

Bone scan index on bone scintigraphy and radiation therapy for bone metastases from cancers other than prostate and breast cancers: a retrospective observational study

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Abstract

Background

A low bone scan index that is associated with a better prognosis in patients with bone metastases from prostate or breast cancer, the former often being osteolytic, has been established. In this study we aimed to use new automatic analysis software (VSBONE BSI; Nihon Medi-Physics, Tokyo, Japan) to investigate whether the pre-radiation therapy bone scan index, derived from bone scintigraphy images, is a prognostic indicator in patients undergoing radiation therapy for bone metastases from cancers other than breast or prostate cancer.

Methods

In this retrospective single institution study, we analyzed data of 51 patients who had undergone whole-body scintigraphy before receiving radiation therapy for bone metastases from cancers other than breast and prostate cancer between 2013 and 2019. Their bone metastases were classified as osteoblastic, osteolytic, or mixed and their pre-radiation bone scan indexes were automatically calculated using newly developed software (VSBONE BSI; Nihon Medi-Physics, Tokyo, Japan). Univariate and multivariate analyses were performed to identify associations between selected clinical variables and overall survival.

Results

We did not find a significant association between BSI and overall survival, possibly because osteolytic lesions may be underestimated by bone scan indexes. However, we did find that younger patients (aged less than the median of 66 years at the time of bone scintigraphy or of diagnosis of bone metastases) had significantly better overall survivals than older patients ($P = 0.016$ and $P = 0.036$, respectively). Additionally, bone scan indexes were significantly lower in patient with solitary or osteolytic bone metastases than in those with osteoblastic or mixed bone metastases ($P = 0.035$ and $P = <0.001$, respectively), and significantly higher in those with lung cancer than in those with other types of cancer (mean BSI 3.26% vs. 1.97%; $P = 0.009$).

Conclusions

The only significant association with survival identified in this study was for age at the time of bone scintigraphy and at time of diagnosis of bone metastases. In particular, we found no association between bone scan index and survival in the whole study cohort.

1. Background

Bone is a common site for metastasis of malignant tumors, 50–75% of malignant tumors metastasizing to bone (1, 2). It has been reported that 30–40% of lung cancers metastasize to bone during their clinical course (3). The modality of choice for evaluation of the presence and extent of bone metastases is bone scintigraphy (BS) using radiopharmaceuticals such as ^{99m}Tc -labeled phosphonates or phosphates because the whole body can easily be scanned in one session. However, because radiopharmaceuticals accumulate at sites of hydroxylapatite deposition, non-metastatic bone lesions caused by trauma and degeneration can appear as hot spots (1, 4). In recent years, hot spots have been characterized and quantified using an artificial neural network (ANN) and an index for the total amount of bone metastases, called the bone scan index (BSI), has been developed (5, 6). For example, bone metastases from prostate cancer are often osteoblastic and readily appear as hot spots. Many reports on the relationship between BSI and prognosis indicate that the prognosis is better in patients with lower BSI (7, 8, 9). However, there have been few reports on BSI and malignant tumors other than prostate cancer. When bone metastases are detected in patients with prostate or breast cancers, the median survival is expected to be years with recent new endocrine therapy and molecular-targeted drugs. In contrast, the median survival is as short as approximately 7 months in patients with lung cancer and hepatocellular carcinoma (10, 11, 12, 13). Therefore, radiation therapy (RT) is often administered to relieve symptoms of bone metastasis from lung cancer and other cancers. In this study, we determined the pre-irradiation BSI and prognosis in patients who underwent RT for bone metastases from malignant tumors other than prostate and breast cancers, such as lung cancer and hepatocellular carcinoma. We used new analysis software VSBONE BSI (Nihon Medi-Physics, Tokyo, Japan) to automatically calculate BSI. To the best of our knowledge, this is the first time this software has been used in the clinical study.

2. Methods

We retrospectively reviewed relevant data of patients treated with local RT for bone metastases between 2013 and 2019, and we selected 51 patients whose bone metastases had been confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) and who had also undergone BS. This study was approved by our institutional Review Board; informed consent was obtained from all patients. We have read the Declaration of Helsinki and followed its guidelines in this investigation. The clinical data of all 51 patients are summarized in Table 1. Age at the time of BS ranged from 32 to 85 years (median 66 years) and there were 33 men (64.7%) and 18 women (35.3%). The most common primary tumor was lung cancer (21 patients, 41.2%) and the second most common liver (nine patients, 17.6%). Seven patients had solitary bone metastasis (13.7%) and 44 multiple bone metastases (86.3%). According to the CT findings, bone metastases were classified into the following three types (14, 15): osteoblastic ($n = 6$, 11.8%), osteolytic ($n = 15$, 29.4%), and mixed ($n = 30$, 58.8%). Concurrent visceral metastases were detected in 36 patients (70.6%).

Table 1
Characteristics of patients treated with radiation therapy for bone metastasis

Characteristics	n = 51 (%)
Age at the time of bone scintigraphy, median years (range)	66 (32–85)
Gender	
Male	33 (64.7)
Female	18 (35.3)
Primary tumor site	
Lung	21 (41.2)
Liver	9 (17.6)
Kidney	4 (7.7)
Bile duct	3 (5.8)
Pancreas	2 (3.9)
Colon	2 (3.9)
Ovary	2 (3.9)
Thyroid	1 (2.0)
Stomach	1 (2.0)
Gallbladder	1 (2.0)
Uterine body	1 (2.0)
Uterine cervix	1 (2.0)
Bladder	1 (2.0)
Bone	1 (2.0)
Unknown	1 (2.0)
Number of bone metastasis	
Solitary	7 (13.7)
Multiple	44 (86.3)
Type of bone metastasis	
Osteoblastic	6 (11.8)
Osteolytic	15 (29.4)
Abbreviations: RT, radiation therapy.	

Characteristics	n = 51 (%)
Mixed	30 (58.8)
Bone scan index, mean % (range)	2.50 (0.00-11.86)
Visceral metastasis	
Yes	36 (70.6)
No	15 (29.4)
Systemic chemotherapy before RT	
Yes	25 (49.0)
No	26 (51.0)
Performance status at RT	
0, 1	33 (64.7)
2, 3, 4	18 (35.3)
RT dose, median Gy (range)	30 (6–40)
Abbreviations: RT, radiation therapy.	

Bone scintigraphy

Each patient was injected with 740 MBq of ^{99m}Tc -methylene diphosphonate (Fujifilm RI Pharma, Tokyo, Japan) or ^{99m}Tc -hydroxymethylene diphosphonate (Nihon Medi-Physics, Tokyo, Japan). Whole-body scintigraphy was performed ≥ 3.5 hours after the administration, using a gamma camera at a speed of 12 or 13.3 cm/min with a low-energy high-resolution collimator, 512×1024 or 256×1024 matrix size, zoom factor 1.00, and 139 keV photopeak with 20% window or 140.5 keV photopeak with 10% window. One of the following two gamma camera units was used; Forte (Philips Japan, Tokyo, Japan) or Discovery NM/CT 670 (GE Healthcare Japan, Tokyo, Japan). Raw image data were transferred to a PC with VSBONE BSI software and analyzed.

VSBONE BSI

The database of VSBONE BSI comprises data of pairs of anterior and posterior BS images of Japanese patients with prostate cancer (16, 17). Additionally, skeletal segmentation from 246 patients with prostate cancer and hot spot extraction from 896 patients with prostate cancer were performed, using a butterfly-type network of fully convolutional networks. Fully convolutional networks have no threshold for hot spots unlike ANN. Hot spots suspected of being metastases are depicted in red, whereas lesions suspected of being false positives are depicted in blue. From these, the BSI is automatically calculated. The BSI of the 51 patients in this study ranged from 0.00–11.86% (mean 2.50%).

Radiation therapy

Systemic chemotherapy was administered to 25 patients (49.0%) after BS and prior to commencing RT. RT was performed to relieve pain or to prevent or improve spinal cord paralysis. Performance status (PS) at the start of RT was evaluated according to the Eastern Cooperative Oncology Group criteria (18). There were 33 patients with $PS \leq 1$ (68.7%) and 18 with $PS \geq 2$ (35.3%). Ten patients received irradiation to multiple sites in one treatment session and eight received irradiation in multiple sessions, the total RT dose ranging from 6 to 40 Gy (median 30 Gy).

Statistical analysis

SPSS version 21.0 (IBM, Armonk, NY, USA) was used for statistical analysis. To identify variables associated with high BSI, univariate analysis with the Mann–Whitney U test was performed using the following patient characteristics: age at BS (median <66 years vs. ≥ 66 years), sex, primary tumor site (lung cancer vs. other tumors), number of bone metastases (solitary vs. multiple), and type of bone metastasis (osteolytic vs. others). The Kaplan–Meier method was used to calculate the probability of overall survival (OS) from the date of BS. Differences in survival between subgroups of patients according to BSI (< mean 2.50% vs. \geq mean), visceral or brain metastases at BS (yes vs. no), systemic chemotherapy before RT (yes vs. no), PS at RT (0, 1 vs. 2, 3, 4), and the above mentioned variables were analyzed using Mantel's log-rank test and multivariate analyses Cox proportional hazard model. A P value of < 0.05 was considered to denote statistical significance.

3. Results

Univariate analysis revealed that the BSI was significantly higher in patients with lung cancer than in those with other tumors (mean BSI 3.26% vs. 1.97%; $P = 0.009$) (Fig. 1 and Table 2). The BSI was significantly lower in patients with solitary and osteolytic bone metastases than in those with other types of metastases ($P = 0.035$ and $P = < 0.001$, respectively) (Fig. 2 and Table 2).

Table 2

Results of univariate analyses of associations between patient characteristics and bone scan index

Patient characteristics	BSI, mean % (range)	P-value
Age at bone scintigraphy (years)		
< 66	3.08 (0.00-11.86)	0.239
≥ 66	1.99 (0.00-5.46)	
Gender		
Male	2.46 (0.00-11.86)	0.430
Female	2.57 (0.29–5.46)	
Primary tumor site		
Lung	3.26 (0.43–8.77)	0.009*
Others	1.97 (0.00-11.86)	
Number of bone metastasis		
Solitary	1.10 (0.00-3.15)	0.035*
Multiple	2.73 (0.00-11.86)	
Type of bone metastasis		
Osteolytic	1.08 (0.00-5.46)	<0.001*
Others	3.10 (0.38–11.86)	
Abbreviations: BSI = bone scan index; CI = confidence interval; RT = radiation therapy. *Significant difference between two groups ($P < 0.05$)		

Overall survival time after BS ranged from 25 days to 2113 days with a median of 221 days. A high BSI (\geq mean) was not correlated with prognosis (Fig. 3 and Table 3). Both univariate and multivariate analyses showed that the younger the patients were when BS was performed or bone metastases diagnosed, the better the prognosis ($P = 0.016$ and $P = 0.036$, respectively) (Fig. 4 and Table 3).

Table 3
Univariate and multivariate analyses of predictors of overall survival after radiation therapy

Prognostic factors	Univariate analysis	Multivariate analysis	
	<i>P</i> -value	<i>P</i> -value	95% CI
Age at bone scintigraphy (years)			
< 66 vs. ≥ 66	0.016*	0.036*	1.052–4.696
Gender	0.271	0.599	0.384–1.737
Primary tumor site			
Lung cancer vs. Others	0.818	0.560	0.342–1.788
Number of bone metastasis			
Solitary vs. Multiple	0.565	0.342	0.260–1.597
Type of bone metastasis			
Osteolytic vs. Others	0.843	0.823	0.472–2.570
Bone scan index			
< 2.50% vs. ≥ 2.50%	0.322	0.908	0.387–2.325
Visceral metastasis			
Yes vs. No	0.263	0.219	0.757–3.370
Chemotherapy before RT			
Yes vs. No	0.580	0.674	0.434–1.716
Performance status at RT			
0, 1 vs. 2, 3, 4	0.124	0.067	0.231–1.052
Abbreviations: CI = confidence interval; RT = radiation therapy. * Significantly different (P < 0.05)			

4. Discussion

Bone metastases often occur in patients with prostate or breast cancer. Postmortem examination reportedly reveals bone metastases in 68% of patients with prostate cancer and 73% of those with breast cancer (19). In particular, bone metastases in patients with prostate cancer tend to be osteoblastic and are highly detectable as hot spots on BS (1, 20). BSI was first developed for characterization and quantitation of these hot spots, and a method using ANN, which was trained on a patients' database, was established (5, 21). In Japan, BONENAVI software (Fujifilm RI Pharma) was developed using ANN trained on a database of Japanese patients with prostate cancer (22). BONENAVI BSI automatically detects hot spots and makes calculations by combining abnormal areas with a high probability of representing

metastases. Recently, databases of Japanese patients with breast cancer and lung cancer have been added and reported to show good accuracy (23). In this study, we used VSBONE BSI, new analysis software, to automatically calculate of BSI for the first time, to the best of our knowledge. VSBONE BSI software also uses ANN trained on databases of Japanese patients and automatically calculates BSI on the basis of the same basic principles as does BONENAVI BSI (16, 17). In this study of patients with cancers other than prostate and breast cancers, BSI was significantly higher in those with bone metastases from lung cancer than in those with bone metastases from other malignant tumors. In general, metastases from other malignant tumors including hepatocellular carcinoma, are predominantly osteolytic, whereas metastases from lung cancer are more likely to have increased hydroxylapatite deposition. In this study, there were patients with BSI 0.00% despite multiple bone metastases from hepatocellular carcinoma having been identified by CT. Possible reported explanations for bone metastases not being detected by BSI are that 2.4% of bone metastases from hepatocellular carcinoma are osteolytic and there are soft tissue components in 38% of patients (13, 24). Our finding of significantly lower BSI with osteolytic lesions in this study is consistent with past reports that BONENAVI BSI of mild osteoblastic lesions from prostate, breast, and lung cancers are significantly lower than osteoblastic or mixed types metastases (14).

Many studies have reported that high BSI is a poor prognostic factor in patients with castration-resistant prostate cancer (4, 7, 9). Some studies have also reported that multiple bone metastases from lung and other cancers have a poorer prognosis than solitary bone metastases (12, 25). We found no correlation between BSI and prognosis in patients in this study, including those with lung cancer; however, osteolytic lesions may have been underestimated.

Few studies have been conducted on BS and RT to date. As for imaging modalities used to evaluate metastatic lesions before treatment with RT for bone metastases, no difference in therapeutic effects between BS, MRI, and ^{18}F fluorodeoxyglucose positron emission tomography have been reported (26). We have reported, we believe for the first time, that age at the time of BS is a significant favorable prognostic factor for RT for bone metastases, suggesting that long-term survival may be expected even in young patients with high BSI. For example, radium-223 (Xofigo; Bayer Pharmaceuticals, Whippany, NJ, USA), which is incorporated into newly formed osteoblastic bone matrix, is associated with longer survival in patients with bone metastases from prostate cancer (27). If radium-223 is approved for treating bone metastases from malignant tumors other than prostate cancer and covered by health insurance in Japan, we can expect prolongation of survival in patients with lung cancer and high BSI.

Conclusions

The only significant association with survival identified in this study was for age at the time of bone scintigraphy and at time of diagnosis of bone metastases. In particular, we found no association between bone scan index and survival in the whole study cohort.

Abbreviations

ANN: artificial neural network; BS: bone scintigraphy; BSI: bone scan index; CT, computed tomography; MRI, magnetic resonance imaging; RT, radiation therapy.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The dataset used during this study are available from the corresponding author on reasonable request.

Competing interests

Drs. Ishibashi, Maebayashi, Kimura, and Okada declare that they have no competing interests.

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No funding was received specifically for this work.

Authors' contributions

NI collected the patients' data and treated the patients and was a major contributor to writing the manuscript. YK and MO interpreted the BS images. TM treated the patients. All authors read and approved the final manuscript.

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Figures

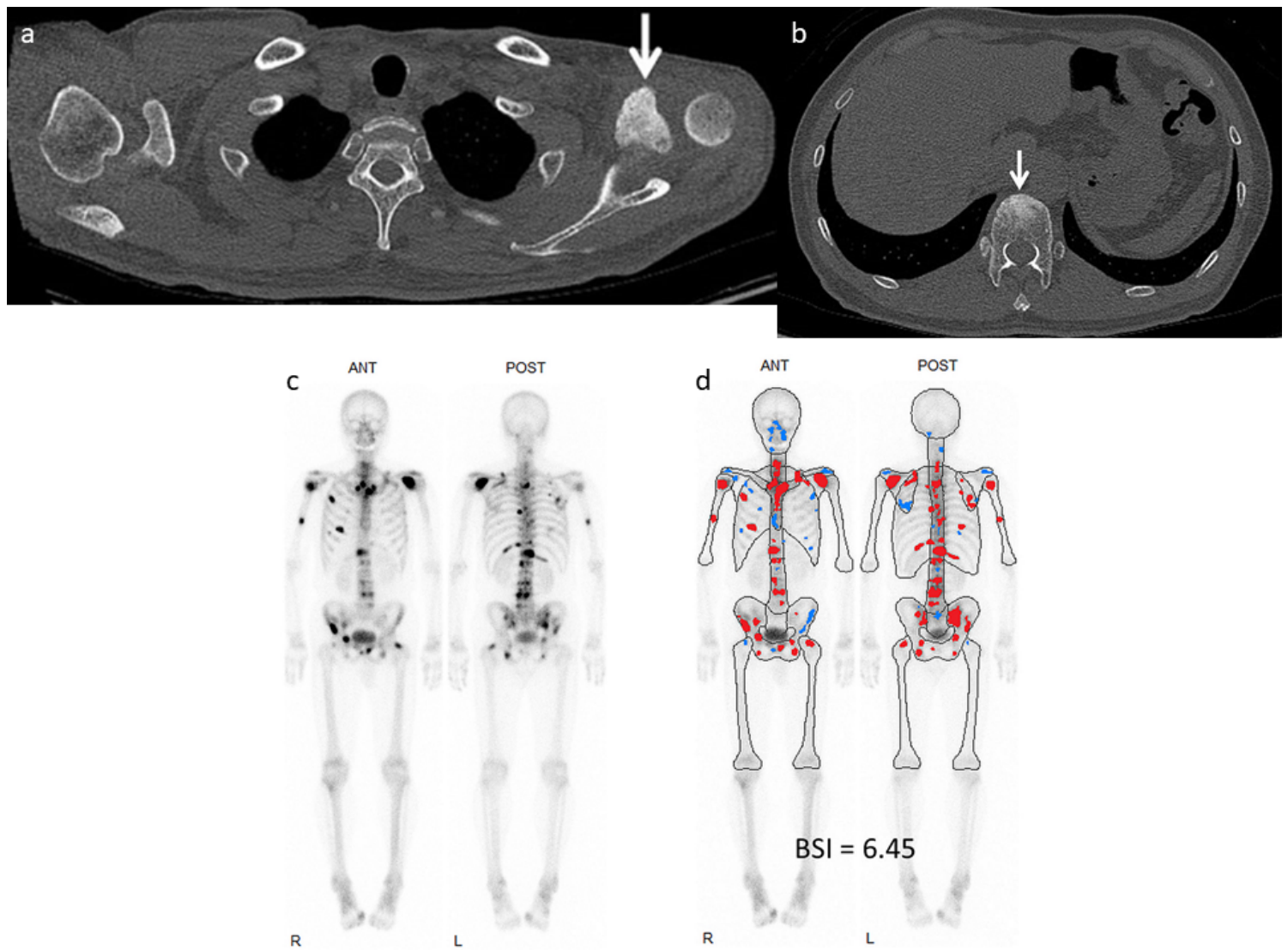


Figure 1

Representative example of a 62-year-old man with lung cancer and multiple bone metastases. Computed tomography showed multiple osteoblastic lesions (a,b). Bone scintigraphy showed multiple hot spots (c) and VSBONE BSI showed these lesions as red and blue. The BSI was extreme high at 6.45% (d).

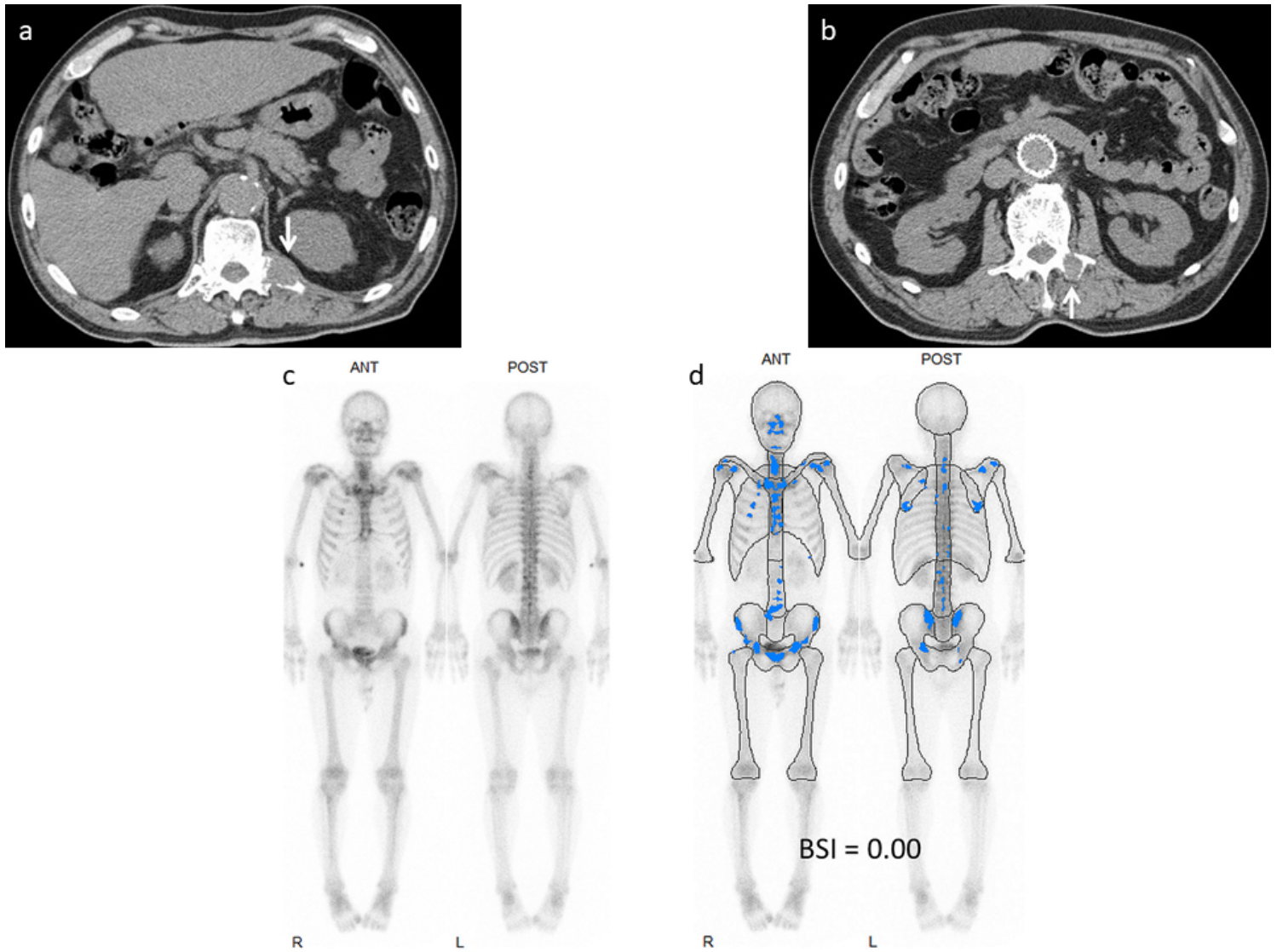


Figure 2

Representative example of a 76-year-old man with hepatocellular carcinoma and multiple bone metastases. Computed tomography showed multiple osteolytic soft tissue masses (a,b). Bone scintigraphy failed to detect these lesions (c) and VSBONE BSI showed hot spots as blue only. The BSI was undetectable at 0.00% (d).

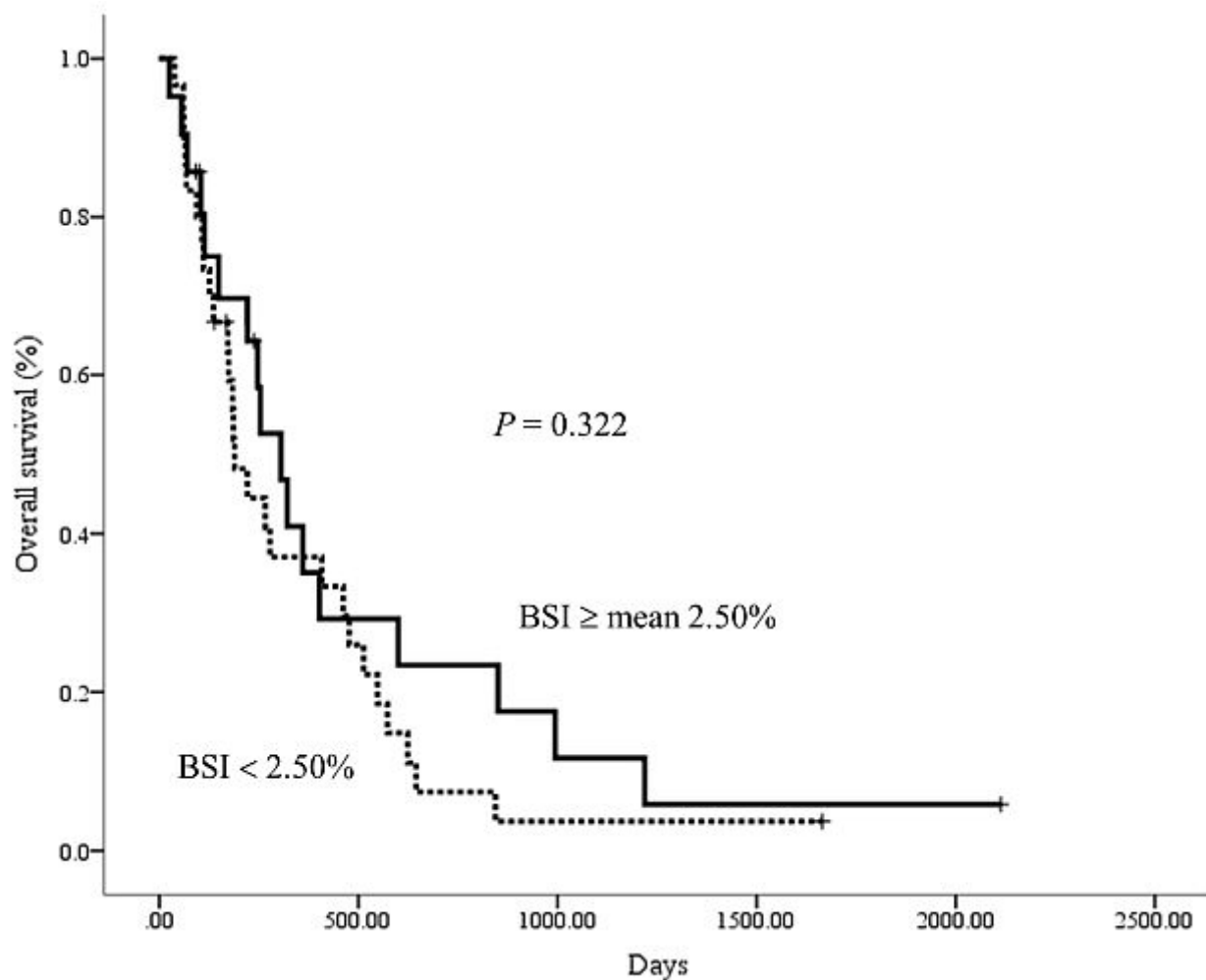


Figure 3

Kaplan–Meier survival curves of patients with BSI < mean 2.50% or \geq mean. The difference between the two groups is not statistically significant ($P = 0.322$).

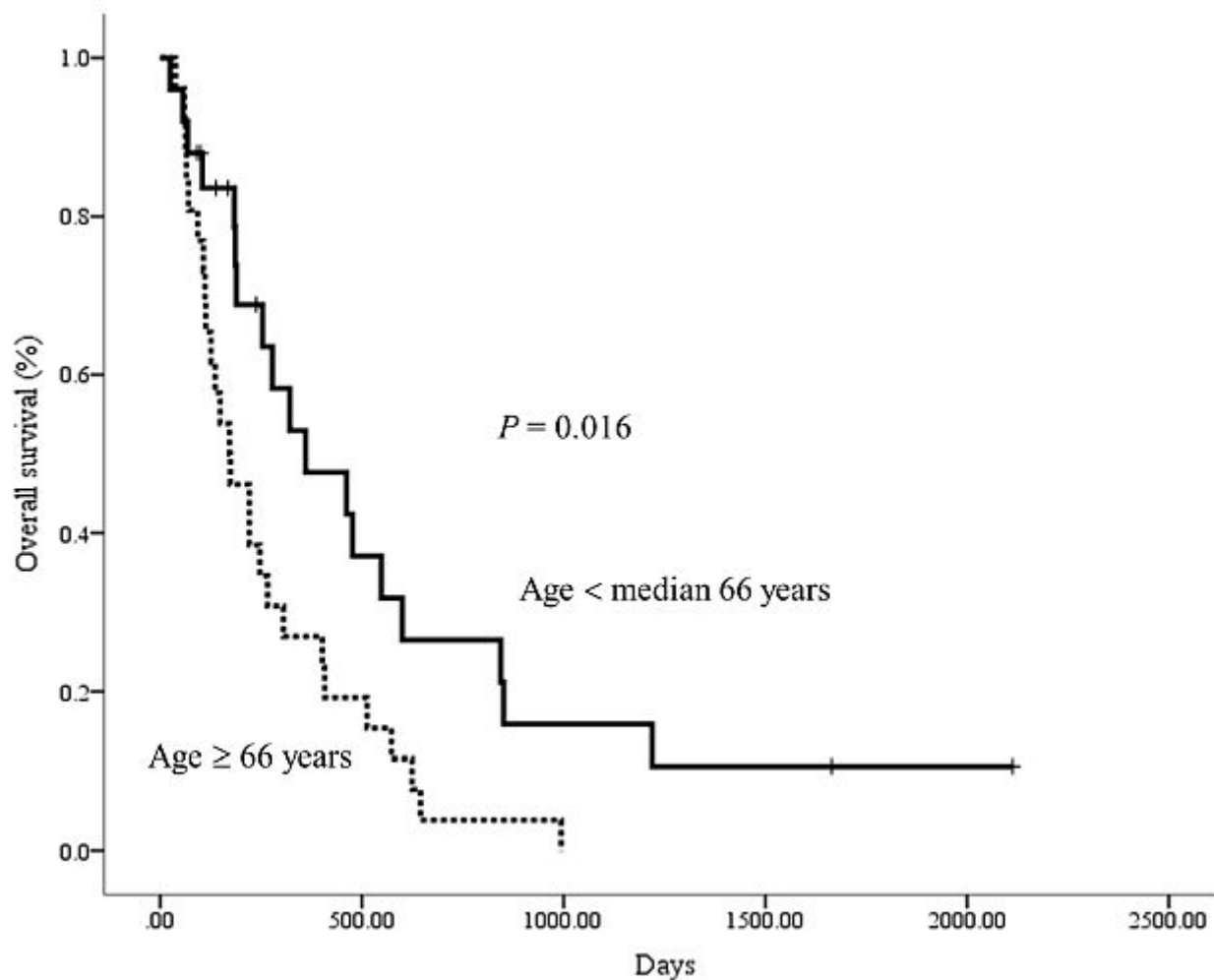


Figure 4

Kaplan–Meier survival curves of patients aged < median 66 years or \geq median at the time of bone scintigraphy. Survival was significantly longer in younger patients ($P = 0.016$).