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Published in:
BJU International

BJU International (2001), **88**, 226–230

Routine bone scans in patients with prostate cancer related to serum prostate-specific antigen and alkaline phosphatase

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Objective To evaluate the need for a bone scan as a routine staging procedure in patients with newly diagnosed prostate cancer in relation to serum prostate-specific antigen (PSA) and alkaline phosphatase (ALP) levels, and thus determine whether a reduction of the use of this staging method is possible in patients with a low probability of osseous metastasis.

Patients and methods The results of bone scans were related retrospectively to levels of serum PSA and ALP in 363 patients with prostate cancer newly diagnosed between 1989 and 1997.

Results Of 363 consecutive patients, 111 had a positive bone scan. In 19 of 144 (13%, 'missed diagnosis') patients with a PSA level of <20 ng/mL the bone scan was positive. In 125 patients (49%, 'false-positives') with a PSA level of >20 ng/mL the bone scan was negative. A threshold level of 100 U/L for ALP gave a better balance for the number of 'false-positives' and 'missed diagnosis'. ALP values correlated better with an abnormal bone scan than did PSA levels; ALP levels of >90 U/L indicated a 60% chance for the presence of bone metastases.

Conclusion Patients with newly diagnosed and untreated prostate cancer should undergo bone scintigraphy if there is bone pain or if ALP levels are >90 U/L. Recent reports discourage the routine use of a bone scan when the serum PSA level is <20 ng/mL. However, the present series suggests there is a greater chance of a positive bone scan in patients with low PSA levels; these findings need further confirmation.

Keywords prostate cancer, staging bone scan, serum prostate-specific antigen, serum alkaline phosphatase

Introduction

Prostate cancer is now the most common cancer and the second leading cause of death from cancer among men in the USA and Europe [1], although a large proportion of the increase seems to represent subclinical cases which formerly remained undetected [2]. With the ageing of the population, the public health burden of prostate cancer will certainly increase in the future with the greater use of diagnostic procedures. The primary objective of clinical staging of prostate cancer is to ensure the patient has the most appropriate treatment modality.

Traditionally, bone scintigraphy is frequently used to detect skeletal metastases. Currently, serum PSA is the marker of choice in prostatic carcinoma. Although there is a direct correlation between the serum PSA concentration and clinical stage, PSA (or its derivatives) is not sufficiently reliable to determine the clinical stage in individual patients [3]. Alkaline phosphatase (ALP), one of the older biochemical tools for investigating and monitoring prostate cancer, has stood the test of time and remains a reliable indicator of osteoblastic activity, as in bone metastases [4]. Because bone scans are normal in the vast majority of patients with newly diagnosed prostate cancer, normal or minimal elevations in serum PSA ($\leqslant 20$ ng/mL) might identify a subgroup of patients with a low risk for a positive bone scan [5]. If the PSA and ALP levels are low this is a time-consuming and expensive staging investigation which might be omitted because of the very low risk of positivity [5,6]. This will have an obvious and significant effect in reducing costs.

The purpose of the present study was to determine whether serum PSA and ALP, and clinical variables such as tumour stage (determined by DRE) and tumour grade from the biopsy specimen, would identify a group of patients with a low probability of having osseous metastases, and thus safely eliminate these scans.

Patients and methods

In all, 363 consecutive patients (median age 72 years, range 48–97) newly diagnosed with prostate cancer and referred for bone scans were reviewed retrospectively, for the period 1989–1997. Clinical charts from these

Accepted for publication 18 April 2001

selected patients were reviewed by one physician. Patients were excluded if they had previous therapy for prostatic disease including androgen ablation therapy, radiation therapy or prostate surgery. Similarly, any patient with newly diagnosed prostate cancer who had abnormal liver function or a lesion on the bone scan suspicious of trauma or of degenerative origin and signs of Paget's disease were excluded. A serum PSA and ALP determination within 2 months before the bone scan was mandatory.

The presence of bone pain was assessed by reviewing the medical history; if no bone symptoms were reported they were recorded as absent. An elevated ALP or bone pain was considered to be a possible indicator of bone metastases. Based on the bone scan results and after comparing areas showing increased skeletal activity with available radiographs, the 363 patients were divided into two groups, i.e. 111 patients with bone metastases, termed 'bone scan-positive', and 252 patients with no bone metastases, termed 'bone scan-negative'.

Bone scintigraphy was carried out as follows; 3–4 h after an intravenous injection with 700 MBq ^{99m}Tc-methylene diphosphonate, anterior and posterior whole-body images were obtained. Detailed images were acquired when considered necessary. With no knowledge of the corresponding biochemical data, the scans were interpreted by the nuclear medicine consultant as negative or positive for skeletal metastases, or as intermediate. In the latter case additional X-ray investigations (plain X-rays, CT) of the relevant 'hot spots' were undertaken to confirm or exclude skeletal metastases.

Clinical data on tumour stage, grade, serum PSA and ALP levels were obtained from the medical charts. Clinical tumour stage was assessed with a DRE undertaken by a urologist and categorized according to the TNM staging system [7]. In 12 patients a clinical tumour stage could not be given and in four there were no data on tumour grade. The diagnosis of prostate cancer was established either by TRUS-guided core biopsy or fine-needle aspiration biopsy, or after TURP for assumed BPH. Histological grades were determined according to the WHO grading system as either well differentiated (G1), moderately differentiated (G2), or poorly differentiated (G3) [8].

Serum PSA concentrations were measured using a equimolar immunoassay from 1989 to 1995 (IMx PSA kit, Abbott Laboratories, UK) and from 1995 to 1997 with the Immulite PSA kit (DPC, Breda, The Netherlands); similar and interchangeable results were obtained with either assay [9]. The normal range for both assays was 0.0–4.0 ng/mL. Serum ALP was measured using a standard commercially available assay, the normal range in our laboratory being 30–110 U/L.

Serum PSA and ALP concentrations are presented as the mean, median and overall range. The serum PSA and ALP distribution for the bone scan groups were compared using the Mann–Whitney *U*-test, with $P < 0.05$ considered to indicate statistical significance. The distribution of tumour stage and grade with positivity of the bone scan is given in cross tables. To determine the most advantageous threshold values for serum PSA and ALP with bone scan findings the relative sensitivity and specificity of the diagnostic test was compared using ROC curves.

Results

For the whole group the mean (median, range) serum PSA level was 239 (31, 0.04–5726) ng/mL and the serum ALP level 144.5 (79, 30–4887) U/L. The number of patients with positive bone scans results for the serum PSA in different ranges is shown in Table 1. The median value of the PSA and ALP concentration in relation to the bone scan results are also given in Table 1. Bone scan-positive patients had a statistically higher level of PSA and ALP than the bone scan-negative patients ($P < 0.001$).

The clinical stage at diagnosis was recorded for 351 patients; most (53%) presented with T3 disease and 7% had T4 disease (Table 1). Tumour grade was recorded for 159 patients; more than half of those with poorly differentiated tumours (55%) had a positive bone scan (Table 1). The risk of having a positive bone scan increased with advancing tumour stage and grade (both $P < 0.001$).

Using ROC curves for all patients, ALP had the best overall correlation with the presence of bone metastases (area under the curve 0.83) compared with PSA (0.76) although the difference between the curves was not significant ($P = 0.26$; Fig. 1a).

Of 144 patients with prostate cancer and a PSA level of <20 ng/mL, 19 had a positive bone scan (13%). Of these 19 patients 14 had PSA values of <10 ng/mL and five had values of 10–20 ng/mL. The relationship between the bone scan results and tumour grade of those patients with PSA levels of <20 ng/mL is given in Table 1.

A serum ALP determination was available in 119 of the men with a PSA level of <20 ng/mL; the distribution of these patients and their bone scan results are shown in Table 1. Of the patients with a normal ALP level, 7% had a positive bone scan, compared with eight of 18 with an abnormal ALP level ($P < 0.001$).

The ROC curves for PSA and ALP with bone metastatic status were significantly different ($P = 0.007$), with areas under the curve of 0.445 for PSA and 0.734 for ALP (Fig. 1b).

Table 1 The serum PSA and ALP levels for patients with positive and negative bone scans, the relationship between the bone scan results and PSA level for all 363 patients, the clinical stage at diagnosis in 351 patients, tumour grade at diagnosis in 359 patients, tumour grade in 144 patients with a PSA level of < 20 ng/mL, and the ALP level for 119 patients with a PSA level of < 20 ng/mL

	Bone scan	
Variable	*positive*	*negative*
No. of patients	111	252
Median (range):		
PSA, ng/mL	130 (0.04–5726)	20 (0.04–894)
ALP, U/L	134 (48–4887)	69 (30–258)
No. (% of category):		
PSA (ng/mL)		
≤ 10	14 (16)	75 (84)
10.1–20	5 (8)	51 (92)
20.1–50	11 (15)	63 (85)
> 50	81 (57)	62 (43)
Clinical stage*		
T1	4 (7)	51 (93)
T2	9 (10)	79 (90)
T3	75 (41)	110 (59)
T4	17 (74)	6 (26)
Tumour grade*		
Well	19 (17)	91 (83)
Moderate	43 (26)	121 (74)
Poor	47 (55)	38 (45)
Tumour grade in patients with PSA < 20 ng/mL*		
Well	4 (7)	53 (93)
Moderate	6 (9)	57 (91)
Poor	9 (38)	15 (62)
ALP level in patients with PSA < 20 ng/mL*		
Normal	7 (7)	94 (93)
Abnormal	8 (44)	10 (56)

*Differences significant at $P < 0.001$.

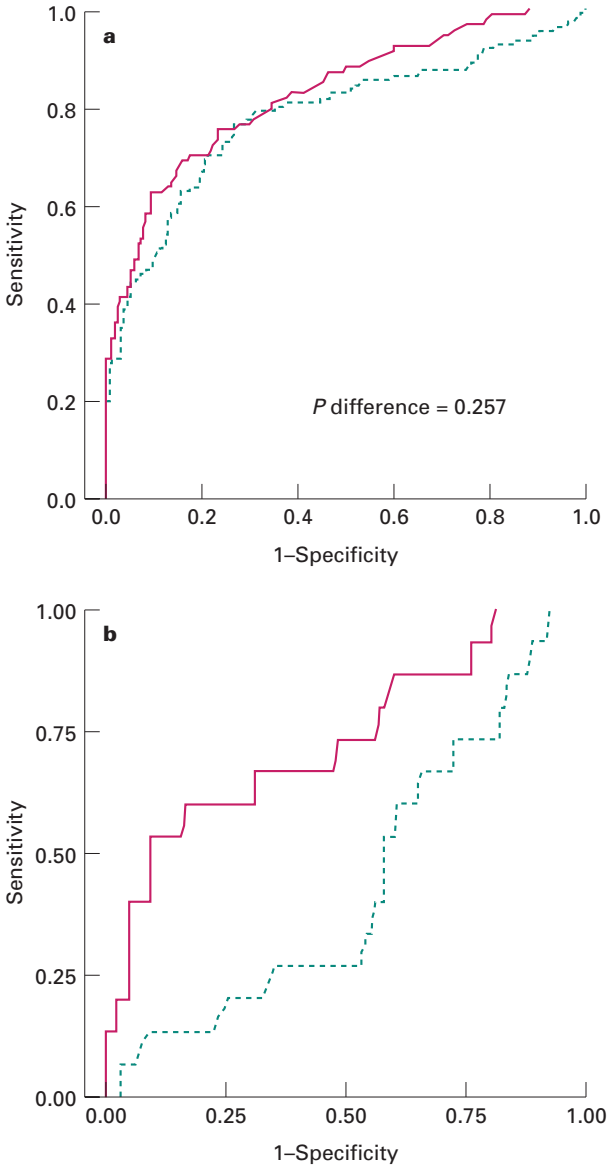

Fig. 1. ROC curves for PSA (green dotted line) and ALP (red solid line) for positive bone scans in **a**, all 363 patients and **b**, patients with a PSA level of < 20 ng/mL.

Discussion

With increased screening for and earlier detection of prostate cancer, the proportion of men needing additional investigations will probably increase. Since the advent of PSA testing, several authors have shown that the PSA level correlates with the relative risk of bone metastases [5,10,11].

Although there are numerous reports addressing bone scan findings in relation to PSA level, in only a few has the serum ALP level also been assessed. ALP is particularly valuable in identifying the subgroup of patients whose metastatic disease relapses while on hormonal treatment, despite a negligible increase in PSA.

In patients with prostate cancer the detection of bone metastases is important for selecting the most appropriate therapy. Because bone scintigraphy is the most sensitive method in clinical practice of detecting these metastases [12–15], it is used frequently at the time of diagnosis. The cost-effectiveness of carrying out routine bone scans only in men with a PSA level of > 10 ng/mL has been shown by Oesterling *et al.* [6,16]. Of 2064 consecutive patients with newly diagnosed untreated prostate cancer and a serum PSA level of < 20 ng/mL, seven (0.8%) had positive results on their bone scan, four of whom had a serum PSA of > 10 ng/mL and five had skeletal pain. Of these seven patients with positive bone scans, only one had a PSA of < 10 ng/mL. At a threshold of 10 ng/mL the observed false-negative rate was 0.5%. Both Chybowski *et al.* [5] and Oesterling *et al.* [16] concluded that a staging bone scan is unnecessary in patients with newly diagnosed

previously untreated prostate cancer, a serum PSA level of $\leqslant 10$ ng/mL and no skeletal symptoms. Recent reports discourage the routine use of a bone scan when the serum PSA level is <10 ng/mL, because this level is a strong negative predictor of a positive bone scan [17]. Many clinicians now limit bone scans to men with a preoperative PSA level of >20 ng/mL and/or bony symptoms, provided the Gleason score is <7 (G1 or G2 tumours) [5,6,16]. This obviously has significant cost-saving implications.

Because it has high sensitivity and a confirmed correlation with tumour burden, various authors attempted to correlate serum PSA concentrations with bone scan findings [5,16,18–21], although these results could not be confirmed in a recent report [22]. The serum PSA concentration provided little information about the presence of bone metastasis and it was doubtful whether a staging radionuclide bone scan could be omitted in patients with a serum PSA value of <10 ng/mL [22].

In the present study the PSA level was <20 ng/mL in 19 (17%) of 111 patients with a positive bone scan (representing metastatic disease). This incidence of bony metastases at this PSA level is higher than previously reported, because there was a high proportion of patients with moderate and poorly differentiated disease. In 59 (63%) of the 94 patients with a positive bone scan the ALP level was also high (>110 U/L). A possible guideline for reducing the need for scans is that in patients with newly diagnosed and untreated prostate cancer bone scintigraphy should be undertaken in those with bone pain or ALP levels of >90 U/L.

In conclusion, ALP levels correlated better than did PSA levels with bone scan results, although not significantly so. All staging bone scan studies in patients with newly diagnosed, untreated prostate cancer and a low serum PSA level are retrospective and consequently may be prone to a possible selection bias. The use of ALP and PSA is only of benefit in patients who are potential candidates for radical treatment, i.e. generally those who are <70 years old, with a PSA of <20 ng/mL and with clinical T2 disease or less. Therefore, a prospective study including this group of patients is needed to confirm the present findings.

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Abbreviations: **ALP**, alkaline phosphatase.