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Retrospective Clinical Evaluation of Painful Bone Metastases Treated with Radiofrequency Ablation Alone or Combined with Cement Injection

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Abstract

Bone metastases are a common cause of severe cancer-related pain, significantly impacting the quality of life of patients. This retrospective study evaluates the effectiveness of radiofrequency ablation (RFA) with or without cement injection for pain relief in 44 patients with symptomatic bone metastases. Patients were treated under CT guidance between January 2019 and December 2021. Pain severity was measured using the Numerical Rating Scale (NRS), and quality of life was assessed with the Oswestry Disability Index (ODI) and the EORTC QLQ-C30 questionnaire. Results showed that RFA significantly reduced pain, with the average NRS score dropping from 8.0 to 2.4 at six months post-treatment. Additionally, patients experienced improved mobility and quality of life, with a notable decrease in ODI scores and enhanced EORTC quality of life measures. RFA, combined with cement injection in some cases, proved to be a safe and effective minimally invasive treatment option for managing cancer pain due to bone metastases.

Keywords: Bone Metastases, Radio Frequency Ablation (RFA), Cement Injection, Cancer Pain Management, Palliative care

Introduction

25% of cancer patients experience pain at the stage of cancer diagnosis, 50% during cancer treatment and 75-80% in the advanced-terminal phase. Pain cannot therefore be considered a symptom just in the advanced-terminal phase. The physician treating cancer patients must be able to manage pain early and be able to treat it appropriately. Despite a correct therapeutic approach, between 3%-5% of patients suffer from persistent and intractable pain; such situations must be recognized early and brought to the attention of the tumor board and interventional pain specialist, at whatever stage of the oncological disease [1]. Cancer pain activates both inflammatory and neuropathic mechanisms, as the tumor growth induces both tissue damage and the release of inflammatory mediators, as well as compresses and infiltrate the sensory nerves. Current clinical evidence suggests that cancer pain should be treated as a disease in its own right because it's a mixed nociceptive–neuropathic pain and less responsive to conventional analgesic therapies such as opioids. With regards to bone metastases, it's therefore important evaluate the pathogenesis of the metastatic bone disease in a multidisciplinary tumor board for discussing treatment options for individual cancer patients. The process of bone metastasis depends on the communication between the tumor cells infiltrating the bone, the bone matrix cells and the nerve fibers that innervate the bone. Tumor cells do not directly damage bone tissue; instead, they primarily activate the RANKL/RANK (Receptor Activator of Nuclear Factor-kappaB ligand) system by producing receptor activator for RANKL, which, by binding with RANK on the surface of osteoclasts, initiates their proliferation and thus triggers their damaging effect on bone. RANKL is a protein member of the tumor necrosis factor cytokine family produced by cancer cells, the osteoblast cell line (i.e. mature osteoblasts and their precursors) and activated T lymphocytes [2]. The lack of RANK for RANKL to bind to inhibited osteoclast differentiation and maturation, causes a deficiency of mature osteoclasts at the bone surface with the consequence of bone resorption. Local acidosis induced by bone resorption stimulates transient receptor potential V1 channel (TRPV1) or and acid-sensing ion channel 3 (ASIC3) and causes cancer-induced bone pain (CIBP). Once the bone is infiltrated, the cancer cells divide and the growing tumor

mass progressively damage the bone structure. Tumor cells, stromal cells and inflammatory cells recruited by tumor cells (macrophages, neutrophils, T-cells, mast cells) produce and release various mediators, including endothelin, bradykinin, proteases, interleukin (IL) 6, hydrogen ions (H +), colony- stimulating factors (CSF), nerve growth factor (NGF). These receptors help to detect and transmit stimulus signals to the spinal cord and thus to the cerebral cortex, where perception occurs. After integration and modulation at the spinal level, the amplified pain messages reach the brain, where the final and patient-reported experience of pain is generated [2-4]. About 25% of patients with bone metastases are asymptomatic, and the diagnosis is usually made by examinations performed for other reasons or during the primary tumor staging. In the remaining 75%, bone lesions are clinically responsible for a series skeletal-related events (SREs). SREs, according to international guidelines, are complications and include pathologic fracture, spinal cord compression and hypercalcaemia of malignancy [5]. SREs and pain have been shown in several studies to significantly worsen the patient's quality of life, reducing functional autonomy, and worsening the patient's psycho-emotional state. Different approaches to the treatment of pain are feasible, both diagnostic and therapeutic, requiring specialized knowledge and techniques. Recent retrospective studies have described excellent clinical outcome with targeted radiofrequency ablation (RFA) of bone metastases. Thanos et al. described a pain reduction in 19/30 patients within 24 hours after RFA. Within one week, all patients reported a significant reduction in pain, together with an improvement in their quality of life [6]. The demand for quality and safety improvement initiatives is needed in the healthcare system and the coordination and delivery of safe, high-quality care demands reliable multidisciplinary teamwork and collaboration within, as well as across, organizational, disciplinary, technical, and cultural boundaries for treating cancer patients. Currently, the aim of bone cancer pain treatment remains palliative at best with systemic therapy (analgesics, hormones, chemotherapy, steroids, and bisphosphonates) as well as local treatments (such as surgery, nerve blocks, and external beam radiation). However, many of these treatments are limited in their efficacy or duration and have significant side effects that seriously limit the cancer patient's quality of life [7]. Radiofrequency ablation of bone metastases is gaining an important role in the oncological pathway of patients with bone metastases. For more than decades percutaneous alcohol injection for the treatment of metastatic disease in some parenchymal organs, including thyroid and liver, has been adopted. More recently, in the last 10 years, radiofrequency ablation technique has been used for the necrosis of osteoid osteoma and later to achieve pain reduction in bone metastases [8, 9]. Palliative therapy for patients with bone metastases are challenging, requiring a comprehensive multidisciplinary approach. Similarly to radiotherapy, percutaneous ablation techniques can act both on the nerve structures responsible for pain-mediated signals (neurolysis) and directly on the tumor for alleviating inflammatory response and debulk the mass. The selection between different ablation techniques (radiofrequency, cryoablation and microwave) should be based on a tailored approach on patient selection but the most used ablative technique for the treatment of bone metastases remains the radiofrequency energy [10]. The combination of RFA and percutaneous cement injection provides, in addition to pain relief, bone strengthening in patients with pathological compression fractures. Indeed, the cement is highly resistant to compressive forces, and it is suitable for fractures involving weight-bearing bones such as the vertebral body, acetabulum and in any bones subject to compressive forces [11].

Materials and Methods

The institutional review board of the hospital approved this study, and the informed consent was obtained from the patients for the retrospective study design. Between January 2019 and December 2021, 44 patients (20 males and 24females) with symptomatic bone metastases were treated with RFA alone or combined with cement injection under CT guidance. The aim of the retrospective single-center study was to investigate the pain relief after percutaneous RFA with or without combined cement injection in 44 symptomatic patients with cancer pain related tobone metastases and the following outcomes were analyzed:

- Pain severity documented with Numerical Rating Scale (NRS) measured preoperatively, 1 and 3 days after theprocedure and 3 and 6 months after the procedure.
- Clinical Outcome Assessment Using the Oswestry Disability Index (ODI) preoperatively and after 1 monthfrom the procedure.
- Quality of Life measured with Cancer quality of life questionnaire core 30 (EORTC QLQ- C30) preoperativelyand after 1 month of the procedure.

Patients eligible for inclusion in this study meet all of the following criteria: (a) patients diagnosed with bone cancer pain with osteolytic and/or mixed (osteolytic and osteoblastic) bone metastases; (b) Numeric Pain Numerical Rating Scale (NRS) score > 4/10 not responding to standard analgesic treatments; (c) oligometastases with no more than two bone metastatic sites; (d) Partial thromboplastin time (PTT) < 50 s, platelet count ≤ 50,000/μL. Exclusion criteria: (a) unstable fracture; (b) pure osteoblastic lesion due to the technical challenges to penetrate the sclerotic bone with an access needle; (c) presence of extra-osseous metastases and lesion located < 1 cm from critical structures such as the spinal cord and nerve roots. All patients were symptomatic and underwent previous anticancer treatments (radiotherapy and chemotherapy). After clinical and radiological evaluation and multidisciplinary discussion, the patients were enrolled for RFA and augmentation of bone metastases. Before the procedure, blood cell count and blood clotting analysis were performed to ensure that antiplatelet and anticoagulant therapy is appropriately stopped before surgery. The procedures were performed under conscious sedation guided by CT scan with the patient in proneposition. The planning of the access needle and RFA probe path were chosen under CT guidance for targeting the lesion and avoid the neurovascular structures (fig. 1A). Once the lesion was identified and needle path was chosen, the bone was perforated percutaneously under CT with 10-gauge access introducer using Seldinger technique. An articulating osteotome was inserting coaxially to the access introducer for creating the desired channels for the targeted ablation with a RFA probe. The RFA device was then advanced through the working cannula of the access introducer into the tumor(s) to be treated (fig. 1B). The steerable RFA device is an articulating navigational and bipolar radiofrequency electrode with two embedded active thermocouples positioned along the length of the electrode, 10mm (proximal thermocouple) and 15 mm (distal thermocouple) from the center of the ablation zone. The device generator displays ablation time, impedance, and the two thermocouple tempera-

ture readings that permit real-time monitoring of the peripheral edge of the ablation zone. The targeted ablation was followed by cement augmentation via the same working cannula for stabilization and prevention of pathological fracture (fig. 1C). In some cases, cement augmentation was not performed as the tumors were small and/or the metastases not involved weight-bearing bones.

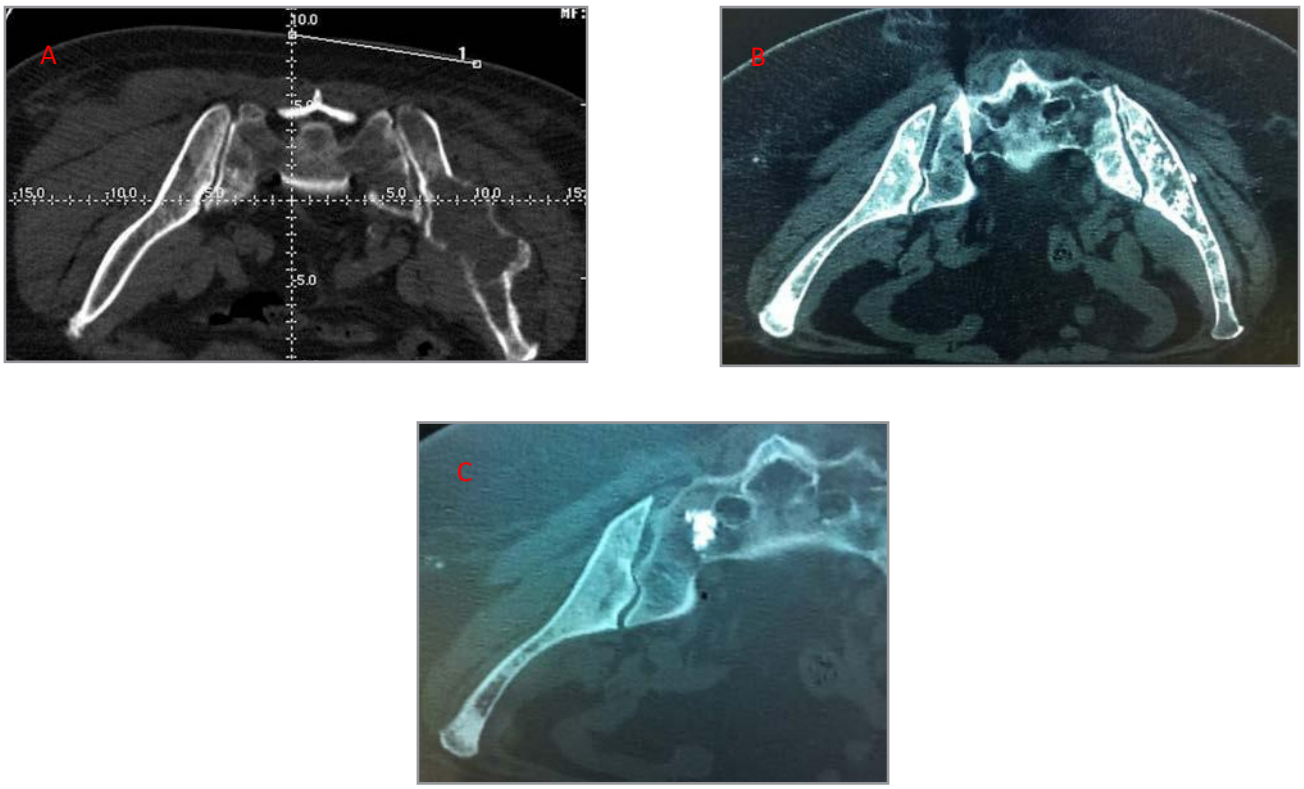

Figure 1: (A) CT image for access needle and RFA probe planning trajectory. (B) Percutaneous sacral access and RFA probe deployment under CTguidance. (C) Injection of high viscosity cement into the sacral metastases ablated.

While a variable number of ablation zones and ablation times were used on the basis of size, shape, nature and location of the lesion, the typical ablation strategy was to target and ablate the most anterior part of the lesion and then retract the RFA probe for ablating the posterior part of the tumor with the respect of all anatomical structures adjacent to the lesion. The total ablation time recorded for each lesion was determined by monitoring the thermocouple readings on the radiofrequency generator with an average of 5min 3sec for small lesions (< 2cm) with amean of ablation time of 25 min 17sec for lesions > 2cm. Repositioning of the RFA probe inside the tumor and overlapping ablation zones were applied to cover the entire metastatic area. For bone metastases at risk of pathological fracture (7/44 patients), the final step of the procedure included the injection of high viscosity bone cement trough the same access cannula into the ablation cavity. After the interventional treatment, patients were observed into our Department for assessing the clinical course and managing potential complications after the procedure.

Statistical Analysis

Mean and 95% confidence intervals (CI) were used to summarize continuous variables of interest, i.e. NRS, ODI and EORTC scores at each timepoint. The change in the distribution of the scores from one timepoint to the following one was evaluated using the two-sample t-test for dependent samples. Analyses were performed using the statistical software R v4.0.2 and p-values <0.05 were considered statistically significant.

Results

The mean age was 66 years old (M = 66, SD = 10) and multiple myeloma was the most common type of tumor (n=16, 36%) followed by breast cancer (n=11, 25%) and lung cancer (n=8, 18%). The most frequent metastatic site was the lumbar spine and iliac wings. Patients' demographics and relative metastatic locations are summarized in Table 1.

Table 1: Patients demographic

ge-Gender	Primary Tumor	Site of Lesion	Treat-ment	NRS Before Treatment	NRS After: 24h, 72h, 2w, 1m, 3m, 6m	EORTC (1-28) Before Treat-ment	EORTC After 1m (1-28)	EORTC (29-30) Before Treat-ment	EORTC After 1m (29-30)	ODI Before Treat-ment	ODI After 1m
53 - W	Multiple Myeloma	L4	RFA	7	3, 2, 2, 2, 2	6	4	42	6	7	4
81 - M	Prostate	L2	RFA + KP	5	2, 2, 0, 2, 2	7	56	6	26	7	3
70 - W	Multiple Myeloma	Iliac Bone	RFA	7	3, 3, 3, 3, 3	6	8	57	3	7	0
76 - M	Pancreas	Acetab-ulum	RFA	8	3, 8, 3, 3, 3	7	5	61	2	7	5
68 - M	Multiple Myeloma	Iliac Bone	RFA	8	4, 2, 2, 1, 1	6	8	46	4	7	5
67 - M	Lung	L4	RFA	8	4, 4, 4, 5, 6	7	3	56	3	7	3
71 - W	Breast	L3	RFA + KP	9	4, 3, 2, 1, 1	7	54	5	17	7	3
63 - M	Multiple Myeloma	L4	RFA + KP	8	4, 3, 1, 1, 1	6	8	57	4	7	8
52 - W											
Breast	Iliac Crest	RFA	9	4, 3, 3, 3, 3	6	56	5	40	7	3	
54 - W	Lymphoma	L3	RFA + KP	8	4, 3, 3, 3, 3	7	61	4	22	7	5
79 - M	Lung	L1	RFA + KP	8	6, 6, 5, 5, 5	6	59	7	37	7	4
77 - W	Multiple Myeloma	L2	RFA + KP	9	2, 2, 1, 1, 1	6	8	60	6	7	3
65 - M	Lung	Iliac Crest	RFA	8	2, 2, 4, 4, 4	7	59	5	22	7	5
77 - W	Multiple Myeloma	Iliac Crest	RFA	7	3, 3, 2, 2, 1	7	55	3	15	7	6
66 - W	Kidney	Sacrum	RFA	9	4, 2, 2, 1, 1	7	45	5	22	7	5
44 - W	Breast	L4	RFA + KP	9	4, 2, 2, 1, 1	7	45	5	28	7	9
66 - W	Multiple Myeloma	L4	RFA	8	4, 4, 2, 2, 1	6	8	45	5	15	7
73 - W	Kidney	Iliac Crest	RFA + KP	9	4, 4, 4, 5, 2	6	45	5	33	7	3
66 - W	Lung	Iliac Crest	RFA + KP	8	3, 3, 2, 2, 2	6	45	5	25	7	8
71 - M	Multiple Myeloma	Iliac Crest	RFA	9	2, 2, 1, 2, 2	7	55	6	25	7	6
76 - M	Lung	Iliac Crest	RFA	8	4, 4, 4, 4, 2	6	45	6	30	7	5
87 - M	Urothelium	Ileum	RFA	9	4, 3, 3, 3, 2	7	55	5	32	7	5
66 - W	Breast	Iliac Crest	RFA + KP	9	4, 4, 2, 2, 1	7	44	7	15	7	1

79 - M	Multiple Myeloma	Iliac Crest	RFA + KP	9	4, 4, 3, 3, 1	7	43	4	25	7	0
73 - W	Lung	L5	RFA	8	4, 4, 4, 4, 3	7	42	4	32	7	8
39 - W	Breast	L4	RFA	9	6, 2, 2, 2, 2	7	41	4	30	7	2
62 - M	Multiple Myeloma	Iliac Crest	RFA + KP	8	7, 6, 5, 7, 6	6	50	3	40	6	3
52 - M	Pancreas	Sacrum	RFA	8	7, 7, 6, 5, 5	6	55	3	40	6	3
47 - M	Stomach	L3	RFA	6	2, 2, 3, 4, 2	6	60	5	22	6	8
68 - W	Multiple Myeloma	L3	RFA	8	4, 4, 3, 3, 4	6	50	5	18	6	0
71 - M	Prostate	L5	RFA	9	3, 3, 3, 3, 4	6	50	5	30	6	8
74 - W	Breast	Shank	RFA	9	3, 3, 3, 4, 4	7	50	5	36	7	2
77 - M	Multiple Myeloma	Iliac Crest	RFA	8	4, 4, 3, 3, 3	7	50	6	28	7	9
69 - W	Lung	Sacrum	RFA	9	4, 4, 4, 4, 4	7	50	6	32	7	6
67 - M	Lung	Iliac Crest	RFA	8	5, 5, 4, 4, 2	6	50	6	22	7	6
59 - W	Breast	Iliac Crest	RFA	7	5, 4, 2, 2, 2	6	50	5	20	7	5
48 - W	Lung	Iliac Crest	RFA	5	3, 3, 2, 2, 2	6	50	5	20	7	0
48 - W	Multiple Myeloma	Iliac Crest	RFA	9	2, 2, 2, 2, 2	7	55	5	32	7	0
71 - M	Multiple Myeloma	L4	RFA	7	4, 3, 3, 1, 1	7	55	5	28	7	2
67 - W	Breast	Iliac Crest	RFA	7	3, 3, 3, 3, 3	7	55	5	31	7	5
70 - W	Endometrium	Iliac Crest	RFA	8	3, 3, 2, 2, 2	7	42	6	27	7	2
71 - W	Sigma	Iliac Crest	RFA	8	3, 3, 3, 2, 2	6	42	6	29	7	8
61 - M	Multiple Myeloma	Iliac Crest	RFA	8	4, 4, 3, 3, 2	6	42	6	38	6	8
80 - W	Multiple Myeloma	Iliac Crest	RFA	8	4, 4, 3, 3, 2	7	44	6	28	6	8

In all patients enrolled in the study, whether they underwent RFA combined with or without cement augmentation, the mean (95% CI) NRS scores had reduced from 8.0 (7.7, 8.3) to 3.7 (3.4, 4.1) after 24 hours from the interventional treatment (reduction was statistically significant, $p<0.001$) and to 3.4 (3.0, 3.8) after 72 hours from the interventional treatment ($p=0.08$ compared to NRS core at 24 hours after the interventional treatment; Fig. 2). A further significant reduction was observed between 72 hours and 2 weeks after the interventional treatment ($p<0.001$). Six months after the interventional treatment, the mean (95% CI) NRS score was 2.4 (2.0, 2.8).

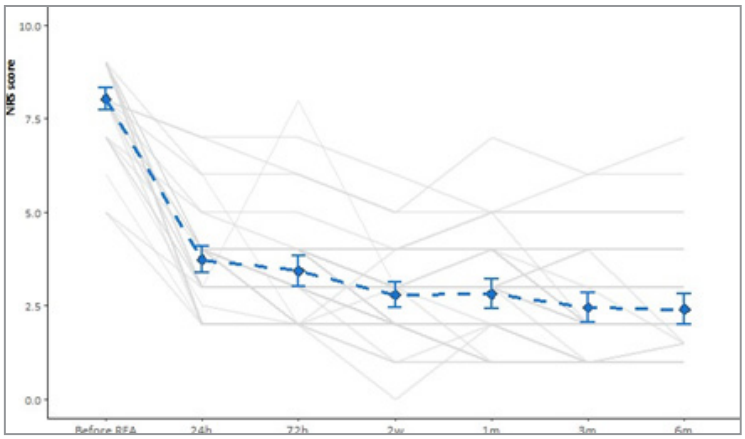

Figure 2: NRS trend before treatment and follow-up until 6 months. The patient indicates the number that corresponds to pain severity.

There was a significant decrease in the ODI score before and one month after the interventional treatment (p<0.001, Fig. xx). Mean (95% CI) ODI score changed from 62.8 (60.9, 64.7) before RFA to 28.0 (25.7, 30.3) after 1 month (Fig.3).

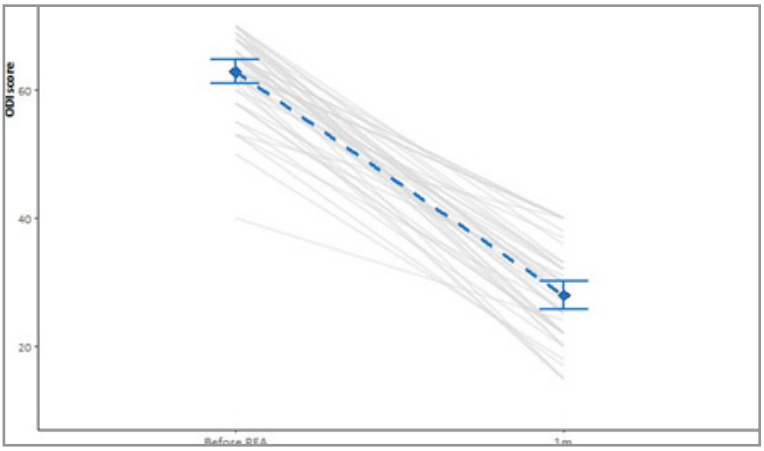

Figure 3: ODI evaluation preoperatively and 1 month after the treatment, representing the improvement of pain intensity.

The quality of life was assessed with the EORTC questionnaire. Before RFA, mean (95% CI) EORTC 1-28 score was 69.1 (67.9, 70.3) and this significantly decreased (p<0.001) to 50.5 (48.6, 52.3) one month after the interventional treatment (Fig xx). EORTC 29-30 score significantly increased (p<0.001) from 4.8 (4.5, 5.2) to 5.6 (5.4, 5.9) (Fig.4).

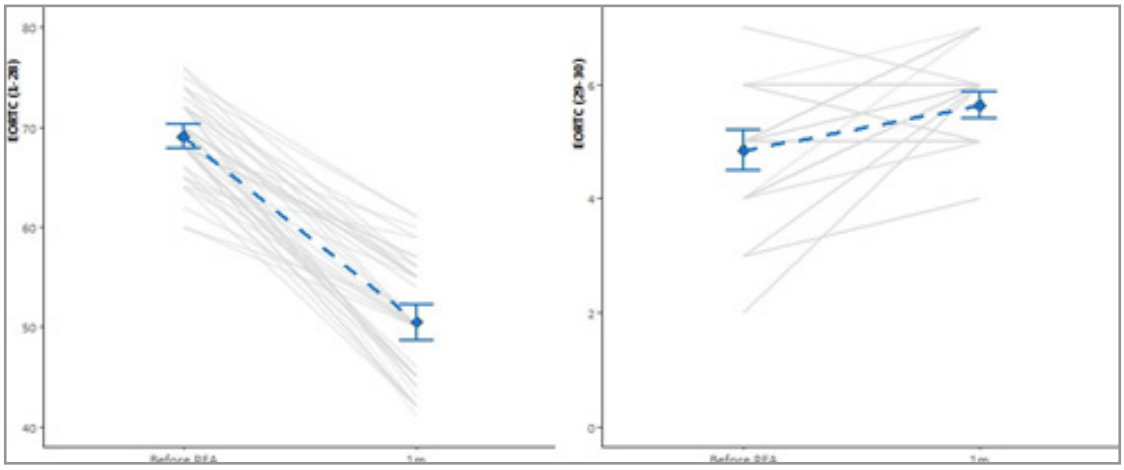

Figure 4: The EORTC Core Quality of Life questionnaire assessment before the interventional treatment and after 1 month, with the measurement of cancer patients' physical, psychological and social functions.

In patients treated with RFA, the area ablated was filled by well-distributed cement. Cement leakage did not occur in any patient. No other complications occurred during the procedure. The patients were followed up for 6 months without any recurrence of pain at the treated site.

Conclusion

Radiofrequency ablation (RFA) has been proved as reliable treatment for the destruction of some soft-tissue tumors, such as liver or lung lesions, when conventional surgery is not an option [12, 13]. In recent years, however, RFA has emerged as a highly successful approach and adopted as a palliative strategy included in the National Comprehensive Cancer Network (NCCN) Practice Guidelines for Adult Cancer Pain and in the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines [5, 14]. Multidisciplinary approach and cross functional meeting is the key for identifying who may benefit from RFA and palliative care. Radiotherapy and chemotherapy are first-line treatments for bone metastasis in patients. When conventional treatments fail, patients are often prescribed high doses of opioid analgesics for pain control. Moreover, opioid therapy often fails to fully alleviate metastasis-related bone pain and leaves without a significant improvement of quality of life [15]. The advantages of RFA for bone metastases include the minimally invasive nature that can be performed with a short hospitalization, low complication rates, no interruption of systemic chemotherapeutic agents, and the ability to combine with other palliative treatmentoptions [16]. Advanced imaging and early detection for pain palliation can optimize the selection of the most appropriate technique in a patient-tailored approach to maximize the efficacy of pain relief. In our clinical experience, radiofrequency ablation with or without combined cement injection in patients with cancer pain related to bone metastases has been demonstrated a safe and effective palliative treatment, reducing pain (Six months after the interventional treatment, the mean NRS score dropped from 8.0 to 2.4 and ODI score changed from 62.8 before treatment to after 1 month follow-up) and improving quality of life (EORTC 1-28 score significantly decreased from to 50.5 one month after the treatment and EORTC 29-30 score from 4.8 to 5.6). Previous studies have highlightedthat RFA for bone metastases results in clinically significant and immediate pain relief and adverse events are rare [17]. In conclusion, RFA with/without vertebral augmentation, is a safe procedure in achieving analgesia in cancer patients with painful bone metastasis. While indicated for patients with bone metastasis who have failed conventionaltherapies, RFA may also be an option for patients who decline radiotherapy. RFA does not prevent patients from receiving chemotherapy or radiotherapy at a later time and should be considered in selecting the most appropriate and effective treatment for cancer patients

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