A New Parameter for Measuring Metastatic Bone Involvement by Prostate Cancer: The Bone Scan Index

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ABSTRACT

In this report, we describe a method for quantitative bone scan interpretation (the Bone Scan Index or BSI) in advanced prostate cancer. The BSI estimates the fraction of the skeleton that is involved by tumor, as well as the regional distribution of the metastases in the bones. The purpose of this report is to describe the development and validation of this method in terms of reproducibility and the application of BSI for determining extent of disease and monitoring disease progression. We analyzed 263 bone scans from 90 patients being studied under four protocols at Memorial Sloan-Kettering Cancer Center for progressive, androgen-independent prostate cancer (AIPC), who had bone scans as a part of their work-up. We determined: (a) the intraobserver and interobserver variability of the BSI; (b) the comparison between a change in BSI and prostate-specific antigen (PSA); (c) the regional distribution of bony metastases in early stage D prostate cancer (<3% skeletal involvement); and (d) the rate of growth of bony metastases from prostate cancer. A cube root transformation of the percentage of skeletal involvement increased. The BSI provides a reproducible new parameter for quantitative assessment of bone involvement by AIPC. These results suggest that the BSI will be useful for stratifying patients entering treatment protocols for extent of tumor involvement. Although further study is necessary, serial bone scan BSI appears capable of quantifying both the progression of bony involvement by tumor as well as the response to treatment.

INTRODUCTION

Prostate cancer has a tendency to spread to the bones, and up to 80% of patients who die from prostate cancer have bone metastases as a result of vascular spread and systemic dissemination. Bone scintigraphy is an effective modality in the detection of skeletal metastasis, frequently providing the first evidence of distant malignant spread. For example, the bone scan has proven to be more sensitive than standard radiographic methods for detecting the initial spread of prostate cancer to bone (1).

Modern bone scanning uses a gamma camera and a Tc-99m bone-seeking agent, usually methylene diphosphonate. An area of increased uptake ("hot spot") develops at the site of metastatic involvement in bone because bone turnover is accelerated near the metastatic site and the scanning agent is incorporated into the bone mineral matrix in this region based on accelerated bone mineral turnover. Modern bone scan techniques can detect an increase in bone mineral turnover as small as 10% in regions that are only a few millimeters in size. In contrast, a relatively large volume of bone (~1 cm³) must demineralize by about 50% before the change can be detected by plain radiographs (2). It is not surprising then, that in regard to prostate cancer, the bone scan is often used to stage patients and monitor the course of bony involvement. Improvements in instrumentation, such as dual-headed gamma cameras that are capable of whole-body scanning, have made rapid staging examinations convenient so that the entire skeleton can be surveyed in less than 15 min. The same instrument can also perform single-photon emission computed tomography. Single-photon emission computed tomography significantly increases the...
sensitivity of bone scanning for detecting metastases, especially in the spine, which is a frequent site of initial metastatic involvement.

As a rule of thumb, if the patient is to have localized treatment for prostate cancer, such as external beam radiation therapy, a bone scan is performed to rule out metastatic involvement of bone (3), especially in patients with a high Gleason’s score and a PSA $> 10$ ng/ml (4).

As therapies improve for bone metastases of prostate cancer, better diagnostic methods are needed to more accurately determine the amount of tumor present at baseline and to monitor the tumor’s response to therapy. In contrast to the important role of bone scans in the detection of tumor involvement of bone, the present use of bone scintigraphy as a way to monitor treatment response in prostate cancer is not optimal. In part this reflects an inherent limitation of bone scintigraphy, which is that the tumor is not directly visualized but only indirectly, because it is the reaction of the bone to the local invasion by tumor that is visualized. Other forms of damage to bone, such as degeneration or trauma, can also cause a positive bone scan. Also, standard methods of bone scan interpretation are most commonly descriptive in that nuclear medicine physicians usually report a simple record of the detected sites of tumor in bones. This method is appropriate for detecting tumor spread to bone but is more difficult to use in monitoring tumor response because it is subjective and nonquantitative. The flare phenomena (5), in which the healing bone becomes strongly positive in the region of a tumor site that is responding to therapy, may delay the diagnosis of a favorable treatment response. Interpretation is difficult because the healing bone can show an increase in intensity that mimics metastatic involvement. For this reason, clinical information about the treatment status of the patient as well as the PSA level is essential for proper interpretation of changes in the scintigraphic pattern during therapy.

To improve the monitoring of the treatment of bone lesions, some authors have developed scoring systems for more objective methods of assessing extent of bone metastases, such as counting the number of lesions in the total skeleton and assessing the regional distribution of the metastases (6). These methods are difficult to apply to the problem of monitoring response to treatment. In part this is because bone lesion counting methods become tedious in advanced disease, and once the lesions become large and coalesce, lesion counting may become impossible.

PSA has been shown to be of clinical value in monitoring patients with prostate cancer who have undergone radical prostatectomy, radiation therapy, and/or hormonal treatment (7–9). Although PSA is probably the best current means for monitoring tumor response and progression, this test also has limitations in monitoring tumor response in bone. Although helpful in detecting tumor and for showing progression, PSA levels do not correlate in absolute terms with the tumor burden, and for a given patient may also be influenced by the amount of benign prostatic hypertrophy in residual prostate tissue. Also, for more advanced tumors, PSA levels can be increased both by soft-tissue and bony metastases; therefore, metastatic disease to bone is not monitored directly.

The aim of the present study was to describe an improved bone scan interpretation technique for quantifying the amount of total skeleton that was involved by osseous metastatic disease (the BSI). We sought to determine the precision and accuracy of this scan interpretation in patients with prostate carcinoma and to compare it with the PSA response during treatment and with the normal adult bone marrow distribution. To explore in this way the biological relevance of the BSI in regard to the pathophysiology of bone metastases in prostate cancer, we used a visual method of analysis, which proved suitable for our initial correlation of BSI with tumor progression and response. An advantage of the visual method was that digitized scans were not required, and we could study a larger series of patient studies, going back several years in some cases.

MATERIALS AND METHODS

Patient Population. Two hundred sixty-three bone scans were performed on 90 patients being treated for AIPC. In all patients, the diagnosis of prostate cancer was confirmed by transrectal biopsy. Blood samples for PSA measurements were obtained from each patient before whole-body bone scintigraphy. Normal serum PSA concentrations ranged from 0 to 4 ng/ml.

Bone Scintigraphy. Bone scans were performed 3 h after the i.v. injection of 740 MBq (20 mCi) of Tc-99m methylene diphosphonate. Whole-body images (and static images when indicated) were obtained using a dual-head gamma camera (ADAC; Genesys) equipped with a low-energy, high-resolution collimator at a scan speed of 20 cm/min. Bone scans were read by independent reviewers who were blinded to the patient’s clinical condition.

Bone Scan Quantitative Analysis. To provide a quantitative measure of the extent of metastatic bone disease, the bone scans were analyzed according to the following criteria. One hundred fifty-eight individual bones in the body were listed by name. The weight of each bone, expressed as a fraction of the weight of the entire skeleton, was determined based on ICRP publication No. 23 (10). The fractional involvement of each bone by tumor was estimated visually from the bone scan. The BSI was then calculated by summing the product of the weight and the fractional involvement of each bone expressed as percentages of the entire skeleton.

Inter- and Intraobserver Variability of Bone Scan Interpretation. The interobserver variation was tested on 69 bone scans from the first 18 consecutive patients (mean age, 69 ± 4) with stage D prostate cancer who were entered on a treatment protocol at MSKCC between January 1990 and February 1994. These bone scans were read by three independent reviewers who were blinded to the patients’ condition, as well as the results of the other reviewers’ readings. This was done after the three observers participated in a training session that last about 3 h and involved 10 images in which they graded the images together to reach consensus.

To assess intraobserver variability, one scan for each of the 18 patients was re-read by two readers at 2-year intervals (the first time in July 1995, and the second time in July 1997). A

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1 The abbreviations used are: PSA, prostate-specific antigen; BSI, Bone Scan Index; AIPC, androgen-independent prostate cancer; MSKCC, Memorial Sloan-Kettering Cancer Center.
simple correlation's analysis was used to assess the intraobserver variability.

Comparison of Changes in Serial BSI to Changes in Serial PSA. A comparison was made between changes in the BSI and PSA in 27 patients with AIPC who participated in a treatment protocol with hydrocortisone followed by suramin at PSA relapse. Twenty-four of these patients had sufficient serial bone scans for comparison (an average of 4.3 bone scans/patient). These bone scans were read by two readers and when there was a discrepancy in BSI, a consensus reading was recorded. There was an average of 28 PSA values per patient. A Pearson's moment correlation analysis was used to correlate the changes in PSA and BSI over time.

Distribution of Metastases in Limited Bone Involvement by AIPC (<3% of the Skeleton). The baseline bone scans of 27 patients with AIPC and limited bone involvement were analyzed in regard to regional distribution within the skeleton, and in particular with respect to the distribution of the normal adult bone marrow. A total of 136 lesions were found and plotted onto a composite representation of the distribution of the normal adult skeleton.

Progression of AIPC. Twenty-one patients were found among patients who were being treated for AIPC who had a baseline scan for which the BSI was 3% or less and who progressed to above 3% in a subsequent scan. In all, a series of 62 bone scans were obtained, and the BSI was plotted as a function of time of observation. The data that was obtained was fit to a Gompertzian equation, which describes an exponentially declining exponential growth rate and appears to describe solid tumor growth patterns relatively well.

RESULTS

Inter- and Intraobserver Variability of BSI. A typical whole-body bone scan from a patient with AIPC is shown in Fig. 1 with the corresponding BSI. The initial involvement in the bone progressed quite slowly from January 24, 1990 to May 20, 1990. When the patient developed a rapidly increasing PSA, a follow-up bone scan was ordered in April 1991, which showed a marked change from prior scans. Also, in the 2-month period to June 27, 1991, there was considerable progression of the lesions in the right upper humerus and right hip. Because there had been no change in management up to this point, flare phenomenon is unlikely as a cause of the bone scan progression.

The interobserver variability of the test is shown in Fig. 2. Fig. 2a shows the three readers' estimates of the percentage of bone involvement with the scans ordered by the average of the three readers' estimates for easier visualization. The ordinate is the BSI, and the abscissa is the scan number, ranked in order of the average of the three readers' scores. As can be seen in Fig. 2, a and b, the average BSI of the three readers varied from 0 to 51% in this series of bone scans. A typical "super-scan" of
prostate cancer would be in the range of 30–50%. The absolute variability among readers increases somewhat at the very highest values. However, Fig. 2b shows that the cube root transformation of the three readers’ estimates of the percentage of bone involvement stabilizes the variance over the entire range of analysis, and this simplifies the interpretation of BSI variation between observers. The curve for reader 1 abruptly goes to zero at scan 27 because no reading was available here. Fig. 2c shows the individual reader’s behavior as a function of the other two, i.e., every reader’s deviation from the cube root of the average BSI of the other two readers, plotted as a function of the average BSI of the other two readers. For the most part, the deviations are scattered along the y = 0 line (x-axis), indicating that any systematic difference between the readers tends to be small. There are some trends that are apparent; for example, at the larger BSI values, reader 3 tended to have a higher value than the average of the other two readers.

After a period of 2 years, the intraobserver variability was minimal, showing a correlation coefficient of 0.97 for reader 1 (Fig. 3a) and 0.99 for reader 2 (Fig. 3b), $P < 0.001$. The same reader agreed with his previous reading of the BSI, even after a considerable time gap. Thus, in summary, the reliability of BSI has been characterized; moreover, there is excellent reproducibility of intraobserver observations.

Comparison of Changes in Serial BSI to Changes in Serial PSA. With regard to the comparison between BSI and PSA, 27 patients with AIPC had scans available, of which 24 patients had sufficient serial bone scans for comparison (an average of 4.3 bone scans/patient). These results have been published previously in abstract form (14). The median time between BSI determinations was 75 (47–110) days, with a 25% median change (18–35%) between studies. The median time between PSA determinations was 11 (7–26) days, with a 6% median change between values per patient. On average, there

Fig. 2  a, percentage of bone involvement as estimated by the three readers with the scans ordered by the average of the three readers’ estimates for easier visualization (x-axis, number of scan; y-axis, percentage of bone involved by tumor). b, cube root transformation of the percentage of bone involvement as estimated by the three readers. c, individual readers’ (1–3) behavior as a function of the other two (i.e., every reader’s deviation from the average of the other two is plotted as a function of the average of the other two).
were 4.3 BSI determinations per patient and 28 PSA values per patient. There was a generally parallel rise in PSA and BSI, with a strong concordance between BSI and PSA change with a Pearson’s moment correlation of 0.71 ($P < 0.01$).

Fig. 4 shows two examples of how the BSI might be used to monitor response. The change in PSA and the BSI show a similar trend in these examples. In Fig. 4a, the gradual increase in PSA and the gradual increase in BSI paralleled one another for about 6 months, at which time there was a rapid increase in BSI involvement, followed later by an increase in PSA. In Fig. 4b, the patient underwent rhenium-186 therapy and showed a dramatic response to treatment, as demonstrated by the decrease in both PSA and BSI over time. The arrows indicate treatment with rhenium-186.

**Distribution of Metastases in Limited Bone Involvement by AIPC with <3% of the Skeleton Initially Involved by Tumor.** The distribution of metastatic lesions within the skeleton was studied in a group of 27 patients with AIPC who were being treated under two treatment protocols at MSKCC. These 27 patients had BSI <3% and were considered to have limited disease, in contrast to the balance of patients in this group with more extensive tumor involvement. The distribution of metastatic lesions in the skeleton was determined. There were a total of 136 lesions in these patients, and the pattern of distribution is shown as a black dot placed at the site of tumor involvement on a model of the skeleton shown in the anterior and posterior projection (Fig. 5a). It can be seen that the distribution is not random in the skeleton; instead, the tumor clusters in the axial skeleton, ribs and proximal limbs. The metastatic pattern shows a remarkable parallel with the distribution of the normal adult bone marrow distribution (Fig. 5b). We have interpreted these results as being consistent with the view that the distribution of early metastatic tumor from AIPC is coextensive with the normal red marrow in the adult and suggests that the marrow may be a particularly favorable environment for growth of AIPC tumor.

**Rate of Progression of AIPC.** In a group of three protocols treated for AIPC, we evaluated patients who were progressing during serial scan studies. Because the natural history of prostate cancer is variable, we defined progression as going from low-volume disease (<3% of skeletal involvement) to progress above 3% in a subsequent bone scan, regardless of bone scan interval. Of the 21 follow-up bone scans, the median first follow-up was 108 days after baseline, with a range of
30–1770 days. The BSI of all available scans in this group of patients was plotted as a function of the time after baseline. In all, 21 patients and 62 scans were analyzed, and the data are plotted in Fig. 6. The data were fitted to a Gompertzian equation of the form $BSI(t) = BSI_0 \exp[a/b(1 - \exp(-bt))]$, where $BSI_0$ represents the BSI at time zero at the baseline, $a$ represents the growth rate at time zero, $b$ represents the rate at which the growth rate slows down, and $t$ is the time in days after the baseline scan. The parameters in the equation that best fit the data were determined by minimizing the sum of the squares of the residuals using the Levenberg-Marquardt method (15).

The fit parameters were as follows: $BSI_0 = 3.3\%$; $a = 0.00485$; and $b = 0.00254$. The progression that was observed was most rapid initially, and then the growth rate gradually diminished as more time elapsed from the index scan. This corresponds to a starting doubling time of 43 days, which rapidly diminished with time. We have interpreted these results to be consistent with a Gompertzian growth pattern in which there is more rapid expansion of tumor in the early phase of growth, reflecting a more highly favorable environment for growth of the AIPC tumor. As time goes by, however, there is a gradual loss of favorable conditions, and the growth slows.

DISCUSSION

We developed the BSI method with two goals in mind: (a) the approach should lend itself to automation; and (b) the method should measure information that is biologically relevant to the pathophysiology of bone involvement by prostate cancer.

The bone scan is widely accepted as a valuable tool for monitoring extent of tumor in bone metastases (16, 17), and a number of authors have developed semiquantitative methodology for assessing bone involvement and response and the extent of tumor involvement (18). In particular, Soloway et al. (6) graded the extent of disease into five categories based on the number of bony metastases read on the bone scintigraphy. Such techniques do have value in permitting a stratification of patients in the extent of bone involvement, and at the extremes, i.e., few lesions versus massive number of lesions, there is a correlation with prognosis. Semiquantitative bone scanning methods based on counting the number of lesions are not easily automated, however. Also, when lesions increase in number and become confluent, the number of lesions can actually drop, even when the patient is progressing. Because of these limitations, simpler methods based on scoring or grading schemes have been
proposed. Knudson et al. (19) divided the skeleton into five skeletal areas: vertebrae, ribs, pelvis, long bones, and skull. Patients were stratified according to the number of skeletal areas involved. Other methods for bone scan interpretation have used simple scoring system ranging from 0 to 2, with 0 representing normal uptake, 1 representing single or several uptakes, and 2 diffuse uptake (20). More recently, Jinnouchi et al. (21) have proposed a different method for quantitation of changes in serial bone scintigrams in patients with carcinoma of the prostate using fixed-size regions of interest placed relative to anatomical landmarks. These methods could be easily automated, at least in principle, but much useful information is lost in these simplified approaches, such as the anatomical information about which bones are involved or progressing, so that correlation can be readily made with other diagnostic information. The net result is that none of these semiquantitative methods have been adopted clinically on a large scale.

The BSI method, which is based on fractional involvement of the skeleton on a bone-by-bone basis, will be more amenable to computerized automation, based on segmentation and thresholding approaches, in comparison with other quantitative techniques developed previously. In fact, a method of threshold analysis, which we believe will permit computerized image interpretation of BSI, has been developed at MSKCC (22). We are in the process of transferring this approach from a silicon graphics platform to a more readily accessible PC environment.

This preliminary study shows that the BSI is a reliable method for quantitative interpretation and assessment of bone scan extent or progression of metastases in patients with prostate cancer. The variability of the three readers was individually assessed in relationship to the average of the other two readers and appears to increase as the BSI increases. Hence a cube root transformation was performed empirically to stabilize the variance, so that a direct comparison between readers could be made. In general, it can be said that the variability between readers is acceptably low. Similarly, the reproducibility based on a linear correlation between two readings of readers 1 and 2, as shown in Fig. 3, is also small, with a mean difference of 1.3% BSI over the range of 2–54%. Thus, intraobserver variability of the visual BSI was excellent and, as expected, was significantly less than the interobserver variability.

In considering how we evaluated the validity of the BSI, certain facts about prostate cancer should be kept in mind. The natural history of clinically evident prostate cancer is gradual progression, from organ-confined tumor to spread both by lymphatics to locoregional lymph nodes and hematogenously to distant sites. Once tumor has spread beyond the prostate gland, it is essentially incurable. Prior to treatment of metastatic prostate cancer, the tumor of individual patients is composed of cells of three distinct phenotypes: androgen-dependent, androgen-sensitive, and androgen-independent (23). Initially, most patients with advanced prostate cancer do respond to androgen withdrawal, because the bulk of the tumor at this stage of the disease is, like normal prostatic cells, androgen dependent, so that the cells stop proliferating and in fact die when androgen is withdrawn. During this phase of treatment, the androgen-sensitive cells stop growing, and the androgen-independent cells are unaffected by the treatment but continue to slowly proliferate. These cells are sensitive to other growth factors, including various stimulatory substances found in the bone and bone marrow. This may explain in part why prostate cancer shows a propensity to spread to bone as the most important and in some cases the sole site of metastatic involvement. The cells initially are seeded to the marrow space, where there is a rich microenvironment that favors growth. The involvement of the bones themselves is a secondary phenomenon, as the tumor cells in the bone marrow expand.

As androgen-independent clones proliferate, often within the bones, the tumor becomes unresponsive to hormonal suppression and androgen-independent sites of tumor evolve. PSA levels begin to rise. In fact, progressive increase in PSA usually begins a few months before symptomatic evidence of relapse occurs. Changes in PSA levels have also been shown to have major prognostic impact, and patients who do not normalize their PSA values after treatment have a poor prognosis (24).

It is also clear from studies by Sabbatini et al. (25) that BSI itself is a powerful independent predictor of the prognosis for such patients and will help select patients who may be candidates for very aggressive therapies because of otherwise poor prognosis. For example, in a separate group of 191 patients with AIPC who were treated with liozazole versus prednisone, and whose data are not included in this report, the BSI values of <1.4%, 1.4–5.1%, and >5.1% divided the study group into patients with corresponding median survivals of 18.3 months, 15.5 months, and 8.1 months, respectively (P < 0.0079).

In assessing the validity of the BSI method as an indicator of bone involvement by prostate cancer, we focused on a comparison of BSI to PSA, because PSA is presently considered to be the best cancer marker for progression. Although the BSI represents a very different feature of bony metastases, changes in BSI show good correlation between the changes in PSA during disease progression. The type of correlation that was used, the Pearson’s moment correlation, is used for rank order correlation and is not sensitive to absolute levels of the variable compared. The correlation was highly significant on a statistical basis. As seen in Fig. 4, the correlation in these individual patients appears to be best in progressing disease, and during response the BSI is likely to be significantly slower to change. However, we did not have a large enough group of PSA responders to systematically study this phenomenon in the present series.

Furthermore, interesting biological correlates can be drawn based on the BSI in terms of a match between the distribution of metastatic disease in early AIPC and the normal adult bone marrow and a Gompertzian pattern of skeletal involvement by AIPC during progression.

In the normal adult, red marrow is found in the central skeleton (skull, thorax, pelvis, and spine) and the upper portion of the femurs, humeri (Fig. 5). In the present study, patients with low-volume tumors (i.e., <3% BSI) displayed a distribution of metastases in a manner corresponding to the distribution of the normal adult bone marrow. This is supportive of the notion that the initial seeding and attachment of the tumor cells occur within the red marrow, followed by expansion during growth to adjacent bone (2).

Finally, the BSI has been graphically explored as a function of time after diagnosis. The progression of bone scan changes in AIPC, from early involvement (<3%) to late involvement (Fig. 6), shows a relatively rapid increase initially, followed by a
slowing of expansion as time elapses from baseline bone scans. The data as plotted match well to a Gompertzian pattern of growth, which describes an exponentially decreasing growth rate and is the usual growth pattern of solid tumor (13).

Based on Fig. 6, it is possible to make recommendations regarding the frequency of bone scanning in following patients with AIPC. During the early proliferative stage of androgen-independent tumor when the PSA begins to rise, bone scan changes occur very rapidly. At this stage, bone scans should probably be obtained every 4–6 weeks to help in deciding when to introduce chemotherapy. However, once the bone scan involvement has progressed to 10%, the rate of growth is considerably slower, and bone scans could be obtained every 3 months. When the bone scan is more than 10%, changes will be considerably slower, and six monthly scans should be sufficient to monitor the process, unless the patient is under active treatment with some evidence of response.

We conclude that the BSI as developed and implemented at MSKCC allows a reproducible estimate of the percentage of skeleton involved by tumor in patients with metastatic prostate carcinoma. This approach appears accurate for demonstrating progression of prostatic cancer metastases to bone. There is a highly significant correlation between changes in PSA, a known parameter of progression, and BSI. Also, BSI data indicate that early tumor involvement of bones is coextensive with the distribution of red marrow. Initial involvement of bone by AIPC is quite rapid, with a doubling time of 43 days or less, followed by a gradual slowing of the rate of involvement. Taken together, the findings of the present study are consistent with the hypothesis that the BSI represents a valid and reliable new parameter for quantitative assessment of bone involvement by AIPC. Accordingly, we are presently evaluating BSI as a tool for bone scan interpretation in situations where monitoring of treatment response is an essential feature of patient management. In addition, it is possible that the BSI may prove to be useful for stratifying patients according to their likelihood of response to particular therapies, based on total extent of tumor in bone, and thus help select the most appropriate therapy for the individual patient.

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