

## Challenges for imaging and therapy of musculoskeletal tumours

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Imaging musculoskeletal tumours has always relied on a variety of morphological and functional imaging modalities for optimum diagnosis and treatment response evaluation. Traditionally, high resolution morphological methods, including radiographs, computed tomography (CT) and magnetic resonance imaging (MRI) have been used to detect and characterise primary musculoskeletal tumours, and nuclear medicine methods have been employed for further characterisation and staging, including bone scintigraphy and  $^{18}\text{F}$ -Fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG PET). Imaging methods for evaluation of therapy response have been less accurate and robust but with the increased use of hybrid imaging, including single photon emission computed tomography (SPECT)/CT, PET/CT and more recently, PET/MRI, there is an increased opportunity to maximise both sensitivity and specificity by combining high-end anatomical, functional and molecular imaging methodology in a single scan acquisition to include primary tumours and whole body imaging for staging.

Whilst MRI has become the major modality for characterisation and local staging of primary musculoskeletal tumours, there is a potential to increase the role of SPECT and PET to grade malignancy, examine heterogeneity within a tumour, to guide diagnostic biopsies and to map

other aspects of abnormal tumour biology. By non-invasively determining the underlying phenotype with novel tracers that can measure underlying biological factors such as proliferation, neoangiogenesis and hypoxia, there is greater potential to predict treatment response to cytotoxic or specifically targeted agents, including radionuclide therapies. Depending on the modes of action of combination cancer therapies, treatment response can also potentially be predicted with companion diagnostics for novel therapies earlier than has previously been possible.

Nuclear medicine has also traditionally played a pivotal part in the management of patients with skeletal metastases.  $^{99\text{m}}\text{Tc}$ -Methylene diphosphonate scintigraphy remains the most commonly used method for skeletal staging and is still considered routine in high risk patients with prostate and breast cancer and in symptomatic patients in other cancers with a predilection for spread to the skeleton. The lack of specificity for cancer using bone-specific tracers that target areas of abnormal osteoblastic activity has been largely overcome with the more routine use of SPECT, and particularly hybrid SPECT/CT where the morphological correlation afforded by CT prevents false positive interpretations due to incidental benign bone pathology [1]. A shortage of  $^{99\text{m}}\text{Tc}$ -Technetium has also promoted the resurgence of interest in the use of  $^{18}\text{F}$ -Fluoride as a bone tracer. Although more costly, the improved image quality, tomographic data, ubiquitous use of the CT component of PET/CT and ability to acquire images less than 1 h after injection, has renewed interest in the use of this tracer in staging the skeleton in cancer patients. In addition, we are able to more specifically target tumour metabolism within bone metastases with metabolic tracers such as  $^{18}\text{F}$ -FDG and  $^{11}\text{C}/^{18}\text{F}$ -Choline. Whilst it remains uncertain whether both bone and tumour-specific tracers are required for optimum sensitivity to detect the associated abnormal

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metabolism in the bone microenvironment as well as the metabolic activity within tumour cells, potentially in bone marrow metastases before the associated reactive bone changes, there is no doubt that the increased use of both tracer types in combination with hybrid imaging has increased diagnostic sensitivity and specificity. In recent years whole body MRI has become possible and with the addition of functional sequences such as diffusion-weighted MRI (DW-MRI) to the standard anatomical acquisitions there is early work suggesting that whole body skeletal staging may now be a realistic option.

Whilst diagnosis has improved, we remain poor at measuring response to treatment in primary musculoskeletal tumours and skeletal metastases, the relatively slow and inaccurate change in bone-specific tracers and the lack of robust data to confirm the validity of tumour-specific tracers being limiting factors. Early work with metabolic and proliferation tracers in primary malignant bone tumours has shown some promise but has not been clinically adopted. This is an area where the combination of anatomical, functional and metabolic information from PET/MRI may be exploited. For example, measuring changes in the apparent diffusion coefficient (ADC) from DW-MRI may provide information on the therapeutic effects of changes in cellular density within a tumour that may complement the metabolic information provided with PET tracers [2] but to date we have not taken advantage of the multimodality, multiparametric information that is available that may allow us to better predict treatment response in bone metastases. There are now a number of second- and third-line treatments for bone metastases for breast and prostate cancer, increasing the requirement for early response assessment to accelerate therapeutic transition in non-responding patients at an early time point. This may prevent unnecessary toxicity, reduce costs of ineffective treatment and potentially improve symptom control and time to progression with effective second-line therapies.

Assessing treatment response also becomes more complex, but potentially more powerful, with the advent of targeted biological anti-tumour therapies and drugs that specifically target the cycle of tumour-associated osteoclast-mediated bone destruction. This results from tumour-derived factors that are released and accelerate the maturation and bone resorptive activity of osteoclasts via the receptor activator of nuclear factor kappa-B (RANK) ligand pathway with subsequent release of bone-derived factors that positively feed back on the tumour to accelerate the cycle. As well as the anti-osteoclast effect of the commonly used bisphosphonates, novel agents that target this pathway have shown activity in bone metastases, for example. denosumab, a monoclonal antibody to RANK ligand. It would therefore seem appropriate to be able to

target the mode of drug action more specifically with imaging probes that report on the relevant part of the tumour or bone (osteoblastic or osteoclastic) process that is being altered. Whilst we commonly use methods that image the osteoblastic and metabolic tumour aspects of the underlying pathophysiology, a potential new method for targeted imaging of osteoclasts involves the use of RGD (arginine-glycine-aspartic acid) tracers that were originally designed to detect tumour neoangiogenesis by targeting the  $\alpha_3\beta_v$  integrin that is also highly expressed on activated osteoclasts. This method has been supported by some preclinical data.

Palliation of bone pain associated with metastases may be achieved with  $^{89}\text{Sr}$ -Chloride and  $^{153}\text{Sm}$ -EDTMP, which have been available for quite some time. While reasonably efficient, such treatments have remained reserved for a fairly limited number of patients, partly because they have not been fully integrated in the therapeutic armamentarium by all oncologists. Change may be on the way however, with the approval of  $^{223}\text{Ra}$ -Dichloride for treating sclerotic metastases. This alpha emitter acts beyond pain palliation as it was shown to significantly increase overall survival in patients with castration-resistant prostate cancer patients and to improve their quality of life, with a very limited toxicity [3]. Another radionuclide option includes  $^{177}\text{Lu}$ , which is increasingly used for labelled peptide therapy of neuroendocrine tumours.  $^{177}\text{Lu}$ -EDTMP has shown very encouraging results for relieving painful bone metastases, with the advantage of low cost and potentially large availability.

In conclusion, whether it concerns imaging or treatment of musculoskeletal tumours, nuclear medicine techniques appear to constantly reinvent themselves, taking advantage of the added value of hybrid imaging methods or applying old tracers with new technology.

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