

# Automated Bone Scan Index as Predictors of Survival in Prostate Cancer

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## Abstract

Prostate cancer (PCa) is the second most diagnosed cancer in men. Early diagnosis and right management of PCa is critical to reducing deaths; the life expectancy is the main factors to be considered in the management of PCa. Among patients who die from PCa, the incidence of skeletal involvement appears to be >85%. Bone scan (BS) is the most common method for monitoring bone metastases in patients with PCa. The extent of bone metastasis was also associated with patient survival until now there is no clinically useful technique for measuring bone tumors and includes this information in the risk assessment. An alternative approach is to calculate a BS index (BSI) and it has shown clinical significance as a prognostic imaging biomarker. Some computer-assisted diagnosis (CAD) systems have been developed to measure BSI and are now available. The aim of this study was to investigate automated BSI (aBSI) measurements as predictors' survival in PCa. Retrospectively cohort studied fifty patients with PCa who had undergone BS between January 2010 and December 2011 at our institution. All data collected was updated up to August 2016. CAD system analyzing BS images to automatically compute BSI measurements. Patients were stratified into three BSI categories BSI value 0, BSI value  $\leq 1$  and BSI value  $>1$ . Kaplan–Meier estimates of the survival function and the log-rank test were used to indicate a significant difference between groups stratified in accordance with the BSI values. A total of 35 subjects deaths were registered, with a median survival time 36 months after the follow-up BS of 5 years. Subjects with low aBSI value had longer overall survival in comparison with the other subjects ( $P = 0.004$ ). aBSI measurements were shown to be a strong prognostic survival indicator in PCa; survival is poor in high-BSI value.

**Keywords:** Artificial neural networks, bone metastases, bone scan, bone scan index, computer-assisted diagnosis, prostate cancer, survival analysis

## Introduction

Prostate cancer (PCa) has become the second leading cause of cancer death in the majority of western countries,<sup>[1]</sup> and there is also a trend toward an increasing number of PCa deaths in Indonesia. Among patients who die from PCa, the incidence of skeletal involvement appears to be >85%.<sup>[2]</sup>

In patients with PCa, bone scan (BS) is the most frequently used imaging technique for detecting or identifying bone metastases, and it is also used to evaluate changes in metastatic spread involving bone tissues.<sup>[3]</sup> Scher showed that BS is more likely than other variables to identify bone lesion as stable disease, even when those variables indicate a beneficial response.<sup>[4,5]</sup>

The BS index (BSI) is a recently validated imaging biomarker and the most objective quantification method currently available for measuring tumor burden in

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bone.<sup>[6]</sup> BSI was developed to quantify the amount of metastases in BSs,<sup>[7]</sup> measures the tumor burden in bone as a percentage of the total skeletal mass and has been shown to be associated with survival of patients with PCa.<sup>[8]</sup>

Inspired by the way biological nervous systems such as human brains process information; an artificial neural network (ANNs) is an information processing system which contains a large number of highly interconnected processing neurons. These neurons work together in a distributed manner to learn from the input information, to coordinate internal processing, and to optimize its final output. Neural network applications in computer-aided diagnosis represent the mainstream of computational intelligence in medical imaging.<sup>[9]</sup> As part of routine clinical work, some computer-assisted diagnosis (CAD) systems have been developed and are now available.<sup>[10]</sup> Sadik *et al.* used a CAD system to identify bone metastases on BS and reported it had a sensitivity of 90% and a specificity of 74%.<sup>[11]</sup> Since a CAD system can easily quantify BS image findings, those can be converted into automated BSI (aBSI) in a more comprehensive and objective way to compare images obtained at different time points during the clinical course.

Recent work has shown that the total aBSI value and aBSI change between BSs are prognostic indicators and can be used as an imaging biomarker for PCa patients.<sup>[12]</sup> The aim of this study was to investigate aBSI measurements as predictors survival in PCa.

## **Materials and Methods**

### **Study population**

All patients with the diagnosis of PCa, who during January 2010 - December 2011 had undergone a whole-body BS at Department Nuclear Medicine and Molecular Imaging Faculty Medicine Universitas Padjadjaran General Hospital Dr. Hasan Sadikin, Bandung, Indonesia, were retrospectively considered for inclusion in the study. If several BS studies had been performed for the same patient, only the first one was used. Sixty patients with images of insufficient quality and twenty patients previously included in the development phase of the aBSI quantification method were excluded, leaving fifty patients in the study population. All patients had histologically confirmed PCa.

### **Data collection**

OS defined as the time from BS to death from any cause except by accident and all data collected by phone was updated up to August 2016. In the survival analysis, all data were censored at a follow-up after 5 years. The

automated method is trained to mimic an expert reader in distinguishing hotspots due to metastases from those caused by factors such as degenerative disease or fractures. A general description of how the computer method is developed and validated, including hot spot detection, feature extraction, and ANNs, is presented by Sadik *et al.*<sup>[11]</sup> the software analyzed images in digital format, and no manual steps were required. The method is implemented in the commercially available software package BONENAVI™ (Fujifilm RI Pharma Co. Ltd., Tokyo, Japan).

### **Bone scan examinations**

BS examinations were performed 3 h after intravenous injection of 740 MBq <sup>99m</sup>Tc-methylene diphosphonate. Whole-body images, at anterior and posterior view scan, were obtained with a gamma camera equipped with low-energy high-resolution parallel hole collimators. Energy discrimination was provided by a 10% window centered on the 140 keV of the <sup>99m</sup>Tc.

### **Computer-assisted diagnosis system**

BONENAVI has been developed using a cohort of Japanese patients based on a single institution's database. This CAD system showed two imaging markers: ANNs and BSI. The ANNs value shows the probability of having skeletal metastasis, and the BSI value shows the bone metastatic tumor burden. The CAD system used was one that can perform completely automated detection and analysis of hot spots and also determines complete classification based on hot-spot analysis findings. The method used for interpretation of BS findings consists of image-processing techniques and ANNs. A multilayer perceptron (MLP) is a special type of feed-forward network employing three or more layers, with nonlinear transfer functions in the hidden layer neurons. MLPs can associate training patterns with outputs for nonlinearly separable data. Feed-forward networks are particularly suitable for applications in medical imaging where the inputs and outputs are numerical, and pairs of input/output vectors provide a clear basis for training in a supervised manner.

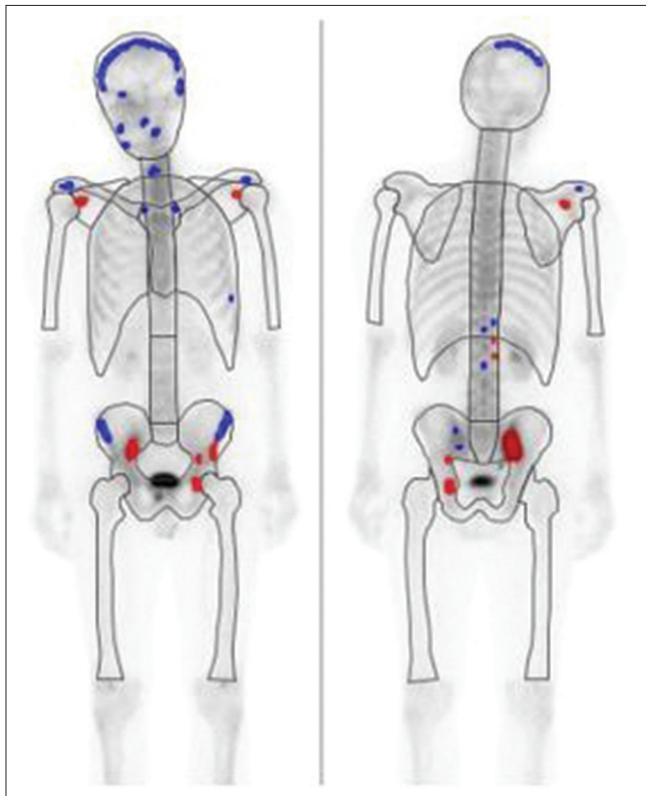
Input factors for ANNs' calculations were size, shape, intensity, and localization of hot spots. An ANNs value was calculated for each hot spot to classify it as a metastasis or not as well as for each patient. The skeletal involvement in each hot spot was calculated as the percentage of the total skeleton; thus, the BSI was calculated as the sum of the skeletal involvement in all hot spots classified by ANNs' values.

The program analyzed anterior and posterior images in digital format, and no manual steps were required. The first step included image segmentation, hot-spot

detection, and feature extraction, then the resulting highlighted features of the images were used as input to ANNs for classifying hot-spot networks. Hot spots classified as possible metastases were indicated as red, while those classified as benign (e.g., degenerative changes, fractures, symmetric hot spots) were indicated in blue [Figure 1].

### Bone scan index calculation

BSI measurement of the total skeletal mass affected by metastatic disease was calculated using the software BONENAVI™ system developed by FUJIFILM RI Pharma. The automated method to calculate BSI, which has been described in detail elsewhere,<sup>[11]</sup> consists of four steps. First, the different anatomical regions of the skeleton such as the skull, ribs, vertebra, and pelvis are segmented. Second, hotspots are detected and features describing them such as intensity, size, shape, and position are calculated. Third, ANNs are used to classify each hotspot as metastatic lesion or not based on the hotspot features. The neural networks have been trained to mimic experienced readers in distinguishing between metastatic lesions and benign hotspots due to, for example, degenerative disease or fracture. Fourth, the BSI is calculated as the sum of volumetric fraction



**Figure 1:** Representative images obtained from 62-year-old patient with prostate cancer. The automated bone scan index value was 0.98% at the time of diagnosis of prostate cancer. Suggestive bone metastases are marked in red whereas symmetric or benign radiotracer uptake is shown in blue

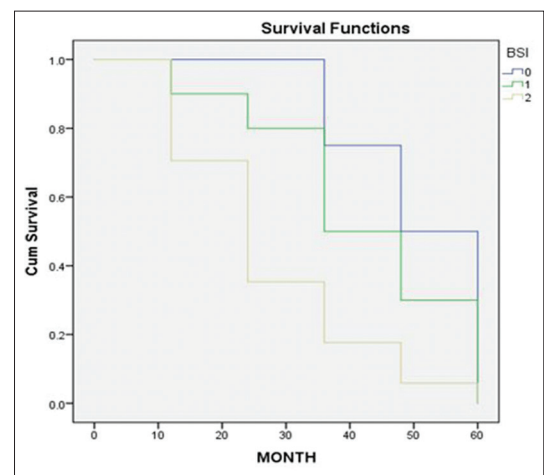
of the skeleton for all hotspots classified as metastatic lesions. In accordance with their BSI values at baseline, these patients were stratified in three BSI categories: BSI = 0, BSI  $\leq 1$ , and BSI  $> 1$ .

### Statistical analysis

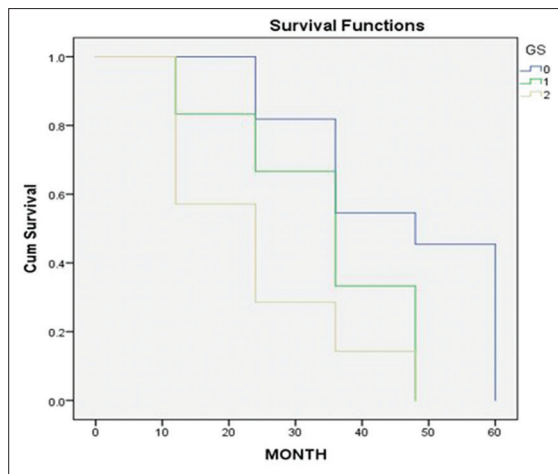
Survival curves were conducted using the Kaplan–Meier method and the differences between two curves were analyzed using a log-rank test. A two-tailed  $P < 0.05$  was considered to indicate statistical significance. Statistical analysis was performed using the IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

## Results

A total of fifty subjects were included in this study. Thirty-five subjects out of the fifty died during the follow-up with a median survival time from the baseline BS scan is 36-month. Based on previously published data on the prognostic value of BSI, we stratified the subjects into three groups based on their baseline BSI: BSI = 0 ( $n = 17$ ), BSI  $\leq 1$  ( $n = 13$ ), and BSI  $> 1$  ( $n = 20$ ), and we could then demonstrate significantly different 5-year survival rates of 52.94%, 28.57%, and 10.53%, respectively  $P < 0.004$  [Figure 2]. Based on their Gleason score (GS), we stratified the subjects into three groups: GS  $< 7$  ( $n = 17$ ), GS = 7 ( $n = 6$ ), and GS  $> 7$  ( $n = 6$ ), and we could then demonstrate significantly different 5-year survival rates of 41.18%, 16.67%, and 0%, respectively  $P < 0.013$  [Figure 3].



**Figure 2:** Kaplan–Meier curves showing subjects survival probability stratified by bone scan index categories. All the fifty subjects included in the study, these subjects were stratified in three bone scan index categories: Bone scan index = 0 ( $n = 17$ ), bone scan index  $\leq 1$  ( $n = 13$ ), and bone scan index  $> 1$  ( $n = 20$ ). These three groups demonstrated significantly different 5-year survival rates of 52.94%, 28.57%, and 10.53%, respectively  $P < 0.004$ , low bone scan index value had a longer overall survival in comparison with the other subjects



**Figure 3:** Kaplan–Meier curves showing subjects survival probability stratified by Gleason score categories. All the 29 subjects included in the study, these subjects were stratified in three Gleason score categories: Gleason score <7 ( $n = 17$ ), Gleason score 7 ( $n = 6$ ), and Gleason score >7 ( $n = 6$ ). These three groups demonstrated significantly different 5-year survival rates of 41.18%, 16.67%, and 0%, respectively  $P < 0.013$ , Gleason score <7 had a longer overall survival in comparison with the other subjects

## Discussion

In clinical practice, prostate specific antigen (PSA) is the most widely utilized surrogate and prognostic marker used to evaluate disease burden and to predict survival prognosis.<sup>[13]</sup> PSA has been shown to correlate with increased risks of bone-related clinical outcomes and overall survival (OS) in patients with metastatic PCa;<sup>[14]</sup> and moreover, in men with nonmetastases PCa, a higher PSA has been found to be associated with a shorter time to bone metastases and reduced OS.<sup>[15]</sup> However, it should be noted that the cohorts of these previous studies consisted of patients with relatively low PSA levels. Hence, are of particular importance given that extremely high PSA levels failed to show associations with all survival endpoints.

GS is a number that is used to indicate the aggressiveness of cancer. Following a biopsy or surgery to remove the prostate, researchers examine the cancer cells and can determine their aggressiveness. GS range from 1 (not very aggressive) to 10 (more aggressive).<sup>[16]</sup> Multivariate analysis revealed oncological features such as clinical T-stage or GS to have only modest effects on survival outcome, which was also consistent with the results of certain previous studies.<sup>[17]</sup>

Tumors with a GS of seven have a significantly worse prognosis than those with a GS of six. Chan *et al.*<sup>[18]</sup> found that the 5-year actuarial risk of progression was 15% and 40% for GS 3 + 4 and 4 + 3 tumors, respectively. Rodrigues *et al.* at 3 years, death from PCa occurred in nearly 36% of patients with GS of eight or greater,

compared with only 11% for those with a GS of lower than eight.<sup>[16]</sup> In the present study shows 5-year OS for GS <7 is 41.18%, and >7 is 0%, respectively  $P < 0.013$ .

BSs is the most frequently used imaging technique to detect bone metastases, can detect such metastases up to 18 months earlier than plain film analysis; however, one of the major drawbacks of conventional BS systems is the high potential for subjectivity when evaluating target bone regions. In addition, BS images reflect the secondary effects of a tumor on the skeleton and return false-positive results in patients with degenerative changes, inflammation, Paget's disease, and trauma.<sup>[19]</sup>

The BSI system was developed to overcome the drawbacks of BS using retrospective data analysis to focus on the differences in accumulation of radioactive materials among tumor metastases, inflammation and normal physiologically associated potentials. Imbriaco *et al.*<sup>[20]</sup> developed and established this novel approach to provide reliable and quantitative assessments of bone involvement using BS, with minimum intraobserver and interobserver variations.<sup>[11]</sup> The CAD system for BS applied in the present study is BONENAVI™, quickly calculates BSI, and does not require manual intervention.

In the others' study, multivariate analysis showed that chemotherapeutic response as evaluated change in a BSI value was significantly and independently correlated with OS. By contrast, bone metastases using the extent of disease grade was not identified as a significant factor contributing to OS in univariate analysis.<sup>[6]</sup> Rigaud *et al.*<sup>[2]</sup> suggest that PCa patients suffering from appendicular metastases experience a shorter life expectancy than those with axial disease only.

Furthermore, Hovsepian *et al.*<sup>[21]</sup> included 102 previously untreated PCa patients having bone metastases with or without lung metastases. They found that patients with >25% involvement of the proximal femur had significantly shorter survival than those with <25% involvement and with no lung metastases.<sup>[7]</sup> A difference between our studies is that we included all PCa patients (fifty) undergoing a BS at our department without restricting the inclusion criterion to a specific PCa group. This study shows OS rates in 5-year between groups of patients is 52.94% (BSI = 0), 28.57% (BSI < 1), and 10.53% (BSI > 1), respectively  $P < 0.004$ . Yamashita *et al.*<sup>[22]</sup> found that the presence of bone metastases outside the pelvis and the lumbar spine is predictive of shorter survival time among the responders to androgen deprivation therapy. This suggests that the localization of bone metastases may be a prognostic indicator if information of therapy response is also added.

## Conclusions

This study have shown that aBSI measurements are a quantitative and objective factor for assessing bone metastases and was shown to be a good prognostic survival indicator in PCa, like its manual counterpart, is a valuable clinical parameter in patients with PCa and OS is poor in high-BSI. Distinct advantages of the aBSI calculation are its 100% reproducibility and rapid processing time. aBSI measurements may prove complementary to PSA measures in blood, which fail to predict survival benefit in patients with PCa.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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