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·*Original Article*·

When is a bone scan study appropriate in asymptomatic men diagnosed with prostate cancer?

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Abstract

Aims: To determine when a bone scan investigation is appropriate in asymptomatic men diagnosed with prostate cancer. **Methods:** Between November 2005 and July 2006, 317 men with prostate cancer underwent a bone scan study; 176 men fulfilled the inclusion criteria. Prostate-specific antigen (PSA) cut-offs as well as univariate and multivariate logistic regression analyses using digital rectal examination finding, biopsy Gleason scores and age were performed to determine when a bone scan study is likely to be of value. **Results:** Only 1/61 men (1.6%) with a serum PSA ≤ 20 ng/mL had a positive bone scan. However, 2/38 men (4.7%) with a serum PSA 20.1–40.0 ng/mL, 3/20 men (15%) with a serum PSA 40.1–60.0 ng/mL, 7/19 men (36.8%) with a serum PSA 60.1–100.0 ng/mL and 19/38 men (50%) with a serum PSA > 100.0 ng/mL had positive bone scans. Univariate and multivariate logistic regression analyses were uninformative in these groups. **Conclusion:** Based on our findings, a bone scan is of limited value in asymptomatic prostate cancer patients presenting PSA ≤ 20 ng/mL. Therefore, this investigation can be eliminated unless a curative treatment is contemplated. Furthermore, digital rectal examination finding, biopsy Gleason score and age are unhelpful in predicting those who might harbor bone metastasis. *(Asian J Androl 2008 Nov; 10: 890–895)*

Keywords: prostate cancer; bone scan; asymptomatic; prostate-specific antigen

1 Introduction

Prostate cancer is the most common cancer in men in the UK and is responsible for 19% of all newly diagnosed male cancers [1]. In 2005, 9 000 cancer deaths were attributed to prostate cancer in England and Wales [2]. There has been a rapid increase in the incidence of prostate cancer over the past 20 years, this being largely attributed to the routine availability of serum prostate-specific antigen (PSA) as a tumor marker. PSA-based screening advances the diagnosis of prostate cancer and leads to a significant reduction in the stage at diagnosis [3].

Prostate cancer has a tendency to metastasize to bone. On presentation, up to 14% of patients have bone metastasis [4]. As a result, radionucleotide bone scanning plays a central role in the staging of prostate cancer. In addition to being the most sensitive method of detecting metastasis [5, 6], bone scans also add prognostic value to patient outcome [7, 8]. Before PSA testing, bone scan imaging was regarded as the primary means of staging

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advanced disease.

Serum PSA has been reported to be the single most useful predictor of metastasis detected on radionucleotide scanning in patients with prostate cancer [9, 10]. Previous authors have suggested a serum PSA rising above 10 ng/mL as an appropriate cut-off value to initiate bone scan investigations in patients with newly diagnosed prostate cancer [8, 11–16]. Furthermore, tumor grade and clinical tumor stage have been successfully used, together with serum PSA, as indicators to predict which patients require investigations for bone metastasis [11, 16–19]. However, other studies suggest that an appropriate PSA cut-off for these patients may be 15 ng/mL or higher [9–10, 18–21], irrespective of tumor stage and grade [9]. Recent European Association of Urology (EAU) guidelines state that in asymptomatic patients with well or moderately differentiated newly diagnosed prostate cancer presenting with a serum PSA < 20 ng/mL, a bone scan may not be indicated [22]. In today's cost conscious National Health Service (NHS), we must consider that bone scans are an expensive investigation (in our institute they cost USD720), and therefore should only be considered if the result will have a strong impact on the management plan. This puts strong emphasis on the need for us to suitably identify those patients who do not require unnecessary investigations. To this end, we determined in a retrospective study PSA cut-offs that are appropriate for bone scan investigation in asymptomatic men with newly diagnosed prostate cancer.

2 Materials and methods

The Leicester General Hospital (UK) bone scan database was used to identify 317 consecutive patients with a diagnosis of prostate cancer who, between November 2005 and July 2006, underwent a bone scan study for the evaluation of suspected bone metastasis. The decision to perform a bone scan was made by urologic clinicians working at our institution, and was irrespective of serum PSA level, digital rectal examination (DRE) finding and Gleason grade. Patients were only included in our study if they were asymptomatic for bone metastasis, had not previously undergone curative treatment and had not received hormonal therapy.

The primary outcome measured was the presence of bone metastasis on bone scan investigation. All radionucleotide bone scans were performed with ^{99}technetium hydroxy methylene diphosphonate and interpreted by a specialist radiologist. Radiological investigations were interpreted as negative or positive for evidence of bone metastasis with reference to plain skeletal radiographs and, if available, computed tomography (CT) or magnetic resonance images (MRI).

Data on serum PSA levels, clinical T stage (tumor, nodes, metastases [TNM] classification) and Gleason score were obtained from patients' case records. PSA readings were carried out using PSA immulite 2000 automated immunoassay analyzers (Diagnostic Products Corporation, Los Angeles, CA, USA). Tissue for histology was obtained either by transurethral resection or transrectal needle biopsy and subsequently assessed by consultant histopathologists. Patients who did not have tissue histology were clinically diagnosed with prostate cancer on the basis of a persistent and significantly elevated PSA (> 40 ng/mL) and abnormal digital rectal examination findings. Patients with a PSA (< 40 ng/mL) and no tissue histology who underwent a bone scan during this period were excluded from the study. Patients were stratified according to age, PSA level, Gleason score and clinical tumor stage.

PSA cut-offs (≤ 10 ng/mL, 10.1–20 ng/mL, 20.1–40 ng/mL, 40.1–60 ng/mL, 60.1–100 ng/mL and > 100 ng/mL), as well as univariate and multivariate logistic regression analysis using DRE staging, biopsy Gleason scores and age, were performed to determine when a bone scan study is likely to be of value in men with newly diagnosed prostate cancer. The data analysis and statistical software program Stata 8 (StataCorp, College station, TX, USA) was used for all statistical analysis.

3 Results

Of 317 patients, 176 fulfilled the inclusion criteria for this study. The rest were excluded owing to either being symptomatic for bone metastasis, having incomplete case notes, inconclusive bone scans or having received previous curative or hormonal therapy for prostate cancer. The mean patient age was 72 years (range: 54–96 years) (Table 1). A total of 32 out of 176 (18.2%) patients showed evidence of bone metastasis on bone scan investigation.

Of 176 patients, 154 (87.5%) underwent core needle biopsy and histological examination that demonstrated adenocarcinoma of the prostate. Biopsy Gleason score was available for all of these patients (Table 1). The remaining 32 patients who did not have tissue histology were

clinically diagnosed with prostate cancer on the basis of a persistent and significantly elevated PSA (> 40 ng/mL) and abnormal DRE findings.

None of the 16 patients with serum PSA ≤ 10 ng/mL had evidence of skeletal metastasis on bone scan and only 1/45 (2.2%) with a serum PSA 10.1–20 ng/mL had a positive bone scan. The only patient with positive bone scan results and serum PSA ≤ 20 ng/mL had Gleason score 9 (4 + 5) and DRE stage T2b disease. However, 2/38 men (5.3%) with a serum PSA 20.1–40.0 ng/mL, 3/20 men (15.0%) with a serum PSA 40.1–60.0 ng/mL, 7/19 men (36.8%) with a serum PSA 60.1–100.0 ng/mL and 19/38 men (50.0%) with a serum PSA > 100.0 ng/mL had positive bone scans. The negative predictive value for these PSA cut-offs are presented in Figure 1. Univariate and multivariate logistic regression analyses using the abovementioned PSA cut-offs, DRE findings and Gleason score were all uninformative in these groups.

Table 1. Characteristics of study group. PSA, prostate-specific antigen.

	Number	% of total
Gleason score		
6	31	17.6
7	68	38.6
8	20	11.4
9	32	18.2
10	0	0
Unknown	25	14.2
Tumor stage		
T1	35	19.9
T2	49	27.8
T3	32	18.2
T4	6	3.4
Tx	54	30.7
Serum PSA (ng/mL)		
≤ 10	16	9.1
11–20	45	25.6
21–40	38	21.6
41–60	20	11.4
61–100	19	10.8
> 100	38	21.6

Using PSA cut-offs alone, we found the negative predictive value of a serum PSA ≤ 10 ng/mL for the absence of skeletal metastasis to be 100% and serum PSA 10.1–20 ng/mL to be 97.8%. When considering Gleason score in these groups, none of the patients with PSA ≤ 20 ng/mL and well (Gleason score 2–4) or moderately differentiated cancer (Gleason score 5–7) showed evidence of metastasis (Table 2).

Using the criterion that bone scans should be omitted with serum PSA ≤ 20 ng/mL would have a negative predictive value of 98.4%. Using this criterion, 61 (34.7%) scans would have been omitted. The cost of performing one scan is USD720, therefore leading to a saving of USD43 920 over a 9-month period.

4 Discussion

We conducted a small retrospective study to determine whether a PSA cut-off of 20 ng/mL can be justi-

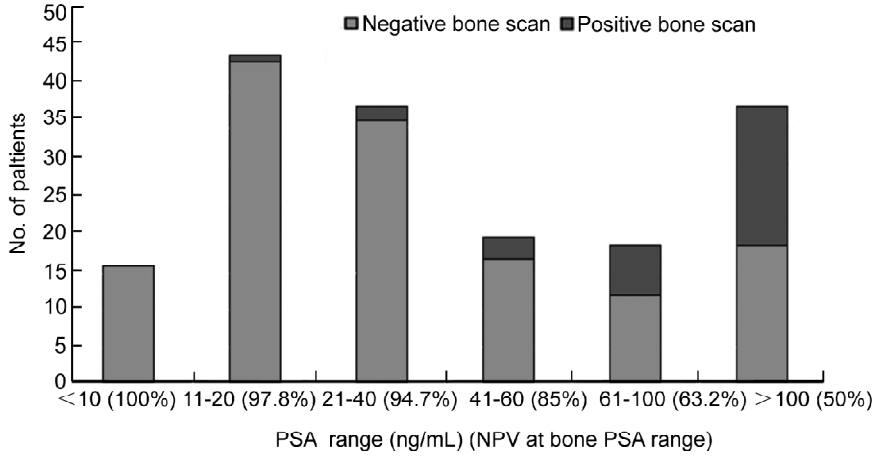

Figure 1. Bone scan results and negative predictive value (NPV) at given prostate-specific antigen (PSA) ranges.

fied for performing a bone scan in patients with newly diagnosed prostate cancer and no symptoms of bone metastasis. Our data support previously published studies demonstrating the close relationship between serum PSA level and bone scan positivity [8–16]. In the present study, only 1/61 (1.6%) patients with a serum PSA ≤ 20 ng/mL had a positive bone scan. Therefore, the negative predictive value of excluding scans with a PSA cut-off ≤ 20 ng/mL was 98.4%. However, if the threshold PSA value was increased to values greater than 20.0 ng/mL, bone metastasis could not be sufficiently excluded (Figure 1).

Tumor stage and Gleason grade have been suggested as useful predictors of bone scan positivity [11, 13, 17–19]. Although the risk of a positive bone scan increases with advanced stage and higher grade, tumor stage and grade are poor independent negative predictors of positive bone scans [13]. In our study, DRE finding and biopsy Gleason score were unhelpful in predicting patients who may harbor metastasis (Tables 2 and 3). This may be a reflection of the low number of patients with high grade or advanced stage disease present in this study. However, the only patient with a positive bone scan and serum PSA ≤ 20.0 ng/mL in our study had Grade 3 (Gleason 4 + 5) cancer.

Table 2. Bone scan results for prostate-specific antigen (PSA) cut-offs and Gleason grade.

PSA (ng/mL)	Gleason score	Negative	Positive
≤ 10	6	6	0
	7	5	0
	8	2	0
	9	3	0
	Not available	0	0
11–20	6	12	0
	7	25	0
	8	3	0
	9	4	1
	Not available	0	0
21–40	6	8	0
	7	20	1
	8	3	1
	9	5	0
	Not available	0	0
41–60	6	2	0
	7	5	2
	8	2	0
	9	3	1
	Not available	5	0
61–100	6	2	0
	7	3	1
	8	1	0
	9	1	3
	Not available	5	3
> 100	6	1	0
	7	4	2
	8	5	3
	9	4	7
	Not available	5	7

Table 3. Bone scan results for prostate-specific antigen (PSA) cut-offs and clinical stage.

PSA (ng/mL)	Clinical stage	Negative	Positive
≤ 10	T1	4	0
	T2	8	0
	T3	0	0
	T4	0	0
	Tx	4	0
11–20	T1	13	0
	T2	20	1
	T3	0	0
	T4	0	0
	Tx	11	0
21–40	T1	9	0
	T2	10	1
	T3	8	1
	T4	0	0
	Tx	9	0
41–60	T1	1	0
	T2	5	0
	T3	5	2
	T4	0	1
	Tx	6	0
61–100	T1	4	1
	T2	0	0
	T3	2	2
	T4	0	1
	Tx	6	3
> 100	T1	2	1
	T2	1	3
	T3	6	6
	T4	3	1
	Tx	7	8

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As a result of the introduction of PSA as a tumor marker for prostate cancer, the majority of patients now present with a low serum PSA. Oesterling *et al.* [12] studied 2 064 patients between 1989 and 1990. In their study, 39% of patients had a serum PSA ≤ 10 ng/mL, compared with only 9.1% in the present study. The lower proportion of patients in the present study with serum PSA ≤ 10 ng/mL may reflect that current clinical practice has been influenced by earlier studies and guidelines [8, 11–17]. Subsequently, clinicians may have been biased against requesting bone scans in patients with lower PSA level, resulting in the majority of bone scan investigations being omitted in patients presenting with PSA < 10 ng/mL. This would account for the low proportion of patients in this group.

PSA thresholds to determine when a bone scan is required have been calculated in previous studies when an appropriately high negative predictive value (NPV) for that given PSA cut-off is recorded. As evident in these studies, there are differences in the negative predictive value at given PSA thresholds [8–16, 18–21]. This may be indicative of the different population groups studied by different authors. A higher percentage of positive bone scans at equivalent PSA thresholds are recorded in studies with a higher percentage of locally advanced prostate cancer [8, 9, 17, 18]. In a study by Bruwer *et al.* [17], 74% of patients were recorded as having stage T3/4 disease. A high proportion of patients with locally invasive cancer in this study was associated with a low NPV (80%) for serum PSA ≤ 20 ng/mL when predicting positive bone scan results [17]. In comparison, studies with a lower percentage of locally advanced tumors show higher NPV of serum PSA ≤20 ng/mL. Haukaas *et al.* [8] studied a group of patients where 38% had stage T3/4. In their study, the NPV of serum PSA ≤ 20 ng/mL was 94% [8]. Similarly, for an identical PSA cut-off, O'Sullivan *et al*. [18] reported an NPV of 93.7% in a group where 33% had T3/4 disease. In a study by Chybowski *et al*. [9], 22% had stage T3 and no patients had T4 disease, and their subsequent NPV for serum PSA <20 ng/mL was 99.7%. In the present study, 22% of patients had T3/4 disease, which is similar to Chybowski *et al*. [9] and, interestingly, our NPV for serum PSA < 20 ng/mL is also similar to their study. Advanced clinical tumor stage has been reported to correlate with bone scan positivity for metastasis and therefore may account for some of these variations in NPV from study to study.

Previous authors have questioned the role of omitting bone scan investigations in patients with low serum PSA. Although Wolff *et al.* [22] reported that 10/237 patients with PSA < 20 ng/mL had positive bone scans for metastasis, their study did not exclude patients with symptoms caused by bone metastasis. On further evaluation, all of their patients with serum PSA < 20 ng/mL and positive bone scans were symptomatic for bone metastasis. Bruwer *et al.* [17] concluded that bone scans could not be excluded in patients with prostate cancer on the basis of a low serum PSA, but this was on the basis of results from a population with tumor characteristics significantly different to most other studies.

Our results strengthen reports from previous authors that state that a PSA of 20 ng/mL is an appropriate cut-off at which to instigate bone scan investigation in newly diagnosed prostate cancer [20, 23]. However, to date, only retrospective studies in this area have been carried out. On reviewing these studies it is evident that differences in the populations studied at the various institutions, and selection bias produced as a result of conducting retrospective studies, indicate that large multi-centred prospective studies are required to clarify these PSA thresholds.

In conclusion, bone scans have been routinely performed to confirm or exclude bone metastasis in patients with clinically localised prostate cancer with a serum PSA value ≥ 10 ng/mL when curative therapy is anticipated. The rationale behind this is to avoid unnecessary procedures in men with carcinoma of the prostate who are unlikely to harbor metastatic disease. However, bone scans are not only time consuming but also expensive. The most significant finding in our study was the NPV of 98.4% for a PSA ≤ 20 ng/mL and a positive bone scan. Therefore, our study demonstrates that a staging radionuclide bone scan in a patient with untreated prostate cancer and a presenting serum PSA ≤ 20.0 ng/mL in the absence of symptoms suggestive of bone metastasis is unlikely to be informative, and should be omitted. Implementation of these criteria against those previously used may have considerable impact on cost saving and waiting times. In patients with a serum PSA > 20.0 ng/mL, being considered for active curative treatment, or those with symptoms suggestive of bone metastasis regardless of PSA value, a bone scan is justified.

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