### Title
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

### Authors
Nakajima, Kenichi / Kaneko, Go / Takahashi, Satoru / Matsuyama, Hideyasu / Shiina, Hiroaki / Ichikawa, Tomohiko / Horikoshi, Hiroyuki / Hashine, Katsuyoshi / Sugiyama, Yutaka / Miyao, Takeshi / Kamiyama, Manabu / Harada, Kenichi / Ito, Akito / Mizokami, Atsushi

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

### Issue date
2018-05

### Resource Type
Journal Article / 学術雑誌論文

### Rights
© 2018 The Authors. International Journal of Urology published by John Wiley & Sons Australia, Ltd on behalf of the Japanese Urological Association. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

### DOI
10.1111/iju.13556

### URL
http://www.lib.kobe-u.ac.jp/handle_kernel/90004898

PDF issue: 2020-05-06
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

Kenichi Nakajima,1 Go Kaneko,2 Satoru Takahashi,3 Hideyasu Matsuyama,4 Hiroaki Shiina,5 Tomohiko Ichikawa,6 Hiroyuki Horikoshi,7 Katsuyoshi Hashine,8 Yutaka Sugiyama,9 Takeshi Miyao,10 Manabu Kamiyama,11 Kenichi Harada,12 Akito Ito13 and Atsushi Mizokami14

The PROSTAT-BSI Investigators

1. Department of Nuclear Medicine, Kanazawa University Hospital, Kanazawa
2. Department of Uro-Oncology, Saitama Medical University International Medical Center, Saitama
3. Department of Urology, Nihon University School of Medicine, Tokyo
4. Department of Urology, Graduate School of Medicine, Yamaguchi University, Ube
5. Department of Urology, Shimane University Faculty of Medicine, Shimane
6. Department of Urology, Graduate School of Medicine, Chiba University, Chiba
7. Department of Diagnostic Radiology, Gunma Prefectural Cancer Center, Ota
8. Department of Urology, National Hospital Organization Shikoku Cancer Center, Matsuyama
9. Department of Urology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto
10. Department of Urology, Gunma University Graduate School of Medicine, Maebashi
11. Department of Urology, Yamashita University School of Medicine, Yamashita
12. Division of Urology, Department of Surgery, Kobe University Graduate School of Medicine, Kobe
13. Department of Urology, Iwate Medical University, Morioka
14. Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

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 99mTc-methylene diphosphonate. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10}

Several prior studies have shown that computer-assisted analysis improves classification and is thus applicable to diagnostics\textsuperscript{5,11–13} Its value has also been investigated in patients with prostate cancer for prognostic purposes,\textsuperscript{6,14,15} and the BSI has proven useful for determining the effects of androgen deprivation and chemotherapy.\textsuperscript{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 \textsuperscript{99m}Tc-methylene diphosphonate, 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.
**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 UMIN000007858.

**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)
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.

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. 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 Uro-Oncology, Saitama Medical University International Medical Center |
|                           | Satoru Takahashi            | Department of Urology, Graduate School of Medicine, Chiba University        |
|                           | Hideyasu Matsuyama          | Department of Urology, Graduate School of Medicine, Yamaguchi University    |
|                           | Hiroaki Shiina              | Department of Urology, Shimane University Faculty of Medicine               |
|                           | Hirohiko Horikoshi          | Department of Breast Oncology, Gunma Prefectural Cancer Center               |
|                           | Atsushi Mizokami            | Kanazawa University Graduate School of Medical Science                      |
| Participating investigators| Kenichi Nakajima            | Department of Nuclear Medicine, Kanazawa University Hospital                |
|                           | Akito Ito                   | Iwate Medical University                                                   |
|                           | Kazuhiro Iwasaki            |                                                                             |
|                           | Tatsuhiko Nakasato          |                                                                             |
|                           | Fusao Murakami              |                                                                             |
|                           | Hiroyuki Motoki             | Ohta Nishinouchi Hospital                                                  |
|                           | 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 Medical University International Medical Center                     |
|                           | Akihiko 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 Kagawa Hospital                                                       |
|                           | Tadashi Fukushima           |                                                                             |
|                           | 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          |                                                                             |
lesions appearing on a bone image compared with a previous image. 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 recommends that measures of metastatic disease burden, such as number of lesions, area and BSI, should provide further information and prospective clinical validation. 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

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    |                                                                  |
|          | Hideno 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 Shiokoku Cancer Center            |
|          | Iku Ninomiya          |                                                                  |
|          | Tadanori Hosokawa     |                                                                  |
|          | Yoshihumi Sugawara    |                                                                  |
|          | Takao Nakashima       | Ishikawa Prefectural Central Hospital                            |
|          | Hiroshi Yagashio      |                                                                  |
|          | Manabu Moriyama       | Kanazawa Medical University Himi Municipal Hospital              |
|          | Yasuo Kuginiuchi      |                                                                  |
|          | Yasushisa Fuji        | Tokyo Medical and Dental University                              |
|          | Soichiro Yoshida      |                                                                  |
|          | Toshiki Kijima        |                                                                  |
|          | Akira Torihara        |                                                                  |
|          | Kaimiyama 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.
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. 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. 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. 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.

The advent of new drugs, such as abiraterone, enzalutamide and cabazitaxel, might increase the possibility of improving bone metastasis. Internal radiation therapy with the alpha-emitter radium-223 is now available in Japan. 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.

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 Tc-methylene diophosphonate and BONENAVI software. A Mizokami has received contributions from FRI. K Nakajima and A Mizokami have received honoraria for lectures from FRI.

References

1. Scher HI, Halabi S, Tannock I et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J. Clin. Oncol. 2008; 26: 1148–59.

2. Mitsui Y, Shina H, Yamamoto Y et al. Prediction of survival benefit using an automated bone scan index in patients with castration-resistant prostate cancer. BJU Int. 2012; 110: E528–34.

3. Eri Y, Humm JL, Imbriaco M, Yeung H, Larson SM. Quantitative bone metastases analysis based on image segmentation. J. Nucl. Med. 1997; 38: 1401–6.

4. Imbriaco M, Larson SM, Yeung HW et al. A new parameter for measuring metastatic bone involvement by prostate cancer: The Bone Scan Index. Clin. Cancer Res. 1998; 4: 1765–72.

5. Scher HI, Halabi S, Tannock I et al. Validation and clinical utility of prostate cancer biomarkers. Nat. Rev. Clin. Oncol. 2013; 10: 225–34.

6. Van den Wyngaert T, Strebel K, Kampen WU et al. The EANM practice guidelines for bone scintigraphy. Eur. J. Nucl. Med. Mol. Imaging 2016; 43: 1723–38.

7. Scher HI, Halabi S, Tannock I et al. Validation and clinical utility of prostate cancer biomarkers. Nat. Rev. Clin. Oncol. 2013; 10: 225–34.