The Clinical Utility of Prostate-Specific Antigen and Bone Scintigraphy in Prostate Cancer Follow-up

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To assess the value of serum prostate-specific antigen (PSA) in prostate cancer follow-up, we prospectively studied 107 consecutive patients with: (1) pathologically confirmed prostate cancer; (2) definitive prostatectomy and/or radiation therapy ≥3 mo prior to bone scanning; and (3) one bone scan and serum PSA sampling within 3 mo of each other. The mean and range of patient follow-up since definitive therapy was 1.6 and 0.5–8 yr, respectively. Abnormal bone scans were correlated with pertinent radiographs. Of 107 bone scans, 16 demonstrated metastatic bone disease. A PSA value of ≤8 ng/ml excluded bone metastases with a predictive value of a negative test of 98.5%. Without radiographic correlation, abnormal bone scans rarely represented metastases if the PSA value was ≤8 ng/ml. In summary, serum PSA concentration determines the need for follow-up bone scanning and assists in scan interpretation in patients status post definitive therapy for prostate cancer.

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Prostatic acid phosphatase (PAP) is a serum marker that has been used to detect prostate adenocarcinoma for the past 50 yr (*1*). PAP, now measured using immunoassay techniques, is elevated in patients with prostate cancer metastases and can be used to monitor their response to therapy, such as orchiectomy or radiation therapy. However, the specificity of the PAP immunoassay is less than desired (*2,3*), and the search for a better prostate cancer tumor marker culminated in the discovery of prostate-specific antigen (PSA) (*4*). PSA is a protease produced by both normal and malignant prostatic epithelial cells, but not by any other cell in the body (*5*). Multiple studies have been performed to compare the clinical usefulness of these two serum markers, PAP and PSA, in patients with prostatic cancer (*6–8*). PSA concentration increases with advancing clinical stage and is proportional to the estimated tumor volume in most series (*6–9*). In contrast, the PAP concentration is elevated in less than 50% of patients with prostate cancer and correlates less closely with tumor volume (*3,10*). However, PSA is not tumor-specific and its value is elevated in 55.8%–86% of patients with benign prostatic hyperplasia (BPH) as compared to PAP's increased value in only 14%–15% of the patients with BPH (*6,8*). In patients with intracapsular prostate cancer, radical prostatectomy leads to a marked fall in PSA values to undetectable levels within several days (half-life 2.2 days). Similar falls in elevated PSA levels are seen following orchiectomy, radiation therapy, or anti-androgen therapy such as Leuprolide or Megestrol Acetate (*8,11–13*).

To determine the clinical utility of serum PSA values and ^{99m}Tc-methylene diphosphate (MDP) bone scans in patients being followed for prostate cancer recurrence after definitive therapy, the following study was conducted.

MATERIALS AND METHODS

One hundred and seven consecutive patients fulfilled the following criteria for study entry: (1) pathologic diagnosis of prostate adenocarcinoma; (2) definitive therapy by a radical prostatectomy (16 patients) and/or radiation therapy (101 patients) at least 3 mo prior to an MDP bone scan and; (3) a MDP bone scan and serum PSA sampling obtained within 3 mo of each other. No changes in chemotherapy or therapeutic interventions (orchiectomy, radiotherapy, etc.) occurred between the bone scan and serum PSA sampling. All PSA samples and bone scans were obtained at greater than 3 mo post-definitive therapy. The mean and range of follow-up since definitive therapy for these 107 patients was 1.6 and 0.5–8.0 yr, respectively. Two patients had an orchiectomy performed 6 and 15 mo, respectively prior to study entry. Abnormal bone scans were correlated with pertinent radiographic studies to determine the presence or absence of degenerative joint disease or metastatic bone disease.

A bone scan was read as positive for metastatic disease if it exhibited two or more focal areas of increased uptake in the axial skeleton not shown to represent benign bone disease on radiologic correlation. Serum samples for PSA concentration were assayed using the Tandem-R PSA technique (Hybritech, Inc.). This immunoradiometric assay employs two murine monoclonal antibodies, each directed against a distinctly different antigenic site on the PSA molecule. PSA molecules bound by both the radiolabeled antibody and the solid phase antibody are detected and the amount of radioactivity measured is directly proportional to

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the PSA concentration present in the test serum. Our normal range is 0–4 ng/ml.

Bone scan findings and serum PSA values of the 107 patients were subjected to receiver-operating characteristic (ROC) curve analysis (Fig. 1). The ROC curve defines the performance of the serum PSA test independently of the threshold (criterion) selected to separate normal from abnormal results (i.e., the upper normal range limit). If only those patients with metastatic bone disease who demonstrate a serum PSA above a certain threshold are considered to be positive by the assay, then the sensitivity and specificity of the assay will vary inversely as the threshold changes.

RESULTS

Of the 107 bone scans performed at study entry, 16 were abnormal and diagnostic of metastatic bone disease; 30 demonstrated focal area(s) of increased uptake in the axial skeleton confirmed by radiographs to represent benign bone disease; and 61 bone scans demonstrated no evidence of bone metastases. The bone scan findings (16 metastatic bone scans and 91 benign bone scans) were then correlated with each patient's serum PSA value. Based on the ROC curve analysis, the 107 patients were divided into three groups: Group 1 exhibited serum PSA concentrations less than or equal to 8 ng/ml (optimal ROC threshold), Group 2 had serum PSA concentrations greater than 8 but less than 40 ng/ml, and; Group 3 had serum PSA concentrations greater than or equal to 40 ng/ml (mean value of 39 patients with PSA >8 mg/ml). There was no significant difference in the mean follow-up times of the three groups (Chi-square, $p>0.5$). Correlation of the PSA concentrations and bone scan findings in these 107 patients is shown in Table 1. A serum PSA concentration greater than 8 ng/ml (ROC-derived optimal threshold) had a sensitivity of 93.8% and a specificity of 73.6% in the detection of metastatic bone disease.

Of the 68 patients in Group 1, only one patient had bone metastases. Thus, a serum PSA concentration of less than or equal to 8 ng/ml excludes the presence of metastatic bone disease with a predictive value of a negative test of 98.5% (chi-square 2 × 2 contingency table, $p\leq0.001$). As the serum PSA concentration increased above 8 ng/ml, the probability of metastatic bone disease also tended to increase with the maximum probability of metastatic bone disease (60%) seen at greater than 10 ng/ml.

TABLE 1
PSA Concentrations and Bone Scan Findings

		PSA CONCENTRATION (NG/ML)		
		≤ 8	>8<40	≥ 40
METASTATIC BONE SCANS	POSITIVE	1	6	9
	NEGATIVE	67	15	9

DISCUSSION

Unfortunately, about 45% of patients with prostate cancer have clinical Stage C or D disease when the diagnosis is first made (*14*). Thus, radionuclide bone scanning is a routine procedure in the initial evaluation of such patients so that the treatment of the primary neoplasm will be appropriate to the level of tumor extent. Subsequent pelvic lymphadenectomy demonstrates that about 50% of patients with initial clinical Stage C disease actually have pathologic Stage D1 disease. At least 80% of patients with pathologic Stage D1 disease will demonstrate distant metastases within 5 yr of follow-up. However, only 20% of patients with pathologic Stage C disease or less will demonstrate distant metastatic disease within the same time frame. Because of the frequency of bone metastases developing during prostate cancer follow-up, bone scans are routinely ordered by many urologists and oncologists periodically to detect bone metastases or to assess the response of a patient's known metastatic bone disease to chemotherapy. Our study and others (*15–18*) would suggest that measurement of serum PSA concentration is quite useful in prostate cancer monitoring. This finding is analogous to the value of serum thyroglobulin in the follow-up of patients with thyroid cancer treated by total thyroidectomy or subtotal thyroidectomy with ^{131}I ablation (*19*). Subsequent to radical prostatectomy with or without radiotherapy for pathologic Stage A or B disease, patients with subsequent serum PSA values of less than 0.4 ng/ml have a very low rate of recurrence at least in short term follow-up studies (*20–21*). Patients with similar staging but treated less aggressively often show measurable serum PSA values indicating residual benign or malignant prostate tissue (*8*). In our study, as the serum PSA concentration exceeded 8 ng/ml, the probability of metastatic bone disease also increased. However, those patients without

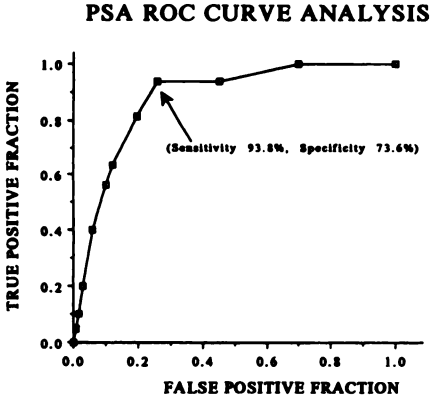

FIGURE 1. As the threshold for an abnormal PSA value is progressively raised from 0 to 200 ng/ml, the true-positive fraction (sensitivity) falls and the false-positive fraction (1-specificity) falls. At 8 ng/ml, the sensitivity and specificity are maximized (most upper left point on ROC curve).

metastatic bone disease as yet are at increased risk as their residual neoplasm is now confined to the primary site and/or pelvic or retroperitoneal lymph nodes. As our mean follow-up time since definitive therapy increases, it is believed that many patients whose initial bone scans were negative for metastatic disease will demonstrate conversion to a metastatic bone scan if their PSA concentration increases with time. Seventeen patients in our study population had a follow-up serum PSA concentration and ^{99m}Tc-MDP bone scan obtained with 18 mo of their entry into the study. One of the five patients who showed a significant rise in serum PSA concentration with time converted from a negative to positive bone scan for metastatic disease. Four patients with metastatic bone disease at study entry underwent bilateral orchiectomy with a marked fall in serum PSA concentration in all and a conversion to a negative bone scan in two of four patients.

One patient in Group 1 demonstrated a bone scan positive for metastatic disease at the time of study entry in February 1988. He had pathologic Stage D2 prostate adenocarcinoma diagnosed in July 1986, following TURP to relieve obstructive uropathy. Following bilateral orchiectomy in November 1986, subsequent bone scans performed in 1987 demonstrated improvement in his diffuse metastatic bone disease. At study entry in February 1988, his serum PSA concentration was 1.6 ng/ml and his bone scan showed residual metastatic disease with a new T9 lesion. Subsequent follow-up demonstrated a progressive rise of his serum PSA concentration to 13 ng/ml and the development of new bone lesions. Thus, in this orchiectomized patient, his rise in serum PSA concentration lagged behind the evidence of new metastatic bone disease. Bone scan progression despite normal PSA values has been reported by others (*15–17*), but these articles do not state whether such discordances are seen in orchiectomized or anti-androgen treated patients. This would suggest that in some orchiectomized patients, progression of metastatic bone scan findings may precede a detectable rise in serum PSA concentration by a few months. Further work needs to be done to determine whether anti-androgen therapy induces a similar discordance.

Twenty-four patients in Group 1 (35.3%) demonstrated focal abnormalities on bone scan that could represent degenerative joint disease or degenerative versus metastatic bone disease. However, correlation with radiographs confirmed degenerative joint findings as the cause of the bone scan abnormalities in all 24 patients. In our series, a patient's serum PSA concentration less than 8 ng/ml when abnormal bone scan findings were detected allowed the nuclear medicine physician to predict with a high degree of certainty that such findings were not related to bone metastases, even in the absence of pertinent radiographs. However, exceptions to this observation have already been noted (*15–17*). Such exceptions (metastatic bone scans despite normal PSA values) may only be seen in orchiectomized or anti-androgen treated patients.

This study also suggests that routine bone scanning in the follow-up of definitively treated patients with prostate cancer is probably not warranted if their serum PSA concentration is less than or equal to 8 ng/ml. Only 1.5% of patients in this series with serum PSA concentration in this range demonstrated metastatic disease as discussed above. However, there is an increased probability (38.5%) of obtaining a positive bone scan for metastatic disease if the serum PSA concentration is greater than 8 ng/ml. Similarly, a rise in serum PSA concentration over time signifies increasing tumor volume and bone scan conversion from normal to metastatic disease is seen commonly in such patients (*16,18*).

In summary, serum PSA concentrations are useful in the follow-up monitoring of patients with prostate cancer treated with definitive therapy. Serum PSA concentrations provide important information in determining the need for follow-up bone scanning and in interpreting abnormal bone scan findings in patients' status post-definitive therapy for prostate cancer.

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