Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated?

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OBJECTIVE

To evaluate the use of radionuclide bone scintigraphy following biochemical recurrence after radical retropubic prostatectomy (RRP) for localized prostate cancer.

PATIENTS AND METHODS

Of 1197 patients undergoing RRP we identified those with biochemical recurrence and who had also had a bone scan. Biochemical recurrence was defined as a prostate specific antigen (PSA) level of ≥0.4 ng/mL. Patients with indeterminate bone scan findings and those in whom the interval between the PSA test and the bone scan was >3 months were excluded. Patient age, PSA level and other relevant pathological details were recorded. Clinical symptoms at the time of bone scan, androgen deprivation after RRP, bone scintigram details and time to recurrence were documented.

RESULTS

Of the 1197 patients, 153 (12.8%) had a biochemical recurrence and 35 (23%) of these had a total of 44 bone scans taken over a mean (sd) follow-up of 70.4 (35.6) months; 34 (77%) bone scans were negative (group 1) and 10 (33%) positive (group 2). In group 1 the mean PSA at the bone scan was 5.2 ng/mL; 76% of the patients had a PSA of <7 ng/mL. In group 2 the mean PSA at the bone scan was 30.7 ng/mL and all patients had a PSA of >7 ng/mL. The only significant difference between the groups was the PSA at the time of the bone scan (P < 0.001).

CONCLUSION

Bone scintigraphy is a sensitive diagnostic tool for detecting prostate cancer metastases to bone. A bone scan in patients with a serum PSA of <7 ng/mL on biochemical recurrence after RRP is unlikely to be positive, whereas a PSA of ≥20 ng/mL is. The presence of skeletal symptoms or a PSA level of >7 ng/mL should prompt the clinician to obtain a bone scintigram.

KEYWORDS
prostate carcinoma, biochemical recurrence, bone scan, radical prostatectomy

INTRODUCTION

PSA is a valuable tool in monitoring patients with prostate cancer [1]; the rate of biochemical recurrence after radical prostatectomy (RP) is 15–40%, depending on several prognostic factors [2,3]. The recurrence may be local or systemic. A recent large series indicated a biochemical recurrence rate of 17% (360/2091); of those who had a recurrence, 66% had biochemical recurrence only, 34% had distant metastasis and 10% had a local recurrence [4]. The most frequent sites of metastasis in prostate carcinoma are lymph node and bone; 90% of patients who die from prostate cancer have bone metastasis [5].

A radionuclide bone scintigram is often requested to detect skeletal metastasis and is the standard initial imaging study for this purpose [6]. In untreated men with prostate cancer, PSA has been shown to be the best predictor of which patients will have a positive bone scan [7]. Most studies that have correlated PSA and bone scan findings have been in patients with clinically organ-confined prostate cancer. There are few reports comparing the PSA level and scan results in patients with biochemical recurrence after surgery.

Small-volume metastatic disease with a minimally elevated PSA is unlikely to be detected by bone scintigraphy [8]. We evaluated the use of radionuclide bone scintigraphy following biochemical recurrence after RP for localized prostate cancer, to correlate the PSA level and the chance of finding bone metastasis on a bone scan.

PATIENTS AND METHODS

We retrospectively reviewed the records of 1197 men who underwent RP by one surgeon (M.S.S) between 1992 and 2003, identifying patients with biochemical recurrence who also had a bone scan. Scintigraphy was requested either by an outside physician/urologist or by our group. The indications for requesting a bone scan in patients with biochemical recurrence after RP were the presence of skeletal symptoms and staging before initiating salvage therapy (e.g. external beam radiation). Biochemical recurrence was defined as a PSA level of ≥0.4 ng/mL [9].

Patients with an indeterminate bone scan and those in whom the interval between the PSA and the bone scan was >3 months were excluded. All patients had a standard bone scan using a 99mTc-labelled agent.

Patient age, PSA, PSA velocity, Gleason score, tumour volume, lymph node involvement, extraprostatic extension (EPE), seminal vesicle invasion (SVI) and surgical margins were recorded. Clinical symptoms at the time of the bone scan, androgen deprivation after RP, bone scintigram details, time to recurrence and the interval between biochemical recurrence and the bone scan result were
documented. Patients were then categorized according to their scan, i.e. group 1 (a negative bone scan) and group 2 (a positive bone scan). The results were assessed statistically using Student’s t-test, the Mann–Whitney U-test and chi-square analysis.

RESULTS

Of 1197 patients, 153 (12.8%) had biochemical recurrence; 35 (23%) of these had a total of 44 bone scans (three who had a bone scan were excluded from the study; one had an indeterminate scan and in two there was >3 months between the PSA assessment and the bone scan). The indications for the bone scan are listed in Table 1. The mean (SD) follow-up after RP was 70.4 (35.6) months. Bone scans were negative in 34 (77%, group 1) and positive in 10 (23%, group 2); the characteristics of the patients are also summarized in Table 1.

In group 1, 76% of the patients had a PSA of <7 ng/mL, and 20 (59%) had androgen deprivation after RP and before the bone scan. No patients had salvage radiation therapy to the pelvis before the bone scan. In group 2 all the patients had a PSA of >7 ng/mL, nine had androgen deprivation and two had salvage radiation therapy to the pelvis before the bone scan. The patient in group 2 with skeletal pain before the scan presented with left shoulder pain and a PSA of 100 ng/mL; no patient in group 1 had skeletal complaints before the bone scan.

The only significant differences between the groups were the PSA value at the time of the bone scan and the PSA velocity (Table 1). There were no statistically significant differences between the groups in the other variables. The distribution of PSA levels and patients with a positive bone scan is summarized in Table 2.

Further analysis of the PSA values associated with the presence or absence of adjuvant hormonal treatment within the two groups showed that in group 1 those who had androgen deprivation had a mean PSA of 5.1 ng/mL and in those who did not it was 5.4 ng/mL; the respective values in group 2 were 32.6 and 14.0 ng/mL.

DISCUSSION

About 8% of white American and 14% of African-American men with prostate cancer have bone metastasis at presentation [10]. The 5-year survival rate for all patients with prostate cancer, regardless of the stage, has improved from 67% in 1974 to 93% in 1994 [11]. Despite this dramatic improvement, in some patients the initial local therapy fails and they develop metastasis.

Metastatic carcinoma is the most common malignancy of the bone. Breast, prostate, lung, kidney and thyroid carcinomas account for 80% of skeletal metastasis [6]; 85–100% of patients who die from prostate cancer have bone metastasis. Pound et al. [12] followed 1997 men after RP; 15% developed biochemical recurrence and 5% developed bone metastases. After biochemical failure the median time to metastasis was 8 years.

The prognosis of patients with bone metastasis is poor; the Prostate Cancer Trialists’ Collaborative Group [13] reported a median survival of 30–35 months for all patients with skeletal involvement who received hormonal therapy. However, in patients with solitary metastasis, the median survival was longer, at ~50 months. Soloway et al. [14] described a semiquantitative grading scale for categorizing patients by the number of metastatic lesions present on the bone scan. They found that patients with fewer than six metastatic deposits had a significantly better 2-year survival than those with more extensive disease.

Classically, the bone lesions of metastatic prostate carcinoma are osteoblastic. Skeletal metastases may be studied by several imaging techniques. Radioisotope bone scintigraphy is the standard initial method for detecting skeletal metastasis. Schaffer and Pendergrass [15] showed bone scintigraphy to be more sensitive than acid and alkaline phosphatase levels, clinical evaluation, conventional

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**TABLE 1** Indications for a bone scan and the patients’ characteristics

<table>
<thead>
<tr>
<th>Indication/characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. bone scans</td>
<td>34</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Indications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rising PSA only</td>
<td>26 (76)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Others*</td>
<td>6 (17)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Staging before radiotherapy</td>
<td>2 (7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>63.9 (5.2)</td>
<td>65.8 (7.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>Mean PSA at bone scan, ng/mL</td>
<td>5.2</td>
<td>30.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (range)</td>
<td>5.3 (0–19.8)</td>
<td>13.3 (7.4–100)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean (SD) PSA velocity, ng/mL/month</td>
<td>0.2 (1.8)</td>
<td>14.1 (32.5)</td>
<td></td>
</tr>
<tr>
<td>Mean Gleason score</td>
<td>8.0</td>
<td>7.6</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean VEPC, %†</td>
<td>35</td>
<td>24</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*Bone scans taken by outside physicians with no specific indications. †Visual estimate of percentage of carcinoma.

**TABLE 2** Distribution of patients according to PSA level

<table>
<thead>
<tr>
<th>PSA level (ng/mL)</th>
<th>Bone scans</th>
<th>All [44]</th>
<th>Positive [10]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–7</td>
<td>26</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7–10</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>10–20</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Biochemical failure after RP. Pound et al. Few studies have attempted to define the available. and MRI are expensive and not widely high specificity (98%) [16,17] but both this bone with moderate sensitivity (65%) and detect prostate carcinoma metastases to tomography using fluorodeoxyglucose can among changes that are caused by treatment, Unfortunately, MRI often cannot distinguish on a bone scan, particularly spinal metastasis. The main role of plain radiography is to support the findings of other imaging studies; it is an unwieldy tool for screening the entire skeleton. MRI is highly sensitive for skeletal metastasis and can detect metastases that are not apparent on a bone scan, particularly spinal metastasis. Unfortunately, MRI often cannot distinguish among changes that are caused by treatment, fracture and tumour. Positron emission tomography using fluorodeoxyglucose can detect prostate carcinoma metastases to bone with moderate sensitivity (65%) and high specificity (98%) [16,17] but both this and MRI are expensive and not widely available.

Few studies have attempted to define the optimal use of a bone scan in the patient with biochemical failure after RP. Pound et al. [18] followed 1916 men after RP for a median (SD) of 5.5 (3.5) years and showed that 56 (3%) had local recurrence. The mean serum PSA at the time of recurrence was 5.8 ng/mL; none of the patients with recurrence had an undetectable PSA. In all, 118 (6%) patients developed distant metastatic disease with a mean serum PSA of 28.6 ng/mL; 80% of those patients had a positive bone scan. All patients with metastases had a high PSA level; the authors concluded withholding a DRE or imaging studies in men with an undetectable PSA after RP [18], but they did not address a specific PSA level at which a bone scan should be obtained.

Öbek et al. [19] followed 501 patients after RP for a mean (SD) of 25.4 (20.8) months; 14.4% of patients had a biochemical recurrence. The DRE was abnormal in four patients; none had an undetectable PSA level. They also concluded that a DRE in the absence of a detectable PSA was unnecessary.

Cher et al. [8] reviewed 144 bone scintigrams taken in 93 patients with biochemical failure after RP; 122 scans were from patients who had not received androgen deprivation after surgery and 117 were negative. The trigger PSA level was defined as the serum PSA that prompted the clinician to obtain a bone scintigram. The mean trigger PSA of the positive and negative bone scan groups was 143 and 6.2 ng/mL, respectively, and the lowest PSA for a positive bone scan was 46.1 ng/mL. PSA was the strongest predictor of a positive bone scan in a multivariate analysis. The authors calculated that at a PSA of ≤10 ng/mL there was a <1% chance of a positive bone scan. Twenty-two bone scans were taken in patients who received androgen ablation after RP and 16 were negative; the lowest PSA associated with a positive bone scan in these patients was 15.47 ng/mL. The authors concluded that in patients with an increasing PSA after RP, bone scintigraphy is of limited use until the PSA increases to >30–40 ng/mL [8].

Kane et al. [20] retrospectively analysed 129 bone scans from 134 patients with biochemical recurrence after RP; 12 (9.5%) were positive. The mean (SD) PSA was 61.3 (71.2) and 4.9 (15.8) ng/mL on patients with positive and negative bone scans, respectively, and significantly different. Of 67 patients with a PSA of <10 ng/mL, three (4.5%) had a positive bone scan. There was also a significantly higher PSA velocity in patients with a positive bone scan, at 22.1 (24.7) vs 0.5 (1.6) ng/mL/month. On logistic regression analysis the PSA and PSA velocity were predictors of the bone scan result. These authors concluded that a bone scan can be omitted for most patients with early biochemical recurrence, as most with a positive bone scan have a high PSA level and a high PSA velocity (>0.5 ng/mL/month) [20].

In the present study there were significant differences between the PSA and PSA velocity of those patients with a positive or negative bone scan. Although in group 2 nine patients had androgen ablation before the bone scan and two had radiation therapy, the PSA was higher than that of group 1. Patients in group 2 had higher PSA values than in group 1 regardless of androgen deprivation therapy. This might suggest that these patients have more aggressive disease and they tend to progress despite adjuvant treatment. There were no significant differences between the groups for the remaining variables. The PSA was never undetectable in the presence of metastatic disease. In this series 76% of patients in group 1 and all in group 2 had a PSA of <7 ng/mL. The lowest PSA level associated with a positive bone scan was 7.4 ng/mL and the highest associated with a negative bone scan was 19.8 ng/mL; nine of the 10 patients in group 2 had a PSA velocity of ≥0.5 ng/mL/month and 64% in group 1 had a PSA velocity of <0.5 ng/mL/month.

There are isolated reports of clinical local recurrence with an undetectable PSA level [21–24]; in the present series none of the patients who had bone metastasis had an undetectable PSA.

Bone pain was present in one patient before the bone scan, and he had a positive bone scan associated with an elevated PSA level. This correlates with previous reports stating that a detectable PSA almost always precedes clinical failure by months to years [19].

In conclusion, a bone scintigram in patients with a serum PSA of <7 ng/mL during biochemical recurrence after RP is unlikely to be positive, whereas it is likely to be if the PSA level is ≥20 ng/mL. Skeletal symptoms or a PSA of >7 ng/mL should prompt the clinician to obtain a bone scintigram.

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CONFLICT OF INTEREST
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Abbreviations: RP, radical prostatectomy; EPE, extraprostatic extension; SVI, seminal vesical invasion.