Bone Scan Index: A Quantitative Treatment Response Biomarker for Castration-Resistant Metastatic Prostate Cancer

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A B S T R A C T

Purpose

There is currently no imaging biomarker for metastatic prostate cancer. The bone scan index (BSI) is a promising candidate, being a reproducible, quantitative expression of tumor burden seen on bone scintigraphy. Prior studies have shown the prognostic value of a baseline BSI. This study tested whether treatment-related changes in BSI are prognostic for survival and compared BSI to prostate-specific antigen (PSA) as an outcome measure.

Patients and Methods

We retrospectively examined serial bone scans from patients with castration-resistant metastatic prostate cancer (CRMPC) enrolled in four clinical trials. We calculated BSI at baseline and at 3 and 6 months on treatment and performed univariate and bivariate analyses of PSA, BSI, and survival.

Results

Eighty-eight patients were scanned, 81 of whom have died. In the univariate analysis, the log percent change in BSI from baseline to 3 and 6 months on treatment prognosticated for survival (hazard ratio [HR], 2.44; $P = .0089$ and HR, 2.54; $P < .001$, respectively). A doubling in BSI resulted in a 1.9-fold increase in risk of death. Log percent change in PSA at 6 months on treatment was also associated with survival (HR, 1.298; $P = .013$). In the bivariate analysis, change in BSI while adjusting for PSA was prognostic at 3 and 6 months on treatment (HR, 2.368; $P = .012$ and HR, 2.226; $P = .002$, respectively), but while adjusting for BSI, PSA was not prognostic.

Conclusion

These data furnish early evidence that on-treatment changes in BSI are a response indicator and support further exploration of bone scintigraphy as an imaging biomarker in CRMPC.

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INTRODUCTION

The axial skeleton, the primary site of active marrow, is the most common distribution of metastatic spread for patients with prostate cancer. At this time, there is no standard means by which osseous lesions can be directly visualized or quantified; thus, there is no qualified imaging biomarker for prostate cancer. Bone scintigraphy is commonly used to assess disease burden and treatment effects, but it is an imperfect modality for quantifying disease or for demonstrating treatment effects. Bone scans do not specifically identify cancer, can paradoxically worsen in the face of response ("flare"), and frequently improve only slowly if at all, despite patients' receiving active treatments. Nonetheless, bone scans are standard, widely used, and reimbursed, and therefore they appear in nearly every clinical trial of castration-resistant metastatic

prostate cancer (CRMPC) as eligibility criteria and response measures.

To mitigate the shortcomings of bone scintigraphy, there has been a recent effort to standardize bone scan interpretation and data collection by using consensus criteria to define progressive disease, control for flare, and establish criteria for data collection.¹ These end points are being validated in several ongoing phase III studies. However, to develop bone scintigraphy as an imaging biomarker, a quantitative measure is needed for comparing baseline and on-treatment status. In the past, methods of quantifying bone lesions have included lesion counting,² lesion scoring on a scale from 0 to 2,³ and lesion rating of negative versus positive.⁴ The bone scan index (BSI) was developed as a quantitative tool to improve the interpretability and clinical relevance of the bone scan.⁵ The BSI is a method of expressing the tumor burden in bone as a percent of the total

Fig 1. (A) Visualization of the bone scan index (BSI). The area of active marrow is shown in red, which is usually the primary distribution of metastatic disease in prostate cancer. The BSI is calculated first by determining the percentage of each bone that is involved by the tracer in relationship to the total skeletal mass, as determined from reference man.⁷ This procedure is done for every single bone, and all of the individual percentages are summed to arrive at a single number that represents the total tumor burden as a percentage of the total skeletal mass.⁵ Notably, approximately 40% of the skeletal mass is active marrow.⁸ (B) Typical sequence of bone scans and BSI calculations for a patient with metastatic castration-resistant prostate cancer. The percentage of total skeletal mass involved by the tracer progresses from 0% to 0.59% to 7.7% and after treatment falls to 5.4%. MDP, methylene diphosphonate; Tc-99m, technetium-99 metastable nuclear isomer.

skeletal mass based on reference man skeletal masses.^{6,7} There is also a relationship to the involvement of a patient's active bone marrow because most metastases are found within the 40% of the skeleton that harbors active red marrow⁸: in the axial skeleton, ribs, and upper humeri and femora (Fig 1). The BSI has undergone preliminary analytic validation in studies that have demonstrated intra- and inter-reader reproducibility. Blinded reviewers experienced less than 10% interobserver variability; intraobserver variability had a correlation coefficient of between 0.97 and 0.94.^{5,9}

These preliminary results for reproducibility and precision justified further development of the BSI, and we have been exploring it in two well-defined contexts of use: as a prognostic indicator and as a response indicator. We have previously demonstrated that the BSI is a useful prognostic measure having shown that, as a single pretreatment value, the baseline BSI was associated with survival.⁹ In this study, we are seeking to qualify BSI as a response indicator biomarker, hypothesizing that change in BSI while on treatment may be associated with survival. For this, we used a population of patients with progressive castration-resistant metastatic disease who had been treated with chemotherapy on four clinical trials at a single center. Patients on these

trials had undergone serial bone scans at regular 12-week intervals. To test our hypothesis, we developed a mathematical model to examine the relationship between survival and on-treatment changes in BSI and prostate-specific antigen (PSA).

PATIENTS AND METHODS

Study Population

For the source data of this retrospective analysis, we used four clinical trials with comparable end points conducted between 1997 and 2005 at Memorial Sloan-Kettering Cancer Center (MSKCC). Although the entry criteria for each trial had subtle differences, all patients had CRMP. All studies had been approved by the MSKCC institutional review board as therapeutic trials; for this analysis, we obtained a separate institutional review board waiver allowing examination of the bone scans, standard imaging, PSA data, and survival data. To qualify for this analysis, patients were required to have osseous metastases at the start of treatment and to have had a total of at least two bone scans to be able to examine change over time.

BSI and PSA Data Collection

In each of the four studies, radionuclide bone scans were collected at baseline (performed just before the start of treatment) and at 3 and 6 months after the baseline scan while on study (+3, +6). PSA levels were obtained at each of the three time points ($\pm$ 4 weeks). Survival time was defined as the time between the start of treatment and the date of death.

For this analysis, a single reader (I.S.M.) calculated the BSI for all bone scans. This was done without knowledge of patients' clinical outcomes and after training on a test set of BSIs that used a standard template developed by another coauthor (S.M.L.) that also provided instruction on making the BSI measurements. We then compared the BSI of the baseline scan with the on-treatment scans (+3 and +6). Percent change in BSI and PSA was determined for the following two intervals: baseline to +3 and baseline to +6.

Statistical Analyses

A proportional hazards model was used to evaluate the relationship between BSI changes and time to death during each on-treatment scanning interval (baseline to +3 and baseline to +6), as well as the prognostic value of the baseline BSI. Percent change of BSI and PSA was logarithmically transformed to correct for skewness.

A Cox model was used to assess the relationship between survival and on-treatment BSI and PSA alterations during each on-treatment scanning interval. The assessment of significance was derived from the Wald test. In the bivariate analyses, the test of significance for a factor was computed by adjusting for the other factor in the model. The analyses were landmarked to begin follow-up at 3 and 6 months after start of treatment. An additional Cox model was used to determine the relationship between survival and baseline BSI and PSA. To portray the relationship between survival time and on-treatment changes in BSI and PSA, a smoothed Kaplan-Meier estimate of the median survival conditional on each covariate was generated.¹⁰ Heuristically, the local median survival times are estimated by using data located in the neighborhood of each covariate value. In addition, the correlation between on-treatment changes in BSI and PSA at each interval was determined by using Kendall's tau correlation coefficients.

RESULTS

Patient Characteristics

We examined data for 138 participants in four clinical trials involving antimicrotubule chemotherapy. We excluded 13 patients for not having osseous metastases and 37 for having insufficient imaging studies, yielding an 88-patient cohort. Figure 2 diagrams the number of patients in each cohort eligible for analysis and the number

Fig 2. Flow chart detailing the available patient cohorts for the baseline, +3 months on-treatment, and +6 months on-treatment analyses. Five patients had missing data at baseline. There is a decrease in sample size from baseline to +3 months to +6 months as patients dropped out of their clinical trials in which the imaging was performed because of disease progression (manifested primarily by an increase in prostate-specific antigen), drug toxicity, or concurrent disease. Alive or dead indicates the patients' vital status at the time the analysis was performed.

of ineligible/discontinuing patients. Table 1 details the cohort's baseline patient demographics, prior treatment histories, type of chemotherapy used, on-treatment BSI and PSA assessments, and vital status.

Survival Analysis of BSI and PSA

Results of the univariate and bivariate survival analyses of baseline BSI, on-treatment BSI changes, baseline PSA, and on-treatment PSA changes are provided in Table 2. A landmark analysis was used, and thus the on-treatment results are conditional on the patient surviving beyond that time. In the univariate analysis, baseline BSI trended toward significance (hazard ratio [HR], 1.15; $P = .08$). On-treatment changes in BSI associated well with overall survival, with comparable estimated HRs at both landmarked times of 3 and 6 months. A patient whose BSI had doubled had approximately a one-third chance of living longer than a patient with no change in BSI (HR, 2.44; $P = .0089$ and HR, 2.54; $P < .001$, respectively). Conversely, if the BSI was reduced, there was an improved probability of survival compared with a stable BSI, as depicted in Table 3. An alternative interpretation is that a doubling in BSI while on treatment represented a 1.9-fold increase in the risk of death.

In the univariate survival analysis, baseline PSA trended toward significance (HR, 1.17; $P = .06$). The changes in PSA at 3 months on treatment did not demonstrate sufficient evidence of association with survival (HR, 1.156; $P = .133$), but the later changes in PSA at 6 months on treatment were associated with survival (HR, 1.298; $P = .013$).

Bivariate Analysis Comparing Baseline and On-Treatment Alterations in BSI Versus PSA

A landmark bivariate analysis was performed to compare baseline BSI and PSA and on-treatment BSI and PSA changes. Neither BSI nor PSA at baseline was associated with survival when both are contained in the model (HR, 1.06; $P = .49$ and HR, 1.16; $P = .13$, respectively). At both on-treatment time points, alterations in BSI while adjusting for PSA were associated with survival (BSI at 3 months: HR, 2.368; $P = .012$ and BSI at 6 months: HR, 2.226; $P = .002$); alterations in PSA were not associated with survival while adjusting for BSI (Table 2).

The relationships between BSI, PSA, and survival are shown in Figure 3, in which all factors are treated as continuous variables. As can

be seen, as the on-treatment BSI values increase, the estimated median survival diminishes. Figure 3 also shows that few bone scans actually improved with treatment. Conversely, on-treatment PSA declines were frequently seen but did not necessarily translate into a significant improvement in survival at 3 months.

Correlation Between On-Treatment BSI and PSA Changes

Kendall's tau statistics were calculated to formally assess the association between changes in BSI and PSA at each on-treatment time interval. There was a modest correlation between BSI and PSA alterations at 3 months on treatment ($\tau = 0.221$; $P = .006$; $n = 79$) and at 6 months on treatment ($\tau = 0.322$; $P < .001$; $n = 66$). The correlations between time intervals for each factor were moderate, with $\tau = 0.43$ ($P < .001$) for PSA and $\tau = 0.62$ ($P < .001$) for BSI.

DISCUSSION

The BSI is a means of capturing bone scintigraphy data as a single reproducible quantitative measure, thus allowing bone scintigraphy to be explored as an imaging biomarker. A critical component of biomarker development is the evidentiary process of linking an analytically valid biomarker to a specific "context of use." This study examined BSI as a response indicator (observing a relationship between on-treatment changes in BSI and survival). The biomarker was studied in a defined cohort of patients with progressive CRMPC who had received chemotherapy with the same class of agent and who had had assessments on treatment at fixed time intervals. BSI changes on treatment were a significant prognostic factor for survival in both the univariate and bivariate analyses. On the basis of a 6-month landmark analysis, a patient with a doubling of BSI from baseline had a 0.34 chance of surviving longer than a patient with no change in BSI. Alternatively, a doubling of BSI while on treatment resulted in a 1.9-fold increase in the risk of death. The change in PSA at 6 months in the univariate analysis was a significant prognostic factor for survival; however, all other on-treatment changes in PSA did not achieve significance.

Table 1. Patient Demographics (N = 88)

Variable (at baseline)	No. of Patients*	No.	%	Median	Range
Age, years				67.70	44-83
Gleason score	83			8	5-10
KPS, %				80	70-90
BSI, %	83			2.81	0.10-46.29
PSA, ng/mL	83			95.95	0.52-2,282.15
Hb, g/dL				12.70	8.5-15.7
Alkaline phosphatase, U/L				99.5	48-2,352
Lactate dehydrogenase, U/L				186.5	65-2,291
Prostate acid phosphatase, ng/mL				8.95	0.7-1,044.7
No. of prior hormonal treatments (at baseline)	84				
0		1	1.2		
1		7	8.3		
2		26	31.0		
3		24	28.6		
> 3		26	31.0		
Previous chemotherapy		38	45.2		
Previous immunotherapy		10	11.9		
Protocol					
Ixabepilone ± estramustine		40	45.5		
Ixabepilone v mitoxantrone		17	19.3		
Paclitaxel, estramustine, and carboplatin		13	14.7		
Paclitaxel, intravenous estramustine, and carboplatin		18	20.5		
On-treatment BSI and PSA (months from baseline)					
BSI					
+3	79			3.28	0.06-46.29
+6	66			5.52	0.06-58.24
PSA					
+3	79			26.32	0.19-2,209.13
+6 months	66			57.14	0.33-1,758.34
Status at end of follow-up period					
Living		7	8		
Deceased		81	92		

Abbreviations: BSI, bone scan index; Hb, hemoglobin; KPS, Karnofsky performance score; PSA, prostate-specific antigen.
 * No. of Patients indicates sample size for specified variable. Analyses are based on full sample (N = 88) unless otherwise noted.

Table 2. BSI and PSA Univariate and Bivariate Survival Analysis

Variable	No. of Patients	HR	SE	P
Univariate analysis				
BSI (months from baseline)				
Baseline only	83	1.15	0.08	.08
Baseline to +3	79	2.44	0.34	.0089
Baseline to +6	66	2.54	0.224	< .001
PSA (months from baseline)				
Baseline only	83	1.17	0.08	.06
Baseline to +3	79	1.156	0.097	.133
Baseline to +6	66	1.298	0.105	.013
Bivariate analysis				
Baseline only				
BSI	83	1.06	0.09	.49
PSA	83	1.16	0.10	.13
Baseline to +3 months				
BSI	79	2.368	0.344	.012
PSA	79	1.139	0.097	.179
Baseline to +6 months				
BSI	66	2.226	0.260	.002
PSA	66	1.111	0.110	.338

NOTE. The percent changes in BSI and PSA were logarithmically transformed.
 Abbreviations: BSI, bone scan index; HR, hazard ratio; PSA, prostate-specific antigen.

weaker indicator requires a larger patient cohort to show its indicative value. The Sabbatini data set (n = 191) was more than twice as large as ours and therefore has more power to demonstrate the statistical significance of baseline BSI. As such, our current data on baseline BSI's prognostic value neither negate nor contradict the results from the prior Sabbatini study; instead, they bolster the strength of the prognostic value we observed for the on-treatment change in BSI.

Changes in BSI while on treatment were significantly associated with survival but on-treatment changes in PSA were not while adjusting for change in BSI. Although PSA declines were frequently seen after 3 and 6 months on treatment, these findings were not strongly correlated to bone scan findings at the same time intervals. Preliminarily, this analysis suggests that even when PSA declines and BSI increases, patients do not live longer. These data underscore the question of whether the occurrence of an on-treatment PSA decline is less relevant than the durability of that decline.

The limitations of the BSI as a biomarker do not escape the shortcomings of the imaging modality itself. Bone scans are still not

Table 3. Relationship Between Δ BSI and Survival Probabilities

Percent Change in BSI	Probability That the Patient Has Longer Survival Relative to a Patient With No Change in BSI
10	0.48
20	0.46
50	0.41
100	0.34
-10	0.52
-20	0.55

NOTE. Probabilities were computed by using the hazard ratio 2.54, derived from the univariate baseline bone scan index (BSI) analysis at 6 months.

Separately and secondarily, we also examined baseline BSI as a prognostic factor to validate earlier work.⁹ We found that baseline BSI and PSA exhibited a trend toward an association with overall survival, although the *P* values were greater than .05. In a previous study of baseline BSI only, Sabbatini et al⁹ found that the baseline BSI was strongly associated with overall survival in both univariate analysis (*P* = .001) and in multivariate analysis for BSI within the range of 1.4% to 5.1% (*P* = .007). Our study examines both baseline BSI and the change in BSI. In our analysis, change in BSI on treatment is a stronger indicator of the risk of death than the baseline BSI value. A

Fig 3. Nonparametric estimation of median time to death against on-treatment (A, B) bone scan index (BSI) and (C, D) prostate-specific antigen (PSA) changes. Each “x” symbol represents a death event, and each “o” symbol represents a patient still alive at the time of analysis.

direct measures of disease and do not change as quickly as other treatment indicators such as PSA, alkaline phosphatase, LDH, and others. In addition, the range of BSI values is smaller than the range of these parameters. To address this limitation, we are currently developing techniques to express BSI not as a fraction of skeletal mass but as a percent of active marrow. This particular study was also limited by relatively small patient numbers and by reliance on retrospective analysis of existing clinical trial data sets. In addition, MSKCC is a single tertiary care facility whose patients and radiology procedures do not necessarily represent those found in community practice. We are working with several institutions on a cross-institutional data set to further evaluate the utility of BSI and to do so in an automated fashion. This effort will broaden the experience of using BSI and will reduce workload, because it currently takes an average of 20 minutes to derive BSI on a per scan basis. In addition, this study did not have enough patients to compare BSI with all known prognostic factors for prostate cancer, such as the serologic indicators above, Gleason score, or other clinical parameters such as performance status.^{11,12}

The purpose of this study was to take the initial steps for beginning to generate evidence toward qualification of BSI as an imaging biomarker in CRMPC, to establish the methodology by which future studies could be done, and to preliminarily explore the two most

commonly used end points in CRMPC clinical trials: imaging and PSA.^{12,13} We intend to further explore BSI by using large data sets from randomized clinical trials in which the radiographic criteria of Prostate Cancer Working Group 2¹ are being validated. These trials have survival as a primary end point, with meticulous attention being paid to recording bone scan data. These data sets will allow us to model on-treatment changes in BSI with all of the prognostic factors for prostate cancer in a multivariate manner. Looking beyond bone scintigraphy, the methods of using highly controlled populations and quantitative imaging end points can be applied to molecular imaging techniques that directly interrogate the cancer cell and overcome many of the limitations inherent in bone scans.

To summarize, this study preliminarily showed that on-treatment change in BSI is strongly associated with overall survival for patients receiving chemotherapy. This study also preliminarily showed that changes in PSA were not associated with survival while adjusting for changes in BSI. This analysis was rigorously controlled by means of a moderately large patient data set, controlled disease state, and multiple scanning time points. It serves as a good foundation for more extensive research on BSI, a quantitative measure of progression in CRMPC. Currently, this biomarker is being automated for prospective study in future trials of cytotoxic and other classes of agents that are now in the prostate cancer therapeutic armamentarium.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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