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ORIGINAL ARTICLE

The diagnostic utility of the flare phenomenon on bone scintigraphy in staging prostate cancer

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Abstract
Purpose Bone scintigraphy (BS) lacks sensitivity for detecting very early skeletal metastases (SM) in prostate cancer (PC) and is often limited by poor specificity. Also scintigraphic flare of SM can occur following effective treatment and mislead an early response assessment. We hypothesised that a flare reaction might amplify the signal from subclinical SM, increasing the sensitivity of BS and that the phenomenon may be specific for metastases.
Methods We conducted a prospective study to determine the frequency of the flare phenomenon in patients with metastatic PC starting hormone therapy and to explore its utility in patients with negative staging scans but considered at high risk of SM and in those with equivocal baseline BS abnormalities. Ninety-nine patients commencing first-line hormone therapy had repeat BS at 6 weeks to score a flare reaction.
Results Of 22 patients with unequivocal SM on the baseline scan, a flare occurred in 9 (41%). Of 36 high-risk localised prostate cancer patients with normal BS pre-treatment, the scan became positive for metastases at 6 weeks in 4 (11%). Of 41 patients with pre-treatment scintigraphic abnormalities of uncertain aetiology, a flare occurred in 8 cases (20%). All eight were confirmed to have SM by follow-up and imaging. Of the 33 remaining patients without a flare, 2 developed SM at 14 months and the remainder did not develop SM in a median follow-up period of 36 months.
Conclusion The flare phenomenon following initial hormone therapy can be used to improve both sensitivity and specificity of BS in PC.

Keywords Bone scintigraphy · Prostate cancer · Skeletal metastases · Flare phenomenon

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Introduction

Bone scintigraphy with ^{99m}Tc-labelled bisphosphonates is widely used to stage patients with prostate cancer considered at high risk of metastases, but it is recognised that it may not detect very small volume skeletal metastases before a sufficient osteoblastic reaction has occurred and other imaging techniques, such as MRI, may be more sensitive for low volume disease in the spine [1]. Although bone scintigraphy is inexpensive, widely available and able to assess the whole skeleton, it is also limited by poor specificity as a number of benign pathologies may mimic metastatic disease, e.g. degenerative disease in the spine or solitary rib fractures. Non-specific and equivocal scintigraphic abnormalities can sometimes be characterised with correlative imaging, e.g. radiographs, CT or MRI, but a number of bone scan lesions remain indeterminate with potential delays in correct staging and subsequent management decisions [2].

The flare phenomenon describes an increase in isotope uptake by metastatic lesions or the appearance of new, previously occult lesions, soon after starting systemic hormone or chemotherapy [3–5]. The phenomenon results from the osteoblastic healing response in a skeletal metastasis causing a localised increase in uptake of bone-specific radiotracers such as the ^{99m}Tc-labelled bisphosphonates.

The flare phenomenon is reported to be greatest up to 3 months after commencing systemic therapy and has usually subsided by approximately 6 months [3, 4, 6, 7]. It has been more widely described in breast cancer [5, 7–9] but is also reported to occur in between 6 and 23% of patients with metastatic prostate cancer being treated with hormones [6, 10, 11].

Following diagnosis of prostate cancer, hormone therapy is indicated not only for metastases, but also for those with locally advanced primary disease, often in combination with radiotherapy [12]. One of the aims of this study was to determine the frequency of the flare phenomenon in patients with bone metastases being treated with hormone therapy. We also aimed to assess whether the occurrence of a flare after starting hormone therapy might improve the sensitivity or specificity of bone scintigraphy in the diagnosis of prostate cancer skeletal metastases.

Materials and methods

Approval was obtained for this study from the local Research Ethics Committee and the national Administration of Radioactive Substances Advisory Committee and all subjects gave written informed consent.

Patients who were commencing hormone therapy on clinical grounds for treatment of prostate cancer were eligible for inclusion. Inclusion criteria were (1) presence of lesions on bone scan considered diagnostic of metastases, (2) presence of equivocal lesions on bone scan not considered diagnostic of metastases but where the management was in any event agreed to be with hormone therapy or (3) high-risk local prostate cancer by the following criteria: T1–3a and prostate-specific antigen (PSA)>50 ng/ml or T3b and PSA>30 ng/ml or Gleason score 8–10 and PSA>20 ng/ml (Table 1). Standard institutional treatment policies included long-term hormone ablation for patients with metastatic prostate cancer or for a palliative approach to locally advanced disease; for attempted curative treatment of high-risk localised disease the combination of hormonal ablation or antiandrogen for 3 years and local pelvic radiotherapy after 1 year was used. Thus all patients had been recommended to have hormone therapy for at least 1 year purely on clinical grounds, and management was not adjusted to conform to our diagnostic protocol or in response to the 6-week bone scan. Additional diagnostic imaging with MRI or positron emission tomography (PET) was not pursued if there was not considered to be an immediate major management implication. Hormone therapy could be either a luteinising hormone-releasing hormone (LH-RH) agonist with an antiandrogen for 4 weeks to counteract early testosterone surge, or full dose antiandrogen alone or combined androgen blockade with an LH-RH agonist and an antiandrogen. A total of 100 men were recruited into the study and 99 were evaluable (mean age: 66.5 years, range: 53–80 years). One patient did not undergo further scans after baseline.

Whole-body bone scintigraphy was performed 3 h after injection of 600 MBq ^{99m}Tc-methylene diphosphonate (MDP). Scans were performed on a dual-head gamma camera with low-energy high-resolution collimators at a table speed of 10 cm/min. Extra spot views were obtained as necessary when required by the supervising nuclear medicine physician. Scans were performed at baseline before starting treatment and repeated 6 weeks and 6 months after commencing hormone therapy. Scans were assessed by one of three experienced nuclear medicine physicians and results reviewed and confirmed at multidisciplinary team meetings attended by nuclear medicine and radiological experts and the latter results used for clinical management and for the purposes of this study if discordance arose. All scan sets were analysed side by side on the same workstation with special care taken to display images at similar intensity settings for normal parts of the skeleton. The baseline scans were assessed qualitatively for the presence or absence of bone metastases. Scans were labelled as equivocal if scintigraphic abnormalities could

Table 1 Description of PSA, Gleason score and staging risk factors as well as frequency of flare in 99 patients according to baseline bone scan findings

Scintigraphic findings	No.	PSA (ng/ml) range (mean)	Gleason score (range)	Stage	No. with flare (%)
Metastases at baseline	22	4.6–4,752 (595)	3+3 to 5+4	T2a N0 to T3b N1	9 (41)
Baseline scan equivocal for metastases	41	5.4–128 (36.1)	3+3 to 5+5	T1c N0 to T3b N1	8 (20)
Normal baseline scan	36	4–178 (36.0)	3+3 to 5+4	T1c N0 to T4 N1	4 (11)

not be confidently categorised as benign or malignant. Abnormalities that were considered typical for benign changes (e.g. adjacent rib fractures, joint-based uptake typical of arthritic or degenerative change) were not included in this category. The 6-week scan was assessed qualitatively for a change in intensity of lesions present on the baseline scan or for the presence of new lesions. The 6-month scan was compared to the baseline and 6-week scans for the intensity and number of skeletal lesions. A flare was recorded if there was an increase in intensity or number of lesions between baseline and 6 weeks and a subsequent reduction in intensity or number at 6 months (Fig. 1). Any scan that showed a progressive increase in intensity or number of lesions over 6 months with a continued rise in PSA was labelled as progressive disease unresponsive to hormone treatment.

Results

Positive baseline scan: 22 patients had unequivocal evidence of skeletal metastases on the baseline scan. Of these, nine (41%) showed a flare response on subsequent bone scans by the above criteria and none showed progressive disease unresponsive to hormones during the 6-month period (Fig. 1).

Negative baseline scan: of the 36 patients considered at high risk who had a normal baseline scan, 4 (11%) became positive at 6 weeks with typical features of bone metastases or new lesions that were subsequently confirmed by other imaging to be metastatic (Fig. 2).

Equivocal baseline scan: 41 patients had baseline bone scans that showed abnormalities in which the features were equivocal and not regarded as typical for bone metastases or for benign skeletal pathology. Of these, eight (20%) showed the flare phenomenon (Table 1). Six of these were confirmed as metastatic disease on other imaging (radiographs, CT or MRI) (Fig. 3) and one showed progressive skeletal disease on subsequent bone scans. One patient had a flare response in a solitary first rib lesion that other imaging, including radiographs and CT scan, was unable to confirm. He developed further skeletal metastases and a rise in PSA 8 months later. Of this group of 41 patients, 33 did not show the flare phenomenon; 2 of these 33 developed skeletal metastases 14 months later. The remaining 31 did not develop metastases on follow-up ranging from 12 to 72 months

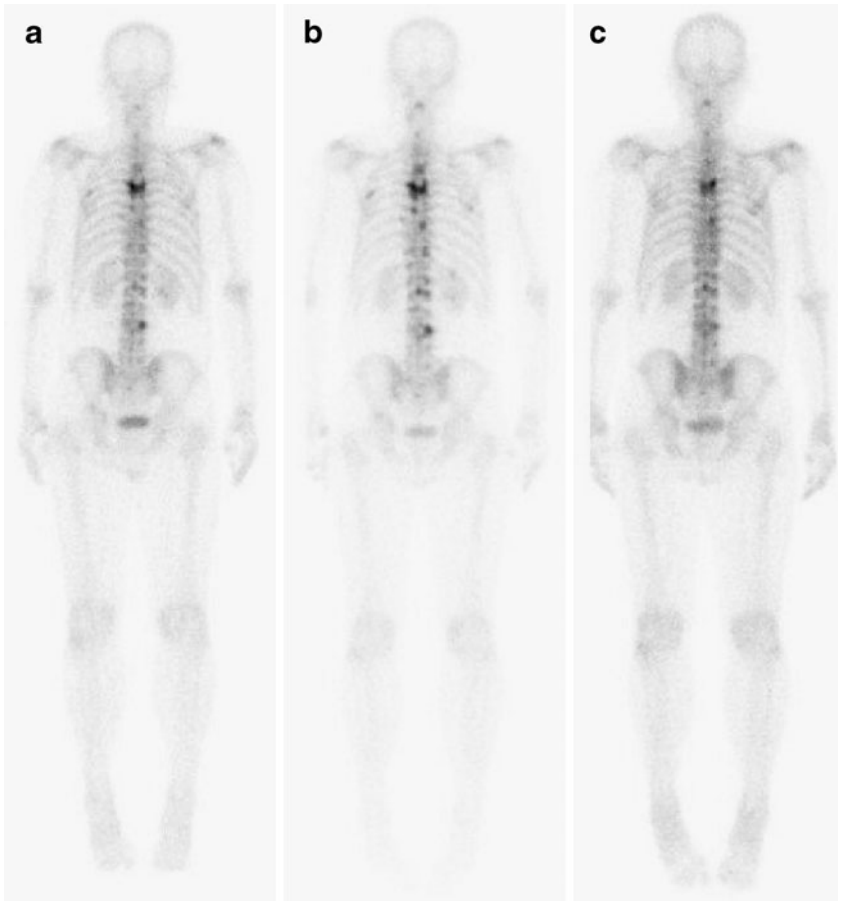

Fig. 1 ^{99m}Tc-MDP bone scans at baseline (**a**), 6 weeks (**b**) and 6 months (**c**) after commencing first-line hormone therapy. There is clear evidence of skeletal metastases on the baseline scan. The metastases show an increase in intensity at 6 weeks which subsequently reduces, typical of the flare phenomenon

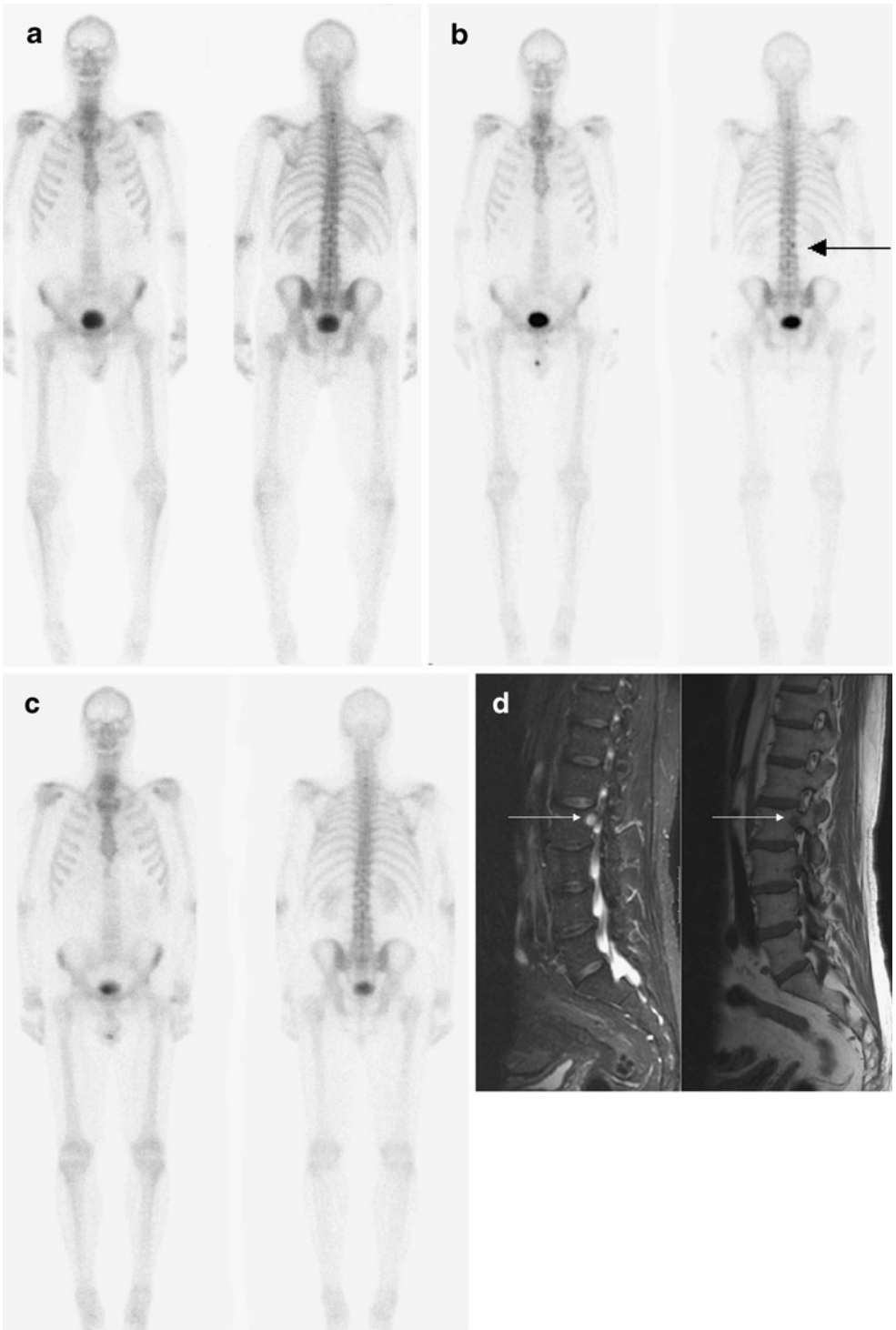

Fig. 2 ^{99m}Tc-MDP bone scans at baseline (**a**), 6 weeks (**b**) and 6 months (**c**) after commencing first-line hormone therapy. The baseline scan is normal but the 6-week scan shows subtle focal increased uptake at L2 on the right (*arrow*). This abnormality has resolved on the 6-month scan. MRI of the spine (**d**) (*left* short τ inversion recovery and *right* T1 images) confirmed typical changes of a metastasis at L2

(median: 36 months). In summary, of the patients who had atypical or equivocal features on the baseline bone scan, seven of eight that showed a flare had bone metastases confirmed and one developed metastases at other sites after 8 months. Two patients without a flare developed metastases in the follow-up period.

Discussion

Correct staging of prostate cancer is crucial for guiding management decisions. Curative treatment options rely on the absence of distant metastases, and as the skeleton is one of the most frequent metastatic sites it is common practice

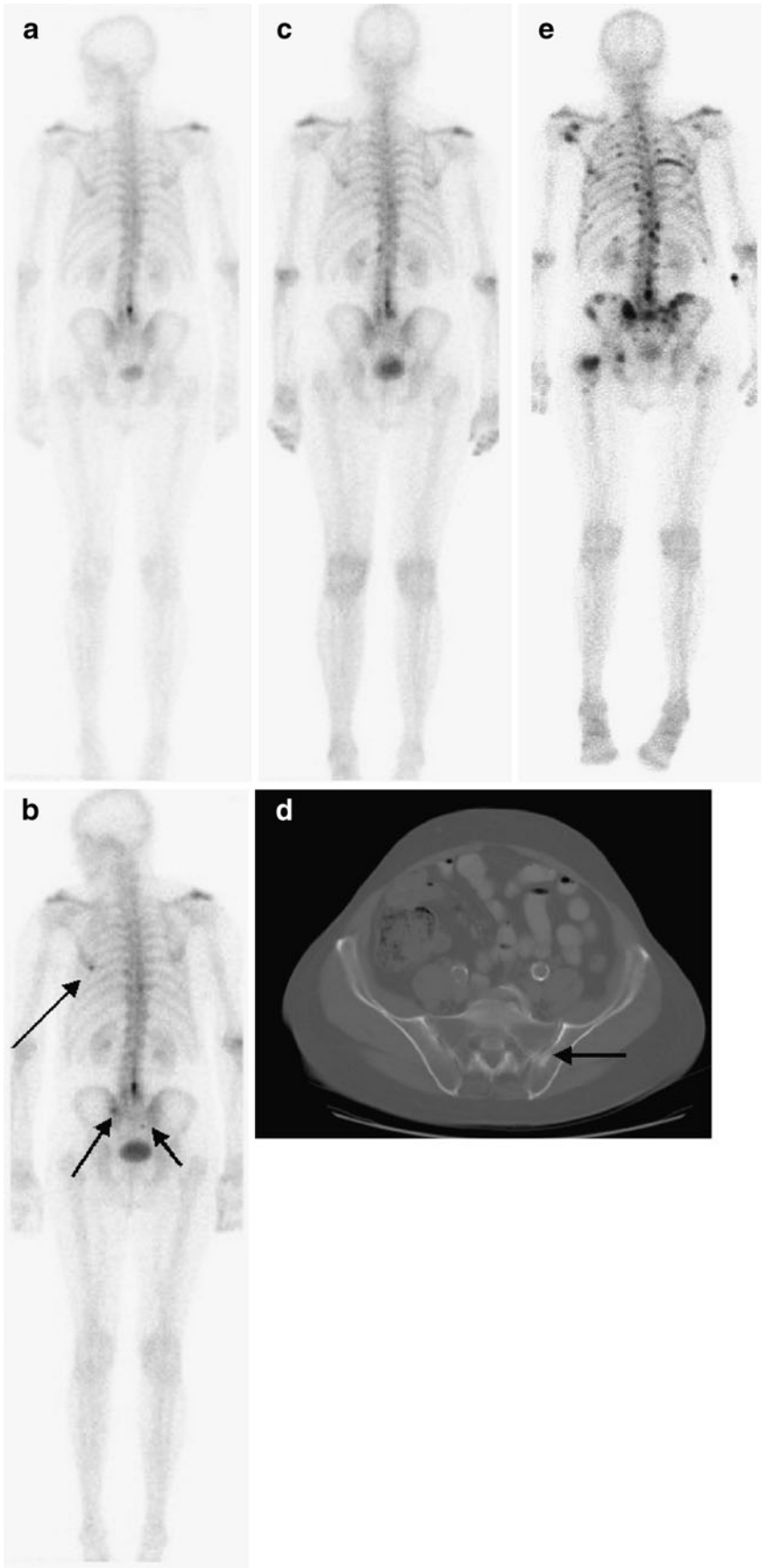

Fig. 3 ^{99m}Tc-MDP bone scans at baseline, 6 weeks and 6 months after commencing first-line hormone therapy. The baseline scan (**a**) shows focal activity in the lower lumbar spine in which it was not felt possible to differentiate a metastasis from benign degenerative changes. The 6-week scan (**b**) shows new lesions in the sacrum, left sacroiliac region and the left seventh rib which then showed a subsequent reduction in intensity at 6 months (**c**) in keeping with a flare. A CT scan (**d**) confirmed a focal sclerotic lesion consistent with a metastasis in the left sacroiliac region. Subsequently the patient developed progressive disease in the skeleton at 1 year (**e**)

to assess the skeleton in all those considered at increased risk [13, 14]. Due to the sensitivity, availability and relatively low cost, this is usually performed with bone scintigraphy. However, bone scintigraphy is not ideal as it is recognised that skeletal metastases may not be detected when the metastatic volume is low [1], when confined to the bone marrow without significant osteoblastic activity, or that false-positive scans can result from coincidental benign skeletal pathology [2].

Scintigraphic bone flare was first described in relation to systemic treatment of metastatic breast cancer in the 1970s [3, 4] and is a recognised phenomenon in patients receiving systemic chemotherapy or hormone therapy in breast [5, 7–9], prostate [6, 10, 11] and other cancers. Its presence may even predict a good treatment response when observed [7], and it is important that physicians are aware that observation of new lesions or increased isotope uptake early after initiation of systemic treatment may not indicate progression of malignant disease.

In this study of patients with prostate cancer starting first-line hormone therapy, 9 of 22 (41%) who had bone metastases at baseline showed the scintigraphic flare phenomenon. Of the remaining patients considered at high risk of bone metastases but with normal baseline scintigraphy, 4 of 36 (11%) showed a flare and in those who had atypical or equivocal bone scan lesions, 8 of 41 (20%) showed a flare. This detection of metastases has implications for management as there is no evidence to support routine prostate radiotherapy in patients with metastatic prostate cancer, whereas radiotherapy is indicated in those with locally advanced disease but no metastases [15].

Overall, 21 of the study population of 99 patients (21%) showed a flare phenomenon. This is a higher proportion of flare reactions than previous reports in patients with prostate cancer and known metastases. Levenson et al. reported 23% [11] and Pollen et al. reported 6% [6] of patients with known metastatic disease showing a flare after combination chemotherapy or hormone therapy and Johns et al. reported 19.2% in patients receiving the LH-RH analogue, leuprolide [10]. All of these studies scanned patients at least 3 months following initiation of treatment. In our study we performed the second scan at 6 weeks and it is possible that some scintigraphic flares begin to resolve by 3 months and that the earlier 6-week time point is more sensitive for the detection of flare. Early bone scan flare before 2 months has previously been described in prostate cancer [16] and although it is uncertain whether this earlier time point for flare would be seen in other types of cancer where osteoblastic metastases do not predominate, it is supported by biochemical data reported by Coleman et al. who showed a peak in bone-specific alkaline phosphatase flare at 1 month in patients with metastatic breast cancer [7]. Care was taken in our study to display serial images at the same intensity settings, but detecting changes in intensity of lesions has a subjective component and it is possible that quantitative or semiquantitative methods to assess changes in uptake may be an even more sensitive way of detecting the flare phenomenon [16].

In our study, 4 of 36 patients with high-risk disease showed the appearance of new bone scan lesions at 6 weeks following a negative baseline scan. All four had bone metastases confirmed by other imaging. The appearance of new lesions as part of the flare response was first described in patients with breast cancer [5]. It is assumed that previously occult lesions become visible due to increased osteoblastic healing as part of the flare phenomenon. In practice, other imaging methods, particularly MRI of the spine, may also be used when initial bone scintigraphy is negative in high-risk patients but is usually limited in anatomical extent [1]. However, it is now possible to perform rapid whole-body MRI acquisitions and although this would appear to be complementary, it is not clear that this method is superior to bone scintigraphy [17]. In patients being treated with hormone therapy, rescanning at 6 weeks remains a potential method to improve bone scintigraphy sensitivity in those at high risk of metastatic disease.

Focal areas of uptake on a bone scan are not necessarily specific for metastatic disease, and this lack of specificity may lead to problems with interpretation, particularly in a relatively elderly population where coexistent skeletal pathology is common. Correlative imaging with radiographs, CT or MRI may be helpful, but there remain some patients in whom bone metastases cannot be definitively excluded. In this study, 41 patients had abnormalities on baseline bone scintigraphy that were either atypical or equivocal and in whom bone metastases could not be excluded. Eight of these (20%) showed a flare at 6 weeks, with seven having metastases confirmed and the other patient developing metastases at other sites within 8 months. The presence of a flare therefore has the potential to improve specificity of bone scintigraphy in a proportion of patients.

Conclusion

We found evidence of scintigraphic flare on repeat bone scan at 6 weeks in prostate cancer patients starting on first-line hormone treatment relatively frequently (21% of the whole population or 41% of those with bone metastases at baseline), compared to previous studies which rescanned at least 3 months after starting treatment.

The presence of a scintigraphic flare after commencing anticancer treatment is specific for bone metastases. A flare at 6 weeks in high-risk patients with prostate cancer who have negative baseline BS, or non-specific abnormalities,

can improve the diagnostic accuracy of bone scintigraphy and could potentially lead to changes in management.

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Conflicts of interest None.

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