients with bone metastases limiting the need for strong narcotic pain management, our findings should be interpreted with caution and should serve as a framework to design future clinical trials.

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