Original Study

Automated Bone Scan Index to Optimize Prostate Cancer Working Group Radiographic Progression Criteria for Men With Metastatic Castration-Resistant Prostate Cancer

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Abstract

The study sought to quantify the total increase in tumor burden represented by prostate cancer working group progression criteria, and to determine the interval increase that best associates with overall survival. An absolute increase of 0.6 in aBSI from the first follow-up scan results in the highest association with survival in patients with metastatic castration resistant prostate cancer.

Introduction: Radiographic progression-free survival (rPFS) by Prostate Cancer Working Group (PCWG) criteria is a radiographic endpoint. The automated bone scan index (aBSI) quantifies osseous disease burden on bone scintigraphy as a percentage of total skeletal weight. Using the aBSI, we sought to quantify increase in tumor burden represented by PCWG progression criteria, and to determine the interval increase that best associates with overall survival (OS). **Patient and Methods:** Retrospective analysis of trials using androgen receptor axis–targeted drugs for metastatic castration resistant prostate cancer patients (mCRPC). aBSI increase in bone disease was assessed from baseline scan to time-to-progression (per PCWG criteria). Threshold for time to aBSI increase were explored and the association between each time-to-threshold and OS was computed. **Results:** A total of 169 mCPRC patients had bone scans available for aBSI analysis. Of these, 90 (53%) had progression in bone meeting PCWG criteria. Total aBSI increase in patients meeting PCWG criteria was 1.22 (interquartile range [IQR]: 0.65-2.49), with a median relative increase of 109% (IQR: 40%-377%). Median aBSI at baseline was 3.1 (IQR: 1.3-7.1). The best association between OS and time-to-progression occurred with an absolute increase in aBSI equal to 0.6 (Kendall's tau 0.52). **Conclusion:** An absolute increase of 0.6 or more in aBSI from the first follow-up scan results in the highest association with OS in patients with mCRPC. The rPFS by PCWG, identified progression at nearly twice this tumor burden, suggesting that aBSI may be used to further develop the PCWG criteria without degrading its association with OS.

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Introduction

Prostate cancer is a bone-tropic disease, accounting for the majority of morbidity and mortality in men with metastatic castration-resistant disease (mCRPC).[1] Bone scintigraphy is the standard imaging modality to assess disease progression. The current standard for assessing progression by bone scan is based on the semiquantitative modified Prostate Cancer Working Group 2 and Prostate Cancer Working Group 3 (collectively PCWG) criteria.[2,3] The definition of progression by these criteria relies on the appearance of new lesions as interpreted by a trained reader. This progression biomarker was validated analytically by showing the reproducibility of the interpretation across readers. It was then clinically validated through a sequence of prospectively designed trials that demonstrated a consistent association with overall survival (OS) across trials, and largely eliminated misinterpretation of "flare" as

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an indicator of treatment failure.[4,5] As a result of the validation evidence generated, the biomarker is now a standard endpoint in clinical trials that is also used by regulatory agencies to support drug approvals.[6,7]

One of the putative explanations for the close association between radiographic progression-free survival (rPFS) and OS is that the PCWG definition of disease progression accounts for tumor flare, or pseudoprogression. The paradoxical increase in Tc99 MDP uptake is a result of bone healing, in response to an effective treatment. This temporary increase in activity is often misinterpreted as a failure of treatment, which can mistakenly lead to discontinuation of an effective therapy. To address flare, PCWG developed the 2 + 2 rule, which enabled patients to remain on treatment despite detection of new lesions on their first posttreatment bone scan if other signs of disease progression were absent. The same first posttreatment scan would become the new baseline to which future scans would be compared. Progression at any time point after the flare period (week 12) is determined on the date additional new lesions are found on any future scan, using the first posttreatment follow-up scan (ie, the flare scan) as the new baseline comparator.

PCWG bone scan progression criteria for rPFS did not utilize changes in the size, volume, confluence, or conspicuity of lesions as indicators of an increase in disease burden, given that such changes were difficult to describe or quantitate. Therefore, a quantitative description of disease burden was not part of PCWG criteria. The field of radiology is undergoing a transformation as automated computing techniques are deployed as assistive technology to image interpretation, to augment human readers. These techniques have the potential to advance imaging biomarkers and enable development of sophisticated, fully quantitative endpoints. The automated Bone Scan Index (aBSI) biomarker is a fully quantitative assessment of a patient's bony disease on a bone scan; it reports lesion number and area as the fraction of the total skeleton weight that is involved by tumor.[8] The aBSI has undergone rigorous preanalytical and analytical validation as a reproducible and accurate measure of the quantitative change in disease burden under various imaging setting and platforms.[9,10] In a recent phase 3 prospective study, aBSI assessment was demonstrated to be a prognostic biomarker in patients with mCRPC.[11] Here we report on our study of the PCWG progression biomarker in comparison to quantitative changes in disease burden using the aBSI in relation to OS.

Materials and Methods

Patients

Patients at Memorial Sloan Kettering Cancer Center (MSKCC) with mCRPC enrolled in phase II/III clinical trials of agents targeting the androgen receptor (AR) signaling axis were assessed for inclusion in this retrospective analysis. All the trials had incorporated PCWG criteria to determine disease progression in bone scans. The bone scan scheduling for the first 6 months were documented at 8 weeks, and after 6 months, the bone scans were performed at 12-week intervals. To qualify for this retrospective study, patients were required to have at least 2 follow-up bone scan images in raw DICOM format. The clinical trials were approved by the MSK institutional review board and a separate waiver was obtained to allow aBSI analysis of available bone scans, along with the collection of PCWG and clinical follow-up data.

Bone Scanning

All whole-body bone scans were obtained at MSKCC after 3 hours of a single intravenous injection of 600 MBq technetium-99m methylene diphosphonate. Whole-body images with anterior and posterior views (scan speed: 10 cm/min, 256 × 1024 matrix), were obtained using a gamma camera equipped with low-energy, high-resolution parallel hole collimators (Maxxus; General Electric, Milwaukee, WI). Energy discrimination was provided by a 15% window centered on the 140 keV of Tc-99m

PCWG Criteria

Changes in lesions considered metastatic on bone scan were assessed serially for progression as described below.

- Early progression of disease (2 + 2 rule) – If ≥ 2 new lesions compared with baseline were observed at the first follow-up scan, then progression was confirmed by a subsequent bone scan demonstrating ≥ 2 additional new lesions.
- Progression at any subsequent time point post flare – If ≥ 2 new lesions relative to the first follow-up bone scan were observed on any follow-up bone scan, and a subsequent confirmatory bone scan verified the continued presence of the ≥ 2 new lesions, then progression was confirmed.

aBSI Analysis

The aBSI platform version 3.3, developed by EXINI Diagnostics AB (Lund, Sweden), was used to generate the aBSI data from available bone scans at concurrent time points of PCWG assessment. The methodology of the automated platform has been described in detail.[8] In brief, neural networks automatically segment the different anatomical regions of the skeleton, followed by detection and classification of the abnormal hot spots. The weight fraction of the skeleton for each metastatic hot spot is calculated and the aBSI is calculated as the sum of all such fractions.

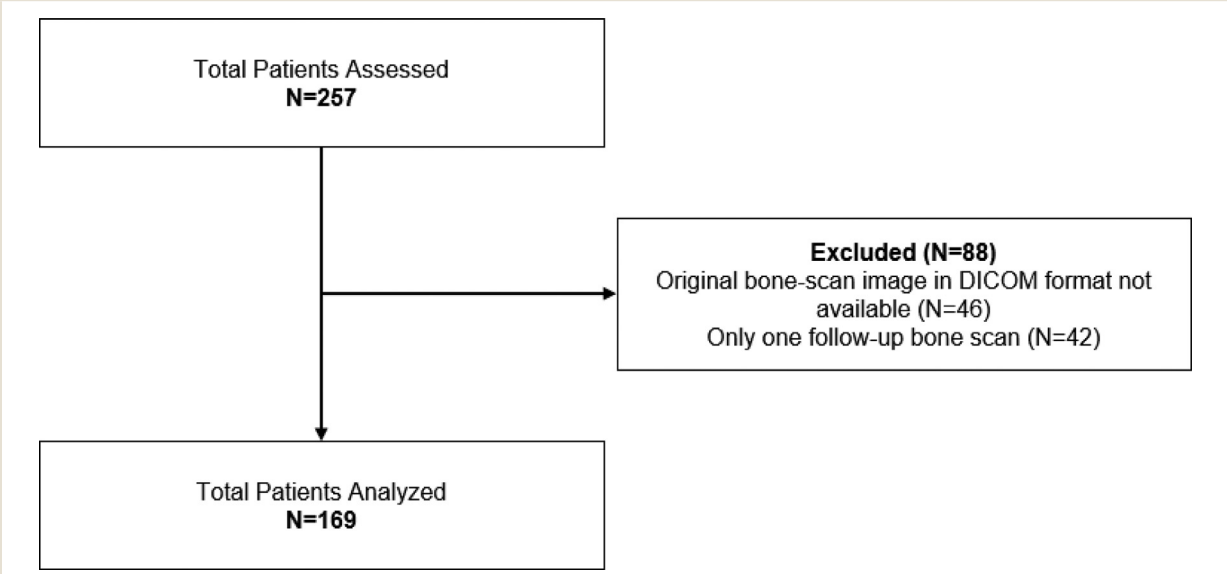
Statistical Analysis

In all evaluable patients, median (M), interquartile range (IQR), and box plots were used to assess the change in aBSI value, both absolute and relative, in determining which patients met the PCWG criteria for bone disease progression. The methodology that we chose to evaluate the association between the quantitative increase in burden of disease with OS was as follows.

(a) First, disease burden was determined by aBSI by examining thresholds of increasing aBSI. These thresholds were absolute increases of 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 with reference to the baseline aBSI, and separately with reference to the first follow-up.

(b) Next, the time interval from the baseline scan and, separately, from the first posttreatment scan for each threshold was examined. For example, the time to aBSI progression corresponding to an absolute increase of 0.6 is defined for each patient as the time t when aBSI(t) – aBSI(ref) > 0.6. A patient who did not exceed the absolute increase threshold was censored at the time of his last scan.

Figure 1 Flowchart to illustrate the qualification of the 169 patients that were evaluable for this study.



(c) Kendall's tau, derived from the Clayton copula, was used as the association measure between the time to progression and OS and accounts for both endpoints possibly being right censored. Kendall's tau ranges between 0 and 1, with the value 1 representing perfect concordance between the time to progression and the OS endpoints.

Statistical analyses were performed using FORTRAN and R software version 3.1.2.

Results

A total of 257 patients with mCRPC were enrolled in 7 clinical trials at MSK of agents targeting the AR signaling axis. Of the 257 patients, 88 were excluded for not having their bone scan images in DICOM format or for not having at least 2 follow-up bone scans as required by the PCWG criteria. Figure 1 details the total assessed patients and the 169 evaluable patients. The clinical characteristics of the 169 evaluable patients with mCRPC are detailed in Table 1.

The median follow-up of serial bone scan in 169 patients was 152 weeks (IQR 78-209 week). The median aBSI at baseline was 3.1 (IQR: 1.3-7.1). Figure 2 represents the summary of aBSI values corresponding to the PCWG assessment of lesion numbers at baseline. The association with survival for each threshold-defined aBSI time to progression in all 169 patients, with reference to increase from baseline and from first follow-up, is summarized in Tables 2 and 3, respectively. The highest observed association between time to aBSI progression and OS was observed at the absolute aBSI increase of 0.6 (Kendall's tau = 0.52) from first follow-up. An aBSI increase beyond 0.6 did not result in significant improvement in the association with OS. The association between the time to bone progression defined by PCWG criteria and OS was also 0.52 (Kendall's tau).

Of the 169 patients, 90 (53%) met the PCWG criteria for disease progression in bone. The 90 patients that met the PCWG criteria demonstrated a median absolute aBSI increase of 1.22 (IQR: 0.65-2.49) and a median relative increase of 109% (IQR: 40%–377%). Of the 90 patients, 35 (38%) met the PCWG criteria for early bone progression (meeting the 2 + 2 rule) and the remaining 55 patients (62%) progressed after the flare period. Table 4 details the increase of aBSI in the course of meeting the PCWG criteria. An example of serial PCWG and aBSI data of a patient that met early progression and a patient that progressed after the flare period is illustrated in Figures 3 and 4, respectively.

In 35 of the 90 patients that met the PCWG early progression criteria, the median aBSI increase from baseline was 1.25 (IQR: 0.55-2.41) at the first follow-up bone scan with ≥2 new lesions. At the subsequent follow-up scan, which requires an additional ≥2 new lesions to confirm early disease progression, the median aBSI increased further to 1.37 (IQR: 0.88-2.48), which represented an increase of 52% (IQR: 52%-99%) relative to the first follow-up scan.

In the remaining 55 of the 90 patients that met the PCWG progression criteria at subsequent time points after the flare period, the aBSI demonstrated incremental increases at the meeting of each PCWG milestone. At the appearance of 1 new lesion, the median aBSI increased by 0.16 (IQR: 0.03-0.39) and at the appearance of ≥2 new lesions the median aBSI increased by 0.47 (IQR: 0.20-1.38). At the subsequent confirmation scan the median aBSI increased by 1.15 (IQR: 0.51-2.49), which represented a total increase of 245% (IQR: 59%-597%) relative to the first follow-up scan. The aBSI increases meeting PCWG criteria are detailed in Table 4.

The remaining 79 patients who did not meet PCWG criteria for progression demonstrated a median absolute change in aBSI

Table 1 Clinical Characteristics of Evaluable Patients

Variable (at Baseline)	Number of Patients (n = 169)	%	Median	Range
Age, years			69.50	46.97-89.01
Gleason score			8	5-10
BSI, %			0.48	0.0-16.83
Prostate-specific antigen, ng/mL			33.38	1.12-1670.61
Hemoglobin, g/dL			12.65	9.0-15.50
Alkaline phosphatase, U/L			82.0	34.0-1068.0
Lactate dehydrogenase, U/L			203.0	88.0-1218.0
Site of metastasis				
Bone only	68	40%		
Bone & soft tissue	71	42%		
Soft tissue only	30	18%		
Prior hormonal treatments				
1	53	31%		
2	55	33%		
3	39	23%		
>3	22	13%		
Prior chemotherapy	49	20%		
No prior chemotherapy	120	80%		
Dead	144	85%		
Alive	25	15%		

Table 2 The Kendall's Tau Correlation of Survival With Time to Absolute BSI Increase From Baseline

Threshold: Absolute Increase From Baseline	Proportion Progressed	Kendall's Tau: Association of Time to BSI Progression vs. OS
0.2	0.75	0.27
0.4	0.70	0.38
0.6	0.63	0.39
0.8	0.58	0.41
1.0	0.54	0.40
1.2	0.53	0.43

Abbreviations: BSI = bone scan index; OS = overall survival.

Table 3 The Kendall's Tau Correlation of Survival With Time to Absolute BSI Increase From First Follow-Up

Threshold: Absolute Increase From First Follow-Up	Proportion Progressed	Kendall's Tau: Association of Time to BSI Progression and OS
0.2	0.58	0.34
0.4	0.47	0.41
0.6	**0.41**	**0.52**
0.8	0.36	0.51
1.0	0.29	0.52
1.2	0.26	0.50

Abbreviations: BSI = bone scan index; OS = overall survival. The bolded numbers highlight the point of the table, that the maximum association is at a BSI of 0.6

Figure 2 The baseline BSI values based on the number of lesions assessed by PCWG at baseline. PCWG = Prostate Cancer Working Group

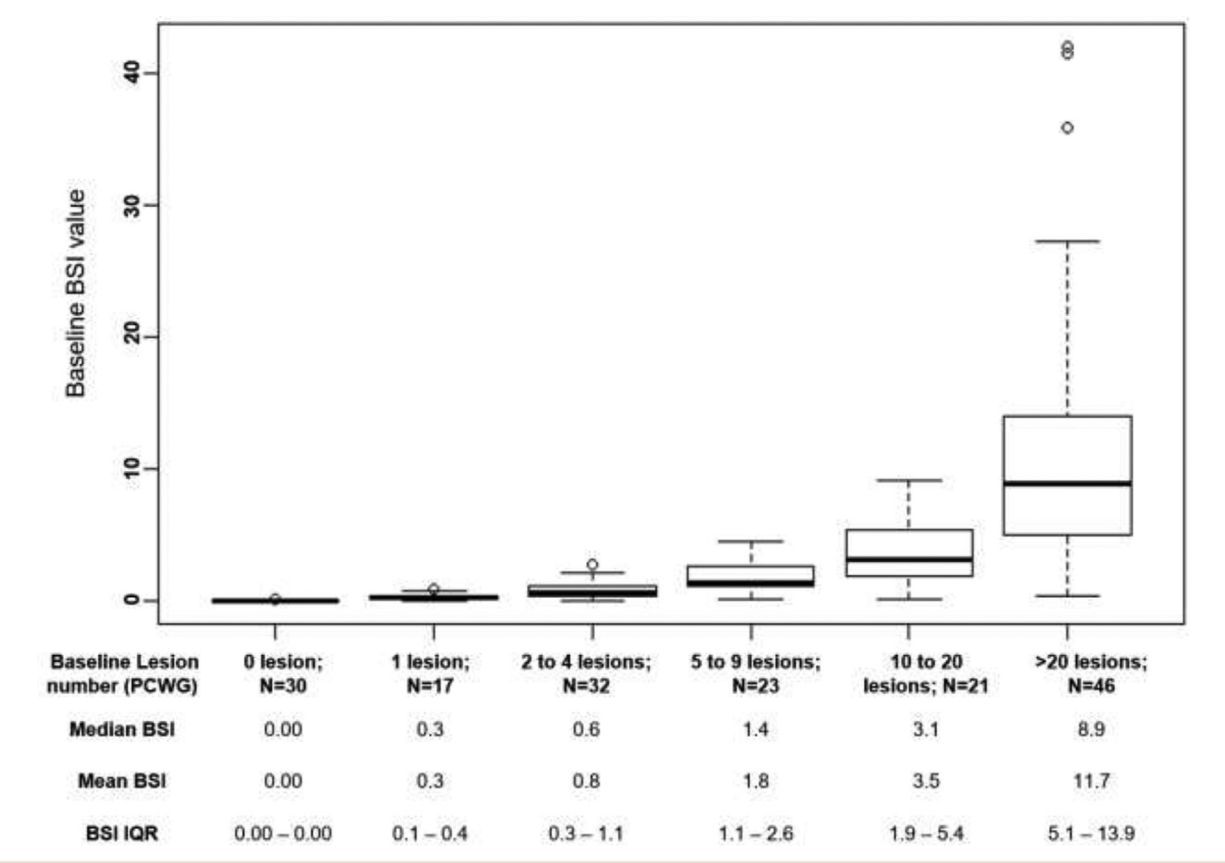


Table 4 Median Relative Quantitative Increase in Disease Burden at Each Milestone of PCWG Progression Criteria

PD by PCWG (n = 90 of 169)	Reference Scan	Assessment at PCWG Milestone	Absolute Increase (IQR)	Median Relative (%) BSI Increase (IQR)
Early PD; N = 35	Baseline	≥2 new lesions	1.25 (0.55-2.41)	79 (63-167)
	1st follow-up	≥2 + ≥2 new lesion	1.37 (0.88-2.48)	52 (21-99)
Post-flare PD; N = 55	1st follow-up	1 new lesion[a]	0.16 (0.03-0.39)	75 (7-175)
	1st follow-up	≥2 new lesions	0.47 (0.19-1.38)	95 (32-286)
	1st follow-up	Confirmation scan (no additional lesion required)	1.15 (0.51-2.49)	245 (59-597)

Abbreviations: BSI = bone scan index; IQR = interquartile range; PCWG = Prostate Cancer Working Group; PD = progressive disease.
[a] Of the 55 patients who met the PCWG criteria for bone progression, 27% (15/55) had an incremental increase of 1 new lesion before meeting the PCWG criteria of ≥2 new lesions.

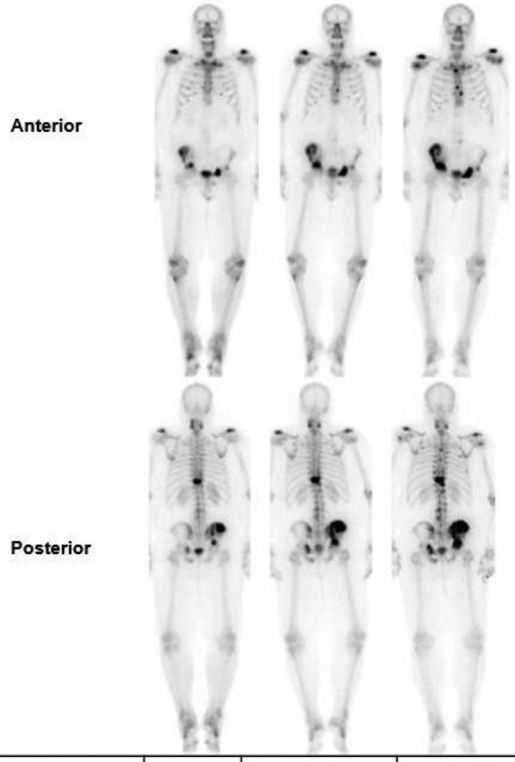
of 0.0 (IQR: 0.00-0.26) at the last available bone scan before end of treatment. Of these, 46% (36/79) demonstrated an increase in aBSI (median = 0.30; IQR: 0.11-1.14) due to increase in disease site/confluence but not due to increase in lesion number, hence not meeting the PCWG criteria.

Additionally, the PCWG reads identified 26 patients (15%; 26/169) with an increase in lesion number at the first follow-up but the subsequent follow-up bone scan did not demonstrate an additional 2 new lesions, hence they did not meet the early progression criteria of PCWG's 2+2 rule. These 26 patients demonstrated a concurrent temporary increase in aBSI at first follow-up (median = 0.67, IQR: 0.16-1.76), followed by a decline in aBSI on the subsequent follow-up bone scan (median= [-] 0.25; IQR: [-] 0.64-0.03), which likely represented flare.

Discussion

To our knowledge, this is the first estimation of the quantitative increase in total bone disease burden that is observed in

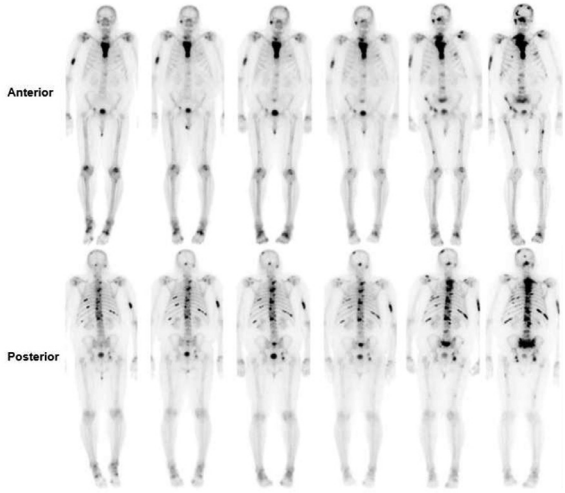
Figure 3 An example of BSI data generated on the concurrent timepoints of PCWG assessment. The patient met bone progression with PCWG 2+2 criteria with 4 new lesions at first follow-up that was confirmed with ≥5 additional lesions on subsequent bone scan. PCWG = Prostate Cancer Working Group



Time Points	BL	1FU (New Lesions compared to BL)	2nd FU (New Lesion Compared to FU1)
PCWG Lesion number	10 to 20	4	>5
Progression by PCWG	NO	≥2 new lesions	≥2+≥2 new lesions
BSI Value	5.8	8.9	10.45
BSI Increase relative to BL	-	53%	80%

meeting PCWG progression criteria. The aBSI allows us to understand how much disease burden has accrued in patients beyond lesion counting. Further, we have demonstrated that such quantitative techniques can be used to refine our definitions of progression without losing the benchmark correlation with OS established by PCWG in the 0.5 range. rPFS by PCWG criteria is dependent on the appearance of 2 (or 2 + 2) new bone lesions.[2,3] This definition represented a major advance for the field in standardizing the interpretation of bone scans, controlling for flare, and creating a semiquantitated endpoint fit for validation studies with an aim towards qualifying as a regulatory endpoint. At the time of its conception, it was not known whether the 2 + 2 or 2 new confirmed lesions was the progression definition that optimally correlated with OS. In this study, we determined the amount of disease progression that occurs in waiting for these definitions to be met. We found that the maximal association between progression of total bone disease burden and OS occurred when the aBSI achieved an absolute increase of 0.6 from the first follow-up scan. Note that this does not provide a clinical implication to discontinue therapy when an increase in aBSI of 0.6 is observed. PCWG has already established that the clinician should discontinue therapy only when the patient is no longer clinically benefiting. Rather, this observation is hypothesis generating, in that PCWG criteria can be further refined in future studies using quantitative methods. This associa-

Figure 4 An example of a patient who met bone progression criteria with the appearance of ≥2 lesions at fourth follow-up (week 48), after the flare period. The continued presence of the new lesions identified at fourth follow-up was confirmed at the subsequent confirmation scan performed 12 wk later; no additional lesions were required.



Time Points	BL	1st FU (New Lesions compared to BL)	2nd FU (New Lesion Compared to FU1)	3rd FU (New Lesion Compared to FU1)	4th FU (New Lesion Compared to FU1)	5th FU (New Lesion Compared to FU1)
PCWG Lesion number	>20	0	0	0	>5	>5
Progression by PCWG	NO	NO	NO	NO	≥2 new lesions	Confirmed
BSI Value	6.2	6.1	7.3	7.6	14.3	21.5
BSI increase relative to 1st FU	-	-	19%	25%	134%	244%

tion between the absolute aBSI increase of 0.6 and OS was nearly identical to the association between PCWG progression and OS in this dataset (Kendall's tau of 0.52), and nearly identical to the PCWG association between rPFS and OS in the COU302 study, which credentialed the criteria as a regulatory endpoint (Kendall's tau = 0.53).[5] Our study demonstrated that an aBSI increase beyond 0.6 (from first follow-up scan) may not result in significant improvement in the association with OS. Notably, at the time of the confirmation scan, the absolute median aBSI increased by 1.15 (IQR: 0.51-2.49), which was well beyond the observed aBSI progression threshold (0.6).

These data have several important implications. The first is an explanation as to why patients may progress clinically even before meeting PCWG progression criteria. In the COU302 study comparing abiraterone/prednisone with placebo/prednisone, 21% to 25% of patients developed clinical progression without ever demonstrating radiographic progression.[5] Using aBSI we have shown that the overall disease burden can significantly increase before PCWG criteria is met. The second implication is that, as we have demonstrated, a significant amount of disease progression occurs after the second lesion is documented, while the patient is waiting for a confirmatory scan to be performed. Note should be made that it is during this period that the median increase in aBSI overshoots the 0.6 threshold, after which the association with aBSI is not improved (ie, further disease progression does not provide a better assessment of the patient's survival).

These data should not prompt a change in PCWG criteria, nor a change in clinical practice. However, these data do signal that further studies should be conducted to optimize the criteria in order to retain a meaningful association between rPFS and OS while minimizing both ineffective treatment and unnecessary progression and clinical events. These data also suggest that total disease burden is feasible to measure and should be further investigated for credentialing as a fully quantitate endpoint for regulatory approval.

Despite the advantages of a fully quantitative imaging biomarker, the automated BSI assessment does not absolve the inherent limitations of bone scan as a non-tumor specific imaging modality. The uptake of technetium 99m in bone scan reflects the increase in the osteoblastic activity in bone. A major advance of the PCWG criteria was distinguishing disease progression from flare in the early on-treatment period. In this analysis, the early progression criteria (2 + 2 rule) demonstrated successive increases in aBSI at the first follow-up scan with the appearance of ≥2 new lesions and at the subsequent follow-up scan with an additional ≥2 new lesions. As a total quantitative assessment of bone scan, the aBSI analysis is also subject to the effects of the flare phenomenon. This was evident in our study, where 15% of patients (N = 26/169) demonstrated a temporary increase in lesion number, which was resolved in the

subsequent follow-up scan. Therefore, similar to the 2 + 2 PCWG criteria, the pattern of successive aBSI increases in the 2 immediate follow-up bone scans, performed at 8-week intervals, is necessary for aBSI to distinguish true early progression of disease from flare or pseudo-progression. Our data support the PCWG recommendation to evaluate progression as increase in bone disease burden from the first follow-up scan rather than the baseline scan. The overall association between time to aBSI increase and OS was higher with reference to the first follow-up values rather than pretreatment baseline values.

The fully quantitative assessment of PCWG3 criteria described in this paper will be increasingly useful as the field begins to transition not only to automated reads of traditional imaging studies, but also begins to explore molecular imaging modalities as direct indicators of tumor response and progression. While molecular imaging has regulatory approval for assessing disease distribution, it has no such indication for assessing therapeutic response. Part of the process of qualifying molecular imaging as a regulatory endpoint will be to define the relationship between a quantitative molecular biomarker and survival. These fully quantitative data of PCWG3 will allow like-with-like comparisons of new proposed molecular imaging biomarkers and PCWG3, to assessed the strength of association with survival.

Conclusion

PCWG-defined radiographic disease progression is a prospectively validated radiographic endpoint and is correlated with OS. We have demonstrated that continuous and quantitative increase of disease burden may achieve similar correlation with OS at an earlier inflection point. An absolute increase of 0.6 or more in aBSI, from the first follow-up scan, results in the highest association with OS in patients with mCRPC. The rPFS by PCWG, identified progression at nearly twice this tumor burden, suggesting that aBSI may be used to further develop the PCWG criteria without degrading its association with OS. Prospective registration studies are being conducted to examine quantitative changes in bone disease burden with aBSI, to further clinical trials endpoints that have meaningful associations with OS without exposing patients to treatment that may not be controlling disease.

Clinical Practice Points

The fully quantitative assessment of PCWG criteria with aBSI described in this paper will be increasingly useful as the field begins to transition not only to automated reads of traditional imaging studies, but also begins to explore molecular imaging modalities as direct indicators of tumor response and progression. While molecular imaging has regulatory approval for assessing disease distribution, it has no such indication for assessing therapeutic response. Part of the process of qualifying molecular imaging as a regulatory endpoint will be to define the relationship between a quantitative molecular biomarker and survival. These fully quantitative data of PCWG will allow like-with-like comparisons of new proposed molecular imaging biomarkers and PCWG, to assess the strength of association with survival.

Authors' contributions

Aseem Anand: Conceptualization, Methodology, Software analysis, Data curation, writing-original draft. Glenn Heller: Statistical analysis, Writing- Original draft preparation. Joseph Fox: Data curation, Reviewing, Editing. Daniel C. Danila: Reviewing, Editing. Anders Bjartell: Writing-Reviewing Editing, Software access. Lars Edenbrandt: Software analysis. Steven M Larson: Conceptualization, Methodology, writing-original draft. Howard I. Scher: Reviewing, Editing. Michael J. Morris: Conceptualization, Methodology, writing-original draft, Supervision.

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Disclosure

Dr. A. Anand is currently an employee at EXINI Diagnostics AB. All other authors have no disclosures to declare. Dr. Morris is a consultant to Curium, Athenex, Novartis, Exelixis, AstraZeneca, and Amgen. His institution has received research funds for the conduct of clinical trials from Bayer, Corcept, Novartis, Janssen, and Celgene.

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