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Total Bone Uptake as a Quantitative Imaging Biomarker for Prostate Cancer With Bone Metastases

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Abstract

Background/Aim: Bone scintigraphy is widely used for evaluating bone metastases in prostate cancer, but conventional planar imaging is limited by its qualitative nature and poor reproducibility for longitudinal assessment. The Bone Scan Index (BSI) provides a semiquantitative measure of skeletal tumor burden, but it does not reflect tracer uptake intensity. Quantitative single-photon emission computed tomography/computed tomography (SPECT/CT) allows volumetric assessment of uptake, and total bone uptake (TBU) derived from GI-BONE (Nihon Medi-Physics Co., Ltd, Tokyo, Japan) may offer a more comprehensive biomarker of skeletal disease activity.

Patients and Methods: We retrospectively reviewed three patients with prostate cancer and bone metastases who underwent serial ^{99m}Tc-HMDP bone SPECT/CT in routine practice between January and September 2025. Clinical data, prostate-specific antigen (PSA) levels, and quantitative indices from GI-BONE, including BSI, metabolic bone volume, and TBU, were extracted from medical records.

Results: In all three cases, serial TBU measurements provided an objective representation of skeletal disease activity over time. Changes in TBU were consistent with the clinical course and treatment response, suggesting that this parameter may be useful for monitoring disease dynamics during follow-up.

Conclusion: GI-BONE-derived TBU may be a practical quantitative biomarker for assessing bone metastatic burden and treatment response in prostate cancer. This case series suggests that TBU can complement conventional bone scintigraphy by providing objective and reproducible longitudinal information.

Keywords: Bone metastases, GIBONE, prostate cancer, SPECT/CT, total bone uptake.

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Introduction

Bone scintigraphy is the standard imaging modality for evaluating bone metastases in prostate cancer. Conventional planar bone scintigraphy remains widely used for detection and follow-up; however, its qualitative or semi-quantitative nature limits objective and reproducible longitudinal assessment. The Bone Scan Index (BSI) has been established as an imaging biomarker for quantifying the extent of bone metastases and has demonstrated prognostic and monitoring value (1, 2). Nevertheless, BSI is based on two-dimensional assessment and does not directly reflect the intensity of radiotracer uptake. Recently, quantitative single-photon emission computed tomography/computed tomography (SPECT/CT) has enabled the calculation of standardized uptake value (SUV) and volumetric parameters, allowing a more comprehensive assessment of skeletal tumor burden (3).

Among these quantitative parameters, Total Bone Uptake (TBU), provided by the GI-BONE (Nihon Medi-Physics Co., Ltd, Tokyo, Japan) software, represents a composite index that reflects both the extent and intensity of radiotracer accumulation in bone lesions. By integrating volumetric and uptake information, TBU may serve as an objective indicator of overall skeletal disease activity. In the present study, we applied this quantitative approach using GI-BONE.

We report three patients with prostate cancer and bone metastases who underwent serial ^{99m}Tc-HMDP bone scintigraphy analyzed using GI-BONE. This case series highlights the potential utility of TBU as an objective imaging biomarker for assessing disease activity and treatment response.

Patients and Methods

Patient selection. This retrospective case series included three patients with prostate cancer and bone metastases. All patients underwent serial ^{99m}Tc-HMDP bone SPECT/CT as part of routine clinical care between January and September 2025. Clinical data, including age, disease status, systemic treatments, prostate-specific antigen (PSA) at each imaging time point, and quantitative values obtained from bone scintigraphy analysis software, were extracted from medical records. The study protocol was approved by the Institutional Review Board of Hamamatsu University School of Medicine (approval No. 25-087).

GI-BONE Bone Scintigraphy Quantification Software. GI-BONE (Nihon Medi-Physics Co., Ltd, Tokyo, Japan) is post-processing software designed for the quantitative assessment of bone scintigraphy. It enables SUV-based quantification of SPECT images by applying a becquerel calibration factor (BCF), which converts count-based images into radioactivity concentration images comparable to PET. The BCF is determined using a cylindrical phantom with a known radioactivity concentration and is subsequently applied to clinical data, allowing SUV normalization based on administered dose and patient body weight.

GI-BONE automatically places volumes of interest (VOIs) on regions exceeding a predefined SUV threshold (4) and measures SUVmax, SUVmean, SUVpeak, and metabolic bone volume (MBV). TBU is calculated from SUVmean and MBV, and when multiple VOIs are present, these values are automatically summed to generate a total TBU (Figure 1).

Results

The first case was first-line treatment for metastatic castration-sensitive prostate cancer (mCSPC). A 68-year-old man presented with neck pain and bilateral upper limb numbness. His baseline PSA level was 4,599 ng/ml, and extensive bone metastases were identified. Combination therapy with degarelix, docetaxel, and darolutamide was initiated. Following treatment, the patient experienced rapid symptomatic improvement, with resolution of neurological symptoms and pain. PSA declined to 0.07 ng/ml. BSI decreased from 1.81% to 0%,

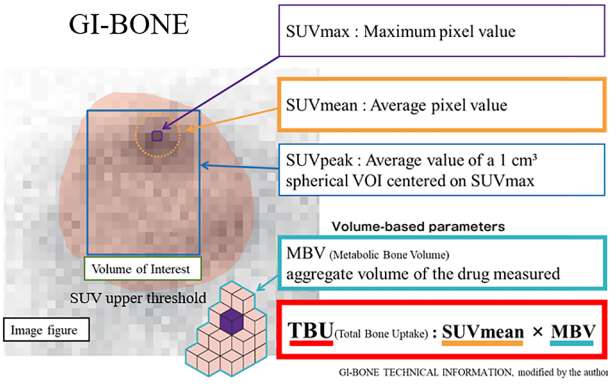

Figure 1. *GI-BONE (Nihon Medi-Physics Co., Ltd, Tokyo, Japan) automatically places volumes of interest (VOIs) on skeletal lesions showing radiotracer uptake above a predefined standardized uptake value (SUV) threshold. The software calculates SUVmax, SUVmean, SUVpeak, and metabolic bone volume (MBV), representing lesion volume above threshold. Total bone uptake (TBU) is derived as SUVmean × MBV. When multiple lesions are detected, individual values are automatically summed to provide the total TBU.*

while TBU showed a marked reduction from 1240 to 2.8, consistent with both clinical and biochemical responses (Figure 2A).

The second case was first-line treatment for metastatic castration resistant prostate cancer (mCRPC). A 78-year-old man with lower back pain was treated with a combination of radium-223 and enzalutamide. PSA initially decreased from 6.7 to 1.89 ng/ml, followed by a gradual increase to 3.6 ng/ml, demonstrating fluctuating kinetics. In contrast, bone pain improved steadily. BSI decreased from 0.33% to 0.05%. TBU declined substantially from 88 to 0 and appeared to correlate more closely with symptomatic improvement than PSA (Figure 2B).

The third case was a late-line setting of mCRPC. A 66-year-old man with diffuse bone and liver metastases received docetaxel. PSA decreased from 2,436 to 1,328 ng/ml. BSI showed only a minimal change (12.92% to 12.43%), whereas TBU decreased from 13,464 to 10,551. Although conventional bone scintigraphy images appeared largely unchanged, quantitative analysis using GI-BONE demonstrated a clear reduction in skeletal tumor burden (Figure 2C).

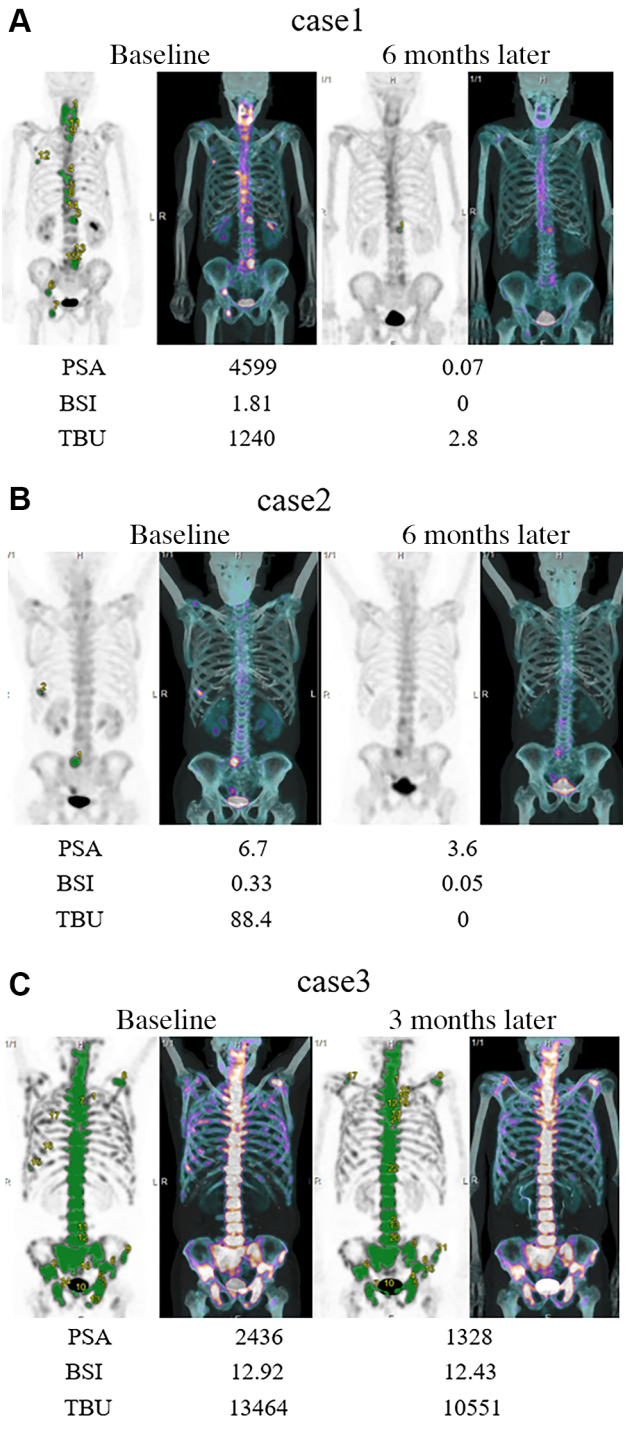

Figure 2. *Serial bone scintigraphy images and corresponding changes in prostate-specific antigen (PSA), Bone Scan Index (BSI), and total bone uptake (TBU) in case 1 (A), 2 (B), and 3 (C). "TBU" refers to the summed TBU calculated as the total across all volumes of interest (VOIs).*

Discussion

Bone scintigraphy remains one of the most widely used modalities for detecting and following bone metastases in patients with prostate cancer because of its broad availability, low cost, and whole-skeleton coverage. However, conventional planar imaging has important limitations, including reduced specificity and difficulty in lesion localization (5), especially in anatomically complex regions such as the spine and pelvis. Superimposition of anterior and posterior structures, as well as benign tracer uptake due to degenerative change, fracture, inflammation, or urinary activity, can reduce diagnostic confidence (6). In this context, SPECT/CT improves lesion localization and characterization by adding three-dimensional anatomical information to functional imaging (7).

BONENAVI and VSBONE are representative computer-aided diagnosis (CAD) systems for planar bone scintigraphy and have been shown to support objective image interpretation. BONENAVI version 2 has been reported to be useful in routine clinical practice (8) although the intrinsic limitations of bone scintigraphy remain unresolved. In particular, false-negative findings may occur in small pelvic lesions, faint uptake lesions, or lesions overlapping with urinary excretion, and segmentation errors can still be encountered in automated analysis (9). Accordingly, planar CAD systems are valuable for screening and initial interpretation, but their performance remains constrained by the two-dimensional nature of bone scintigraphy.

By contrast, GI-BONE provides a three-dimensional quantitative SPECT/CT-based approach. Because lesions are evaluated volumetrically, overlapping foci can be separated and assessed individually, which is a major advantage over planar methods (10). Quantitative SPECT/CT studies in prostate cancer have shown that uptake metrics can differentiate metastatic lesions from degenerative changes with high specificity, and SUV-based thresholds have been proposed for distinguishing active metastases from benign uptake (6). These findings support the use of GI-BONE for quantitative assessment of skeletal tumor burden.

At the same time, the threshold-based nature of GI-BONE should be recognized. Because all lesions above a predefined cutoff are extracted, benign degenerative or inflammatory changes may also be included, potentially increasing false-positive findings (11). Therefore, quantitative output should not be interpreted in isolation. Correlation with CT morphology, lesion distribution, clinical findings, and direct review by experienced readers remains essential to ensure diagnostic accuracy (12). In this sense, GI-BONE should be regarded as a tool that complements expert interpretation rather than replacing it.

In the present case series, TBU decreased in all three patients in association with treatment response and clinical improvement, despite differences in disease stage and treatment line. In the second case, TBU appeared to reflect improvement in bone pain more closely than PSA, which showed fluctuating kinetics. In the third case, TBU demonstrated a measurable decline despite minimal change in BSI and largely unchanged visual findings on conventional bone scintigraphy, suggesting that it may detect subtle changes in skeletal tumor burden that are not readily apparent on planar imaging.

These findings suggest that TBU may be useful for longitudinal monitoring of bone metastases in prostate cancer. Unlike planar-based indices such as BSI, TBU integrates both the extent of disease and the intensity of radiotracer uptake, allowing a more comprehensive assessment of skeletal tumor activity (3, 11). This quantitative and volumetric characteristic may be particularly valuable when conventional imaging appears stable or when PSA does not adequately reflect disease status (2). The observed utility of TBU across both castration-sensitive and castration-resistant settings also suggests that it may be applicable throughout the disease course. Quantitative SPECT/CT has likewise been reported to be useful in treatment-response assessment, including during radium-223 therapy, further supporting its role as a longitudinal imaging biomarker (3).

These observations are consistent with previous reports demonstrating the utility of quantitative SPECT/CT in differentiating metastatic from benign bone lesions

and in assessing treatment response (11). TBU has also been suggested to be more sensitive than BSI for detecting changes in metastatic bone burden (3). Collectively, these findings support the role of quantitative SPECT/CT-derived parameters as imaging biomarkers in prostate cancer, with TBU representing a promising metric for disease monitoring (11).

Taken together, BONENAVI and VSBONE may be particularly useful at diagnosis because they provide automated interpretation of planar bone scintigraphy and may help standardize lesion detection, whereas GI-BONE may be more advantageous for follow-up because it enables three-dimensional quantification and serial assessment of uptake change. These tools may therefore be complementary rather than mutually exclusive: planar CAD systems may support initial detection, while quantitative SPECT/CT may be more suitable for response monitoring and longitudinal disease evaluation.

Several limitations should be acknowledged. First, this study is limited by its small sample size and retrospective design, which may restrict the generalizability of the findings. Second, variability in imaging acquisition protocols, reconstruction parameters, and VOI delineation methods may influence quantitative measurements, highlighting the need for standardized methodologies. Third, the descriptive nature of this case series precludes definitive conclusions regarding the comparative superiority of TBU over established biomarkers. Despite these limitations, the consistent association between reductions in TBU and clinical improvement across heterogeneous clinical scenarios suggests that TBU provides clinically meaningful information complementary to PSA, BSI, and conventional imaging. In particular, its ability to reflect symptomatic changes and to detect treatment response not readily apparent on planar imaging underscores its potential value in routine follow-up.

Conclusion

This case series suggests that TBU derived from quantitative bone SPECT/CT may serve as a promising imaging biomarker for monitoring disease activity and treatment response in prostate cancer with bone metastases. Further prospective studies with larger cohorts are warranted to validate these findings and to establish standardized approaches for clinical implementation.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Shunsuke Watanabe conceived and designed the study, collected and analyzed the clinical data, and drafted the manuscript. The co-authors contributed to data interpretation and critically revised the manuscript for important intellectual content. All Authors reviewed and approved the final manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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