European Journal of Cancer (2014) xxx, xxx–xxx

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Position Paper

Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: A review and position statement by the European Organisation for Research and Treatment of Cancer imaging group

F.E. Lecouvet [a,*], J.N. Talbot [b], C. Messiou [c], P. Bourguet [d], Y. Liu [e], N.M. de Souza [c,f], on behalf of the EORTC Imaging Group

[a] *MRI Unit, Dept of Radiology, Centre du Cancer and Institut de Recherche Expérimentale et Clinique (IREC), Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium*
[b] *Dept of Nuclear Medicine, Hôpital Tenon, AP-HP & Université Pierre et Marie Curie, Paris, France*
[c] *Dept of Radiology, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, United Kingdom*
[d] *Dept of Nuclear Medicine, Cancer Center Eugène Marquis and University of Rennes 1, Rennes, France*
[e] *EORTC, TR, Radiotherapy and Imaging Department, EORTC Headquarters, Brussels, Belgium*
[f] *MRI Unit, Institute of Cancer Research and Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, United Kingdom*

Received 10 February 2014; received in revised form 25 June 2014; accepted 2 July 2014

KEYWORDS
EORTC
Cancer
Bone
Metastases
Imaging
Treatment
Response
RECIST
MRI
PET

Abstract Assessment of the response to treatment of metastases is crucial in daily oncological practice and clinical trials. For soft tissue metastases, this is done using computed tomography (CT), Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) using validated response evaluation criteria. Bone metastases, which frequently represent the only site of metastases, are an exception in response assessment systems, because of the nature of the fixed bony defects, their complexity, which ranges from sclerotic to osteolytic and because of the lack of sensitivity, specificity and spatial resolution of the previously available bone imaging methods, mainly bone scintigraphy. Techniques such as MRI and PET are able to detect the early infiltration of the bone marrow by cancer, and to quantify this infiltration using morphologic images, quantitative parameters and functional approaches. This paper highlights the most recent developments of MRI and PET, showing how they enable early detection of bone lesions and monitoring of their response. It reviews current knowledge, puts the different techniques into perspective, in terms of indications, strengths, weaknesses and

* *Corresponding author:* Address: Dept of Radiology, Cliniques Universitaires Saint Luc, Hippocrate Avenue 10/2942, B1200 Brussels, Belgium. *E-mail address:* frederic.lecouvet@uclouvain.be (F.E. Lecouvet).

http://dx.doi.org/10.1016/j.ejca.2014.07.002

Please cite this article in press as: Lecouvet F.E. et al., Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: A review and position statement by the European Organisation for Research and Treatment of Cancer imaging group, Eur J Cancer (2014), http://dx.doi.org/10.1016/j.ejca.2014.07.002

complementarity, and finally proposes recommendations for the choice of the most adequate imaging technique.

1. Introduction

Evaluation of response to therapy is a pivotal component of cancer imaging. For the last 20 years, Response Evaluation Criteria in Solid Tumours (RECIST) criteria have been used for soft tissue metastases, but bone lesions remain 'non-measurable' [1,2]. Therefore, in cancers such as prostate and breast where metastases occur preferentially or exclusively in the bone, response assessment is difficult. Serum biomarkers where available (e.g. Prostate Specific Antigen (PSA) in prostate cancer) provide a means for monitoring treatment response; bone resorption biomarkers such as n-telopeptide (NTX) have also been explored [3]. However, serum biomarkers do not address heterogeneity of response at different sites as resistant clones emerge. Advances in Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), along with their increased availability, have led to their use for response assessment of bony metastases. Evaluation of bone metastasis response and the development of criteria of bone response are current priorities in the EORTC Imaging group, because they are required for several ongoing multicentre studies. This paper therefore discusses current state-of-the-art MRI and nuclear medicine imaging approaches for detecting and evaluating response in bone metastases.

2. Methods of detecting bone metastases

2.1. Magnetic Resonance Imaging (MRI)

Morphological approaches use measurements of tumour number and size, paralleling measurements for 'soft tissue' metastases. Functional techniques (Dynamic contrast-enhanced (DCE)-MRI and diffusion-weighted (DW)-MRI) widely studied in soft tissue disease [4–6], provide assessments of response that predate volume changes [7,8] but have only recently been extended to the study of bone metastases [9–13].

2.1.1. Morphologic MRI

Morphologic MRI is superior to radiographs, computed tomography (CT) and bone scintigraphy (BS) because it detects the early replacement of marrow fat and haematopoietic cells by tumour, prior to trabecular changes. T1 changes are independent of associated sclerosis and are applicable across tumour types [14]. On T1-weighted (T1-W) images, high contrast between lesions and normal marrow enables derivation of an index of tumour load [12]. T2-weighted (T2-W) and short tau inversion recovery (STIR) images reflect lesion composition (water content, fibrosis and sclerosis) rather than marrow replacement, and show variable signal [15]. Although whole body coverage is feasible, limiting coverage to the axial skeleton where metastases predominate minimises examination time to 20 min [16] and outperforms BS [17] (Fig. 1). A $T2^*$ measurement may be used to quantify bone sclerosis and has shown changes in bone density that parallel those found on CT [18].

2.1.2. Diffusion-weighted MRI (DW-MRI)

DW-MRI is sensitive to thermal motion (diffusion) of water molecules. In biologic tissues barriers such as endothelium, cell membranes, components of the extracellular matrix and intracellular organelles restrict diffusion; increase or decrease in these barriers modifies the degree of water diffusion leading to a reduction or retention of MR signal. Tumour foci are visualised as increased signal-intensity on DW-MRI images with a corresponding decrease in the measured Apparent Diffusion Coefficient (ADC), which represents the rate of signal loss with increasing diffusion weighting [19]. As the diffusion properties of bone metastases are significantly different to age-matched normal marrow [20], DW-sequences are now almost routinely used as an adjunct to conventional T1-W images [15]. However, DW-MRI lacks specificity, emphasising the need for morphologic sequences [21,22].

2.1.3. Perfusion MRI (DCE-MRI)

DCE-MRI requires injection of a paramagnetic contrast agent which shortens T1 relaxation of tissue water. The mass transport of this agent through the vascular, extravascular and extracellular spaces and the differences in water and contrast compartmentalisation in the tissues [6] are used to model the vascular and interstitial properties of tissues. The most frequently reported parameter K^{trans} is constructed from a lumped representation of perfusion and permeability and has been validated as an imaging biomarker of tumour vasculature (angiogenesis) and of the early effects of treatment on vascularisation [6,23]. DCE-MRI has no role in the detection and global quantification of bone metastatic disease, as anatomic coverage is limited, and standardisation of acquisition techniques across different platforms and centres is challenging.

2.2. Nuclear medicine

Techniques reflect the functional/biologic properties of tissues and are based on two different physical

Please cite this article in press as: Lecouvet F.E. et al., Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: A review and position statement by the European Organisation for Research and Treatment of Cancer imaging group, Eur J Cancer (2014), http://dx.doi.org/10.1016/j.ejca.2014.07.002