Skeletal metastases: what is the future role for nuclear medicine?

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Although planar bone scintigraphy with ^{99m}Tc -labelled bisphosphonates has been the mainstay for imaging skeletal metastases for nearly four decades, it has been limited by poor specificity and has been losing ground to the improving anatomical imaging modalities such as multi-slice CT and newly developing whole body MRI imaging techniques [1, 2]. The addition of SPECT to planar bone scintigraphy improves sensitivity and specificity to a degree [3] but has not been able to negate the need for anatomical imaging correlation, leading to extra imaging procedures for the patient and a subsequent delay in clinical management decisions. The advent of hybrid SPECT/CT and PET/CT would therefore seem to be a natural progression towards optimal assessment of skeletal metastases, incorporating both functional information for sensitivity and anatomical information for specificity in a single comprehensive test. Hybrid MRI scanners are also in development and may have more to offer in view of MRI's particular sensitivity for bone-marrow-based disease.

Hybrid SPECT/CT with diagnostic quality CT has partly been driven by the success of PET/CT, and as a relatively recently available modality, the evidence for incremental benefit in imaging bone metastases is only just starting to accrue [4–7].

Utsunomiya et al. have shown an incremental benefit of fused SPECT/CT compared to separate SPECT and CT images or planar and SPECT images [4]. Fused images allowed greater diagnostic certainty with fewer equivocal lesions, better interobserver agreement and greater overall diagnostic accuracy in diagnosing benign and malignant bone lesions as measured by ROC analysis. Fused SPECT/CT allowed indeterminate lesions to be classified as benign or malignant in 17/82 lesions for one observer and 8/82 for another observer. The correct classification of benign lesions was more frequent for both observers, thus predominantly improving specificity.

In a similar retrospective study of bone SPECT/CT, Romer et al. analysed 52 indeterminate skeletal lesions on SPECT in 44 patients being staged for malignancy [5]. Approximately two-thirds of lesions were classified as benign and in only four lesions was it not possible to classify them as benign or malignant with SPECT/CT.

As bone scintigraphy remains in frequent use and is readily available for staging many cancers, it seems likely that it will continue to have a significant and enhanced clinical role in its new form of SPECT/CT as combined SPECT/CT scanners become more widely available.

However, interest in evaluating skeletal metastases with PET/CT techniques is increasing. It is possible to take advantage of two aspects of metabolic changes associated with bone metastases with two readily available PET tracers, namely ^{18}F -fluoride and ^{18}F FDG. With a similar mechanism of uptake to ^{99m}Tc -labelled bisphosphonates, ^{18}F -fluoride has been available as a bone-specific tracer for many years and the properties of ^{18}F FDG as a tumour-specific agent are well recognised.

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The skeletal clearance of ^{18}F -fluoride ion is similar to $^{99\text{m}}\text{Tc}$ -labelled bisphosphonates in that it reflects a combination of local blood flow and osteoblastic activity [8]. The pharmacokinetics differ from $^{99\text{m}}\text{Tc}$ -labelled bisphosphonates in that there is little protein binding, and unlike bisphosphonates, renal tubular reabsorption occurs. Evidence suggests that ^{18}F -fluoride undergoes high first-pass extraction in bone, approaching 100% at physiological blood flow rates, and similar to $^{99\text{m}}\text{Tc}$ -labelled bisphosphonates, there is chemisorption into bone crystals with the formation of fluorapatite. This process occurs preferentially at sites of actively mineralising bone [9, 10].

In the era before hybrid PET/CT, a number of comparisons of ^{18}F -fluoride PET and planar +/- SPECT bone scintigraphy were performed in the diagnosis of skeletal metastases. These generally showed an improved diagnostic accuracy for the PET method, particularly when compared to planar scintigraphy alone [11–14].

In a study of 34 patients with breast cancer, ^{18}F -fluoride PET detected 64 metastases in 17 patients compared to planar bone scintigraphy, which only detected 29 metastases in 11 patients. ^{18}F -fluoride PET led to a change in management in 12% of patients overall [11]. The greatest incremental benefit of ^{18}F -fluoride PET is in the spine and pelvis compared to the skull, thorax and extremities [12].

However, this raised the question of whether the improved spatial resolution of PET and inherent tomography were responsible for the greater accuracy or whether this was due to a difference in the pharmacokinetics and bone uptake mechanisms between the types of tracer. To some extent an answer to this question was suggested in a subsequent analysis by Schirrmester and colleagues in patients with lung cancer [13]. Of 53 patients with lung cancer, 12 had bone metastases for which there were six false-negatives with planar scintigraphy, one false-negative with planar scintigraphy augmented with SPECT and no false-negatives with ^{18}F -fluoride PET. Six patients had management altered as a result of ^{18}F -fluoride PET and five due to SPECT. The difference between PET and SPECT as measured by the area under the ROC curves was not statistically significant. These findings suggest that the differences between bone scintigraphy and ^{18}F -fluoride PET were mainly technical rather than due to mechanistic differences in the tracers. The same group took this analysis further in a group of 103 patients with lung cancer and on this occasion showed a statistically significant increase in the area under the ROC curve with ^{18}F -fluoride PET compared to SPECT and planar scintigraphy but it was noted that this was at higher incremental costs [14].

Unsurprisingly, when combined with CT, as hybrid ^{18}F -fluoride PET/CT, diagnostic accuracy is improved when compared to PET alone [15, 16]. The anatomic data

provided by the low-dose CT component allowed better discrimination of benign and malignant lesions and usually obviated the need for a subsequent full-dose diagnostic CT in a group of 44 patients with various primary cancers [15]. Incremental value of ^{18}F -fluoride PET/CT was found in a further study of patients with prostate cancer when compared to planar bone scans, single and multi-field of view SPECT and ^{18}F -fluoride PET without CT [16].

Whilst many of the reported studies are either retrospective or involve only a limited number of patients, a randomised, prospective, multicentre study of over 500 patients with breast, prostate and lung cancers is underway in the United States comparing $^{99\text{m}}\text{Tc}$ MDP planar bone scintigraphy with ^{18}F -fluoride PET/CT and the results are awaited with interest [17].

In the detection of skeletal metastases, ^{18}F FDG is thought to act as a tumour-specific tracer and therefore has the potential advantage of being able to detect small bone marrow metastases before an osteoblastic reaction has occurred (in contrast to bone-specific tracers) or metastases that are predominantly osteolytic in nature with little or no osteoblastic reaction. However, ^{18}F FDG PET may not be as sensitive as MRI in detecting small bone marrow lesions in some tumour types [18].

Much of the literature describing PET and skeletal metastases compares bone scintigraphy with ^{18}F FDG PET in patients with breast cancer [19–21]. The majority of studies indicate that ^{18}F FDG PET is more accurate, although some show this is predominantly due to improved specificity rather than sensitivity [19, 20]. It would appear that the sensitivity for lytic metastases is better with ^{18}F FDG PET but that osteoblastic metastases are less ^{18}F FDG-avid with resultant poor sensitivity compared to bone scintigraphy [21–28]. Although there seems little doubt that lytic and sclerotic metastases behave differently with regards to ^{18}F FDG uptake and that osteoblastic breast cancer lesions may be associated with a better prognosis [22], prior treatment probably influences this relationship [25]. Other tumours where ^{18}F FDG PET or PET/CT have shown superior diagnostic accuracy compared to bone scintigraphy include lung cancer [29, 30], thyroid cancer [31], nasopharyngeal carcinoma [32] and oesophageal carcinoma [33]. However, one study found no apparent advantage of ^{18}F FDG PET over bone scintigraphy in a variety of tumour types [34] and another found bone scintigraphy with SPECT more sensitive in breast cancer due to the poor sensitivity of ^{18}F FDG PET for osteoblastic lesions [28].

There is as yet little data available to determine the value of combined ^{18}F FDG PET/CT compared to ^{18}F FDG PET alone in bone metastases but at least one study suggests a complementary role for the PET and CT components of the examination by finding a much higher positive predictive

value when PET and CT findings are concordant (98%) compared to PET positive/CT negative discordant cases (PPV=61%) and PET negative / CT positive cases (PPV=17%) [35]. A further study showed an improved specificity in the spine of patients with varied tumours when using ^{18}F FDG PET/CT compared to ^{18}F FDG PET alone [36].

However, many cancers are now routinely staged with ^{18}F FDG PET/CT and the pertinent question is whether this method is sufficiently accurate in evaluating skeletal disease such that bone-specific methods, including bone scintigraphy (+/- SPECT and SPECT/CT) or ^{18}F -fluoride PET (or PET/CT), are superfluous.

In non-small-cell lung cancer staging it would appear that routine skeletal assessment with bone scintigraphy in symptomatic and asymptomatic patients can help avoid unnecessary surgery [37]. However, it has been shown that not only bone-specific PET imaging with ^{18}F -fluoride [14] but tumour specific imaging with ^{18}F FDG, are more accurate than bone scintigraphy in patients with lung cancer [29, 30]. As potentially curable NSCLC is now almost routinely staged with ^{18}F FDG PET/CT, the obvious question is whether bone-specific imaging, with SPECT, ^{18}F -fluoride PET or hybrid methods with CT, are required at all.

In this issue of the journal, Kruger and colleagues present some interesting data comparing bone scintigraphy with SPECT of the axial skeleton, ^{18}F -fluoride PET and ^{18}F FDG PET/CT in patients with a new diagnosis of NSCLC [38]. Despite some limitations in retrospective design, individual patients not having all three tests, the use of ^{18}F -fluoride PET rather than ^{18}F -fluoride PET/CT and $^{99\text{m}}\text{Tc}$ MDP SPECT rather than SPECT/CT, there is supportive evidence that ^{18}F FDG PET/CT could at least replace bone scintigraphy in this group of patients.

Overall, ^{18}F FDG PET/CT was found to be more sensitive than ^{18}F -fluoride PET but in spite of all the metastases being lytic in nature, there were four patients who had metastases identified with ^{18}F -fluoride PET but not with ^{18}F FDG PET/CT. Although the number of patients who were ^{18}F -fluoride-positive but ^{18}F FDG-negative is small and we do not know if these corresponded to a particular histological subtype, it would seem too early to say that full nodal, visceral and skeletal staging of lung cancer can be performed by ^{18}F FDG PET/CT alone. It seems possible that additional ^{18}F -fluoride PET or PET/CT might be able to help avoid futile curative therapy regimes but clearly a prospective trial of state-of-the-art imaging with $^{99\text{m}}\text{Tc}$ -MDP SPECT/CT, ^{18}F -fluoride PET/CT and ^{18}F FDG PET/CT is required to clarify remaining questions and to guide us on the optimal way to assess the skeleton for metastases. It seems likely that nuclear medicine will continue to provide a significant contribution towards evaluation of skeletal metastases, almost certainly with hybrid imaging.

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