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Research article

Diffusion-weighted magnetic resonance imaging in painful bone metastases: Using quantitative apparent diffusion coefficient as an indicator of effectiveness of single fraction versus multiple fraction radiotherapy

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ABSTRACT

Purpose: Bone metastases are a common cause of cancer-related pain. The aim of this study is to determine the optimal radiotherapy schedule for the treatment of painful bone metastases and verify if could cause different biological effects on bone. This has been achieved using functional Magnetic Resonance Imaging (MRI) with diffusion-weighted imaging (DWI).

Patients and methods: Fifteen patients received Multiple Fractions Radiation Therapy (MFRT) with a total dose of 30 Gy in 10 daily fractions of 3 Gy given over 2 weeks and 15 patients received a Single Fraction Radiation Therapy (SFRT) with a dose of 8 Gy. Quantitative Apparent Diffusion Coefficient (ADC) values after SFRT or MFRT were compared with response to treatment (pain relief), assessed by Visual Analogue Scale (VAS) before radiotherapy and at 1 and 3 months after the completion of treatment.

Results: The two schedules had equal efficacy in terms of pain control, without any difference at 1 and 3 months post radiotherapy. In both treatments, pain reduction was related to an increase in the ADC. However, the median ADC value had an increase of 575 points between the baseline and 3 months (from 1010 to 1585, $p = 0.02$) in the 30 Gy group, while it was only 178 points (from 1417 to 1595) in the 8 Gy group.

Conclusions: The increase in the ADC values after radiotherapy corresponds to increased cell death. Despite an equal pain control, MFRT treatment seems to be more effective to achieve cancer cells kill. Our preliminary data could also explain the higher retreatment rates in SFRT vs MFRT in long survivors.

1. Introduction

Bone is the most common metastatic site from different cancer primaries and bone metastases (BoM) can cause severe and debilitating effects, including pain, spinal cord compression, hypercalcemia and pathologic fractures [1]. Radiotherapy (RT) provides successful and time efficient palliation of painful BoM, with very few side effects [2]. Despite the clinical evidence supports the use of Single Fraction Radiation Therapy (SFRT), practice patterns vary greatly worldwide, showing reluctance to prescribe SFRT [3]. The choice of palliative radiotherapy treatment is conditioned by various clinical factors like symptom burden, extent of disease, life expectancy, Performance Status (PF), comorbidities, toxicity, prior treatment and patient wishes. Institution and training-related factors, but also individual physician beliefs may play a role [4]. Furthermore, most of the randomized controlled trials have focused on pain relief and only few have evaluated the impact of BoM fractionation on patient's quality of life [5–11]. Westhoff et al. [11,12] analyzed, in the Dutch Bone Metastasis Study database, the effect of radiation therapy on QoL and showed that response resulted in better QoL for all domains compared with non responders, with any clear factors, other than probably primary tumor and performance status, predicting a pain response. Radiation therapy can offer a good pain response but most domains of QoL do not improve after treatment with the exception of slightly improvement of psychosocial QoL. The evaluation of pain response to treatment with the Visual Analogue Scale (VAS) or other questionnaires on quality of life is subjective. In addition, the pathogenesis of metastatic bone pain remains unclear and the mechanism of pain relief after RT is uncertain. For these reasons, palliative RT for bone metastasis still remains an area of active clinical investigation and at the present time there is still no

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objective evidence in literature regarding the influence of fractionation on bone structure. The aim of this study is to verify if different radiotherapy fractionation schedules could cause different biological effects on bone. Functional MRI with diffusion-weighted imaging (DWI) and quantitative Apparent Diffusion Coefficient (ADC) measurement provides a new tool to better understand bone microenvironment, characterize the microstructure of metastatic tissue and estimate changes in cellularity due to cellular death in response to treatment [6]. Changes in ADC values after SFRT or Multiple Fractions Radiation Therapy (MFRT) were compared with changes in value of the Visual Analogue Scale (VAS) for pain.

2. Methods and materials

This prospective study was approved by our institutional ethics committee and all patients gave written informed consent.

Patients with histologically proven primary cancers and radiologically confirmed non-complicated bone metastases were prospectively enrolled. The following exclusion criteria were considered: primary diagnosis of myeloma, evidence of contraindications to MRI (e.g., pacemaker, cochlear implant, etc.), incomplete MRI acquisition, no histopathological diagnosis of primary cancer, incapacity to give consent to treatment, patients with Karnofsky performance status less than 50% life expectancy of less than 6 months, clinical or radiological evidence of spinal cord compression, pathological fracture or impending fracture in the planned RT site, requiring surgical intervention prior to radiotherapy.

No randomization was performed; the patients were allocated to one of the two radiotherapy schedules, on the basis of clinical decision made by the radiation oncologist, especially considering the fitness of patient to receive MFRT, life expectancy, lesion size, tumor burden outside the bone and the availability of relatives' support.

The mean age at the beginning of radiotherapy was 51.6 years (range: 30.6–81.1 years) and the mean Karnofsky Performance Status was 60% (range: 50–90%).

The primary tumor sites and the localizations of bone metastases are summarized in Table 1. Before treatment and at 1 and 3 months after completion of radiotherapy, each patient was examined whit MRI-DWI scanning (3T unit, Discovery 750, GE Healthcare, Milwaukee, WI, USA) with conventional sequences (axial and coronal T1-weighted sequences, axial and coronal T2-weighted sequences, axial and coronal T1- and T2-weighted sequences with fat signal saturation), and DWI. Radiation therapy was delivered with a 3D conformal multiple field technique and 6 or 15 MV energy photons were used. Between September 2015 and August 2016, 164 patients, with different histologically proven primary cancer received palliative RT. Of these, thirty consecutive patients, meeting the inclusion criteria and for whom it was possible to perform a MRI at the of clinical evaluation, received MFRT or SFRT. Five patients refused the proposed protocol.

Table 1
Baseline patients demographic and treatment characteristics.

Characteristic		SFRT	MFRT
Median age (yrs) (range)		51.6 (range: 30.6–81.1)	
Gender	Male	7	9
	Female	8	6
Primary Tumor	Brest	4	5
	Lung	3	4
	Prostate	5	4
	Colon		1
	Stomach		1
	Thymus	1	
	Rectum	2	
Site of delivery	Pelvis	6	8
	Femur	3	1
	Humerus	3	2
	Spine	3	4

Fifteen patients received MFRT with a total dose of 30 Gy in 10 daily fractions of 3 Gy given over 2 weeks and 15 patients received SFRT with a dose of 8 Gy. Treatment outcome was evaluated in terms of symptom palliation and pain severity was assessed using the VAS score.

VAS values were recorded at baseline and at 1 and 3 months post-treatment, before MRI examination, to avoid multiple access to hospital. Patients characteristics were summarized by means of cross-tabulations for categorical variables or by means of quantiles for continuous variables. Non-parametric tests were applied for comparisons between treatment groups. Box plots were used for comparing distributions of ADC values between treatment groups. All tests were 2-sided, accepting $p < 0.05$ as indicating a statistically significant difference and confidence intervals were calculated at 95% level. All analysis were performed using the SAS software (release 9.4 − SAS Institute, Cary, NC, USA).

3. Results

The median value for the ADC before treatment was 1010 and 1417 for the 30 Gy and 8 Gy group respectively. At 1 month post treatment, the ADC was increased in both groups, with a median value of 1635 and 1581 respectively. At 3 months post treatment, no significant difference was reported between the two treatment schedules, with an ADC median value of 1585 for the 30 Gy group and 1595 for the 8 Gy group (Fig. 1) (Table 2). However, the median ADC had an increase of 575 points between the baseline and 3 months (from 1010 to 1585, $p = 0.02$) in the 30 Gy group, while it was only 178 points (from 1417 to 1595) in the 8 Gy group (Fig. 2). Both groups reported a median value of 8 on the Visual Analogue Scale (VAS) with the scale of 0–10. The two schedules had equal efficacy in terms of pain control. The median VAS value at one month was 3 for the 8 Gy group and 1 for the 30 Gy group, while at three months the median was 0 in both groups. There was no statistically significant differences between the two groups at 1 and 3 months ($p = 0.15$ and $p = 0.61$) (Fig. 3). Changes in pain medication was recorded at three months in all patients with complete interruption of analgesic drugs in 70% of MFRT patients and 68% of SFRT and reduction in the use of analgesic drugs in 30% and 32%, respectively. During this short follow-up no retreatment due to recurrent pain was performed.

4. Discussion

Bone metastases are a common cause of cancer-related pain. Palliative radiotherapy is a cornerstone in the treatment of painful BoM. Multiple randomized controlled trials (RCTs) and meta-analyses have shown that SFRT is as effective as MFRT for relief of painful BoM [8–10,13–15]. This is reflected in guidelines from Choosing Wisely Canada, the national Choosing Wisely campaign and the American Society for Therapeutic Radiology and Oncology which recommend SFRT for uncomplicated BoM [15]. However, despite this evidence there are still concerns regarding the use of SFRT [9]. The pathogenesis of metastatic bone pain remains unclear [16,17] and the mechanism of pain relief after RT is uncertain [18–22]. The destruction of tumor cells followed by bone remodeling occurs; the rapid speed of onset and the maintenance of pain relief post-RT with the absence of a dose response suggest that tumor cell kill is not the only factor. Other possible mechanisms include an effect on sensitive host cells producing pain mediators, direct effect on osteoclast activity, or disturbance of the neuronal transmission of pain [23]. A placebo effect may also be possible. Even the re-calcification effect seems to produce a significant influence even though there is no conclusive data about this effect. When considering changes in bone density, all studies showed the same trend: bone density seemed to increase after treatment with radiotherapy but scientific data underlining this stabilizing effect are scarce. Historical literature data reported radiotherapy decreases the bone