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Predicting the prognosis of prostate cancer bone metastasis using the bone scan index (BSI) and hot spots(HS) calculated using VSBONE® BSI from Tc-99m-HMDP bone scintigraphy

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Short Title: Predicting the prognosis of prostate cancer bone metastasis using VSBONE

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Abstract

Introduction

The bone scan index (BSI) is widely used as a quantitative indicator of bone metastasis, therapeutic effect assessment, and prognosis prediction in prostate cancer. However, the BONE NAVI, which calculates BSI, only supports bone scintigraphy using Tc-99m-methylene diphosphonate (MDP). We developed the VSBONE® BSI, which calculates BSI from bone scintigraphy using Tc-99m-hydroxymethylene diphosphonate (HMDP). The purpose of this study was to demonstrate that the BSI calculated using VSBONE® BSI and hot spots (HS), which indicates the number of abnormal accumulations, are useful prognostic factors for patients with prostate cancer bone metastasis, similar to BONE NAVI.

Methods

We analyzed 322 patients who underwent bone scintigraphy for prostate cancer bone metastasis at our hospital. Initial bone scintigraphy was performed using Tc-99m-HMDP. All cases were retrospectively examined for their outcome and time to the final outcome. The results obtained were compared with the BSI and HS calculated using VSBONE® BSI.

Results

When the patients were divided into two groups, HS > 2 and HS ≤ 2, the HS ≤ 2 group had a significantly longer survival time ($P < 0.001$). In addition, when divided into two groups, BSI > 0.46 and BSI ≤ 0.46, the survival time of the BSI ≦ 0.46 group was significantly longer ($P < 0.001$).

Conclusion

BSI and HS obtained using VSBONE® BSI may be useful as prognostic predictors, similar to those obtained using BONE NAVI.

Introduction

Bone scintigraphy is used to identify bone metastasis in prostate cancer and the extent of disease is used to quantify the evaluation [1-2]. BONE NAVI, which is used to calculate the bone scan index (BSI), was developed as an accurate automatic diagnostic software [3-4]. Although BSI is recognized as an imaging biomarker and a prognostic factor [5-6], BONE NAVI only uses Tc-99m-methylene diphosphonate (MDP) bone scintigraphy. Figure 1 shows the structural formula of Tc-99m-MDP. Therefore, we developed the VSBONE® BSI, which calculates BSI from bone scintigraphy using Tc-99m-hydroxymethylene diphosphonate (HMDP). Tc-99m-HMDP exists as a chelate a compound composed of methane-1-hydroxy-1,1-diphosphonic acid disodium (Figure 2) and technetium oxide ion (Figure 3). In this study, we examined whether VSBONE® BSI is as useful as a prognostic indicator as BONE NAVI [7-10].

Material and methods

1. Patients

We recruited 527 patients who underwent initial bone scintigraphy using Tc-99m-HMDP to identify prostate cancer bone metastases between January 2010 and June

2018. 527 cases include those who underwent bone scintigraphy before treatment of the first onset of prostate cancer and those who underwent bone scintigraphy for re-stage diagnosis of recurrent lesions. Among them, 174 patients who was transferred to another hospital during the observation period, 14 patients who died of other diseases, and 17 patients with unknown outcomes were excluded. Finally, 322 cases were included and analyzed. The final outcome comprised 72 deaths and 250 surviving patients at the time of the survey. This is a retrospective study in which bone scintigraphy images results obtained during routine examinations were analyzed. For the 72 deaths, the number of days from initial bone scintigraphy to death was examined. For the 250 survivors, the number of days from the initial bone scintigraphy to the time of the survey was determined. Figure 4 shows a flowchart of a patient group assignment.

This study shows that it is possible to study survival time by calculating and comparing the cutoff value of survival time by BSI and HS, which are quantitative indicators obtained from bone scintigraphy, and the effect of treatment. The purpose is to clarify that VSBONE can be used as a tool for judgment and prognosis prediction. Therefore, this study includes cases of recurrence of bone metastases and cases before and after hormone therapy and chemotherapy.

2. Bone scintigraphy

Whole-body anterior and posterior bone scan images were acquired within 3 to 5 hours of intravenous injection of 740 MBq Tc-99m-HMDP. The imaging devices employed were ADAC Forte and Phillips BrightView X equipped with low-energy high-resolution collimators. The imaging parameters of the Forte were as follows: scan speed of 20 cm/min, 1024 × 1024 matrix, and a 140-keV photopeak with a 20% window and those of the BrightView X were as follows: scan speed of 20 cm/min, 1024 × 512 matrix, and a 140-keV photopeak with a 20% window.

3. Diagnosis of bone metastasis using VSBONE® BSI

VSBONE® BSI is software with a deep learning-based artificial intelligence developed to calculate BSI and hot spots(HS) on bone scintigraphy using Tc-99m-HMDP[7-8]. In the analysis protocol, the process of recognizing the skeletal anatomical structure on bone scintigraphy images and the process of detecting an abnormal accumulation of RI were performed using VSBONE processing. Subsequently, the BSI calculation and data output were performed by VSBONE View software using the VSBONE analysis results [9-10].

To use the software, digital imaging and communications in medicine (DICOM) data of the anterior and posterior images of the whole-body bone scintigraphy image were

transferred to a personal computer on which the software was installed. On the result, an area determined to be a bone metastasis was displayed in red as a "hot spot requiring a high degree of attention," and an area determined not to be a bone metastasis was displayed in blue as a "hot spot requiring a low degree of attention." On the Figure 5, BSI was 10.01% and the HS was 48. The results of the analysis of the previous test are also displayed. The previous bone scintigraphy and BSI in this patient showed that the number of HS was 0 and no bone metastases were observed. Injection leakage and RI distribution to the bladder and kidney were not recognized as abnormal RI accumulation in bone metastases. Although the automatically calculated BSI and HS were used, if there was an error in the result calculated by VSBONE® BSI, it was possible to edit the HS as needed. The process was then completed and the report image saved. In addition, multiple tests can be analyzed, and changes over time in BSI are displayed as graphs and tables shown in Figure 6.

The initial bone scintigraphy of the targeted 322 cases were reviewed by two nuclear medicine specialists for the presence or absence of bone metastases and analyzed using VSBONE® BSI to calculate BSI and HS.

4. Statistical analysis

A statistical software package (JMP SAS Institute., Cary, NC, USA) was used for all

statistical analyses. Receiver operating characteristics (ROC) analysis was performed for HS and BSI, and the cutoff value with the highest sensitivity was determined. The survival rate was determined from the obtained cutoff value using the Kaplan–Meier method.

5. Result

The 322 patients ranged in age from 43 to 88 years; the average age was 70.75, and the survival period was 27 to 3526 days, with an average of 2312.67 days (6.33 years). In 248 patients with no abnormal accumulation on bone scintigraphy, no bone metastasis was observed in the VSBONE® BSI analysis. Patients without bone metastases ranged in age from 43 to 88 years, with an average age of 70.01 years, and minimum survival time of 304 days (death due to the disease) and a maximum of 3526 days (survival cases), with an average of 2501.48 days (6.85years) (Table1).

Bone metastasis was diagnosed using bone scintigraphy in 74 cases. As a result of VSBONE® BSI analysis, bone metastasis was diagnosed, and BSI and HS were calculated. Bone metastases were finally diagnosed with additional computed tomography or magnetic resonance imaging or additional follow-up at the site of bone metastasis.

The 74 patients with bone metastases were 52 to 88 years of age (average, 73.16

years) and had a minimum survival time of 27 days (cases with a primary disease) and a maximum of 3488 days (survival cases), with an average of 1679.89 days (4.6 years). When the ROC analysis was performed on HS and the value of HS = 2 was used as the cutoff, AUC (0.725) and sensitivity (0.932) were highest shown in Figure 7.

When the patient group was divided into two groups of HS > 2 and HS ≦ 2, the group with HS > 2 included 47 patients and the survival time ranged 27 days (clinical cases) to 3291 days (survival cases), with an average of 1362.51 days (3.73 years). The group with HS ≦ 2 had 275 patients with a survival time of 304 days (death of the disease) to 3526 days (surviving cases), with an average of 2475.06 days (6.78 years).

When the Kaplan–Meier method was applied, the group with HS ≤ 2 had a significantly longer survival time ($P < 0.001$) shown in Figure 8.

When ROC analysis was performed on BSI and a value of BSI = 0.46 was used as the cutoff, AUC = 0.722 and sensitivity = 0.928, which was the highest sensitivity obtained shown in Figure 9.

When divided into two groups, BSI > 0.46 and BSI ≦ 0.46, the group with BSI > 0.46 included 54 patients, and the survival time ranged 27 days (death due to the original disease) to 3411 days (surviving cases), with an average of 1340.31 days (3.67 years). There were 275 patients in the group with BSI ≦ 0.46, with a survival time ranging

304 days (patients with bone metastases in bone scan) to 3526 days (survivors), with an average of 2508.59 days (6.87 years).

When the Kaplan–Meier method was applied, the group with BSI $\leqq$ 0.46 had a significantly longer survival time ($P < 0.001$) shown in Figure 10.

6. Discussion

Among malignant bone metastases, bone destructing lesions caused by osteoclasts and sclerosing lesions caused by osteoblasts can be mixed, but bone metastasis in prostate cancer is generally characterized by osteoblastic bone metastasis [11–12]. Regarding the drugs used for bone scintigraphy, hydroxyapatite crystals, which are the main components, accumulate at active sites of bone regeneration, such as osteoblastic lesions. Bone scintigraphy is the first choice for prostate cancer patients with bone metastasis, with the advantage of being able to locate systemic bone metastases at the same time.

BSI calculated using BONE NAVI is widely used as an index for the diagnosis of bone metastases, treatment effect evaluation, and prognosis prediction in prostate cancer [13–14]. However, BONE NAVI is a software that only supports scintigraphy with Tc–99m–MDP. At present, In Japan, approximately 30,000 bone scintigraphy examinations are performed annually. Tc–99m–MDP and Tc–99m–HMDP are used for bone

scintigraphy and their shares are almost the same for both drugs. We thought that it would be clinically useful to be able to calculate BSI from bone scintigraphy using Tc-99m-HMDP and developed VSBONE® BSI with the Tokyo University of Agriculture and Technology [7-10].

In this study, we used VSBONE® BSI for the initial bone scintigraphy procedure performed for the purpose of identifying bone metastasis in prostate cancer. We calculated the BSI and HS and examined the correlation with prognosis in the target patients. When the patient group was divided into two groups of HS > 2 and HS ≦ 2, the survival time of the HS ≦ 2 group was significantly longer in the Kaplan-Meier survival analysis. When the patient group was divided into two groups of BSI > 0.46 and BSI ≦ 0.46, the survival time of the BSI≦ 0.46 group was significantly longer in the Kaplan-Meier survival analysis.

BSI using BONE NAVI has been applied not only to the prognosis of prostate cancer bone metastases, but also to the evaluation of treatment effects and the prognosis of patients with breast cancer bone metastasis [15-17].

BONE NAVI is also a tool for calculating BSI and comparing survival time, and since there is a comparison with HS as its base, VS BONE can also be used as a tool for similar comparison. It is not possible to directly compare the two except to perform

MDP and HMDP simultaneously in one patient and calculate the BSI with each tool, but this is a wasteful exposure and is ethically unacceptable.

However, there is no difference in the mechanism of accumulation in bone metastasis between MDP and HMDP, and BONENAVI and VSBONE calculate BSI based on the same definition, so it is fully speculated that the results show the same tendency.

Conclusion

These results suggest that VSBONE® BSI may be useful in assessing the prognosis of patients with prostate cancer bone metastases.

Acknowledgement

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Statement of Ethics

We obtained written informed consent from all the participants in accordance with the Code of Ethics of the World Medical Association. All procedures performed in this study were in accordance with the ethical standards of our institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

This study has been approved by the Ethics Committee sponsored by the Graduate School of Medicine, Osaka City University, under the name of ″Validation of an automated diagnostic system for abnormal accumulation sites in nuclear medicine images, certification number 2019-40″.

Conflict of interest Statement

The authors have a financial conflict of interest to disclose concerning the study.

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Author Contributions

1. Shigeaki Higashiyama: manuscript writing, data collection, conceived and designed the analysis, and design of the research.

2. Atsushi Yoshida: data collection and manuscript writing.

3. Joji Kawabe: main conceptual idea and design of the research.

Data Availability Statement.

All data generated or analysed during this study are included in this. Further enquiries can be directed to the corresponding author.

References

1 Soloway MS, Hardeman SW, Hickey D, Raymond J, Todd B, Soloway s, et al. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer. 1988 Jan 1;61(1):195-202.

2 Takahashi Y, Yoshimura M, Suzuki K, Hashimoto T, Hirose H, Uchida K, et al. Assessment of bone scans in advanced prostate carcinoma using fully automated and semi-automated bone scan index methods. Ann Nucl Med. 2012 Aug;26(7):586-93.

3 Sadik M, Hamadeh I, Nordblom P, Suukula M, Höglund P, et al. Computer-assisted interpretation of planar whole-body bone scans. J Nucl Med. 2008 Dec;49(12):1958-65

4 Sadik M, Suurkula M, Höglund P, Järund A, Edenbrandt L. Improved Classifications of Planar Whole-Body Bone Scans Using a Computer-Assisted Diagnosis System: A Multicenter, Multiple-Reader, Multiple-Case Study. J Nucl Med. 2009 Mar;50(3):368-75.

5 Wakabayashi H, Nakajima K, Mizokami A, Namiki M, Inaki A, Taki J, et al. Bone scintigraphy as a new imaging biomarker: the relationship between bone scan index and bone metabolic markers in prostate cancer patients with bone metastases. Ann Nucl Med. 2013 Nov;27(9):802-7

6 Sabbatini P, Larson SM, Kremer A, Zhang ZF, Sun M, Yeung H, et al. Prognostic

Significance of Extent of Disease in Bone in Patients with Androgen-Independent Prostate Cancer. J Clin Oncol. 1999 Mar;17(3):948-57.

7 Shimizu A, Wakabayashi H, Kanamori T, Saito A, Nishikawa K, Daisaki H, et al. Automated measurement of bone scan index from a whole-body bone scintigram. International Journal of Computer Assisted Radiology and Surgery. Int J Comput Assist Radiol Surg. 2020 Mar;15(3):389-400.

8 Sekuboyina A, Rempfler M, Kukačka J, Tetteh G, Valentinitsch A, Kirschke Jan S, et l. Btrfly Net: Vertebrae Labelling with Energy Based Adversarial Learning of Local Spine Prior.. Proceedings of the 21th International Conference on Medical Image Computing and Computer Assisted Interventions; 2018 Sep 13-17; Granada, Spain.pp.649-57. Available from: https://arxiv.org/abs/1804.01307

9 Yoshida A, Higashiyama S, Kawabe J. Clinical trial of a new BSI analysis software for 99mTc-HMDP. Japanese Archive of cases conference of clinical nuclear medicine. Available from: https://doi.org/10.32291/nmj.1.0_28

10 Higashiyama S, Yoshida A, Kawabe J. Study of the Usefulness of Bone Scan Index Calculated From 99m-Technetium-Hydroxymethylene Diphosphonate (99m Tc-HMDP) Bone Scintigraphy for Bone Metastases from Prostate Cancer Using Deep Learning Algorithms. Curr Med Imaging. 2021;17(1):89-96.

11 Imbriaco M, Larson SY, Yeung HW, Mawlawi OR, Erdi Y, Venkatraman ES, et al. A new parameter for measuring metastatic bone involvement by prostate cancer: the Bone Scan Index. lin Cancer Res. 1998 Jul;4(7):1765-72.

12 Garnero P, Buchs N, Zekri J, Rizzoli R, Coleman RE Delmas PD. Markers of bone turnover for the management of patients with bone metastases from prostate cancer. Br J Cancer. 2000 Feb;82(4):858-64.

13 Koizumi M, Miyaji N, Murata T, Motegi K, Miwa K, Koyama M, et al. Evaluation of a revised version of computer-assisted diagnosis system, BONENAVI version 2.1.7, for bone scintigraphy in cancer patients. Ann Nucl Med. 2015 Oct;29(8):659-65.

14 Mitsui Y, Shiina H, Yamamoto Y, Haramoto M, Arichi N, Yasumoto H, et al. Prediction of survival benefit using an automated bone scan index in patients with castration-resistant prostate cancer. BJU Int. 2012 Dec;110(11 Pt B):E628-34.

15 Ulmert D, Kaboteh R, Fox JJ, Savage C, Evans J Michael, Lija H, et al. A Novel Automated Platform for Quantifying the Extent of Skeletal Tumour Involvement in Prostate Cancer Patients Using the Bone Scan Index. Eur Urol. 2012 Jul;62(1):78-84.

16 Armstrong AJ, Kaboteh R, Carducci MA, Damber J-E, Stadler WM, Hansen M, et al. Assessment of the bone scan index in a randomized placebo-controlled trial of tasquinimod in men with metastatic castration-resistant prostate cancer (mCRPC).

Urol oncol. 2014 Nov;32(8):1308-16

17 Okada Y. Bone scan index is a prognostic factor for breast cancer patients with bone metastasis being treated with zoledronic acid. Open J Rad 2015;5:149-58.

Figure Legends

Fig. 1

The structural formula of 99mTc-MDP.

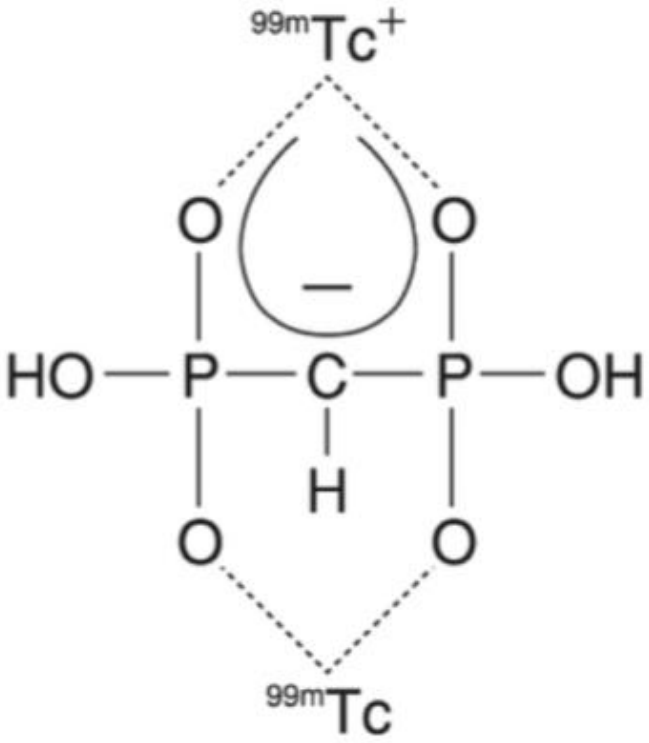


Fig. 2.3

99mTc-HMDP exists as a chelate compound composed of methane-1-hydroxy-1,1-diphosphonic acid disodium (Fig.2) and technetium oxide(Fig.3).

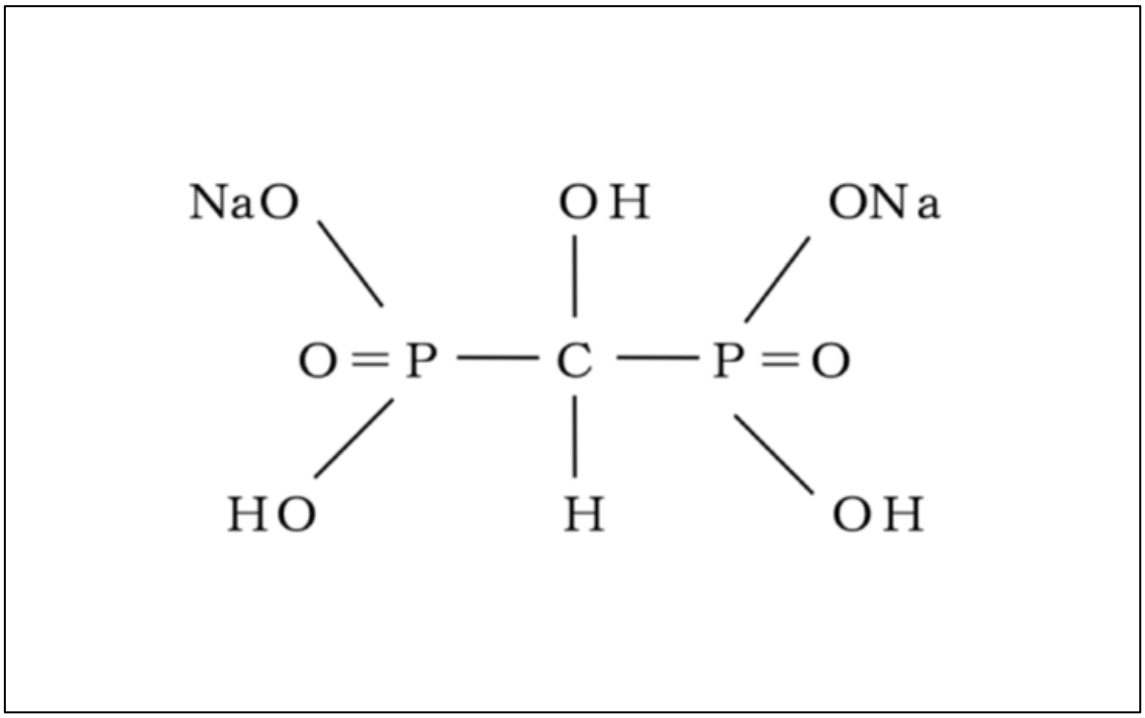


Fig.2

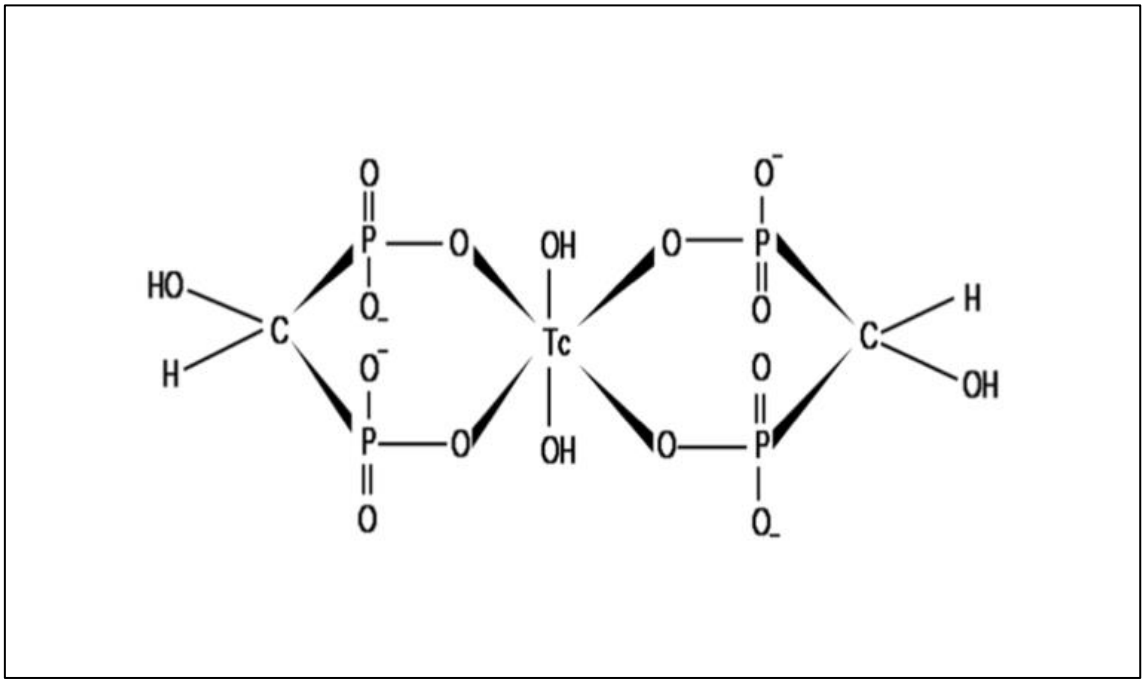


Fig.3

Fig.4

Flow chart detailing the patients included in the analysis

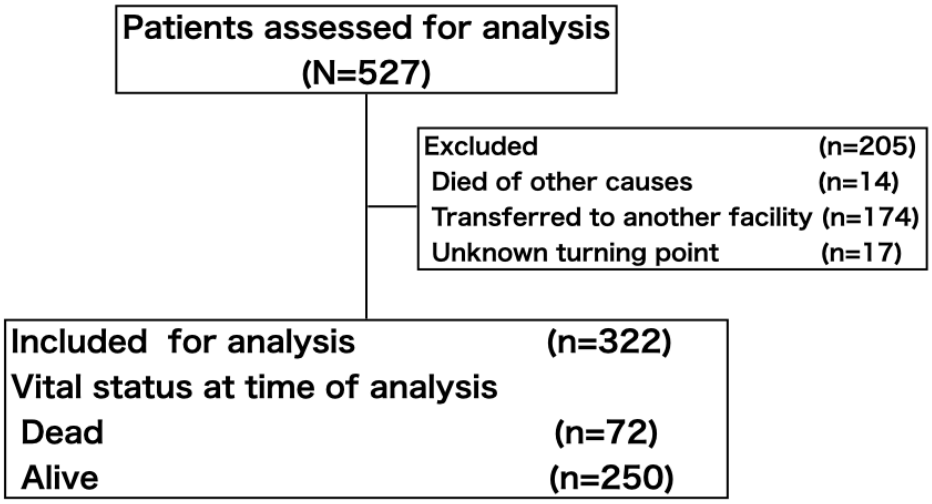


Fig. 5

A: Bone scintigraphy. B: Results of analyzed bone scintigraphy.

A case of bone metastases from prostate cancer is shown.

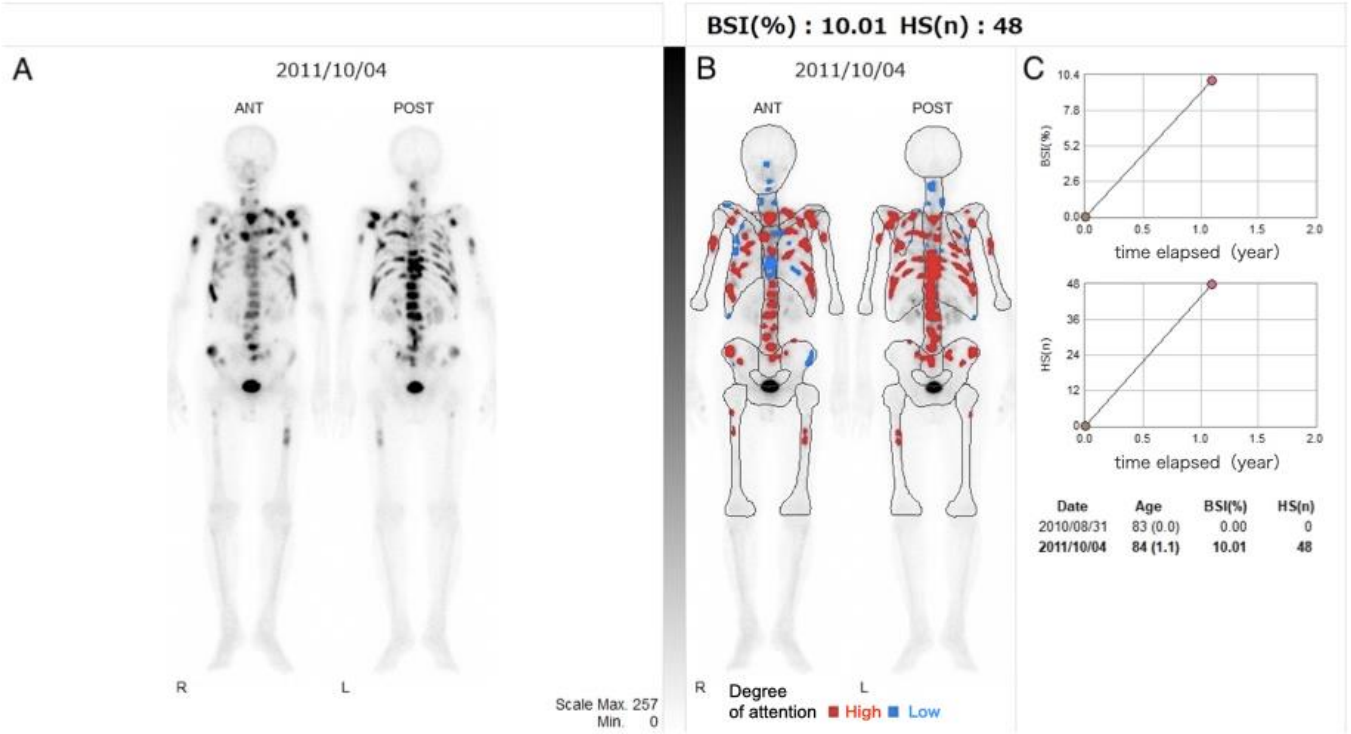

BSI(%) : 10.01 HS(n) : 48
A
2011/10/04
ANT
POST
R
L
Scale Max. 257
Min. 0
B
2011/10/04
ANT
POST
R
L
Degree of attention High Low
C
BSI(%)
time elapsed (year)
HS(n)
time elapsed (year)
Date Age BSI(%) HS(n)
2010/08/31 83 (0.0) 0.00 0
2011/10/04 84 (1.1) 10.01 48

Fig.6

A: Results of analyzed bone scintigraphy

B: Graphs and tables of the bone scan index (BSI) and number of hot spots (HS).

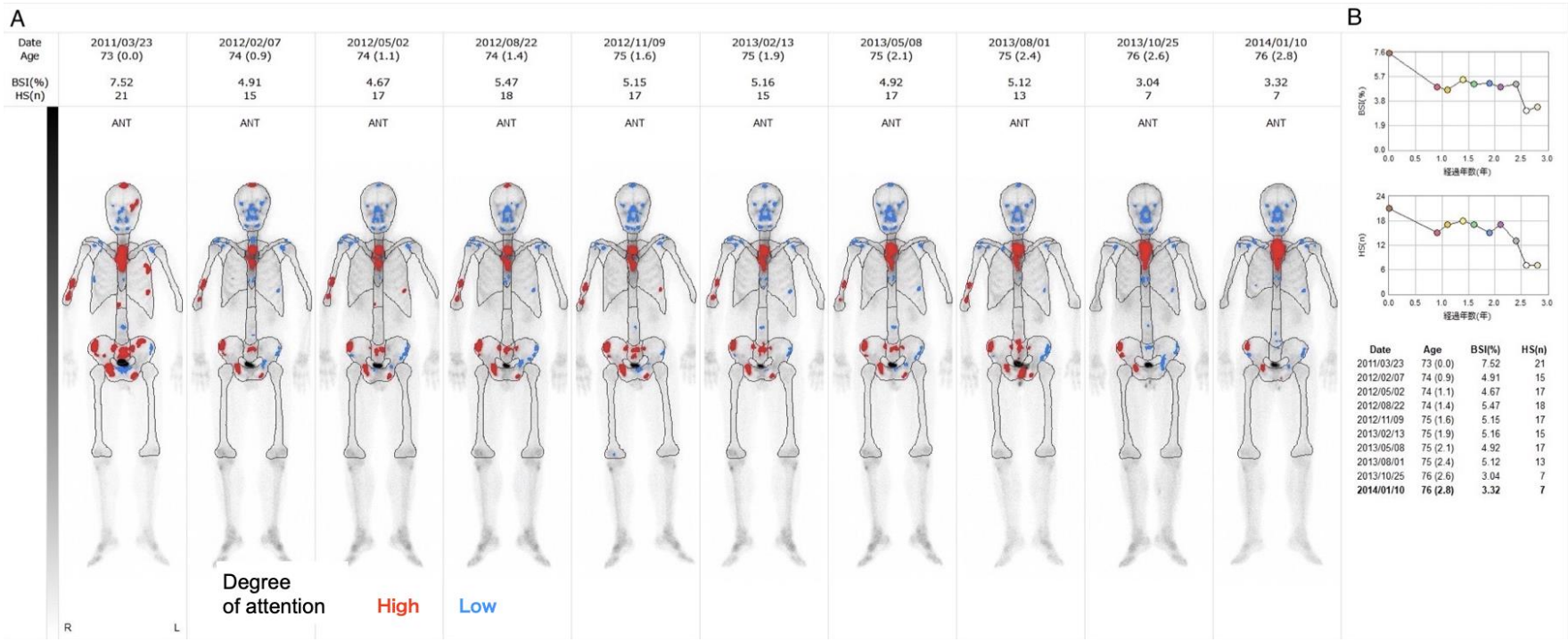


Fig.7

ROC analysis was performed on the number of HS. HS = 2 was used as the cutoff, producing the highest area under the curve (AUC; 0.725) and sensitivity (0.932).

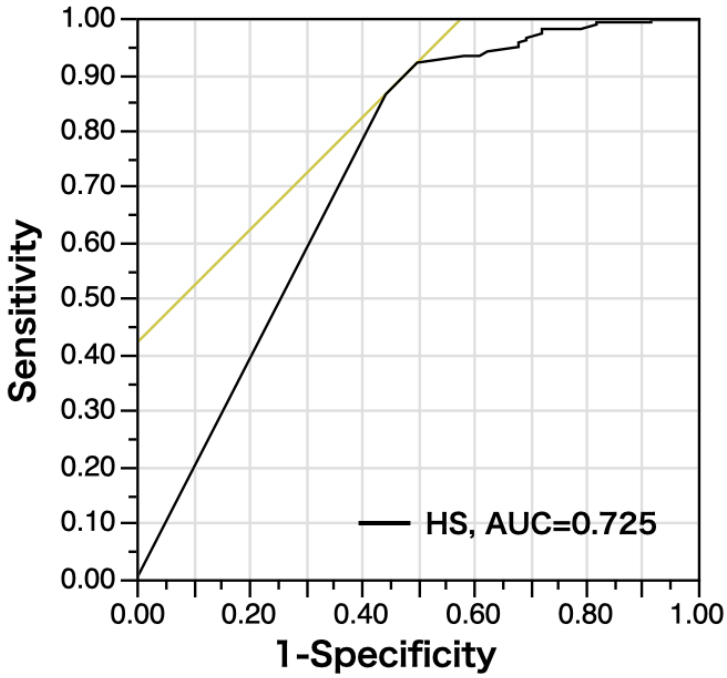


Fig.8

Kaplan–Meier method was applied. The group with hot spots (HS) ≤ 2 had a significantly longer survival time ($P < 0.001$).

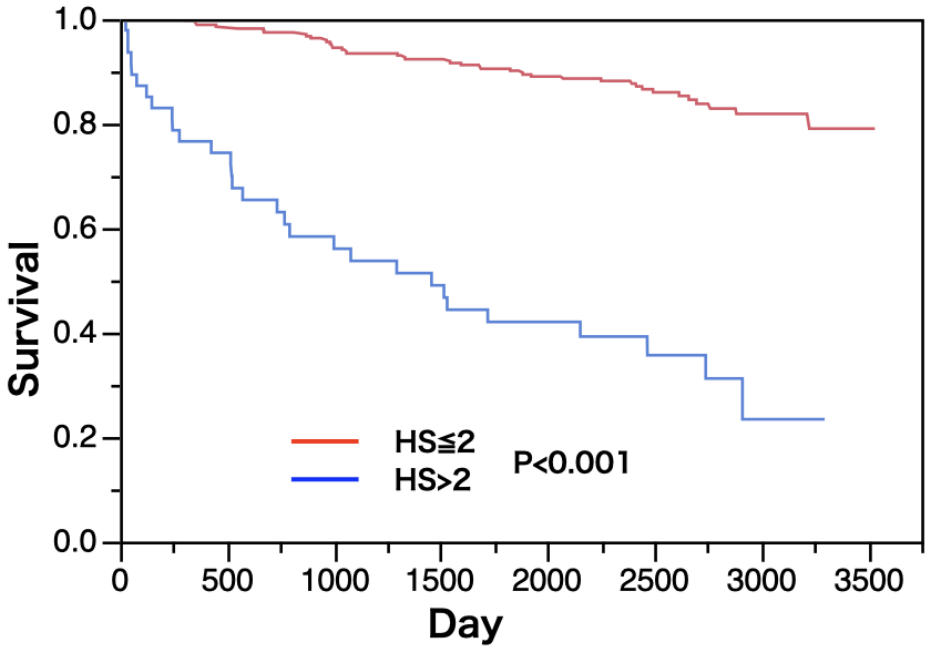


Fig.9

ROC analysis was performed for the BSI. BSI = 0.46 was used as the cutoff, producing the highest area under the curve (AUC; 0.722) and sensitivity (0.928).

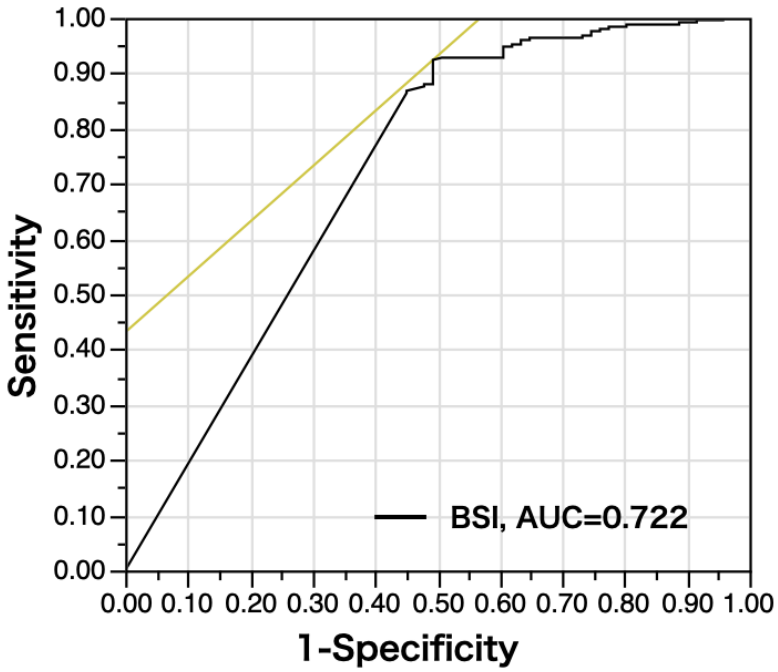
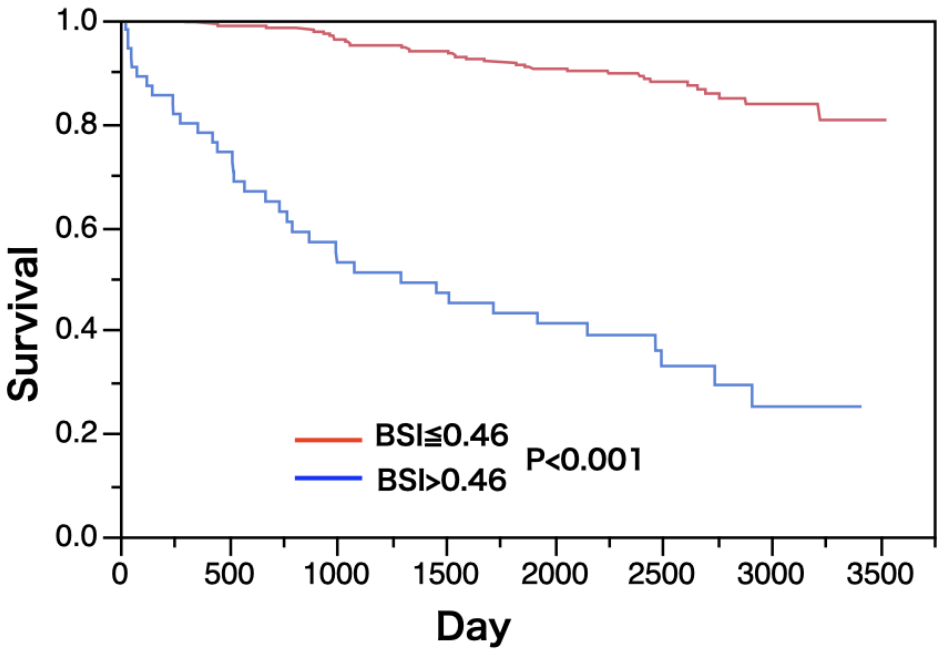


Fig.10

The survival curve was determined by Kaplan–Meier. The BSI ≤ 0.46 group had a significantly longer survival time (P < 0.001).



	Total (n=322)	Bone metastasis - (n=248)	Bone metastasis + (n=74)
Age, years			
Median	70.75	70.01	73.16
Range	43-88	43-88	52-88
Survival time(day)			
Median(day,year)	2312.67, 6.33	2501.48, 6.85	1679.89, 4.6
Range(day)	27-3526	304-3526	27-3488

Details of cases and survival time in this study

Table 1.