Review article

Evaluation of usage of bone scan index in assessment of metastatic prostate cancer

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Abstract

Introduction: Prostate cancer has been the leading type of cancer to affect male population, and as such, it is a subject to efforts to furthermore diagnostic tools already in existence as well as development of new ones which will Aid early diagnostic, treatments as well as a follow up procedures and clinical trials. Bone scan index is a useful and objective biomarker used as a valuable tool for determination as to precise bone involvement in advanced cases, as well as a tool to predict the outcome in prostate cancer patients in clinical trials.
Methods: This paper is a non-experimental (qualitative) research, that is, a scientific review of the literature.
Results: The results we analyzed in this paper were collected from published academic journals.
Conclusion: As a new imaging biomarker, bone scan index has potential to predict therapeutic effects and survival of patients with prostate cancer. Using measurable diagnostic image parameters, the bone scan index is important for determining metastatic bone changes in prostate cancer patients.
Keywords: Bone scan index, cancer prostate, biomarkers

Introduction

Nearly 1.4 million people are diagnosed with cancer every year in the USA. Of these, half of patients suffer from a cancer that frequently metastasizes to bones (1). In fact, bones are the third most common site of metastatic malignancy after lungs and liver. Bone metastases can occur in just about any primary malignancy. The most common cancers to metastasize to bones are breast, prostate, thyroid, lung, and kidney cancer. In autopsy studies the incidence in breast and prostate cancers is as high as 73 % (2).

Prostate cancer (PCa) is the most prevalent nondermatologic cancer in males. At presentation, ~10% of patients have bone metastases, and almost all patients who die of prostate cancer have skeletal involvement (3). The clinical course of patients with metastatic prostate cancer can be relatively long, and several prognostic factors have been identified, including performance status, tumor grade, hemoglobin, serum lactate dehydrogenase, prostate-specific antigen, and alkaline phosphatase (4–6). It is the most common noncutaneous cancer, and the second most frequent cause of death from cancer among men in the USA. In Japan, 11,507 men were estimated to die of prostate cancer in 2014, making this disease the sixth leading cause of death from cancer (7). Prostate cancer is a bone tropic cancer, and nearly 85% of patients with fatal prostate cancer are reported to have bone metastases (8). Several studies have attempted to correlate the extent of skeletal metastatic involvement with survival in patients with advanced prostate cancer. A staging system based on distribution of bone metastases according to bone scintigraphy (axial versus appendicular) showed a significant association with survival (9). A different system based on the number of lesions identified by bone scintigraphy was also predictor of survival (10). However, although both systems were able to discriminate between patients at the extremes of their respective scales, neither was particularly effective at

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discriminating between patients toward the center of the range. Among the patients who die from PCa, the incidence of skeletal involvement appears to be > 85% (11,12) . The standard treatment for patients with PCa with metastatic spread to the bones is androgen deprivation therapy (ADT); however, the vast majority of patients with PCa with bone spread finally become resistant to androgen deprivation and progress to castration-resistant PCa (CRPC) (13).

Early diagnosis of prostate cancer has increased since the introduction of the prostate-specific antigen (PSA) blood test >25 yr ago, but many patients still fail the initial treatment and progress to castration-resistant prostate cancer (14). One of the most challenging management tasks for researchers and pharmaceutical companies is to find new effective treatments for this aggressive stage of the disease, due to the potentially rapid development of metastasis where bone tissue is the most commonly affected (15,16). After the development of metastatic castration-resistant prostate cancer (mCRPC), patients commonly initiate secondary hormonal manipulation or chemotherapy. At this stage, the therapeutic landscape has changed considerably since the introduction of new drugs in the last few years (17). These systemic treatments are not always well tolerated, and many patients soon acquire resistance; therefore, most of these patients need additional therapeutic options (18). In mCRPC patients, clinical or biologic parameters related to bone metastases have a major prognostic value (19). Bone scintigraphy (BS) is a widely used method for assessing metastatic spread to the skeleton, but there is still a lack of standardisation in its analysis. Interpretations of BS images are currently based mainly on a traditional visual analysis that is both subjective and interpreter dependent (20).

For monitoring progression of bone metastases on prostate cancer patients, serum prostate-specific antigen (PSA) is widely used as a biomarker in prostate cancer. Although prostate cancer can become refractory (castration-resistant prostate cancer), serum PSA provides limited information related to bone metastases. At present, PSA level has been considered an essential and practical marker for management of patients with PCa, but an elevated PSA level itself cannot always determine whether the region of bone, lymph nodes or visceral organ is metastatic spread or local recurrence. In addition, although PSA is the best marker for PCa monitoring, it is not PSA that represents or reflects the comprehensive status of PCa aggressiveness.

Considering the bone as the most prevalent site of metastatic spread in PCa, we think that a more detailed approach to analysing bone metastasis would contribute to improvements in prognosis and even confer a survival benefit on the affected patients (13). Prostate cancer has a high risk of spreading metastases to the bone. An autopsy study of 1589 patients showed that 90% of prostate cancer patients aged 40 years or older had bone metastases (21). The bone metastases of prostate cancer are most often characterized as extended osteoblastic lesions radiographically. Although management of the bone metastases is making progress, advanced diseases with bone metastases remain incurable. In the cases of bone metastases there are risks of pathological skeletal fracture, intractable bone pain, and spinal-cord compression during the clinical course (22). The most common form of metastasis from prostate carcinoma is on the bones, which occurs in about 80% of terminal prostate carcinoma patients. The median survival of prostate cancer patients with bone metastasis is 2–3 years and the 5-year probability of survival is 30%. The mortality rate of patients with bone metastasis on the first medical examination is expected to be 90% after 10 years. Therefore, the prognostic prediction of prostate carcinoma by bone scintigraphy may be vital. However, the optimal method for detecting, quantifying, and grading tumor metastasis of bones is difficult. There were several attempts to quantify bone metastasis by bone scintigraphy, with different results (23, 24). The use of extent of disease (EOD) grade is useful for the prognostic prediction of prostate carcinoma. However, this method is subjective, and interobserver variation can be substantial (25).

Bone metabolic markers are useful to evaluate the activity but not the extent of bone metastases. Bone scintigraphy has been used as a primary imaging procedure for evaluating extent of bone metastases of the whole body in the case of an elevated serum PSA after diagnosis of prostate cancer. The extent of disease (EOD) on initial bone scintigraphy was used to stratify patients with prostate cancer (26). In addition, a computer-aided diagnosis system on bone scintigraphy images has been developed for improving the interpretations of bone scan images, which can help with understanding the spread of bone metastases. The system can indicate “Bone Scan Index (BSI)” which provides a quantitative measure of the percentage of the adult skeleton involved by bone metastases. Although it has been difficult to monitor therapeutic responses with bone

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metastases radiologically, BSI has potential to predict therapeutic effects and survival of patients with prostate cancer as a new imaging biomarker. However, few papers have yet to show the relationship between BSI and bone metabolic markers (27).

Bone scintigraphy is a very common examination for patients with prostate cancer to verify or exclude suspected metastatic disease. For patients with bone metastases the extent of the tumor burden is associated with survival (28,29). The Bone Scan Index (BSI) was developed in order to quantify the amount of metastases in bone scans (30). BSI measures the tumor burden in bones as a percentage of the total skeletal mass and has been shown to be associated with survival of patients with prostate cancer (31). Automated BSI methods (32) have been developed to further increase the objectivity and clinical use of bone scans for patients with prostate cancer. Recent work has shown that the total BSI value and BSI change between bone scans are prognostic indicators and can be used as an imaging biomarker for prostate cancer patients (33-35).

Bone scintigraphy, however, is commonly used to assess skeletal tumour burden in prostate cancer patients, both in clinical routine and in nearly every clinical trial. In order to extract as much clinical information as possible from the bone scans, the Bone Scan Index (BSI) was developed as a quantitative tool to improve the interpretability and clinical relevance of the bone scan. BSI is a method of expressing the tumor burden in the bones as a percentage of the total skeletal mass (36).

Bone scintigraphy was also successfully used for the determination of the extent of metastatic bone disease that has shown to correlate with disease prognosis and proved to be a useful indicator of response to treatment (37-39).

An alternative approach to quantifying the progression of metastatic disease is to calculate a bone scan index (BSI) reflecting the burden on the skeleton. The tumor burden is expressed as a percentage of the total skeletal mass. This method was recently evaluated in patients with prostate cancer receiving chemotherapy, and the results showed that on-treatment change in BSI was closely associated with overall survival (40). The same study also showed that changes in PSA were not associated with survival, while adjusting for changes in BSI, indicating the value of BSI as a response indicator (41).

Visual image analysis for the detection of new lesions and the calculation of BSI is time consuming and subjective and involves inter-observer variability. We therefore recently presented an automated method for calculation of BSI (42). The method was designed to analyse one scan at a time, and it was shown that the automated method provides important clinical information comparable to that of visual BSI scoring (41).

BSI is calculated by first calculating the area of a hotspot classified as a metastatic lesion and then calculating the area of the corresponding skeletal region obtained from the segmentation of the skeleton (e.g. the skull or pelvis). Dividing the former by the latter and multiplying the result by a constant representing the weight fraction of the present skeletal region with respect to the weight of the total skeleton (43) gives an estimate of the volumetric fraction of the skeletal region occupied by the hotspot (41).

This method has now been further developed so that a comparison of two wholebody bone scans from the same patient is carried out automatically (41).

A template normal scan is used to establish correspondences between time points. As part of the method presented in a previous study, the template scan is warped to fit each individual scan using a non-rigid registration algorithm. Separate warps are used for anterior and posterior images (42). The aim of this study is to provide assessment as to involvement of bone scan index to diagnostic procedures and the gradation to which bone scan index is relevant for determination of the metastatic changes on bones in patients with advanced prostate cancer.

Materials and methods

This paper is a non-experimental (qualitative) research, that is, a scientific review of the literature. Upon creating the research, different databases were used, including Pub Med, Medline, using key words "bone scan index", "prostate cancer", "bone metastate", "scintigraphy". The research is limited to articles published in English.

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Results

Table 2. Variables are relative to the objective of the research

Author	Study name	Aim	Research method	Results
Armstrong AJ, Anand A, Edenbrandt L, Bondesson E, Bjartell A, Widmark A, et al (2018)	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. [44]	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).	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-naive 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.	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).
Anand A, Morris MJ, Larson SM, Minarik D, Josefsson A, Helgstrand JT, et al. (2016)	Automated Bone Scan Index as a quantitative imaging biomarker in metastatic castration-resistant prostate cancer patients being treated with enzalutamide. [45	In the present study, we retrospectively evaluated the discriminatory strength of the automated BSI in predicting overall survival (OS) in mCRPC patients being treated with enzalutamide.	Retrospectively, we included patients who received enzalutamide as a clinically approved therapy for mCRPC and had undergone bone scan prior to starting therapy. Automated BSI, prostate-specific antigen (PSA), hemoglobin (HgB), and alkaline phosphatase (ALP) were obtained at baseline. Change in automated BSI and PSA were obtained from patients who have had bone scan at week 12 of treatment follow-up. Automated BSI was obtained using the analytically validated EXINI BoneBSI version 2. Kendall's tau (τ) was used to assess the correlation of BSI with other blood-based biomarkers. Concordance index (C-index) was used to evaluate the discriminating strength of automated BSI in predicting OS.	Eighty mCRPC patients with baseline bone scans were included in the study. There was a weak correlation of automated BSI with PSA (τ=0.30), with HgB (τ= −0.17), and with ALP (τ= 0.56). At baseline, the automated BSI was observed to be predictive of OS (C-index 0.72, standard error (SE) 0.03). Adding automated BSI to the blood-based model significantly improved the C-index from 0.67 to 0.72, p = 0.017. Treatment follow-up bone scans were available from 62 patients. Both change in BSI and percent change in PSA were predictive of OS. However, the combined predictive model of percent PSA change and change in automated BSI (C-index 0.77) was significantly higher than that of percent PSA change alone (C-index 0.73), p =0.041.
Miyoshi Y, Yoneyama S, Kawahara T, Hattori Y, Teranishi J, Kondo K, et al. (2016)	Prognostic value of the bone scan index using a computer-aided diagnosis system for bone scans in hormone-naive prostate cancer patients with bone metastases. [46]	This study aimed to evaluate the pretreatment BSI as a prognostic factor in hormone-naive prostate cancer patients with bone metastases.	The study included 60 patients with hormone-naive, bone metastatic prostate cancer that was initially treated with combined androgen blockade therapy. The BONENAVI system was used for calculating the BSI. We evaluated the correlation between overall survival (OS) and pretreatment clinicopathological characteristics, including patients' age, initial prostate-specific antigen (PSA) value, Gleason scores, clinical TNM stage, and the BSI. Cox proportional hazards regression models were used for statistical analysis.	The median follow-up duration was 21.4 months. Clinical or PSA progression occurred in 37 (61.7%) patients and 18 (30.0%) received docetaxel. Death occurred in 16 (26.7%) patients. Of these deaths, 15 (25.0%) were due to prostate cancer. The median OS was not reached. In multivariate analysis, age and the BSI were independent prognostic factors for OS. We evaluated the discriminatory ability of our models, including or excluding BSI by quantifying the C-index. The BSI improved the C-index from 0.751 to 0.801 for OS. Median OS was not reached in patients with a BSI ≤1.9 and median OS was 34.8 months in patients with a BSI >1.9 (p = 0.039).
Mads H. P; Janne R; Lars E; Poul F. Høilund-Carlsen, Oke G; Allan J; Lars L. (2016)	Bone Scan Index predicts outcome in patients with metastatic hormone-sensitive prostate cancer. [47]	To evaluate the Bone Scan Index (BSI) for prediction of castration resistance and prostate cancer-specific survival (PCSS).	In all, 88 patients with prostate cancer awaiting initiation of androgen-deprivation therapy due to metastases were included. WBS was performed using a two-headed c-camera. BSI was obtained using the automated platform EXINI bone (EXINI Diagnostics AB, Lund, Sweden). In Cox proportional hazard models, time to castration-resistant prostate cancer (CRPC) and PCSS were modelled as the dependent variables, whereas prostate-specific antigen (PSA) level, Gleason score and BSI were used as explanatory factors. For Kaplan–Meier estimates, BSI groups were dichotomously split into: BSI < 1 and BSI ≥1. Discrimination between prognostic models was explored using the concordance index (C-index).	The mean (range) age of the patients was 72 (52–92) years, the median (range) PSA level was 73 (4–5 740) ng/mL, the mean (range) Gleason score was 7.7 (2–10), and the mean (range) BSI was 1.0 (0–9.2). During a mean (range) follow-up of 26 (8–49) months, 48 patients became castration resistant and 15 had died; most (13) from prostate cancer. In multivariate analysis including PSA level, Gleason score and BSI, only prediction by BSI was statistically significant. This was true both for time to CRPC (hazard ratio [HR] 1.45, 95% confidence interval [CI] 1.22–1.74; C-index increase from 0.49 to 0.69) and for PCSS (HR 1.34, 95% CI 1.07–1.67; C-index increase from 0.76 to 0.95).
Mariana R; Mattias O; Reza K; Aseem A; Ingela Franck-Lissbrant, Jan-Erik D; Anders W; Camilla Thellenberg-Karlsson, Lars B; Thomas St; Till E; Per W; Lars E; Elin T; Anders B. (2016)	Bone Scan Index as an Imaging Biomarker in Metastatic Castration-resistant Prostate Cancer: A Multicentre Study Based on Patients Treated with Abiraterone Acetate (Zytiga) in Clinical Practice [48]	To evaluate the value of BSI as a biomarker for outcome evaluation in mCRPC patients on treatment with AA according to clinical routine.	We retrospectively studied 104 mCRPC patients who received AA following disease progression after chemotherapy. All patients underwent whole-body bone scintigraphy before and during AA treatment. Baseline and follow-up BSI data were obtained using EXINI BoneBSI software (EXINI Diagnostics AB, Lund, Sweden)	Patients with an increase in BSI at follow-up of at most 0.30 (n = 54) had a significantly longer median survival time than those with an increase of BSI >0.30 (n = 50) (median: 16 vs 10 mo; p = 0.001). BSI change was also associated with OS in a multivariate Cox analysis including commonly used clinical parameters for prognosis (Cindex = 0.7; hazard ratio: 1.1; p = 0.03). The retrospective design was a limitation.

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Discussion

Automated bone scan index has a solid foundation to be a gold standard in standard imaging modality, with the potential to build on the current bone scan assessment at the baseline eligibility and after-treatment monitoring. It both provides a quantitative measure of the percentage of the bone metastases involvement in the adult skeleton and has the potential to predict therapeutic effects and survival of patients with prostate cancer as a new imaging biomarker, as well as showing to be beneficial in clinical evaluation for optimising treatment and patient counselling. Bone scintigraphic assessment using BSI is becoming increasingly standardized, and it enables acquiring more objective data for the treatment and prognosis of the patient.

Conclusions

Bone scan index estimation is based on the known proportional weights of each of the 158 bones, and calculated as a sum of the fractional contribution of each bone expressed as a percentage of the entire skeleton. As a new imaging biomarker, bone scan index has potential to predict therapeutic effects and survival of patients with prostate cancer.

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