Utilization of Bone Scans in Conjunction with Prostate-Specific Antigen Levels in the Surveillance for Recurrence of Adenocarcinoma After Radical Prostatectomy

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Follow-up evaluation of patients who have undergone radical prostatectomy routinely consists of serial bone scintigraphy and, more recently, prostate-specific antigen (PSA) levels. The utility of serial bone scans in combination with PSA levels is retrospectively reviewed in 118 men treated by radical prostatectomy for clinical Stage A or B disease who, at the time of surgery, had no evidence of metastatic disease. Of the 118 patients, 75.4% had no abnormality on either test (mean follow-up 32.4 mo), 9.3% demonstrated a detectable or rising PSA level with negative bone scans (mean followup 35 mo), and 8.5% exhibited a detectable and or rising PSA level and positive bone scan (mean follow-up 30.7 mo). Follow-up bone scans were read as either positive or indeterminate with undetectable PSA levels in 6.8% of patients (mean follow-up 27.3 mo). Critical review of the equivocal studies suggests that postoperative PSA levels more truly represent the clinical situation than bone scans. Following radical prostatectomy, routine bone scintigraphy provides little additional information when PSA levels are negative. If PSA becomes detectable or the patient develops symptoms, bone scintigraphy should then be performed.

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Serial bone scintigraphy has been a standard component of follow-up evaluation in patients who have undergone radical prostatectomy for prostatic adenocarcinoma (*1–3*). However, the development of the polyclonal radioimmunoassay technique of measuring prostate-specific antigen (PSA) levels recently has been suggested as a more accurate means of postoperative monitoring in prostate cancer patients (*4–6*). Such advances require reevaluation of current surveillance protocols. The utility of serial bone scans in combination with PSA levels is evaluated in patients who were treated by radical prostatectomy and who, at the time of surgery, had no evidence of metastatic disease.

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METHODS

Prostate cancer was diagnosed and determined to be organ-confined (clinical Stage A or B disease) based on digital rectal examination and bone scan in 118 men prior to radical retropubic prostatectomy. Cancer volumes in the prostatectomy specimens of these patients ranged from 0.04 cc to 45.4 cc, with a mean volume of 5.12 cc as measured by the Stanford technique as previously described (*7*). Ten percent (12 of 118) of the patients exhibited unsuspected microscopic nodal metastases on final pathology. Postoperative follow-up consisted of physical examination and measurement of serum PSA levels every 3 mo for the first year, every 4 mo for the second year, and then every 6 mo thereafter. Bone scans were obtained 6 mo postoperatively, then annually. Occasional exceptions to this schedule exist due to the performance of non-reviewed scans at other facilities. Such exclusions were random events and should not influence the results of the study. Additional bone scans were obtained whenever PSA levels changed from undetectable to detectable in a patient. The follow-up period ranged from 12 to 72 mo with an average of 32 mo.

Venous blood samples for PSA measurements were drawn on an ambulatory basis, prior to rectal examination or instrumentation, and stored at −20°C until assays were performed. The PSA level was subsequently measured by the Yang polyclonal radioimmunoassay at the Stanford Urology Laboratory as previously described (*8,9*). A nondetectable PSA was considered any concentration less than 0.3 ng/ml. In selected patients, radioimmunoassay for prostatic acid phosphatase (PAP) was performed on the same frozen serum sample. The normal range for PAP is 0–2.5 ng/ml.

Bone scintigraphy was performed 3 hr after the injection of 25 mCi of ^{99m}Tc-methylene diphosphate. Whole-body images and spot views as indicated were obtained with a large field of view gamma camera (Technicare Omega High Resolution or Siemens Omniview High Resolution). The photopeak was centered at 140 keV with a 20% window. Each bone scan was reviewed in consensus by two investigators without knowledge of prior bone scan reports or PSA results. The results of prior bone scans were blinded to prevent bias in the interpretation. However, in clinical

practice previous studies would certainly be considered in the interpretation. A total of 264 scans were reviewed and read as positive for metastatic disease, negative, or indeterminate. Positive scans exhibited multiple asymmetric lesions predominantly involving the axial skeleton. Criteria for a negative reading included completely normal distribution of radiopharmaceutical or patterns of uptake which could be classified as typical for such conditions as post-surgical orthopedic changes, posttraumatic changes, Paget's disease, or, most commonly, degenerative arthritis. Indeterminate scans included those patterns which were unexplainable on the basis of a benign process and, while not clearly characteristic for metastatic disease, did appear suspicious. The clinical history (excluding PSA levels) was subsequently reviewed for confirmation of the initial reading or reclassification of indeterminate studies. The threshold for labeling bone scans as indeterminate or positive may be slightly lowered, since by this study design the interpretation was made without benefit of prior scintigrams or the PSA level.

RESULTS

The 118 patients were divided into four groups, depending on the results of serial bone scans and PSA levels (Table 1). Follow-up times are from the date of radical prostatectomy.

Negative Bone Scans with Undetectable PSA Levels

Eighty-nine of the 118 patients (75.4%) showed no abnormality in either test (follow-up: 12-72 mo, mean 32.4 mo). Only one patient (1%) was found to have a single microscopic nodal metastasis. They are all currently considered free of recurrent cancer.

Negative Bone Scans with Detectable and/or Rising PSA Levels

In 11 patients (9.3%), the PSA level began to rise, but bone scans have not shown any evidence of metastases (follow-up: 18-64 mo, mean 35 mo). On final pathology, 36% (4 of 11) of these patients exhibited microscopic nodal metastases.

Positive or Indeterminate Bone Scans with Undetectable PSA Levels

Eight of the 118 patients (6.8%) had follow-up bone scans which were read as either positive (4 patients) or indeterminate (4 patients), but these patients have continued to have nondetectable levels of PSA (follow-up: 17-51 mo, mean 27.3 mo). The findings in each of these cases are listed in Table 2. Upon more critical review of the scans in these eight patients, three (Patients 1–3 in Table 2) were likely to represent degenerative changes but were still felt to be suspicious for metastatic disease (Figs. 1 and 2). The remaining five cases (Patients 4–8 in Table 2) exhibited radiopharmaceutical uptake that was not typical for any particular diagnosis but could represent either metastases or other processes such as occult trauma or Paget's disease (Figs. 3–6). The presence of metastases could not be confirmed by plain radiographs on any of the patients and no patients had clinical evidence of recurrent disease or progression on follow-up scintigraphy. This re-review was performed for academic interest and did not affect the initial classification of the scans.

Radioimmunoassay PAP levels obtained from the frozen serum samples of these eight patients were all normal (range 0.3 to 1.1 ng/ml). None of these patients demonstrated microscopic nodal metastases on final pathologic review.

Due to these findings, certain patterns, especially asymmetry of radiopharmaceutical uptake in the ischia (Fig. 1)

TABLE 1
PSA Levels and Bone Scintigraphy Results in 118 Patients After Radical Prostatectomy

	Undetectable PSA	Detectable/Rising PSA	Total
Negative bone scans	89*	11*	100
Positive/Indeterminate bone scans	8*	10†	18
Total	97	21	118

* None of these patients were felt to have true skeletal metastases.
† All of these patients were felt to have true skeletal metastases.

TABLE 2
Age and Findings in Eight Patients with Positive or Indeterminate Scintigrams Who Had Undetectable PSA Levels

Patient no.	Age	Bone scan interpretation	Findings
1	66	Indeterminate	Asymmetry of ischia (Fig. 1)
2	64	Indeterminate	Asymmetry of ischia
3	68	Positive	Multiple vertebrae (Fig. 2)
4	72	Positive	Right 4th rib, 5th lumbar vertebra (Fig. 3)
5	60	Positive	1st Lumbar vertebra, right parietal, and left 8th rib (Fig. 4)
6	68	Positive	Proximal right femur (Fig. 5)
7	57	Indeterminate	Right 11th rib
8	60	Indeterminate	Distal femoral metaphysis (Fig. 6)

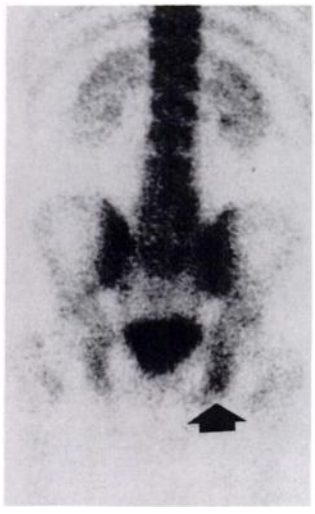

FIGURE 1. A 66-yr-old patient with an undetectable PSA level and asymmetric radioisotope uptake in the ischia (arrow).

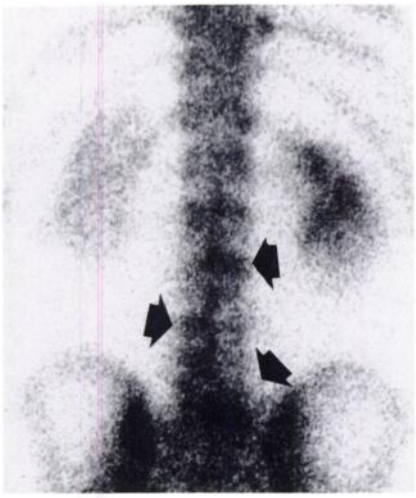

FIGURE 2. A 68-yr-old patient with increased uptake in multiple vertebrae (arrows) with an undetectable PSA level.

are no longer deemed particularly suspicious for metastases.

Positive or Indeterminate Bone Scans with Detectable and/or Rising PSA Levels

In 10 patients (8.5%), PSA began to rise and bone scans were read as either positive (8 patients) or indeterminate (2 patients) (follow-up: 14 to 51 mo, mean 30.7 mo). The rise in PSA preceded bone scan detection by an average of 12.7 mo (range: 3 to 24 mo) in 7 of the 10 patients. Interim negative bone scans were obtained following the initial rise in PSA level in 3 of these 7 patients. Two patients exhibited a simultaneous rise in PSA and development of lesions on bone scan. In one patient, a follow-up bone scan was read as indeterminate 3 mo prior to the development of detectable PSA levels.

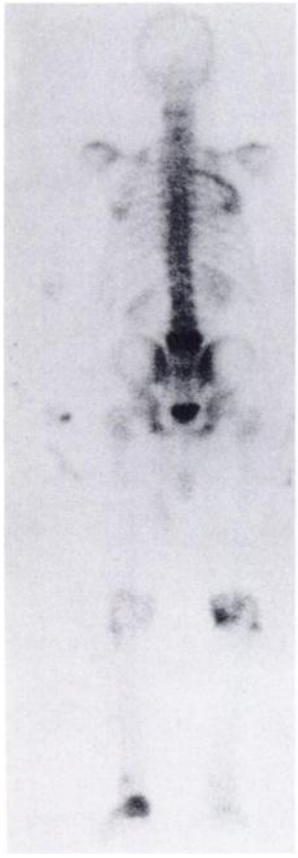

FIGURE 3. A 72-yr-old patient who demonstrated a suspicious bone scan appearance of the right 4th rib and 5th lumbar vertebra despite a negative PSA level.

In 70% (7 of 10) of this group, final pathology revealed microscopic nodal metastases.

In 5 of the 10 patients with both rising PSA and positive bone scans, hormonal therapy was subsequently initiated either as oral diethylstilbestrol administration or bilateral orchiectomy. The response was monitored by PSA and bone scintigraphy. In three of these five, PSA levels diminished minimally at the initiation of hormonal therapy, then began to rise. These three patients exhibited progression of disease on follow-up bone scans. PSA levels in two patients fell to undetectable levels and follow-up bone scans demonstrated marked improvement.

DISCUSSION

The initial evaluation of a patient diagnosed with prostate cancer should include both bone scintigraphy and a PSA level. These two tests have also been used routinely in the evaluation of prostate cancer patients after radical prostatectomy. In this retrospective study of 118 patients who underwent radical prostatectomy, PSA levels were found to be an essential part of postoperative follow-up. Bone scintigraphy was not as useful unless preceded or accompanied by elevated PSA levels.

In 21 of the 118 post-radical prostatectomy patients, the PSA level began to rise. In 10 of these 21 patients (47.6% or 8.5% of the total study group) bone scintigrams became positive. Despite the time delay in the development of a positive bone scan after the initial rise in PSA, which may be in part due to the difference in timing of the studies, we feel that serial bone scintigrams are indicated in patients with an elevated postoperative PSA. A negative bone scan in the face of a rising PSA frequently signifies a recurrence localized to the prostatic bed (*5*) and may indicate the need for treatment aimed at a local recurrence. However, a similarly rising PSA and a positive bone scan suggests the need for more systemic treatment such as androgen-deprivation therapy. Consequently, bone scans provide important information for treatment decisions in post-radical prostatectomy patients with elevations of PSA. Neither bone scans nor PSA levels may be indicated if the physician believes that delayed hormonal therapy, waiting until the patient becomes symptomatic, rather than early therapy is appropriate.

Continued PSA monitoring in patients undergoing irradiation or anti-androgen therapy has been shown to be an important prognostic indicator (*10,11*). This finding was confirmed in this study by the improvement in bone scan appearance in those patients whose PSA levels diminished and stabilized following androgen deprivation, whereas the number and intensity of sites of radiopharmaceutical up-

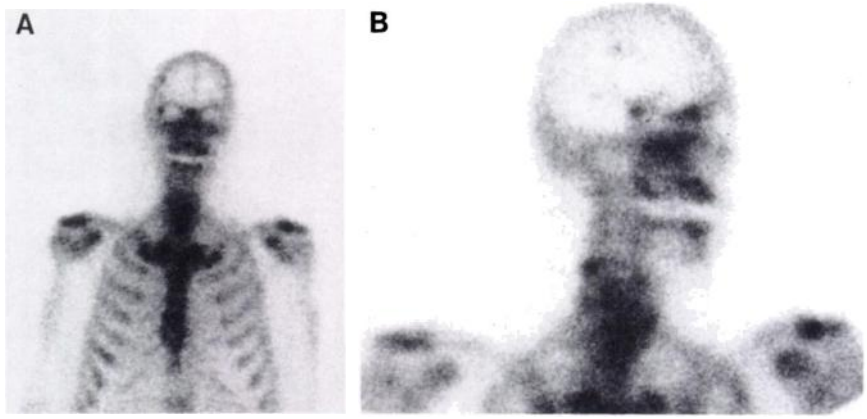

FIGURE 4. A 60-yr-old patient in whom bone scintigraphy revealed increased uptake in the parietal bone on the anterior (A) as well as the oblique view (B). In addition, there was an abnormality in the 1st lumbar vertebra and left posterior 8th rib. PSA was negative.

take increased in those patients who demonstrated only a partial, transient fall in PSA. The false-negative PSA rate may be higher in this group, however, and further study is needed to evaluate the usefulness of follow-up bone scans in this clinical setting (*11*).

PSA levels remained undetectable in 97 of the 118 post-radical prostatectomy patients in this study. In 89 of these 97 patients (91.8% or 75.4% of the total study group), bone scans confirmed the absence of skeletal metastases. However, in 8 of the 97 patients (8.2% or 6.8% of the total study group), bone scintigrams were read as positive or indeterminate when PSA was undetectable. This group poses a particular problem for the clinician. The patient age group stricken with prostate cancer is the same as that prone to progressive degenerative bone and joint disease which, if severe and in the lumbosacral area, can be difficult to differentiate from metastases. Plain skeletal radiographs of the area of suspicion may clarify the nature of the abnormality detected by bone scintigraphy. Prior to the availability of PSA measurement, bone biopsy was recommended in prostate cancer patients in whom an abnormal bone scintigram was the only evidence of disease (*12*). A less invasive approach, magnetic resonance imaging has been utilized more recently to clarify the presence or absence of bone metastases in prostate cancer patients with equivocal bone scans (*13*). In patients with no other evidence of metastatic disease, a false-positive bone scan can lead to undue anxiety, additional invasive and expensive studies, and inappropriate treatment.

Thus, a negative postoperative bone scan gives little added information to negative PSA levels and a positive postoperative bone scan must be interpreted along with PSA levels to ensure that appropriate therapy is advised. A change in appearance of the bone scintigram from a negative one preoperatively is not inevitably due to metastases. In addition, a bone scan costs $790, whereas a PSA level costs $55 (Stanford University Hospital, December 1990). For these reasons, we feel that bone scans are not warranted postoperatively in patients with negative serial PSA levels and negative preoperative bone scans.

There is differing evidence on whether or not poorly differentiated metastatic prostate cancer cells can completely lose the ability to produce PSA (*14–16*). PSA has been shown to be normal in 2% of patients with untreated stage D2 disease and even higher following hormonal ablation (*17*). However, there has been only one reported case of documented bone metastases and *nondetectable* PSA levels following radical prostatectomy (*18*). This pos-

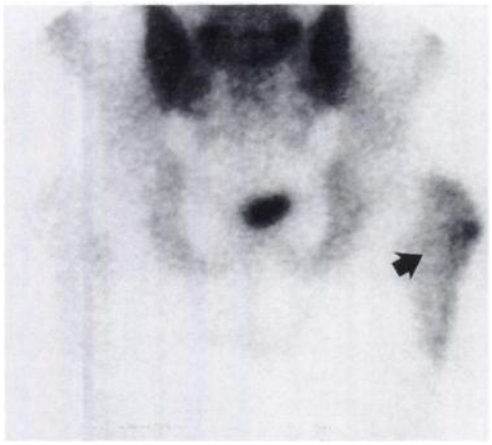

FIGURE 5. A 68-yr-old patient exhibiting increased uptake in the proximal right femur (arrow) and an undetectable PSA level.

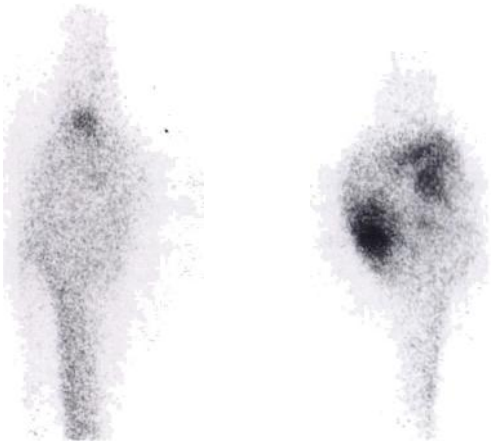

FIGURE 6. A 60-yr-old patient with a negative PSA level and a suspicious scintigram at the distal femoral metaphysis.

sibility is one argument for continued ordering of "routine" bone scans postoperatively in this setting. Certainly any patient complaining of bone pain despite a nondetectable PSA level may still require bone scintigraphy for diagnosis. Another potential problem is the production of PSA autoantibodies that could mask the detection of PSA. Such antibodies have been problematic in the radioimmunoassay of other serum markers such as thyroglobulin in thyroid cancer patients. In 30% of thyroid cancer patients, anti-thyroglobulin autoantibodies can falsely lower thyroglobulin measurements (*19*). However, a survey for the presence of anti-PSA reveals that this autoantibody occurs in only 7.4% of the normal male population and exists in such minute concentrations that there is little potential to produce a falsely undetectable PSA level. Additionally, there is no significant difference between the anti-PSA antibody levels before and after prostatic surgery (Graves HCB and Stamey TA, unpublished results).

CONCLUSION

When the preoperative PSA is not markedly elevated, the bone scintigram is negative preoperatively, and PSA levels remain undetectable after prostatectomy, there is a high probability that the patient is free of disease (*5,9*). False-negative scans are very rare (*20*). Follow-up evaluation with PSA measurement alone is advised since bone scans rarely, if ever, provide unique information. If the PSA becomes detectable or if the patient develops symptoms referable to the skeletal system, bone scintigraphy can be repeated. The preoperative scintigram is then very valuable for comparison. Although recent studies suggest that preoperative PSA levels are more useful for staging (*21*), bone scintigraphy is still an important part of the routine preoperative evaluation for any future comparison.

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