

LIMITED VALUE OF BONE SCINTIGRAPHY AND COMPUTED TOMOGRAPHY IN ASSESSING BIOCHEMICAL FAILURE AFTER RADICAL PROSTATECTOMY

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ABSTRACT

Objectives. To define the utility of bone scan and computed tomography (CT) in the evaluation of patients with biochemical recurrence after radical prostatectomy.

Methods. A retrospective analysis of the Center for Prostate Disease Research database was undertaken to identify patients who underwent radical prostatectomy between 1989 and 1998. Patients who developed biochemical recurrence (two prostate-specific antigen [PSA] levels greater than 0.2 ng/mL) and underwent either bone scan or CT within 3 years of this recurrence were selected for analysis. The preoperative clinical parameters, pathologic findings, serum PSA levels, follow-up data, and radiographic results were reviewed.

Results. One hundred thirty-two patients with biochemical recurrence and a bone scan or CT scan were identified. Of the 127 bone scans, 12 (9.4%) were positive. The patients with true-positive bone scans had an average PSA at the time of the bone scan of 61.3 ± 71.2 ng/mL (range 1.3 to 123). Their PSA velocities, calculated from the PSA levels determined immediately before the radiographic studies, averaged 22.1 ± 24.7 ng/mL/mo (range 0.14 to 60.0). Only 2 patients with a positive bone scan had a PSA velocity of less than 0.5 ng/mL/mo. Of the 86 CT scans, 12 (14.0%) were positive. On logistic regression analysis, PSA and PSA velocity predicted the bone scan result ($P < 0.001$ each) and PSA velocity predicted the CT scan result ($P = 0.047$).

Conclusions. Patients with biochemical recurrence after radical prostatectomy have a low probability of a positive bone scan (9.4%) or a positive CT scan (14.0%) within 3 years of biochemical recurrence. Most patients with a positive bone scan have a high PSA level and a high PSA velocity (greater than 0.5 ng/mL/mo). UROLOGY 61: 607–611, 2003. Published by Elsevier Science Inc.

With the advent of prostate-specific antigen (PSA) testing, a significant stage migration has occurred in prostate cancer such that the number of patients presenting with metastatic disease decreased 52% between 1990 and 1994.¹ The proportion of patients presenting with localized prostate cancer has likewise increased. Currently, most

patients presenting with prostate cancer undergo local therapy with the intent to cure. In 1992, 36.6% of patients with localized and regional disease were treated with radical prostatectomy (RP). Moul² estimated that if approximately 200,000 men are diagnosed with prostate cancer in the United States per year, more than one third will

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receive RP and 20% to 40% of these may eventually develop biochemical recurrence. Thus, 13,000 to 26,000 men annually may have PSA-only recurrence after RP.

The assessment of patients with PSA-only "biochemical" recurrence after RP is challenging. To choose the most appropriate additional therapy in this setting, the clinician's goal is often to categorize the recurrence as local or systemic. Important information to consider includes the patient's pretreatment PSA level, pathologic stage and grade, and the results of pretreatment radiographic imaging. Most patients with a pretreatment PSA level less than 20 ng/mL have not undergone a preoperative bone scan or computed tomography (CT) scan because numerous studies have documented the low utility of these studies for patients with "low-risk" newly diagnosed prostate cancer.³⁻¹⁰ Additionally, many patients with low-stage and grade disease have pelvic lymphadenectomy omitted at the time of RP, potentially confounding the assessment of patients with biochemical recurrence.¹¹

The radiologic assessment of patients with biochemical recurrence after RP has traditionally included both a radionuclide bone scan and abdominal and pelvic CT to determine the presence of local recurrence and lymphatic, solid organ, and bone metastases.^{12,13} However, recent studies have questioned the utility of bone scans in patients with low serum PSA levels after RP.¹⁴

Although we have routinely performed bone and CT scans to assess patients with biochemical recurrence after RP, it has been our impression that these radiologic tests are rarely helpful in disease management. In addition, they have significant financial costs and require patient time, discomfort, and inconvenience. We sought to determine the utility of bone scan and abdominal pelvic CT in locating disease recurrence in patients with biochemical recurrence after RP.

MATERIAL AND METHODS

An analysis of the Center for Prostate Disease Research multicenter prostate cancer database¹⁵ was carried out to identify patients who had undergone RP for clinically localized (cT1-3N0M0) prostate cancer between 1989 and 1998 at four participating medical centers (Naval Medical Center San Diego, Walter Reed Army Medical Center, Madigan Army Medical Center, and Brooke Army Medical Center). Patients with biochemical recurrence were the focus of this study. Biochemical recurrence was defined as two serum PSA values greater than 0.2 ng/mL or a single PSA level greater than 0.5 ng/mL.

The Center for Prostate Disease Research is a congressionally mandated, Department of Defense-funded research program to study prostate cancer in the United States military healthcare system and has been described fully elsewhere.¹⁶ A component of the program is a multicenter prostate cancer database that is maintained at nine military hospitals nationwide. Demographic, clinical, and pathologic data were entered

retrospectively for all patients treated before 1994 and have been entered prospectively at all participating facilities since 1998. The institutional review board at each institution has approved the Center for Prostate Disease Research database, and each prospectively entered patient provided informed consent. Standardized data collection forms include registration, biopsy, clinical and pathologic staging, treatment, and follow-up information. We classified the pathologic stage using the 1992 TNM staging system¹⁷ and used the Gleason grading system.¹⁸ RP was performed using a retropubic or perineal approach by multiple surgeons and pelvic lymph node dissection was performed at the discretion of the surgeon. Routine postoperative follow-up was performed at 3, 6, 9, and 12 months for the first year, every 6 months for the next 2 years, and annually thereafter unless recurrence was identified.

Patients with biochemical recurrence who had a nuclear medicine bone scintigraphy study (bone scan) or contrast abdominal and pelvic CT scan performed within 3 years of the date of biochemical recurrence were identified. We chose 3 years because we were primarily interested in the utility of the initial radiographic assessment of biochemical recurrence. The standard at each institution during the period of review was whole body bone scan with additional spot images as required after the administration of technetium-99m methylene diphosphate (MDP). The CT scan technique typically used axial images obtained at a 7 to 10-mm slice thickness from the dome of the diaphragm to the floor of the pelvis after intravenous, oral, and rectal contrast. The results of the bone scan and CT were determined to be either positive or negative after review of the officially recorded results from each institution.

Serum PSA levels immediately before the imaging study were determined. The PSA velocity was calculated from the two most recent PSA levels before the radiographic study divided by the number of months between them as listed in units of nanograms per milliliter per month. If a patient received hormonal therapy before the radiographic study or if PSA data within 3 months of the radiographic study were unavailable that patient was not included in the PSA calculations.

Demographic and clinical data on patients with biochemical recurrence were collected, including preoperative clinical stage, grade, and PSA; pathologic stage and grade; and postoperative PSA levels. The rank sum test was used to test for differences in PSA, PSA velocity, and stage by bone and CT scan results; Fisher's exact test was used to test for differences in grade. Logistic regression analysis was used to assess the effectiveness in predicting bone and CT scan results by PSA level, PSA velocity, and stage.

RESULTS

One hundred thirty-four patients with biochemical recurrence after RP were identified who had received a bone scan or CT scan within 3 years of the date of biochemical recurrence. The dates of surgery ranged between 1988 and 1998. Of 127 bone scans, 12 (9.5%) were positive. Ten were suspicious, but plain radiography or magnetic resonance imaging found no evidence of metastatic disease. The patients with positive bone scans had significantly greater PSA levels and greater PSA velocities than patients with negative bone scans (Table I). In logistic regression analysis, both PSA and PSA velocity were strong predictors of bone scan findings ($P < 0.001$ for both). Pretreatment PSA,

TABLE I. Post-treatment PSA and PSA velocity by bone scan and CT scan result

	Positive	Negative	P Value*	R ² Value
Bone scan result				
PSA (ng/mL)	61.3 ± 71.2 (8)	4.9 ± 15.8 (69)	<0.001	
PSAv (ng/mL/mo)	22.1 ± 24.7 (9)	0.5 ± 1.6 (56)	<0.001	
Logistic regression analysis				
PSA (ng/mL)			<0.001	0.264
PSAv (ng/mL/mo)			<0.001	0.419
CT scan result				
PSA (ng/mL)	27.4 ± 47.9 (8)	4.9 ± 14.9 (49)	<0.001	
PSAv (ng/mL/mo)	1.8 ± 4.2 (8)	0.7 ± 1.9 (40)	<0.001	
Logistic regression analysis				
PSA (ng/mL)			0.733	0.003
PSAv (ng/mL/mo)			0.047	0.085

KEY: PSA = prostate-specific antigen; PSAv = PSA velocity; CT = computed tomography.

Data presented as the mean ± SD, with the number of patients in parentheses.

*P values between positive and negative computed with rank sum test; P values and R² values of logistic regression analysis computed between PSA and PSAv.

pathologic stage, and grade were not significantly different by bone scan outcome ($P = 0.943, 0.254, 0.287$, respectively), nor were pretreatment PSA and pathologic stage significant predictors of bone scan outcome ($P = 0.469$ and 0.252 , respectively). Of the 9 patients with calculable PSA velocities and a positive bone scan, only 2 had a PSA velocity less than 0.5 ng/mL/mo, and only 3 of 59 patients with negative bone scans had PSA velocities greater than 0.5 ng/mL/mo.

For those patients whose date of bone scan could be accurately determined, the frequency of a positive bone scan by year after recurrence was 3.5% (2 of 57) in year 1, 12.5% (3 of 24) in year 2, and 18.2% (2 of 11) in year 3. In the 12 patients with positive bone scans, the location of the positive study was not recorded for 6. Of the remaining 6 patients, 4 had multiple sites of abnormalities, with the most common locations the pelvis, ribs, and spine.

Of 86 CT scans, 12 (14.0%) were positive within 3 years of biochemical recurrence. Three of the positive CT scans confirmed palpable local recurrences alone and one confirmed bone metastasis previously identified by bone scan. Only 8 (9.3%) of the 86 CT scans provided new information to the clinician. The PSA and PSA velocity data for the patients with CT scans are summarized in Table I. PSA and PSA velocity were significantly different for positive versus negative CT scan results. PSA was not a significant predictor of a positive or negative CT scan result individually and PSA velocity was barely so. However, when used together in a logistic regression analysis, they were able to predict the CT scan result ($P = 0.03$). Similar to the findings with bone scan, pretreatment PSA, pathologic stage, and grade were not significantly different by CT scan outcome ($P = 0.772, 0.937, 0.554$, respectively), nor were pretreatment PSA

and pathologic stage significant predictors of CT scan outcome ($P = 0.432$ and 0.867 , respectively). The frequency of a positive CT scan result by year from recurrence was 11.1% (3 of 27) in year 1, 25% (3 of 12) in year 2, and 20% (1 of 5) in year 3. The location of CT abnormality was recorded in 10 of 12 patients. The most common sites of abnormality were local recurrence, lung, liver, and lymph nodes.

COMMENT

The evaluation of patients with biochemical failure after RP is a challenge. Terris *et al.*¹⁹ in 1991 recommended that bone scans be routinely obtained in patients with detectable PSA levels after RP. In their 21 patients with a rising PSA after RP, 10 had positive or indeterminate studies (48%). However, of those patients with a positive bone scan, 7 of 10 had positive lymph node metastasis at the time of RP. Partin *et al.*¹² evaluated 51 men with PSA-only recurrence after RP who were followed expectantly until local or distant recurrence was identified. Thirty-five patients were ultimately found to have a positive bone scan. A combination of PSA velocity, pathologic stage, and Gleason grade best distinguished local from distant recurrence in this group. Although the average PSA just before a positive bone scan was 123 ng/mL, they recommended yearly bone scans for patients with biochemical recurrence, because 34% of the men with positive bone scans had a serum PSA of less than 10 ng/mL at the time of the scan. However, similar to the study by Terris *et al.*,¹⁹ 21 (60%) of 35 patients with positive bone scans had pathologic node-positive disease.

A more recent study suggests a more limited role for bone scan in the early evaluation of these patients. In an analysis of 144 bone scans in 93 pa-

tients with biochemical recurrence after RP, Cher *et al.*¹⁴ found that only 4% of the bone scans were positive. Of the 5 patients with a positive bone scan, 3 had positive lymph nodes at the time of RP. In parallel with our findings, both PSA and PSA velocity were strong predictors of bone scan results. They concluded that the likelihood of a positive bone scan in patients with PSA recurrence after RP was less than 5% until the PSA was greater than 40 ng/mL. Our study yielded similar results and confirmed that the likelihood of a positive study is low in the first 3 years after biochemical recurrence (10.4%) and very low in the first year after biochemical recurrence (3.5%).

Pound *et al.*²⁰ recently published their data on the natural history of disease progression in men with PSA recurrence after RP. The median actuarial time from biochemical recurrence after RP to the development of metastatic disease was 8 years, and the time from metastatic disease to death was another 5 years. They showed that the time to biochemical progression, grade, and PSA doubling time were predictive of the likelihood and time to the development of metastatic disease. It is therefore not surprising that the likelihood of an abnormal study is dependent on the interval between recurrence and the imaging study.

We found both PSA and PSA velocity to be independent predictors of bone scan results, although PSA velocity was more powerful in a logistic regression model. Interestingly, PSA was not an independent predictor of CT scan results, although used together in multivariate analysis PSA and PSA velocity were able to predict the CT scan results ($P = 0.03$).

As expected, bone scan detected abnormalities most commonly in the pelvis, ribs, and lumbar spine and CT scan most commonly identified local recurrence, lymphadenopathy, and lung or liver metastases. CT scan was also able to identify bone metastases in 2 patients.

Our population of patients with PSA recurrence is typical of contemporarily treated RP patients, having a low risk of nodal metastasis at surgery. It appears from published reports that the chance of a positive imaging study may be higher in patients with node-positive disease. In our series, only 3 of 65 patients undergoing pelvic lymphadenectomy were found to have positive nodes and none of these 3 patients had either a positive bone scan or CT scan. Thus, our number of node-positive patients was too small to evaluate adequately the impact of nodal status on radiographic assessment.

CT has poor sensitivity for the detection of local recurrences. Kramer *et al.*²¹ retrospectively evaluated 22 patients with biopsy-confirmed local recurrence and found that CT was positive in only 36%, indeterminate in 23%, and negative in 41%. John-

stone *et al.*²² also reviewed 18 patients after RP who underwent CT to evaluate biochemical recurrence and found only 2 (11%) of 18 were positive. However, despite the relatively low yield of CT scanning in this setting, Johnstone *et al.*²² suggested that CT should be performed in patients being evaluated for adjuvant radiotherapy so that the radiation ports can be expanded if necessary or the patient excluded if distant disease is recognized.

It is likely that the continued downward stage migration evident in the PSA era will result in even lower rates of positive imaging studies than seen in our patients, many of whom underwent surgery in the early 1990s. The cost and inconvenience of bone scans and CT scans are also significant. On the other hand, imaging techniques, particularly CT, have improved substantially, which may enhance its sensitivity for the detection of recurrent disease.

The results of our study suggest that the most appropriate radiographic evaluation in this setting depends on the clinical situation. Patients with a low serum PSA level in the first year after biochemical recurrence have a very low likelihood of bone metastasis, and the bone scan can usually be omitted. The possible exception to this is patients with pathologically positive lymph nodes. Patients with a PSA velocity of less than 0.5 ng/mL/mo also have a very low likelihood of an abnormal bone scan (3.4%, 2 of 58), and bone scans can reasonably be omitted in these patients. Certainly, if a patient has biochemical recurrence after RP and chooses observation or hormonal therapy, radiographic studies can be omitted unless the results will change therapy. Similarly, most CT scans performed for patients with biochemical recurrence after RP are of little utility and have little bearing on therapeutic decisions.

A weakness of our study is the lack of standardization of the techniques and interpretation of the bone scans and CT scans. This limitation is inherent in retrospective studies spanning a wide interval and involving geographically separate sites. It does, however, allow the results to be relevant to the general urologic community. Also, the date of each study was missing from the database in some patients, which did not allow them to be included in some of the evaluations. This is, however, the largest study of the utility of both bone scans and CT scans for assessing post-RP biochemical recurrence yet published.

CONCLUSIONS

Patients with biochemical recurrence after RP have a low probability of having a positive bone scan (9.4%) or new information demonstrated on CT scan (9.3%) within 3 years of biochemical re-

currence. If the serum PSA level at the recurrence evaluation was less than 10 ng/mL, only 4.5% of our patients had a positive bone scan (3 of 67). Most patients with a positive bone scan have a high PSA level and a high PSA velocity (greater than 0.5 ng/mL/mo). Thus, radiographic assessment with bone scan and CT scan can be omitted for most patients with early biochemical recurrence after RP.

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