Scoring systems of quantitative bone scanning in prostate cancer: historical overview, current status and future perspectives

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Abstract
Whole-body bone scintigraphy using technetium-99m-methylene-diphosphonate (^{99m}Tc-MDP) is the most widely used radionuclide imaging modality applied in patients with prostate cancer. With this technique, the choice of methods to estimate the extend of the metastatic disease on the skeletal system includes various different approaches, classified in two main categories: First, the quantitative measurements of tracer uptake, defined either as the percentage of the injected dose of tracer, or as the more complicated plasma clearance techniques and second, the various semi-quantitative scoring systems of the bone scan images. These scoring systems can be based either on visual counting of bone lesions, or on the estimation of a numerical index that expresses the fractional involvement of each bone by tumour, called "Bone Scan Index" (BSI); the latter can be produced either visually (manually) or by the more sophisticated techniques of fully- or semi-automated (computerized) forms. *In this review*, a brief chronological overview of the aforementioned methods is presented, along with the main advantages, drawbacks and the prognostic implications of each method. There remains, however, the challenge of defining, developing and validating the optimal measurement methodology in order these scoring systems to obtain a wider clinical use.

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Introduction

In patients with prostate cancer (PCa), whole body bone scan (WBS) is the most frequently used imaging technique for detecting or identifying bone metastases, for monitoring of tumor response to treatment and for predicting the survival, both in clinical routine and in nearly every clinical trial. However, as treatments for bone metastases of PCa improve, better diagnostic methods are needed to more accurately determine the tumor burden at baseline and to monitor the tumor's response to treatment.

Although WBS are highly sensitive for the detection of metastatic lesions, there is little consensus on a standard approach to image analysis; the interpretation of changes in the intensity and size of metastatic lesions on bone scans can be a difficult task causing variability between different readers, with unacceptably high false-negative interpretations [1]. Whole body scan images are essentially interpreted by subjective evaluation focusing on the intensity and/or the size of osseous lesions, which makes it difficult to compare images in a long term period of time. While initial detection of bone metastases is important, a thorough and standardized quantification of the progress of metastatic disease that downgrades the clinical status of the patient would also be utmost beneficial.

Methods of estimating the extend of skeletal disease (EOD)

Measurement of tracer uptake

Historically, quantitative radionuclide bone studies of bone have used one of two different approaches, the first being the quantitative measurement of plasma clearance from the relationship between the time–activity curve in a selected ROI and the blood input curve and the second being the semi-quantitative measurement of skeletal uptake defined as the percentage of injected dose of the tracer in a specified region of interest (ROI). Athough uptake is technically much simpler to measure than plasma clearance, it is important to ask whether the choice of a simpler method entails any loss of information [2].

The question of measuring skeletal uptake or plasma clearance has existed for years in studies using bone scanning radiopharmaceuticals. In 1980 the bone uptake of ^{99m}Tc-MDP was monitored quantitatively in PCa patients undergoing treatment. The uptake

was expressed as a function of the administered dose [3]. Another relatively simple technique measured the 24h whole body skeletal uptake of ^{99m}Tc-MDP as an objective marker for bony metastases in patients with PCa in comparison to clinical outcome. Whole body count measurement was performed 5min and 24h after administration, and was expressed as the percentile uptake by the skeleton at 24h. Interestingly, the skeletal uptake values at 3-6 months in the group of responders decreased by 18%, while in patients with PCa relapse or progression these values increased by 19% [4]. This simplified approach however never came to routine clinical practice because of the missing useful anatomical information about the involved bones. In another method called "Dynamic quantitative bone scintigraphy" a ROI was defined over each vertebra from T10 to L5. The count rate per pixel and per unit injected activity, corrected for radioactive decay and for varying depths, and background subtracted was calculated for each ROI and measurement periods were determined. Prostate cancer patients with osseous metastases had higher vertebral uptake (count rate) pre- and post-operatively, while the patients without evidence of skeletal metastases did not show any significant change throughout the study [5] (Fig. 1).

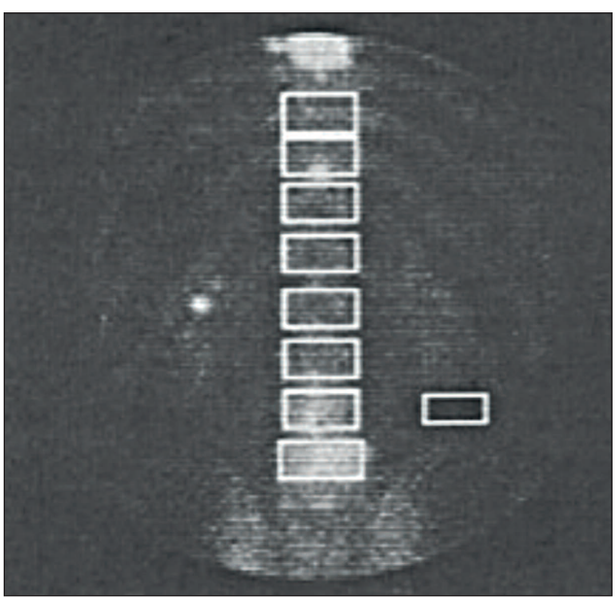

Figure 1. "Dynamic quantitative bone scintigraphy": A ROI was defined over each vertebra from T10 to L5; background region was placed between the projection of the kidney and crista iliaca [5].

The standardized uptake value (SUV) is defined as tissue activity (kBq/mL) x body weight (kg)/injected activity (MBq) and is equivalent to the measurement of tracer uptake per unit of metastatic volume. Although SUV is frequently used to quantify PET studies, most fluoride-18 fluorodesoxyglucose (^{18}F-FDG) studies have used the alternative plasma clearance technique first described in 1992 [6]. Since years, ^{18}F-FDG dynamic positron emission tomography (PET) has been the technique of choice for physiologically precise quantitative studies of the skeleton [7]. This method is technically more demanding than a SUV measurement, requiring a 60min dynamic PET acquisition together with continuous blood sampling to accurately define the arterial input function. In addition, a compartmental modeling programme is required for computation of the results. Few studies have directly compared ^{99m}Tc-MDP and ^{18}F-FDG as quantitative bone tracers, but there is evidence that whole skeleton plasma clearance measured with ^{18}F-FDG is nearly twice higher than that measured with ^{99m}Tc-MDP [8], probably reflecting the more diffusible fluoride ion [2].

Because whole-body counters are no longer widely available, several authors have described equivalent methods for measuring ^{99m}Tc-MDP retention based on whole-body gamma-camera bone scanning [9-11]. All these techniques which measure tracer uptake are based like on SUV, on three-phase WBS obtained at various time periods after the injection of ^{99m}Tc bone radiopharmaceutical. Using ROI techniques and fitted time-activity curves, bone uptake was calculated as the total whole body activity minus both soft tissue activity and urinary excretion. The results of these methods were in good agreement with the findings of the standard 24h whole body retention measurements. Nowadays, by combining serial gamma-camera imaging with blood sampling, one can also measure ^{99m}Tc-MDP plasma clearance both for the whole skeleton and for selected ROI [12].

At present, we can choose between ^{99m}Tc-MDP and ^{18}F-FDG as possible tracers, and between straightforward quantifying approaches such as SUV or the more complicated plasma clearance techniques. Quantitation with radionuclides provides a novel tool for studying regional and whole skeleton bone turnover that complements the information provided by biochemical markers. There remains, however, the challenge of developing and validating simpler methods that may have wider clinical use.

Visual inspection

To improve the objective assessment and monitoring of the EOD, many, more or less simple semiquantitative visual scoring systems have been developed. Visual semiquantitative methods do have value in permitting a stratification of patients in the extent of bone involvement, with significant prognostic implications, which will be discussed below. Another advantage of all these methods was that digitized scans were not required, and a larger series of patient studies could be studied, going back several years in some cases. The most acknowledged of these scooring systems are presented bellow, in chronological order (Table 1).

The abovementioned techniques of visual analysis by counting the number of bone lesions are common methods to estimate the EOD. However such simplified approaches have severe drawbacks, which did not allow their clinical adoption on a large scale: a) They constitute subjective and arbitrary interpretations of the bone scans, based on the experience of the physician, with significant interobserver variablility [21]. In one meta-analysis of multiple Swedish institutions, substantial variations in the interpretation of bone scans were shown among 37 observers, according to readers' experiences [22]. b) Efforts to minimize the interobserver variability of the reading usually necessitate more than one independent bone scan readers [21]. c) The problem of subjectivity is further complicated by the three-dimensional nature of many bone structures (eg. pelvic bones

or skull) and also in cases with greater skeletal involvement. For example, it can be very difficult to accurately count the number of bone metastases on planar WBS when lesions increase in number, or when they become confluent (e.g. with the number of them actually dropping, even when the disease is progressing). d) The mere number of lesions does not always adequately correspond to the tumour extension in the skeleton; it is an oversimplification to count this number instead of measuring the total area involved because much useful clinical and prognostic information is being lost and e) Visual methods are not easily automated [23].

Table 1. *Discription of the main visual scoring systems*

Year	Description of the scoring systems	Ref.
1988	Classification into four groups by using as cut-off the absolute number of bone lessions: Grade 0, normal; Grade 1, < 6 lesions, each involving less than 50% of a vertebral body; Grade 2, 6-20 lesions; Grade 3, > 20 lesions but not a superscan (diffuse symmetrical uptake without visualisation of the kidneys); and Grade 4, a superscan	[13]
1991	Classification of lessions as negative, positive, or intermediate	[14]
1991	Scoring of the skeleton from 0 (normal uptake) to 2 (diffuse metastatic uptake)	[15]
1991	Division of the skeleton into five areas (vertebrae, ribs, pelvis, long bones and skull) and stratification according to the number of skeletal areas involved	[16]
1993	On the basis of the pattern of spread on the initial bone scan (pelvic bones versus distal sites)	[17]
1993	On the basis of axial versus appendicular regions	[18]
1996	Fixed-size ROI placed relative to anatomical landmarks for (semi-) quantitation of changes in serial WBS	[19]
2000	Classification into two groups (<10 or ≥10 bone metastases)	[20]

CAD: computed aided diagnosis

Manual BSI

As an answer to the aforementioned drawbacks, the other common method of EOD grading is the by far more sophisticated technique of BSI, as first described by Imbriaco et al [24]. The basic principles of this method go back to the late seventies, in a study of Fogelman et al [25], who first described a semi-quantitative diagnostic index for metabolic bone disease derived from the WBS. Each bone scan was inspected for seven common metabolic features which were scored from 0-normal up to 2- markedly abnormal and the sum of the scores for each metabolic feature was defined as the "Metabolic Index". Twenty years later, a novel visual method was developed to quantify the extent of skeletal involvement by tumor more accurately than visual counting of the lessions [24]. This method relied on the known proportional weights of each of the 158 bones derived from the so-called "reference man", a standardized skeleton in which autopsy-based individual bone weights were reported for the average adult [26]. The bones were considered individually and assigned a numerical score, representing the percentage involvement with tumor, multiplied by the weight of the bone (derived from that "reference man"). The fractional involvement of each bone by tumour was estimated visually from the WBS. The BSI measurement was then calculated by summing the product of the weight and the fractional involvement of each bone expressed as percentages of the entire skeleton.

The BSI was initially developed as a visual semi-quantitative tool to improve the interpretability and clinical relevance of the WBS in estimating metastatic burden in patients with advanced PCa. It showed good reproducibility and a parallel change with PSA, thus allowing WBS to be explored as an imaging biomarker for global tumour involvement in bone [24]. The BSI allows easier computerized automation with acceptably low variability between readers in comparison to rough visual analyses developed previously.

The important message implemented here and verified from following studies [27-29], is that until now BSI has proved to be a prevalent and useful research tool, also amenable to technical modifications [30, 31] (Fig. 2). It has the potential to enhance the value of WBS, especially in situations where monitoring of treatment response is an essential feature of PCa patient management. Finally, it is a powerful independent predictor of the prognosis for such patients, which will help select which of them may be candidates for more aggressive antineoplastic treatments. However, the visually derived BSI has several drawbacks that also render the procedure less than ideal [27, 28]: a) It is still a subjective task, with perhaps greater interobserver variablility than visual counting the number of bone lesions. b) It is more tedious and time-consuming to analyse the data. c) It necessitates special training to be applied to routine clinical work, thus making it a difficult and complicated process. d) Further limitation constitutes the expense of special image-processing programmes.

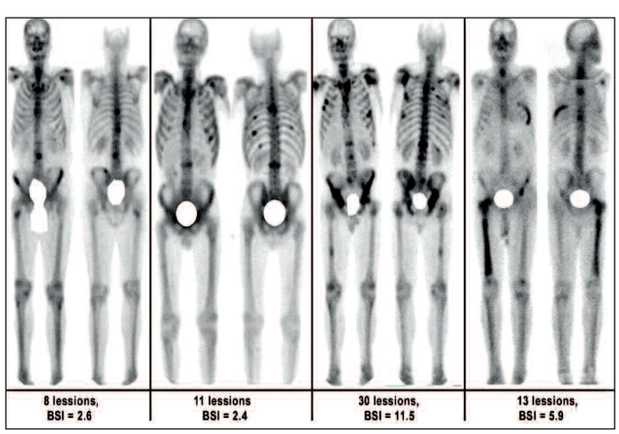

Figure 2. Whole-body bone scans of four representative patients with the corresponding lesion counts and BSI values [31]. BSI values were calculated according to a modified method of reference nr. 24.

Computerized BSI

Apart from a heraldic digitalized model to quantify bone disease from the WBS which finally stayed out of the clinical pactice [32], the "Computerized Bone Scanning" (CBS) was first described in a paper of 1984 [33], as a technique used to measure quantitative changes in bone scans, by means of percentile decrease in measured counts. Nowadays, with the general term "Computer Aided Diagnosis" (CAD), a new diagnostic tool has evolved to interpret digital medical images as a "second opinion" in assisting radiologists' image interpretations [34]. In the USA, CAD softwares have been used for several years as a part of clinical routine for the analysis of myocardial perfusion scintigrams and for detecting breast cancers by mammography [35, 36]. Thus, any automated method for calculation of the BSI is also welcomed.

In most modern automated systems, 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. 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 [37] gives we can obtain an estimate of the volumetric fraction of the skeletal region occupied by the hotspot. The results of many studies show that such an automated method can be used to detect new lesions and changes in BSI in serial bone scans. Some more sophisticated techniques use computer-assisted image analysis to calculate the percentage of bone metastases on bone scintigram, thus determining more accurately the amount of bone metastases and monitoring the response to treatment. After the year 2003 many research groups have presented a series of CAD systems in the field of Nuclear Medicine. The most distinctive of them are chronologically presented in the following Table 2:

***Table 2**. Description of the main CAD systems*

Year	Brief description of CAD system	Reference
2003	The percentage of the positive area on the bone scan (%PABS) was quantified automatically by using an image-analysis programme for measurements of all positive areas on bone scans transferred by manual tracing to a comprehensive map of the entire bone metastasis (Fig. 3).	[21, 38]
2004	A system called "Characteristic-Point-Based Fuzzy Inference System" (CPFIS) was employed to implement the diagnosis with warning marks and abnormal scores of the images of WBS to direct physician's attention towards these locations. (Sensitivity=91.5%)	[39]
2007	A CAD system included algorithms for automated segmentation of the head, chest, spine, pelvis and bladder, automatic thresholding and detection of hot spots, for the detection of interval changes in successive WBS by use of a temporal-subtraction image (Sensitivity=95.3%).	[40]
2008	A CAD system called "Artificial Neural Networks (ANN)" performed fully automated detection and analysis of hot spots in digital format and determined complete classification based on hotspot analysis. The size, shape, intensity, and localization of each hot spot and the intensity characteristics of the region in which the hot spot was located were calculated using a region-specific threshold algorithm.	[41]
2009	A more precise segmentation of the skeleton than previous reference made it possible to use improved algorithms for detection of hot spots and to present information in greater detail regarding the localization and distribution of hot spots. The resulting image features were assigned between four grades of diagnostic certainty, from Grade 1 (without findings of bone metastases) to Grade 4 (bone metastases highly suspected).	[42]
2012	EXINI bone™ (EXINI Diagnostics AB, Lund, Sweden), originally developed in 1997 [27] as a fully automated CAD software package, was commercially available from 2012. The technology was assembled to identify, quantify and classify hotspots as lesions. Twenty to 30 features describing each hotspot (eg, size, shape, max counts, median counts, shape and localisation) were calculated and used as inputs to the ANN system. This automated method mimiced an expert reader in distinguishing hotspots due to metastases from those caused by other factors such as degenerative disease or fractures (Fig. 4).	[43]
2012-2013	Bonenavi (Fujifilm RI Pharma Co., Ltd., Tokyo, Japan) is a fully automated system which used reconstructed images obtained from a CAD system based on a database including more than 1,500 patients from a multi-center project to establish a Japanese-tailored customized variation of EXINI software [44, 45]. BSI was calculated as the percentage of weight of summed abnormal hot spots to the entire skeleton [46-47] or as the sum of the skeletal involvement of all hot spots classified by the software as metastases [45]. As calculated by this system, BSI significantly correlated with EOD, with only slight interobserver variation. This CAD system improved the physicians' sensitivity in detecting metastases from 78% to 88% (Fig. 5).	[44-47]

CAD: computed aided diagnosis

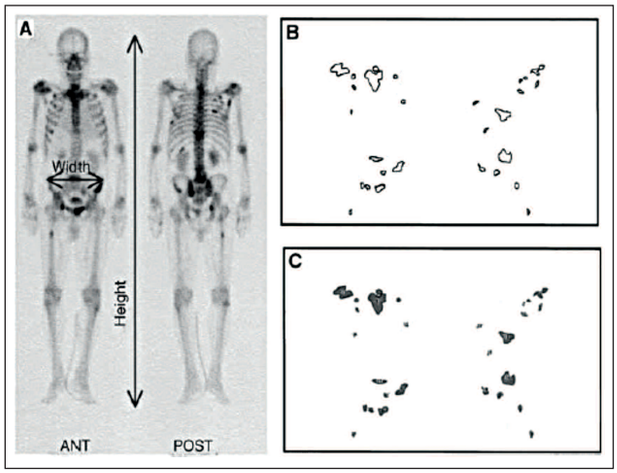

Figure 3. The automatic calculation of %PABS: Direct computer-processed tracings on a comprehensive map of the entire bone metastasis (right), of hot spots shown on WBS (left) [38].

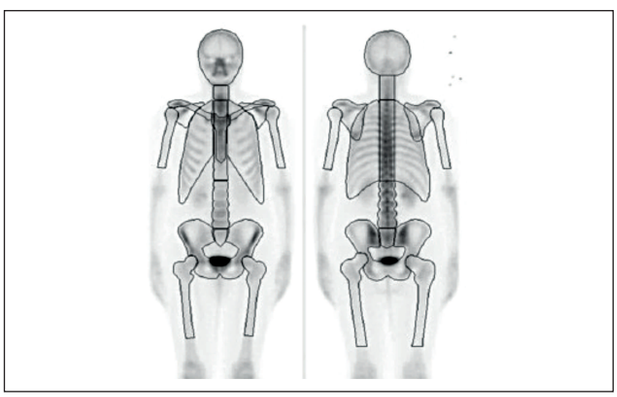

Figure 4. An atlas with 12 skeletal regions used for automated segmentation of WBS according to EXINI bone™ programme [43].

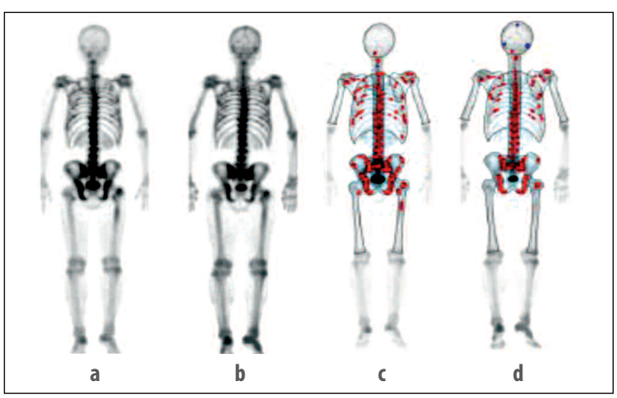

Figure 5. A patient with PCa and multiple bone metastases. 5a: Baseline visual image. EOD Grade is 3; however, it is very difficult to accurately count the number of metastatic lesions because the extent of metastases is diffuse and poorly defined. 5b: Post-treatment visual image (after 6 months). EOD remained Grade 3; however on follow-up it is difficult to compare scans 5a and 5b visually. 5c: Semi-automatically processing of baseline image (BSI=10.4%). 5d: Semiautomatically processing of post- treatment image. In contrast, the CAD detection of metastases is relatively easy, and BSI can be calculated semiautomatically; BSI=7.8%, objective response; the effectiveness of the treatment was supported by the decrease in BSI and serum PSA and ALP levels [44].

The main advantages of the fully- or semi-automated CAD systems applied in Nuclear Medicine are their simplicity, accuracy and reproducibility in estimating the percentage of EOD in patients with advanced PCa. They reduce inter-observer variation, improve the physician's sensitivity in detecting metastases in planar WBS and decrease false-positive results, so that non-metastatic patients to be reclassified into lower BSI groups. In addition to the high reproducibility and rapid processing times (<10sec versus 5min–30min for the manual method, depending on the EOD) [43], an automated BSI calculation can promote its utility as a valuable tool in both clinical practice and research with specific focus on the ability of these systems to accurately detect changes in the skeletal tumour burden over time, in particular, after treatment. Furthermore the relationship between manual and automatic BSI values was shown to be higher for bone scans with manual BSI scores <10 [43]. However, it is worth noting that BSI calculation (either manual or automated) has still five main limitations: a) The BSI relies on an estimate of healthy skeletal mass, which certainly varies among men [43]. Especially absorption in the trunk area tends to be different, and this area varies significantly by races [46]. b) Bone scans are still not direct measures of disease and do not change as quickly as other treatment indicators such as PSA, alkaline phosphatise or LDH [29]. c) Studies including cases from multiple centers to evaluate if the CAD system showed the same performance on images acquired with different gamma-cameras or different protocols are not yet available. d) Such a system does not replace physicians who still remain responsible for lesion analysis and final interpretation of digital examination, so that interpretations made by experienced physicians to be always used as the "gold standard" [36, 48, 49]. e) And of course there still exist the intrinsic limitations of bone scan procedure, common in all kinds of EOD measurement, most notably the false-positive and false negative factors affecting the technique.

However, most of these problems can be improved by concrete methodology, such as: a) By restricting inclusion criteria, b) By comparing BSI changes simultaneously or subsequently with serologic bone metabolic markers, c) By corellations with the Gleason score, d) By using the performance status scoring systems, i.e. the scoring of bone pain according to the severity and frequency of bone pain, daily mobility and the type/dosage of administered analgesic drugs [50, 51, 31], e) By further advancing the diagnostic performance of the CAD systems applied in Nuclear Medicine [47].

Application of the CAD methods as clinical decision support tools appears to have significant potential and merits further research. Future developments in this field along with sufficient training databases and relative cost-benefit analyses may lead to clinically usefull decision-support tools, simplifying a valuable but cumbersome technology with shortcomings that had prevented until recently its widespread clinical use.

Prognostic implications

With the use of a digital model measuring the EOD on the bone scan, it was already in 1981 possible to derive quanti-

tative criteria for response in bone metastases of patients with metastatic PCa. It was then also suggested that serial quantitative bone scans should be done, in preference to radiographs, to assess the response of bone metastases to systemic treatment [32]. The different patterns of bone metastases, metastatic load and their prognostic significance, in terms of disease progression and disease specific survival, were examined in many consecutive studies; the most acknowledged of them are chronologically presented bellow (Table 3):

Table 3. *Description of the main patterns of adverse scintigraphic prognostic predictors in patients with PCa*

Year	No of patients	Adverse scintigraphic prognostic predictors in patients with PCa	Reference
1984	10	Stability or increase in count rate, in sequential computerized bone scanning (versus decrease in count rate, that had a better prognosis)	[33]
1988	166	The 2 years survival rates for EOD Grades 1 to 4 (see Table 1) were 94%, 74%, 68%, and 40%, respectively *Comment: discrimination was lost in the middle groups*	[13]
1991	521	Positive bone scan (mere presence of bone metastases)	[14]
1991	80	Diffuse bone involvement (versus focal, that had a better prognosis)	[15]
1991	76	PCa patients with >2 bony lesions (versus those with 1-2 skeletal metastases)	[16]
1993	169	A metastatic patern either diffuse or involving more distal sites, such as the skull or the sternum (versus that with an isolated metastasis in the pelvis or on the dorsal vertebrae)	[17]
1993	76	PCa patients with bone metastases outside the pelvis and the lumbar spine (versus those with lesions confined in these areas) *Comment: no statistical difference was observed with disease grading according to the traditional classification of EOD [13]*	[18]
1993	34	An increase in count rate over the lower thoracic and all lumbar vertebrae 4h after injection of ^{99m}Tc-MDP was associated with disease progression and survival < 1 year	[52]
2002	86	PCa patients with appendicular bone metastases (versus those with axial disease; 29 versus 53 months, respectively). *Comment: Prediction was also not possible when the same old grading system [13] was used*	[53]
2007	1006	Among 10 independent prognostic factors which were identified in multivariate analysis, the number of metastatic sites had a significantly worse survival HR (1.63 if > 2 sites)	[54]
2008	40	The combination of 4 prognostic factors in PCa patients under hormonal palliative treatment (WBS with more than 6 "hot" spots, Gleason Score, TNM staging and serum PSA) increased the overall prognostic validity compared to each single factor alone.	[55]

As regards the BSI value (manual or automated), it has been amply reported to contain prognostic information in patients with hormone-refractory metastatic PCa, in addition to that of conventional prognostic markers such as clinical T stage, Gleason score, and PSA [38, 43, 56, 57] and it has therefore drawn the attention of oncologists and urologists. A key issue will be whether serial changes in the BSI can be used to monitor treatment effects. This is important because of the controversies surrounding the use of posttherapy change in PSA as an outcome measure for clinical trials and the difficulties in interpreting changes in radionuclide bone scans in a reproducible way. In an effort to make the interpretation more standardised, the Prostate Cancer Clinical Trials Working Group (PCWG2) has defined progression in bone as the simplified model of the presence of two or more new lesions on a bone scan compared with a prior scan [58]. Nonetheless, the differences in survival rates of PCa patients with metastatic disease according to pre-treatment BSI values, or post-treatment BSI changes were also examined in many consecutive studies; the most acknowledged of them are chronologically presented bellow (Table 4):

Table 4. *Description of the prognostic power of BSI in PCa patients*

Year	No of patients	Brief discription of prognostic power of BSI in PCa patients, in terms of mean overall survival (OS)	Reference
1999	191	OS was 18.3 months, if BSI<1.4%. OS was 15.8 months, if 5.1%>BSI>1.4%. OS was 8.1 months, if BSI>5.1%.	[28]
2003	56	After hormonal treatment OS was longer, if %PABS<4.6%, versus %PABS>4.6% (relative risk ratio, 2.603).	[38]
2003	42	After hormonal treatment OS was longer, if %PABS declined by > 25% versus a %PABS decline by <25%.	[21]
2012	88	After hormonal treatment, the log-transformed percentile change in BSI from baseline to 3 and 6 months was prognostic for shorter OS (relative risk ratios, 2.44 and 2.54 respectively). Alternatively, a doubling of BSI while on treatment resulted in a 1.9-fold increase in the risk of death. *Comment 1: The baseline BSI value was a weaker indicator of OS.* *Comment 2: Respective changes in PSA were not correlated with OS when adjusted for BSI.*	[29]
2012	42	After hormonal treatment OS was longer, if the automated BSI (aBSI) decreased. *Comment 1: aBSI was a stronger indicator of OS than EOD grade [13].* *Comment 2: aBSI was an earlier sign of disease progression than rising PSA level.*	[59]
2013	130	5-year OS was 42%, if BSI<1%. 5-year OS was 31%, if 1%<BSI<5%. 5-year OS was 0%, if BSI>1%.	[60]
2013	266	After treatment with docetaxel, the 2-year OS was 57%, if BSI decreased, versus 18%, if BSI increased. *Comment: the PCWG2 classification was not prognostic for 2-year OS (respective rates were 35% and 38%, for patients fulfilling or not the criterion of two or more new lesions on WBS).*	[61]

In future larger, prospective or retrospective studies, the time range between baseline scan and start of treatment as well as between baseline scan and follow-up scans should also be more standardised. Moreover, the imaging biomarkers reflecting the skeletal EOD and their percentagile changes could also be correlated to serological biomarkers such as PSA and bone turnover markers, perhaps by the use of mathematical tools such as the logarithmic, or cube root transformation to stabilize the variance of analysis, with the first relative results being quite promising [62, 47].

The importance of prognostic models rests on their ability to capture clinically relevant and measurable variables for routine use and to make treatment decisions after prospective and independent validation. Consequently it might be speculated that with continued development, the imaging indeces of EOD may be most useful by individualising therapies and ultimately, by providing a more systematic way to determine response outcomes. Thus, such a practice has the potential to prove the imaging analogue of PSA kinetics in PCa for predicting survival after therapeutic trials. Quantitative WBS can be eventually used as a promising imaging biomarker, which will be important in terms of gaining valuable overall diagnostic and prognostic experience, especially when the final form of it becomes widely used under proper standarization of the methology.

In conclusion, all the aforementioned findings have shown the feasibility of capturing bone scintigraphy data as a single semi-quantitative imaging biomarker and generate evidence that such a measurement of tumour burden in the skeleton after bone-affecting therapies can be used to risk-stratify patients more efficiently than only using M-staging based on evidence of the presence or absence of metastatic spread. Although the results of most of the abovementioned studies are encouraging, their clinical value is hampered from many general limitations: The histopathological heterogeneity of prostatic disease, lack of an imaging gold standard, lack of prospective studies based on large patient groups and long follow-ups, bias in patient selection and finally the various and arbitrary methodologies of measurement and of cut-off values make evaluation of the relative literature challenging and render any attempt for serious and systematic comparisons, e.g. meta-analyses, arduous or even prohibiting.

The author declares that he has no conflicts of interest.

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The "Hippocratic plane tree" in the island of Kos, under the branches of which Hippocrates was teaching. The tree is now supported with iron fences but still has green leaves.