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Phase 3 Assessment of the Automated Bone Scan Index as a Prognostic Imaging Biomarker of Overall Survival in Men With Metastatic Castration-Resistant Prostate Cancer

A Secondary Analysis of a Randomized Clinical Trial

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Key Points

Question

Is the automated Bone Scan Index an independent prognostic determinant of overall survival in men with metastatic castration-resistant prostate cancer?

Findings

In this secondary analysis of 721 participants in a randomized clinical trial, the automated Bone Scan Index was significantly associated with overall survival and remained independently associated with overall survival in a multivariable survival model. The automated Bone Scan Index was also significantly associated with additional clinical end points.

Meaning

This study supports the prognostic utility of the automated Bone Scan Index in the design and eligibility of clinical trials of systemic therapies for patients with metastatic castration-resistant prostate cancer.

Abstract

Importance

Prostate cancer commonly metastasizes to bone, and bone metastases are associated with pathologic fractures, pain, and reduced survival. Bone disease is routinely visualized using the technetium Tc 99m (^{99m}Tc) bone scan; however, the standard interpretation of bone scan data relies on subjective manual assessment of counting metastatic lesion numbers. There is an unmet need for an objective and fully quantitative assessment of bone scan data.

Objective

To clinically assess in a prospectively defined analysis plan of a clinical trial the automated Bone Scan Index (aBSI) as an independent prognostic determinant of overall survival (OS) in men with metastatic castration-resistant prostate cancer (mCRPC).

Design, Setting, and Participants

This investigation was a prospectively planned analysis of the aBSI in a phase 3 multicenter randomized, double-blind, placebo-controlled clinical trial of tasquinimod (10TASQ10). Men with bone metastatic chemotherapy-naïve CRPC were recruited at 241 sites in 37 countries between March 2011 and August 2015. The statistical analysis plan to clinically evaluate the aBSI was prospectively defined and locked before unmasking of the 10TASQ10 study. The analysis of aBSI was conducted between May 25, 2016, and June 3, 2017.

Main Outcomes and Measures

The associations of baseline aBSI with OS, radiographic progression-free survival (rPFS), time to symptomatic progression, and time to opiate use for cancer pain.

Results

Of the total 1245 men enrolled, 721 were evaluable for the aBSI. The mean (SD) age (available for 719 men) was 70.6 (8.0) years (age range, 47-90 years). The aBSI population was representative of the total study population based on baseline characteristics. The aBSI (median,

1.07; range, 0-32.60) was significantly associated with OS (hazard ratio [HR], 1.20; 95% CI, 1.14-1.26; $P < .001$). The median OS by aBSI quartile (lowest to highest) was 34.7, 27.3, 21.7, and 13.3 months, respectively. The discriminative ability of the aBSI (C index, 0.63) in prognosticating OS was significantly higher than that of the manual lesion counting (C index, 0.60) ($P = .03$). In a multivariable survival model, a higher aBSI remained independently associated with OS (HR, 1.06; 95% CI, 1.01-1.11; $P = .03$). A higher aBSI was also independently associated with time to symptomatic progression (HR, 1.18; 95% CI, 1.13-1.23; $P < .001$) and time to opiate use for cancer pain (HR, 1.21; 95% CI, 1.14-1.30; $P < .001$).

Conclusions and Relevance

To date, this investigation is the largest prospectively analyzed study to validate the aBSI as an independent prognostic imaging biomarker of survival in mCRPC. These data support the prognostic utility of the aBSI as an objective imaging biomarker in the design and eligibility of clinical trials of systemic therapies for patients with mCRPC.

Trial Registration

ClinicalTrials.gov Identifier: NCT01234311

This secondary analysis of a randomized clinical trial assesses the automated Bone Scan Index as an independent prognostic determinant of overall survival in men with metastatic castration-resistant prostate cancer.

Introduction

More than 90% of men with lethal metastatic castration-resistant prostate cancer (mCRPC) have bone metastasis.[1] Bone scanning of preinjected technetium Tc 99m (^{99m}Tc) is the standard imaging modality for bone metastases in prostate cancer and is ubiquitously used in clinical trials to stage and monitor the course of skeletal disease burden. This technique measures tumor activity indirectly based on osteoblastic activity in the tumor microenvironment. The current standard of bone scan assessment relies on manual assessment of counting metastatic lesion numbers,[2] which remains semiquantitative and open to variability because of subjective interpretation. Variability in the assessment of tumor burden can limit the clinical utility of bone scans in accurate staging of mCRPC. As the therapeutic options in mCRPC increase, more accurate and reproducible assessment of total skeletal disease burden is needed.

The Bone Scan Index (BSI) is a quantitative assessment of bone scan data that represents the total tumor burden as the fraction of total skeleton weight.[3] The BSI methods were developed to represent the total pathophysiology of bone involvement in prostate cancer as a single numeric index, which can be objective in staging and monitoring of disease. In preliminary studies,[4,5] the BSI has shown clinical utility as a prognostic and progression biomarker to assess the association between therapy and bone burden. Despite demonstrating clinical utility, the application and dissemination of the BSI in clinical practice have been limited because of the laborious manual calculations, which have been reported to take up to 30 minutes per scan in patients with extensive bone metastasis.[6]

The BSI methods have been automated with artificial neural networks to detect and classify metastatic hot spots in bone scans, with minimal manual supervision.[6] Analytical validation demonstrated that the automated BSI (aBSI) platform gives accurate and reproducible assessments in low-burden to high-burden disease ($r = 0.99$; $P < .001$) and minimizes interoperator variability ($\kappa = 0.96$; $P < .001$).[7,8] Compared with manual BSI calculation, the output from the aBSI platform is several magnitudes faster (5 seconds per scan), and it is 100% reproducible in repeated testing of the same scan, irrespective of the reader.

Several preliminary studies[9,10,11,12,13] have shown aBSI assessment to be a prognostic biomarker for mCRPC. However, the scope of all previous studies in demonstrating the clinical utility of the aBSI as a prognostic biomarker has been limited because of the nature of retrospective ad hoc analyses. In addition, previous investigations of the independent association of the aBSI with overall survival (OS) have lacked predictive models that include all known significant prognostic biomarkers in mCRPC.[14]

The primary objective of the present study was to perform a prospectively defined analysis to clinically assess the aBSI as an independent prognostic determinant of OS in men with mCRPC. In the multivariable setting, the aBSI was also evaluated against all known prognostic biomarkers and clinical end points in mCRPC. The aBSI analysis was incorporated into a phase 3 multicenter randomized, double-blind, placebo-controlled clinical trial of tasquinimod (10TASQ10 study) in mCRPC.

Methods

Study Design

This investigation was a prospectively planned analysis of the aBSI in a phase 3 multicenter randomized, double-blind, placebo-controlled clinical trial of tasquinimod (10TASQ10 study), a small-molecule inhibitor of myeloid suppressor cell activity and immune-mediated angiogenesis. The 10TASQ10 study[15] has been previously described in detail. Briefly, men with bone metastatic chemotherapy-naive CRPC were recruited at 241 sites in 37 countries between March 2011, and August 2015, and were assigned 2:1 to receive tasquinimod or placebo until progression or toxic effects. The analysis of aBSI was conducted between May 25, 2016, and June 3, 2017.

The statistical analysis plan to clinically evaluate the aBSI was prospectively defined and locked before unmasking of the 10TASQ10 study. As the primary objective of this statistical analysis plan, baseline aBSI was evaluated against OS, defined as time from random assignment to death. The aBSI was also associated with the following other clinical end points: (1) prostate cancer–specific survival; (2) radiographic progression-free survival (rPFS), defined as time from random assignment to radiologic progression or death, where radiographic progression was defined as soft-tissue progression (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1),[16] bone progression detected with confirmatory bone scans (Prostate Cancer Working Group 2-3 [PCWG2-3]),[2] or radiographically confirmed spinal cord compression or fracture resulting from malignant progression; (3) time to symptomatic progression; and (4) time to opiate use for cancer pain.

The 10TASQ10 study was approved by the institutional review board or ethics committee at each participating center and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry, and the study was registered under ClinicalTrials.gov identifier NCT01234311.

Image Analysis

The aBSI analysis was conducted masked to study treatment and outcomes. All digital images from bone scans were quality checked to ensure that the anterior and posterior bone scans were saved in the standard Digital Imaging and Communications in Medicine (DICOM) format with uncompressed pixel data. Image files failing one or more of these criteria were excluded from the analysis. The aBSI analysis was performed using the automated platform developed by EXINI Diagnostics AB, Lund, Sweden, a subsidiary of Progenics Pharmaceuticals, Inc (New York, New York). The aBSI was assessed according to the software provider's instructions by an experienced bone scan reviewer (L.E.) masked to study treatment, other scan data, biomarker data, and clinical outcome. The methods for the aBSI analysis of bone scans have been described previously.[6] Briefly, the different anatomic regions of the skeleton are segmented, and abnormal hot spots are detected and classified as metastatic or benign lesions. The mass fraction of the skeleton for each metastatic hot spot is determined, and the aBSI is calculated as the sum of all such fractions.

Statistical Analysis

The statistical analysis plan to evaluate the aBSI was prospectively defined and locked before unmasking of the 10TASQ10 study. Baseline statistics included percentages for categorical data and medians for continuous data for the study, the aBSI population, and each aBSI quartile.

Spearman rank correlation was used to evaluate the association of baseline aBSI with other baseline prognostic biomarkers. These comprised (1) tumor pain using a visual analog scale (VAS); (2) Karnofsky performance status (KPS); and (3) blood-based disease biomarkers, including albumin, prostate-specific antigen (PSA), lactate dehydrogenase (LDH), C-reactive protein (CRP), hemoglobin (Hb), alkaline phosphatase (ALP), bone-specific ALP (BAP), neutrophils, lymphocytes, and neutrophil to lymphocyte ratio (NLR).

Cox proportional hazards regression models based on stratification factors for randomization (KPS, visceral metastases, and geographic region) were used to analyze the associations of the aBSI with OS and other time-to-event end points. Covariates that had a skewed distribution were $\log_2$ transformed. In addition, the aBSI was split into 4 quartiles (Q1, Q2, Q3, and Q4). Quartile was used as a reference to evaluate linearity and stratification of clinical end points.

An explorative analysis was performed to assess the discriminatory ability to predict the survival outcome for the aBSI and the standard assessment of lesion number at baseline. The manual lesion counting denoted with "greater than 20 or too many metastases to count" was assigned a value of 25. To accommodate a comparative analysis between the aBSI and lesion number, the aBSI data were truncated at 15 to avoid a large influence for extreme values. The concordance index by Uno et al[17] was used to compare the 2 variables. To further evaluate the influence of the aBSI on OS, adapted subpopulation treatment effect pattern plot (STEPP)[18]

was performed as an exploratory analysis. The population was divided into 15 groups based on baseline aBSI, with 5% overlap resulting in subgroups of approximately 17% of the patients, to describe the approximate median survival from low to high aBSI.

The aBSI was also evaluated in a prospectively defined multivariable survival model that was generated through backward selection, where factors with $P > .001$ were removed and the aBSI was always included. The Akaike information criterion (AIC) and the Uno concordance index were used to evaluate the prognostic model with and without the aBSI to assess whether the aBSI has an additive prognostic influence on OS. The AIC and the concordance index estimate the quality of each survival model, relative to each of the other models, and thus provide a means for selecting the best model (the one with the lowest AIC score and the highest concordance index). A sensitivity analysis with more standard covariates was performed. $P < .05$ was regarded as significant hazard ratios (HRs), and 2-sided 95% CIs were calculated for each model. No correction for multiplicity was performed. All statistical analyses were conducted using a software program (SAS, version 9.4; SAS Institute Inc).

Results

Baseline Characteristics

Of the 1245 men enrolled in the phase 3 trial, 739 had valid bone scans for quantitative aBSI analysis; 506 of the 1245 (40.6%) were excluded because of the lack of a suitable bone scan in the standard DICOM format. Another 18 men had superscans and were excluded because of the inability of the aBSI to capture diffused high bone burden, leaving 721 men evaluable for this analysis (Figure 1). The mean (SD) age (available for 719 men) was 70.6 (8.0) years (age range, 47-90 years).

Patient characteristics of the total population, the aBSI population, and the aBSI quartiles are summarized in eTable 1 in the Supplement. Of the 721 aBSI-evaluable patients, 402 had 10 or more bone lesions, with the median aBSI being 1.07 (range, 0-32.60). Patients were divided into the following 4 equally sized nonoverlapping aBSI quartiles: 180 in Q1 (median, 0.05; range, 0-0.27), 181 in Q2 (median, 0.58; range, 0.28-1.07), 180 in Q3 (median, 2.06; range, 1.08-3.96), and 180 in Q4 (median, 6.72; range, 3.97-32.60). Representative anterior and posterior bone scans from each of the aBSI quartiles are shown in eFigure 1 in the Supplement.

Associations of the aBSI With Clinical Prognostic Factors

Baseline aBSI correlated strongly with the number of bone lesions at study entry (Spearman rank correlation, 0.68; $P < .001$), indicating a strong association with the standard measure of bone burden. The aBSI also had strong correlations (0.67-0.69) with serum levels of ALP and BAP at baseline. The correlation between the aBSI and PSA level was moderate at 0.48. Correlations of the aBSI with LDH, CRP, and Hb levels and with tumor-related pain (VAS score) were all weak (eTable 2 in the Supplement).

Primary Outcome of the Association of Baseline aBSI With OS

In the prospectively defined univariate analyses to determine the association of baseline aBSI with OS, the risk of death (from any cause) was found to increase by 20% per doubling of the aBSI (HR, 1.20; 95% CI, 1.14-1.26; $P < .001$). Estimated median OS for aBSI Q1 was 34.7 months; for aBSI Q2, 27.3 months; for aBSI Q3, 21.7 months; and for aBSI Q4, 13.3 months. The median OS values corresponded to a 65% reduction in the risk of death for patients in aBSI Q1, 56% reduction in Q2, and 40% reduction in Q3 compared with patients in Q4 (Figure 2A).

The exploratory STEPP (subpopulation treatment effect pattern plot) analysis showed longer OS in patients with low aBSI at baseline (eTable 3 and eFigure 2 in the Supplement). The patients in subgroups with a mean baseline aBSI of 0.2 or lower had a median OS longer than 30 months, while the patients in subgroups with a mean baseline aBSI of 5.6 or higher had a median OS shorter than 15 months. In addition, the discriminative ability of the aBSI (C index, 0.63) in prognosticating OS was significantly higher than that of the manual lesion counting (C index, 0.60) ($P = .03$) among 709 men. The univariate and bivariate Cox proportional hazards regression model analysis and the corresponding concordance index are summarized in Table 1.

Multivariable Cox proportional hazards regression models for OS using all the significant univariate covariates were generated through backward selection. Factors that were dropped from the model were (in order): pain (VAS score), Hb levels, visceral metastases, geographic region (all but Eastern Europe), historical PSA slope, NLR, ALP levels, and KPS. The multivariable survival model resulted in the following 5 variables that were independently associated with OS: Eastern Europe as the geographic region, values for albumin, serum PSA, LDH, and CRP (Table 2). The aBSI remained independently associated with OS (HR, 1.06; 95% CI, 1.01-1.11; $P = .03$) after adjustment for these significant variables. The AIC score for the survival model with the aBSI was 3 U lower than the AIC score for the regression model that excluded the aBSI. The concordance index was 0.01 U higher for the model with the aBSI. An explorative but more conventional clinical multivariable model that included VAS score of 4 to 10, albumin and LDH values exceeding 281 U/L (upper limit of normal), Hb, KPS of 80 or less, and PSA showed similar results (HR, 1.06; 95% CI, 1.01-1.12 per log2 aBSI change; $P = .03$), with the AIC score improving 3 U and a concordance index of 0.71 for both models. (To convert LDH level to microkatals per liter, multiply by 0.0167.)

Secondary Outcomes

Finally, we evaluated baseline aBSI for associations with other clinically important outcomes. Table 3 lists associations with the aBSI as a continuous variable and by quartiles for these outcomes. The aBSI was associated with prostate cancer–specific survival (HR, 1.20; 95% CI, 1.14-1.26; $P < .001$) (Figure 2B), time to symptomatic progression (HR, 1.18; 95% CI, 1.13-1.23; $P < .001$) (Figure 2C), and time to opiate use for cancer pain (HR, 1.21; 95% CI, 1.14-1.30; $P < .001$) (Figure 2D). As expected, baseline aBSI was not associated with risk of soft-tissue progression (HR, 0.96; 95% CI, 0.90-1.03; $P = .25$); hence, there was a moderate association with rPFS (HR, 1.08; 95% CI, 1.03-1.13; $P = .002$). Multivariable analyses on the secondary end points using the significant covariates in Table 2 strengthened the aBSI as an independent variable for time to symptomatic progression and time to opiate use for cancer pain (HR, 1.18 and 1.21, respectively; $P < .001$), with the concordance index increasing 0.02 U for both.

Discussion

Our study met the primary objective of the prospective analysis plan and demonstrated a strong prognostic association of the aBSI with OS, and we confirmed this independent association of the aBSI with OS in a multivariable model with other clinical, serological, and geographic prognostic factors. We found that the aBSI was strongly associated with bone disease burden and osteoblastic serum bone biomarkers, such as ALP level, but was only modestly associated with other clinical factors, such as LDH and PSA values. While the number of bone metastases is strongly correlated with the aBSI, we found that the aBSI provides additional prognostic discrimination beyond lesion counting. For example, a patient with a single large-bone metastasis with a high aBSI may have a worse prognosis than a patient with 3 small-volume bone metastases, corresponding to a lower aBSI. Notably, pain scores were only weakly associated with the aBSI, reflecting the clinical observation that some men with a high degree of skeletal metastasis may exhibit little to no pain, while other men with oligometastatic bone metastases may have substantial pain. Therefore, the aBSI provides a rapid quantitative measure of bone burden with clear prognostic utility and is strongly associated with time to new bone metastases, time to symptomatic progression, and time to opiate use for cancer pain.

A number of therapies in mCRPC have demonstrated significant OS benefit, including the approved radiopharmaceutical radium 223, which incorporates into hydroxyapatite and targets areas with high bone turnover. The availability of and exposure to such effective therapies in mCRPC necessitate more accurate staging tools for effective sequencing of available therapies in clinical practice and for evaluating the efficacy of novel therapeutic agents. The aBSI together with other established clinical prognostic factors and potential predictive biomarkers[19,20] may improve our ability to identify subgroups of men with more homogeneous outcomes for clinical trial design and stratification and for patient management.

The results for our primary objective agree with previous retrospective ad hoc analyses that have demonstrated the prognostic significance of the aBSI in mCRPC.[9,10,11,12,13] The prospectively defined evaluation in the present phase 3 study validated the independent association of the aBSI with OS in a multivariable analysis and demonstrated the additive value of the aBSI to the prognostic model, with a significant improvement in the AIC, a measure of predictive discrimination.

The exploratory STEPP analysis demonstrated the clinical value of the aBSI as a continuous quantitative radiographic biomarker that is associated with OS. The aBSI has the potential to build on the current standard of bone scan assessment at baseline eligibility and after treatment monitoring. The current standard of assessment by PCWG (Prostate Cancer Working Group) criteria is semiquantitative (assessment of 2 new lesions) and unidirectional because it defines only progression and not response. As a continuous quantitative assessment, the aBSI can inherently account for the increase in the total tumor burden by quantitating the increase both of existing lesions and of new lesions. Subsequent analyses are ongoing to define and validate the aBSI increase as a progression end point biomarker for determining response and benefit to systemic therapies in men with bone mCRPC.

In addition, our study demonstrated stratification of OS and other clinical end points based on the aBSI quartiles. In the OS analysis, using patients in Q4 as a reference, the risk of death increased with decreasing quartile. As summarized in Table 3, patients in Q1, Q2, and Q3 had a

65%, 56%, and 40% reduction in risk of dying, respectively, compared with patients in Q4. Similarly, the aBSI quartiles optimally stratified the risk of prostate cancer–specific survival, time to symptomatic progression, and time to opiate use for cancer pain. The aBSI quartiles presented herein—Q1 (0.00-0.27), Q2 (0.28-1.07), Q3 (1.08-3.96), and Q4 (3.97-32.60)—can be evaluated prospectively as a baseline prognostic factor to assess response to novel therapies. These data support the clinical utility of the aBSI given its association with clinically relevant outcomes that are critically important in patient care.

Limitations and Strengths

Our study had some limitations. Forty-one percent (506 of 1245) of bone scans were not evaluable because of image quality issues, including missing anterior or posterior images, lack of DICOM format, and poor image quality. This confirms the lack of due diligence in obtaining imaging data in standard-quality format for standardized analysis like that of the aBSI. However, baseline characteristics and the follow-up OS data of the aBSI and total trial populations were determined to be similar, suggesting that the missing bone scans did not result in any systematic bias. While the phase 3 trial did not demonstrate a survival benefit of therapy,[15] permitting both treatment arms to be combined for this biomarker analysis, further prospective studies of the clinical utility in community settings are needed, with close attention to standard DICOM format digital bone scans for software interpretation and scoring.

An inherent limitation of the aBSI is the nature of bone scanning, which reflects the increase in the osteoblastic activity, and thus is an indirect tracer of bone tumor burden. In response to an effective treatment, the bone scan can show a temporary increase in tracer activity, reflecting the healing process during the first 8 to 12 weeks. This temporary increase in activity, commonly referred to as the flare phenomenon, is not distinguishable from the early disease progression. In recognition of the limitations of bone scintigraphy, PCWG2-3 advocated shifting the focus of clinical trials from response assessments to time to radiographic progression. Ongoing work will develop the aBSI bidirectional response and progression criteria similar to PCWG2-3 that define the need for metrics to define clinically relevant improvements or increases in the aBSI that are most associated with clinical outcomes, and which account for the need for confirmatory scans demonstrating further progression from the initial postbaseline scan if new lesions develop over time. Confirmatory aBSI metrics should help to better differentiate the aBSI flare phenomenon from true aBSI progression. Finally, the automated platform fails in the setting of very high tumor burden, as in 18 patients herein who had superscans. In such bone scans, the neural network of the aBSI platform struggles to find a reference value for the normal bone that allows segmenting of the tumor. Assigning these scans a high aBSI threshold value, rather than excluding them, may be reasonable given the poor outcomes in patients with superscans.

Our study had multiple strengths that suggest clinical applications and utility. First, this is the largest study to date to evaluate the aBSI and the only prospective one based, to our knowledge, on a predefined statistical plan. The study was sufficiently powered to demonstrate an independent prognostic association with OS after adjustment for standard clinical prognostic factors. However, further work is needed in community settings investigating the effectiveness and clinical utility of the aBSI assessment in changing patient management, identifying patients appropriate for novel or bone-targeting therapies, and determining patient response to therapy. Second, we developed defined aBSI quartiles that may be prospectively used as eligibility

criteria for clinical trials of systemic therapies and bone-targeted outcomes based on the risk of death and skeletal-related events. Clinical trials may stratify based on aBSI values at baseline and other clinical factors or may select patients more likely to benefit from bone-targeted approaches based on the aBSI. Third, we provide an informed and accurate quantitative imaging report from the bone scan, which may be monitored over time. Efforts are ongoing to perform the prospectively defined analysis of on-treatment change in the aBSI as a determinant of OS.

Conclusions

This study offers strong evidence that the aBSI provides prognostic information for OS, prostate cancer–specific survival, and time to symptomatic progression to patients and health care providers. The aBSI is only moderately or weakly associated with standard clinical biomarkers, such as tumor pain and LDH and PSA values, and thus has independent clinical value for determining prognosis and is strongly associated with bone metastatic burden and risk of future bone metastases. Incorporating the aBSI into clinical practice to supplement nuclear medicine reports may permit a more objective analysis of bone scan changes over time and their clinical relevance to patient care. Finally, this study could be a part of an evidentiary process qualifying the aBSI as an imaging biomarker in the context of mCRPC studies.

Notes

Supplement.

eTable 1. Patient Characteristics and OS of the Total Trial Population (TTP), the aBSI Population, and by aBSI Quartiles

eTable 2. Spearman Rank Correlation of aBSI at Baseline With CRPC Biomarkers Assessed at Baseline or Diagnosis

eTable 3. OS Association With Baseline aBSI as a Continuous Variable (STEPP Analysis)

eFigure 1. Representative Examples of Bone Scan Images in Each aBSI Quartile

eFigure 2. OS Association With Baseline aBSI as a Continuous Variable (STEPP Analysis)

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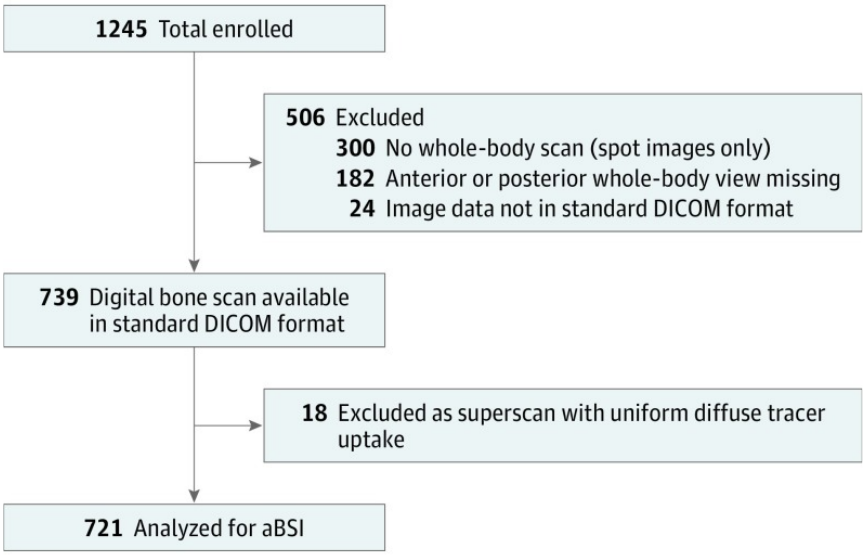
Figures and Tables

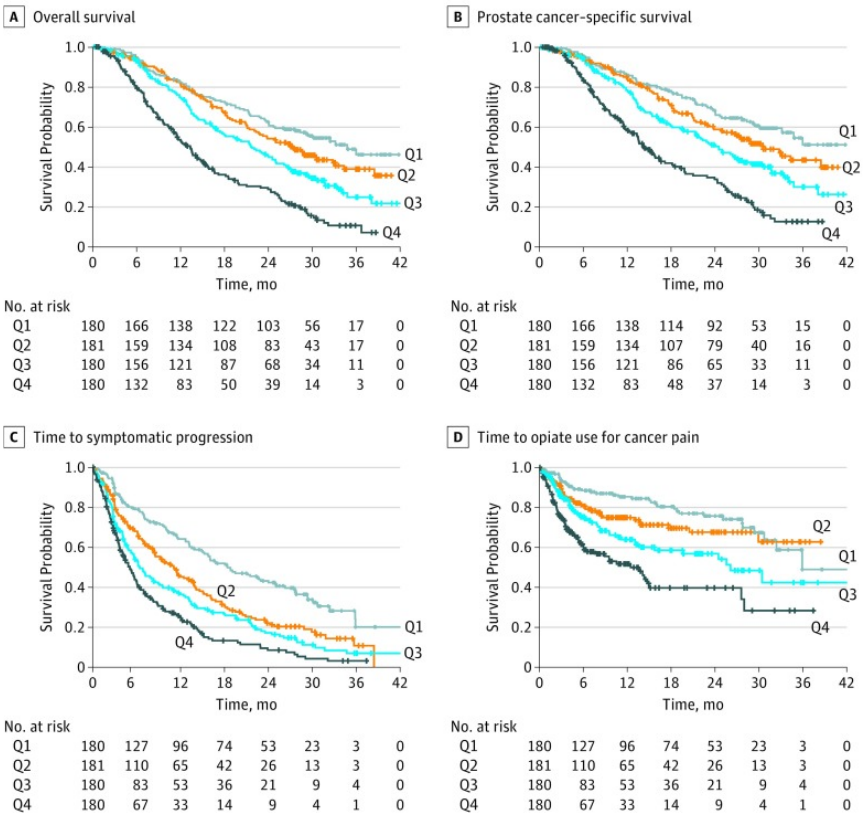
Figure 1.



Flow Diagram of Participants

Shown are the total and evaluable patients in the study. aBSI indicates automated Bone Scan Index; DICOM, Digital Imaging and Communications in Medicine.

Figure 2.



Associations of the Automated Bone Scan Index as Quartiles With Clinical Outcomes

Hash marks on each line represent the censored events indicated in the curves. Q indicates quartile. Q1 (n = 180) median aBSI, 0.05; Q2 (n = 181) median aBSI, 0.58; Q3 (n = 180) median aBSI, 2.06; Q4 (n = 180) median aBSI, 6.72.

Table 1.

Univariate and Bivariate Analyses Comparing the aBSI With the Number of Bone Lesions Among 709 Men

Analysis	Covariates	HR (95% CI)	*P* Value	C Index
Univariate	Lesion No.[a]	1.05 (1.03-1.06)	<.001	0.60
	aBSI[b]	1.15 (1.11-1.19)	<.001	0.63
Bivariate	Lesion No.[a]	1.02 (1.00-1.04)	.02	0.63
	aBSI[b]	1.12 (1.08-1.17)	<.001	

Abbreviations: aBSI, automated Bone Scan Index; HR, hazard ratio.

[a]Lesion numbers denoted with “greater than 20 or too many metastases to count” were assigned a value of 25.

[b]To accommodate the comparative analysis because of the lesion number threshold, aBSI values of 15 or higher were assigned a value of 15.

Table 2.

Multivariable Cox Proportional Hazards Regression Model Analysis of Overall Survival Among 721 Men

Variable	HR (95% CI)	*P* Value
Log_2 aBSI	1.06 (1.01-1.11)	.03
Eastern Europe geographic region[a]	2.04 (1.67-2.49)	<.001
Log_2 Albumin	0.09 (0.04-0.24)	<.001
Log_2 Prostate-specific antigen	1.11 (1.06-1.17)	<.001
Log_2 Lactate dehydrogenase	1.98 (1.65-2.37)	<.001
Log_2 C-reactive protein	1.13 (1.08-1.19)	<.001

Abbreviations: aBSI, automated Bone Scan Index; HR, hazard ratio.

[a]Reference category is the rest of the world.

Table 3.

Hazard Ratios for the Primary and Secondary Outcomes According to the aBSI as a Continuous Variable and by Quartiles Among 721 Men

Outcome	Analysis	Median, mo	HR (95% CI)	*P* Value	C Index
Overall survival	Quartiles	22.9	NA	<.001	0.62
	Q1 vs Q4	34.7	0.35 (0.27-0.47)	NA	NA
	Q2 vs Q4	27.3	0.44 (0.33-0.58)	NA	NA
	Q3 vs Q4	21.7	0.60 (0.47-0.79)	NA	NA
	Q4	13.3	NA	NA	NA
	Log_2 aBSI	22.9	1.20 (1.14-1.26)	<.001	0.63
Prostate cancer–specific survival	Quartiles	25.8	NA	<.001	0.62
	Q1 vs Q4	>40	0.34 (0.25-0.47)	NA	NA
	Q2 vs Q4	30.6	0.44 (0.33-0.60)	NA	NA
	Q3 vs Q4	24.5	0.61 (0.46-0.80)	NA	NA
	Q4	14.4	NA	NA	NA
	Log_2 aBSI	25.8	1.20 (1.14-1.26)	<.001	0.63
Radiographic progression-free survival	Quartiles	5.6	NA	.03	0.54
	Q1 vs Q4	6.4	0.64 (0.48-0.86)	NA	NA
	Q2 vs Q4	6.2	0.75 (0.56-1.02)	NA	NA
	Q3 vs Q4	5.7	0.79 (0.59-1.06)	NA	NA
	Q4	4.4	NA	NA	NA
	Log_2 aBSI	5.6	1.08 (1.03-1.13)	.002	0.55
Soft-tissue progression (RECIST 1.1)	Quartiles	16.6	NA	.46	0.53
	Q1 vs Q4	14.6	1.21 (0.81-1.81)	NA	NA
	Q2 vs Q4	16.6	0.96 (0.63-1.48)	NA	NA
	Q3 vs Q4	22.0	0.92 (0.60-1.42)	NA	NA
	Q4	16.4	NA	NA	NA
	Log_2 aBSI	16.6	0.96 (0.90-1.03)	.25	0.52
Time to symptomatic progression	Quartiles	9.1	NA	<.001	0.62
	Q1 vs Q4	18.4	0.37 (0.28-0.48)	NA	NA
	Q2 vs Q4	11.1	0.59 (0.46-0.76)	NA	NA
	Q3 vs Q4	6.4	0.74 (0.58-0.94)	NA	NA
	Q4	5.1	NA	NA	NA
	Log_2 aBSI	9.1	1.18 (1.13-1.23)	<.001	0.62
Time to opiate use for cancer pain	Quartiles	32.4	NA	<.001	0.64

Abbreviations: aBSI, automated Bone Scan Index; HR, hazard ratio; NA, not applicable; Q, quartile (see the Baseline Characteristics subsection of Results for medians and ranges for the 4 quartiles); RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1 in the study by Nishino et al.[16]