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(Citation)
International Journal of Urology,25(5):492-499

(Issue Date)
2018-05

(Resource Type)
journal article

(Version)
Version of Record

INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2018) 25, 492–499 doi: 10.1111/iju.13556

Original Article: Clinical Investigation

Role of bone scan index in the prognosis and effects of therapy on prostate cancer with bone metastasis: Study design and rationale for the multicenter Prostatic Cancer Registry of Standard Hormonal and Chemotherapy Using Bone Scan Index (PROSTAT-BSI) study

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Abbreviations & Acronyms
ANN = artificial neural network
BSI = bone scan index
CRP = C-reactive protein
CT = computed tomography
MRI = magnetic resonance imaging
PROSTAT-BSI = Prostatic Cancer Registry of Standard Hormonal and Chemotherapy Using Bone Scan Index
PSA = prostate-specific antigen

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Received 27 September 2017; accepted 9 February 2018. Online publication 6 April 2018

Objective: To present the study design and rationale of Prostatic Cancer Registry of Standard Hormonal and Chemotherapy Using Bone Scan Index, a prospective study aiming to determine the role of the bone scan index, the amount of bone metastasis, in the treatment and prognosis of prostate cancer patients.

Methods: A total of 237 patients were recruited at 30 hospitals in Japan. All had prostate cancer with bone metastasis and were scheduled to undergo either hormonal therapy (group H) or chemotherapy (group C). Bone scans were carried out with ^{99m}Tc-methylenediphosphonate. Follow-up studies are planned to continue for 3 years, and changes in biochemical and tumor markers in response to hormonal therapy and chemotherapy will be recorded in addition to skeletal-related events, recurrence, disease progression and death.

Results: The basic characteristics of the patients (n = 200) at the time of registration during December 2016 were as follows: mean age 71 ± 8 years; median bone scan index calculated on-site 1.9% (range 0.02–13.3%); median number of hot spots 18 (range 1–128); median prostate-specific antigen 155 ng/mL (range 0.04–22 412 ng/mL); and the most frequent Gleason score 9 (47%). The prostate-specific antigen value was higher in group H than group C (288 *vs* 33 ng/mL, $P < 0.0001$), whereas bone scan indexes were comparable (1.7 *vs* 2.3%, not significant) between the two groups. Liver metastasis was more frequent in group C than group H (6.1% *vs* 0.8%, $P = 0.035$).

Conclusions: The baseline characteristics of the Prostatic Cancer Registry of Standard Hormonal and Chemotherapy Using Bone Scan Index database have been established. This collaborative study can now proceed with clarifying the role of the bone scan index for patient management including treatment strategies and prognosis.

Key words: imaging biomarker, oncological therapy, quantitation, scintigraphy, survival.

Introduction

Recent advances in oncological therapies have contributed to the increased survival of patients with various types of cancer. However, the incidence of bone metastasis of prostate, breast and other cancers continues to increase and cause a significant deterioration in

the quality of life of patients due to skeletal-related symptoms, bone pain, pathological fractures, compression by masses and hypercalcemia. The early diagnosis and identification of appropriate surrogate markers linked to relevant outcomes by monitoring bone metastasis are vital for patients with bone metastasis.[1]

Bone scans still play a major role in the screening and follow up of patients with possible or definite bone metastasis, even in the era of multimodal imaging. Whereas the diagnostic sensitivity of bone scans is generally considered good, they are limited in terms of difficulties with quantifying metastasis and a lack of specificity.[2] Although the extent of disease can be determined to some degree by counting hot spots, the complex nature of radiotracer accumulation hampers the general applicability of bone scans.[3,4]

A quantitative software package comprising an ANN has been introduced to quantify bone metastasis, and it has proven useful in terms of diagnostic and prognostic bone scintigraphy.[5–7] This software is called BONENAVI (FUJIFILM RI Pharma, Tokyo, Japan) in Japan, and was revised from the original EXINI bone software (EXINI Diagnostics, Lund, Sweden) in a multicenter project involving a large Japanese database.[8,9] The software automatically segments whole-body images, identifies abnormal hot spots, characterizes hot lesions and calculates the total amount of abnormal or metastatic lesions.[10]

Several prior studies have shown that computer-assisted analysis improves classification and is thus applicable to diagnostics.[5,11–13] Its value has also been investigated in patients with prostate cancer for prognostic purposes,[6,14,15] and the BSI has proven useful for determining the effects of androgen deprivation and chemotherapy.[16] However, few prospective multicenter studies have examined the value of the BSI. A multicenter registry (PROSTAT-BSI) comprising data derived from patients who have prostate cancer with bone metastasis in Japan has been established. The treatment effects of standard hormonal therapy and chemotherapy, as well as patient prognosis, will be analyzed based on data extracted from this registry. The present report describes the study protocol, rationale for this multicenter project and initial findings at the time of entry.

Methods

Participants

We enrolled patients who were untreated, or intended to undergo hormonal therapy for pathologically confirmed prostate cancer with bone metastasis and chemotherapy of metastases that was refractory to standard hormonal therapy.

Inclusion criteria

The inclusion criteria included one imaging with ^{99m}Tc-methylenediphosphonate, and at least one documented bone metastasis confirmed by X-ray CT and/or MRI.

Exclusion criteria

The exclusion criteria included age <40 years at the time of bone imaging; abnormal posture or extraskeletal accumulation causing failure of computer analysis and being judged unsuitable for participation by the principal investigator at a participating institution.

Informed consent

The study protocol including the purpose of this study, methods, anticipated outcomes, and freedom of choice to participate and opt out of the study at any time was explained to the patients, and written informed consent was obtained from all those who elected to participate.

Study design

This is a multicenter observational study within the context of routine medical practice. Regular bone scintigraphy and medical examinations will proceed as indicated below. The strategies for hormonal therapy and chemotherapy were determined independently of the multicenter registry. The treatments and medical examinations were not randomized.

End-points

The primary end-points are post-treatment changes in BSI compared with baseline and event-free and PSA progression-free survival. Secondary end-points include changes in BSI determined by an ANN, other parameters of PSA, bone metabolic markers and overall survival from baseline until the end of post-treatment follow up for 3 years. Dates of recurrence and events are recorded.

Schedule of examinations

Figure 1 shows whole-body bone scintigrams with BONENAVI analysis, PSA (tumor marker), bone metabolic markers and blood cell counts will be quantified 3 months before and after treatment for 1 year, and then once annually for the next 2 years. Bone metabolic markers include urinary N-terminal telopeptide, creatinine, serum cross-linked telopeptide parts of type I collagen, serum bone alkaline phosphatase, alkaline phosphatase and calcium. X-ray CT and MR images are assessed at least before and, if required, after treatment. Liver and lymph node metastases were confirmed by X-ray CT and/or MRI, and follow-up studies. All assessments will proceed regardless of relapse or recurrence during follow up. Bone scintigraphy will be implemented according to the nuclear imaging procedure guidelines of the Nuclear Medicine Technology Association in Japan.

Termination of the study

If an investigator at a participating institution judges that a patient is unable to continue the study, then the patient will withdraw, and the rationale for such withdrawal and the course of the patient will be recorded in case reports. The effectiveness of the monitoring and management strategies will be judged at the time of termination. The patients will continue to be regularly examined even after the study is completed.

	Registration	Follow-up				
	Pre-treatment diagnosis	3 – 12 months (every 3 month period)	12 months	24 months	36 months	At the time of recurrence
Bone scintigraphy + BONENAVI analysis	R	R	O	O	O	R
Tumor marker: PSA	R	R	O	O	O	R
Bone metabolic marker	R	R	O	O	O	R
Blood cell count, CRP	R	R	O	O	O	R
X-ray CT and/or MRI	R	O	O	O	O	O

R: Required
O: Optional but as much as possible

Fig. 1 Study protocol and timing of examinations.

Data handling

All data were anonymized at participating hospitals before transfer to the central laboratory. Serial numbers without specific personal patient information were used for data processing and statistical analysis after anonymization.

Adverse events

Appropriate medical therapy will be applied if adverse events arise during the study and recorded in medical charts, as well as case reports.

Ethics

All study protocols comply with the Declaration of Helsinki (2008) and Ethics Guidelines Regarding Clinical Research in Japan (revision, 2008). The Ethics Committee at Kanazawa University (the core center) approved the study. Approval has been obtained from the institutional review boards or ethics committees at all participating hospitals.

Registry

The present study was registered on 1 May 2012 in the University Medical Information Network as UMIN00000-7858.

Imaging data analysis

All imaging data including bone scintigraphy, X-ray CT and MRI are uploaded to a cloud-type file management system after the original data are anonymized. Micron (Tokyo, Japan) is managing the data. The quality of the medical images is controlled for subsequent analysis.

The ANN probability, BSI and number of hot spots in each institution are calculated using BONENAVI software. However, all parameters will be processed again under the same conditions using the latest version of the software after all scintigraphic data are accumulated. In principle, although the automatically calculated BSI is used for analysis, abnormal regions can be manually adjusted when urinary contamination and artifacts apparently overlap. Figure 2 shows a sample analysis.

Statistical analysis

All values are shown as medians with ranges or as the mean ± standard deviation. Pairs of variables were compared using *t*-tests and analysis of variance. Data without normal distribution were assessed by non-parametric analyses using Wilcoxon/Kruskal–Wallis tests (rank sums). Contingency tables were analyzed using Pearson statistics. $P < 0.05$ was considered significant. Data were analyzed using JMP version 11 statistics software (SAS Institute, Cary, NC, USA).

Results

Participating hospitals

A total of 237 patients were registered from 36 hospitals in Japan through their urology, radiology and nuclear medicine departments (Table 1). By December 2016, the registry comprised 200 patients with a mean age of 71 ± 8 years (range 48–89 years), who had undergone either hormonal therapy (65%) or chemotherapy (35%).

Distribution of ANN probability, BSI and number of hot spots

The median ANN probability of abnormality or bone metastasis (0, normal; 1, abnormal) was 0.98 (range 0.03–1), confirming that most of the patients had bone metastasis (Fig. 3). The median BSI calculated on-site was 1.9% (range 0.02 –13%), and the median number of hot spots was 18 (range 1 –128).

Background of patients

Median PSA was 155 ng/mL (range 0.038–22 412 ng/mL) (Fig. 4). Lymph node metastasis other than regional nodes as well as lung and liver metastases were found in 29%, 13% and 3% of the patients, respectively. Gleason scores ranged from 3 to 10, and the most frequent was a score of 9 (47%), followed by 8 (29%) and 10 (12%) (Fig. 4). The median concentrations of bone alkaline phosphatase, telopeptide parts of type I collagen 6 and urinary N-terminal telopeptide were 28 μg/L (range 5–805 μg/L), 6 ng/mL (range 2–83 ng/mL)

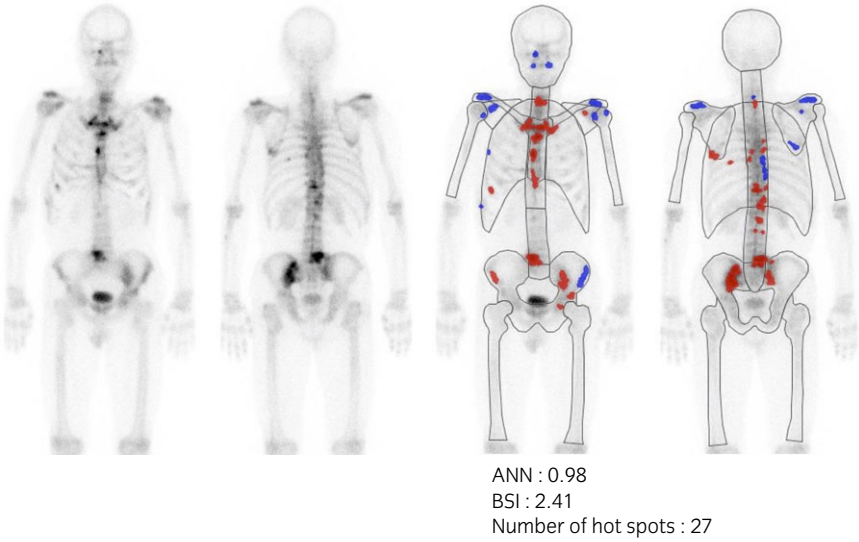

Fig. 2 BONENAVI software used in the PROSTATE-BSI study. Probability of metastasis shown as red (high) or blue (low) in a patient with prostate cancer BSI is increased to 2.41% with 27 hot spots.

and 41 nmol/bone collagen equivalents/mmol creatinine (range 6–1531 nmol/bone collagen equivalents/mmol creatinine), respectively.

Hormonal therapy and chemotherapy

Patients were classified based on whether they received hormonal therapy (group H, $n = 130$) or chemotherapy (group C, $n = 70$). The median PSA value was higher in group H than in group C (288 *vs* 33 ng/mL; $P < 0.0001$, Wilcoxon/Kruskal–Wallis test), whereas BSI values were comparable (1.66% *vs* 2.34%, not significant; Fig. 5). The frequency of liver metastasis was higher in group C (than group H [6.1% *vs* 0.8%, $P = 0.0349$; Pearson test]), but the frequency of lymph node metastasis other than regional nodes and lung metastasis was comparable between the groups (Fig. 6).

Discussion

The purpose of this report was to present a study design and rationale for the PROSTAT-BSI study with initial backgrounds of the registered patients. This study aimed to establish a prognostic database of patients with prostate cancer and bone metastasis. Clinical background data including serum and urinary biochemical values, tumor markers, and imaging data were systematically registered. Patient baseline conditions for hormonal therapy and chemotherapy significantly differed with respect to PSA level and the frequency of liver metastasis. Changes in conventional markers and bone scintigraphy, skeletal related adverse events, and overall survival rates over a period of 3 years will be analyzed based on the accumulated information.

Although this study is observational and without randomized intervention, the procedures conformed to standard urological clinical practice in most Japanese hospitals. The frequency of bone scintigraphy in the present study is every 3 months for the first year, which might be slightly higher than that in routine clinical practice. However, this frequency is sometimes clinically applied, and rapid changes that occur soon after starting hormonal therapy and chemotherapy should be recognized to understand the effects of therapy. More importantly, without quantitation, repeated imaging of bone metastasis within a few months is rarely useful, but quantitation within a shorter period might be able to reflect progress or improvement.

Therefore, the patients received a detailed explanation of the study protocol. They confirmed that they understood the protocols, that participation is voluntary and that they can opt out at any time, without affecting their care and treatment.

Several advantages and limitations are associated with using bone scintigraphy as an index of bone metastasis. Although various types of imaging modalities are routinely available, bone scintigraphy is one of the first choices in Japan for whole-body surveys of bone. X-ray CT provides a more precise picture of bone destruction and osteoblastic findings, and MRI might illustrate bone marrow involvement more clearly. Although bone scintigraphic findings are less specific for bone metastasis, whole-body surveys of bone metastasis are simple and practical in the clinical setting, and X-ray CT or MRI can be added should further confirmation of metastasis is required. Bone scintigraphic assessment using BSI is becoming increasingly standardized, and it enables more objective data, particularly for patients with prostate cancer.[2,3,17] Although ^{18}F-fluorodeoxy glucose positron-emission tomography can detect original tumor sites and metastases, variable uptake and false positive results have prevented it becoming the primary indication for patients with prostate cancer.[18,19] Given the current clinical environment in Japan, we selected bone scintigraphy among imaging modalities to provide a surrogate marker for bone metastasis.

Some quantitative approaches using software are required to determine total amounts of metastasis. Although some studies have determined the extent of disease based on six, 20 and >20 hot spots and super scan, precise classification is sometimes difficult.[20] The Prostate Cancer Working Group 2 defines bone metastatic progression as at least two new

Table 1 Steering committee and participating hospitals

Function	Name	Institution
Principal investigator	Atsushi Mizokami	Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science
Steering Committee		
	Kenichi Nakajima	Department of Nuclear Medicine, Kanazawa University Hospital
	Yota Yasumizu	Department of Uro-Oncology, Saitama Medical University International Medical Center
	Tomohiko Ichikawa	Department of Urology, Graduate School of Medicine, Chiba University
	Satoru Takahashi	Department of Urology, Nihon University School of Medicine
	Hideyasu Matsuyama	Department of Urology, Graduate School of Medicine, Yamaguchi University
	Hiroaki Shiina	Department of Urology, Shimane University Faculty of Medicine
	Hiroyuki Horikoshi	Department of Breast Oncology, Gunma Prefectural Cancer Center
Participating investigators	Atsushi Mizokami	Kanazawa University Graduate School of Medical Science
	Kenichi Nakajima	Department of Nuclear Medicine, Kanazawa University Hospital
	Akito Ito	Iwate Medical University
	Kazuhiro Iwasaki	
	Tatsuhiko Nakasato	
	Fusao Murakami	Ohta Nishinouchi Hospital
	Hiroyuki Motoki	
	Satoru Takahashi	Nihon University School of Medicine
	Tsuyoshi Matsui	
	Kenya Yamaguchi	
	Tomonori Sato	Shirakawa Kosei General Hospital
	Munehisa Ueno	Saitama Medical University International Medical Center
	Go Kaneko	
	Yukio Kageyama	Saitama Cancer Center
	Akihiro Ichikawa	
	Haruo Kato	Gunma University Graduate School of Medicine
	Takeshi Miyao	
	Tetsuya Higuchi	
	Kiyoshi Koshida	Kanazawa Medical Center
	Yoshitaka Aoki	University of Fukui Faculty of Medical Sciences
	Shota Konishi	Fukui-ken Saiseikai Hospital
	Hideki Kanda	Mie University Graduate School of Medicine
	Tomihiko Yasufuku	Konan Kakogawa Hospital
	Tadashi Fukuhara	
	Yasuhiko Oka	
	Eiro Sakai	
	Masayoshi Yokoyama	Ehime University Graduate School of Medicine
	Noriyoshi Miura	
	Tadahiko Kikugawa	
	Masao Miyagawa	
	Hiroaki Shiina	Shimane University Faculty of Medicine
	Miho Hiraki	
	Naoko Arichi	
	Hajime Kitagaki	
	Hideyasu Matsuyama	Graduate School of Medicine, Yamaguchi University
	Hiroaki Matsumoto	
	Yoshihisa Kawai	
	Matakazu Furukawa	
	Shingo Ashida	Kochi Medical School, Kochi University
	Tsutomu Shimamoto	
	Yoriko Murata	
	Yoshiaki Kawano	Graduate School of Medical Sciences, Kumamoto University
	Yutaka Sugiyama	
	Tatsuma Kurahashi	
	Kazutaka Fukuyama	
	Keita Chikaura	
	Shinya Shiraishi	
	Yasuyuki Yamashita	

Table 1 (Continued)

Function	Name	Institution
	Hideki Sakai	Nagasaki University Graduate School of Biomedical Sciences
	Tomoaki Hakariya	
	Takashi Kudo	
	Hideki Enokida	Graduate School of Medical and Dental Sciences, Kagoshima University
	Yoshiaki Nakabeppu	
	Hidero Minami	Noto General Hospital
	Kenichi Harada	Kobe University Graduate School of Medicine
	Junya Furukawa	
	Satoru Takahashi	
	Takeyuki Ishida	Saiseikai Takaoka Hospital
	Ichikawa Tomohiko	Graduate School of Medicine, Chiba University
	Koji Kawamura	
	Takuro Horikoshi	
	Katsuyoshi Hashine	National Hospital Organization Shikoku Cancer Center
	Iku Ninomiya	
	Tadanori Hosokawa	
	Yoshifumi Sugawara	
	Takao Nakashima	Ishikawa Prefectural Central Hospital
	Hiroshi Yaegashi	
	Manabu Moriyama	Kanazawa Medical University Himi Municipal Hospital
	Yasuaki Kuginuki	
	Yasuhisa Fujii	Tokyo Medical and Dental University
	Soichiro Yoshida	
	Toshiki Kijima	
	Akira Toriihara	
	Kamiyama Manabu	Yamanashi University School of Medicine
	Hirofumi Ikuta	University of Occupational and Environmental Health
	Naohiro Fujimoto	
	Takatoshi Aoki	
Statistical analyst	Shiro Hinotsu	Center for Innovative Clinical Research, Okayama University
Statistical advisers	Satoshi Teramukai	Kyoto Prefectural Medical University
	Kenichi Yoshimura	Kanazawa University Hospital

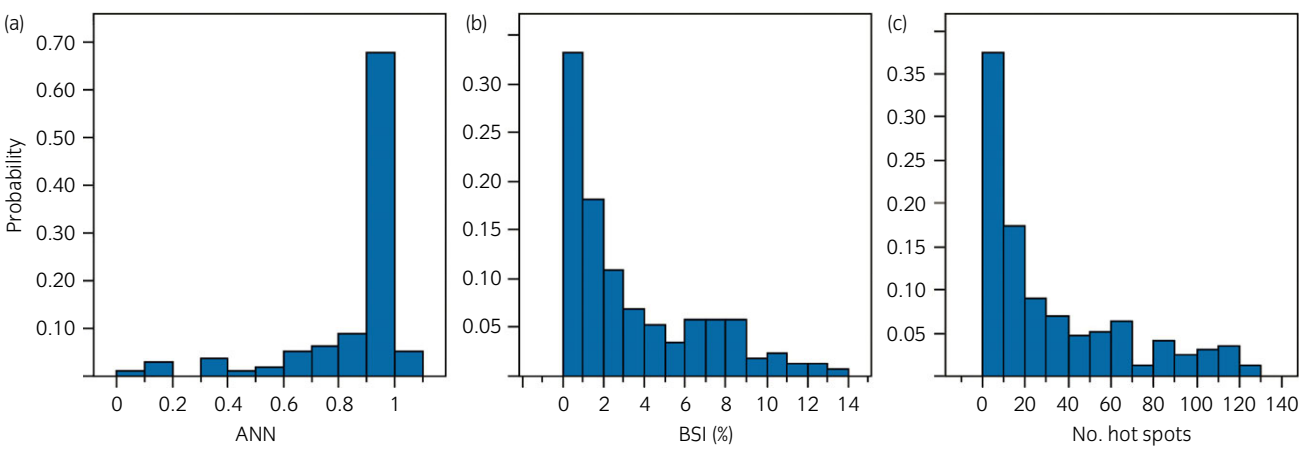

Fig. 3 Distribution of (a) ANN probability, (b) BSI and (c) number of hot spots.

lesions appearing on a bone image compared with a previous image.[3] A bone image as the sole indicator of progression is not necessarily objective and reproducible, because simultaneous metastatic improvement and worsening in a series of bone images hampers the judgment of therapeutic effects. The Prostate Cancer Working Group 3 recommends that measures of metastatic disease burden, such as number of lesions, area and BSI, should provide further information and prospective clinical validation.[21] The present study uses the BSI based on the ANN system of probability. The BSI is derived from an automated analysis of whole-body scintigrams. Counting hot spots to visually define sites of positive

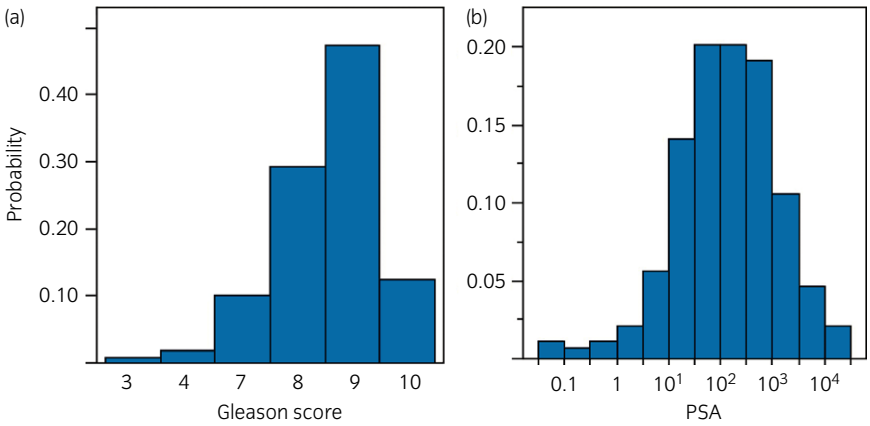

Fig. 4 Distribution of (a) Gleason scores and (b) PSA.

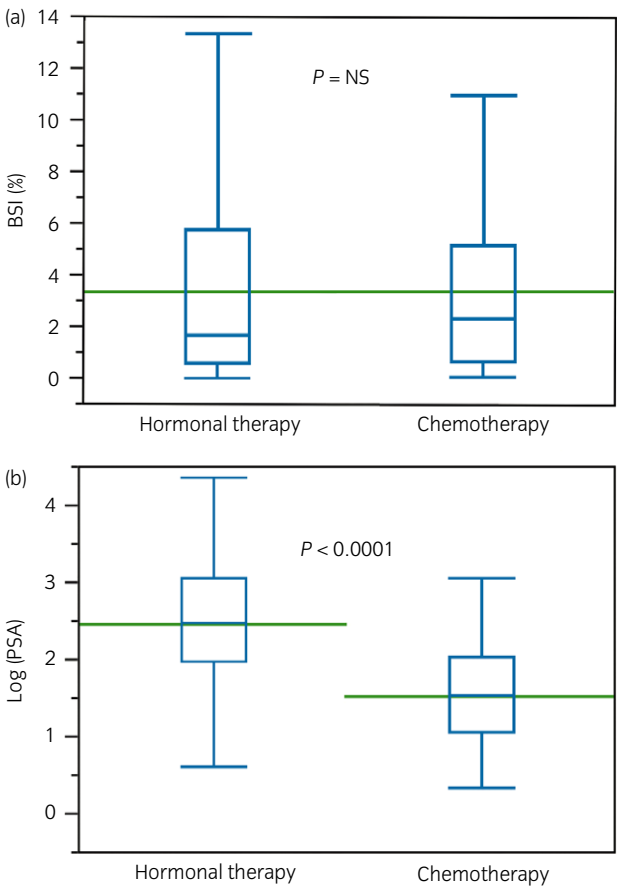

Fig. 5 Comparison of (a) BSI and (b) log PSA between hormonal therapy (n = 130) and chemotherapy (n = 70).

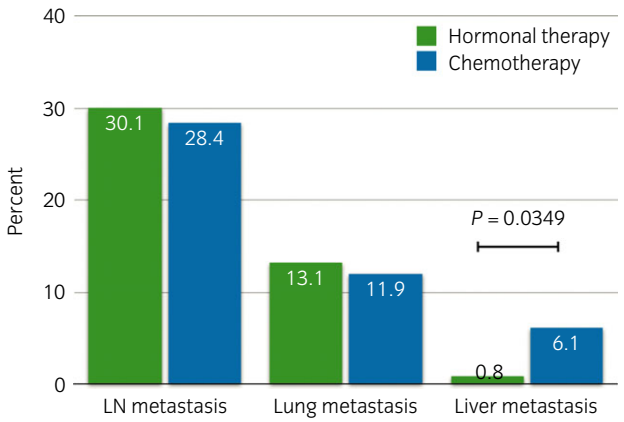

Fig. 6 Frequency of metastasis to lymph nodes (LN) other than regional nodes, lungs and liver of patients receiving hormonal therapy and chemotherapy.

metastasis is not always easy, because display count settings considerably influence visual impressions. Repeated measurements over longer follow-up periods are simple matters for fully automated software that has been trained to process red hot spots as having a probability of >0.5 of being metastatic bone lesions.[5,9] The possibility of radioactive accumulation due to typical degenerative changes and in joints is generally low, but it might be judged as abnormal (or as metastasis) in some patients. Therefore, although some cautions are required for interpretation, we selected to apply automated analysis to enhance the reproducibility and objectivity of the results.

Initial evaluation of therapeutic responses to hormonal therapy and chemotherapy with agents such as docetaxel will be important for deciding whether to continue, stop or modify therapeutic strategies. We will evaluate the relationship between treatment courses and changes in BSI and other bone metabolic biomarkers using the data acquired in the present study. The role of BSI should be further explored, because the PSA level is not the optimal indicator of prognosis and changes in BSI comprise a potentially better indicator of the responses of metastatic castration-resistant metastatic prostate cancer to treatment.[17] The effectiveness of the BSI for monitoring therapeutic responses and other tumors or bone markers can be evaluated. The flare phenomenon with a tentative increase in bone accumulation sometimes occurs within 3 months of therapy, and usually decreases after several months. Thus, every 3 months is considered the optimal frequency for undergoing bone scintigraphy.

Finally, the baseline conditions of the patients in groups H and C significantly differed with respect to PSA levels and the frequency of liver metastasis, whereas BSI values were comparable. In particular, a lower PSA value during chemotherapy suggested the importance of biomarkers that

accurately reflect the amount of bone metastasis. The recommendations of the St. Gallen Advanced Prostate Cancer Consensus Conference 2015 emphasize the importance of regular treatment monitoring and risk-adapted approaches.[22] When treatment is stopped, at least two of three criteria, such as PSA progression, radiographic progression and clinical deterioration, should be considered. Therefore, the BSI could be a promising quantitative marker of radiographic progression. Based on the background conditions in the present study, the role of BSI for monitoring treatment and estimating risk will be analyzed at the completion of follow up.

The advent of new drugs, such as abiraterone, enzalutamide and cabazitaxel, might increase the possibility of improving bone metastasis.[16] Internal radiation therapy with the alpha-emitter radium-223 is now available in Japan.[23] Although these novel therapeutic possibilities are not included in the present study, methodological advances in using BSI to monitor the treatment of bone metastasis could enhance its future application as a bone biomarker in patients with prostate cancer, and finally contribute to additional treatments that could prolong survival.[10]

A Japanese registry of patients with prostate cancer and bone metastasis has been established and their baseline characteristics were determined. The relevance of BSI as a biomarker of bone metastasis will continue to be assessed by its ability to reflect changes in biochemical and tumor markers. Prognostic evaluations related to serious events will also be analyzed.

Acknowledgments

DICOM data were anonymously collected and stored on a server at Micron, Tokyo, Japan. The authors thank Mika Tanaka of Micron for collecting the data and managing the databases, and Kazunori Kawakami, FUJIFILM RI Pharma Co., Ltd. (FRI), Tokyo, for technical support with using BONENAVI software. We are grateful to Norma Foster for editorial assistance. The PROSTAT-BSI study is partly supported by FRI, through the Innovative Clinical Research Center of Kanazawa University Hospital, Kanazawa, Japan.

Conflict of interest

K Nakajima and A Mizokami collaborate with FUJIFILM RI Pharma Co., Ltd. (FRI), Tokyo, Japan, a supplier of ^{99m}Tc-methylenediphosphonate and BONENAVI software. A Mizokami has received contributions from FRI. K Nakajima and A Mizokami have received honoraria for lectures from FRI.

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