Prognostic value of computer-aided diagnosis system for bone scans (BONENAVI) in hormone-naive prostate cancer patients with bone metastases

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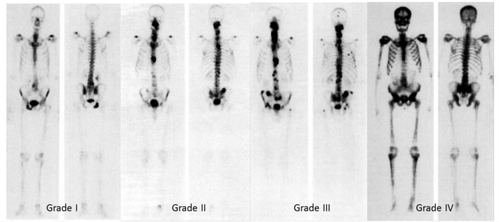
Introduction and objective

- Prognosis of advanced prostate cancer is predicted by classical risk factors such as clinical stage, Gleason scores, metastatic sites, and serum prostate-specific antigen (PSA) levels. A bone scan is also a common method for evaluation about spread of bone metastases and EOD (extent of disease) classification which was proposed by Soloway and colleagues has been widely used for risk stratification of osseous metastases . Although EOD classification provide the subjective and qualitative information, objective and quantitative parameters for evaluation of bone scan are needed.
- Recently, BONENAVI which is computer-aided bone scan evaluation system has been expected to be an objective and quantitative clinical tool for evaluation of bone metastasis in prostate cancer patients.
- The bone scan index (BSI) and number of hotspots are the variables calculated by BONENAVI software.
- In this study, we evaluated the usefulness of BSI and number of hotspots which were calculated by BONENAVI as prognostic factors in hormone-naive prostate cancer patients with bone metastases.

Figure1. Representative image of EOD classification in bone scan



Methods

Patients: We analyzed 86 patients diagnosed as hormone-naive prostate cancer with bone metastases between 2005 and 2013 at Yokohama City University Medical Center and Yokohama Municipal Citizen's Hospital. The clinicopathological characteristics of all patients are shown in table 1.

Treatment and outcome: Each hospital had a same treatment protocol. All patients except one case were treated with androgen deprivation therapy (medical or surgical castration with or without anti-androgen) initially. After failed initial androgen ablation therapy, almost all patients were subsequently treated with substitution of anti-androgen, anti-androgen withdrawal therapy, and/or oral low-dose steroid. Some patients received a bisphosphonate and cytotoxic therapy such as docetaxel or estramustine after development to CRPC (castration-resistance prostate cancer). In the terminal state, palliative therapy and pain control with morphine, palliative external beam radiation, and strontium were used as appropriate. In this study, enzalutamide, cabazitaxel, abiraterone, radium223, and Sipuleucel-T were not used because these agent were not approved in Japan before 2013. Treatment and outcome of all patients in this study are summarized in table 2.

BONENAVI: Computer-aided bone scan evaluation system were developed in 2011.
BONENAVI could provide three quantitative parameters;
1) ANN value: probability of bone metastasis (range 0-1).
2) BSI: percentage of the total skeletal mass.
3) number of hotspots.

- BONENAVI could detect bone metastatic lesions as red hotspots, while benign lesions were indicated in blue by Artificial Neural Network (ANN).
- Representative image from BONENAVI is shown in figure 2.

Figure 2: Representative image of BONENAVI

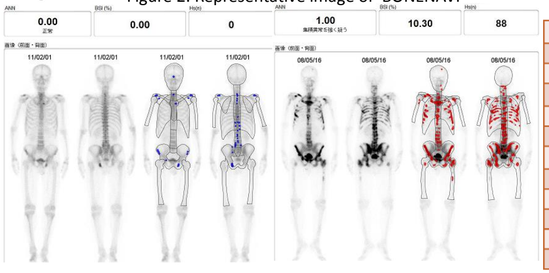


Table 1: Patients characteristics

Median age (years, range)	73 (42.3-89.0)
Median observation period (months, range)	20.7 (0.9-104.3)
Median initial PSA (ng/mL, range)	277.0 (9.7-4206.0)
Gleason scores, no. (%)	
7	10 (11.6)
8	31 (36.0)
9	29 (33.7)
10	16 (18.6)
Clinical T stage, no (%)	
T3	67 (77.9)
T4	19 (22.0)
Clinical N stage, no (%)	
N0	43 (50.0)
N1	43 (50.0)
Clinical M stage, no(%)	
M1b	77 (89.5)
M1c	9 (10.5)
Median BSI (%, range)	2.8 (0.0-14.6)
Median No. of hot spots (range)	25 (0-123)

Table 2: Treatment and outcome

Initial therapy (n=86)	
Androgen ablation therapy	85 (98.8%)
Abiraterone alone	1 (1.2%)
Treatment after development CRPC (n=49)	
Docetaxel	21 (42.9%)
Bisphosphonates or denosumab	22 (44.9%)
Outcome at analysis (n=86)	
Death by other causes	4 (4.7%)
Prostate cancer death	21 (24.4%)
Non-CRPC	32 (37.2%)
CRPC	27 (31.4%)
Unknown	2 (2.3%)

Statistical analysis: We investigated that the usefulness of BSI and hotspots as prostate cancer-specific survival predictors by multivariate analysis. Cox proportional hazards regression models were applied to multivariate analyses to evaluate the usefulness of BSI and number of hotspots which calculated by BONENAVI as prostate cancer-specific survival predictor.
This study was approved by each of the participating institution's review boards.

Results

- EOD was strongly correlated with BSI and No. of hotspots (Figure 3). EOD was not included to multivariate analysis in this study because of multicollinearity. For same reason, BSI and No. of hotspots were not analyzed simultaneously.
- In univariate analyses, BSI and No. of hotspot were significantly associated with prostate cancer-specific survival (Table 3). Figure 4 revealed Kaplan-Meier curve for cancer-specific survival, stratified by BSI and No. of hotspots .
- In multivariate analyses, only BSI and No. of hot spots were extracted for independent prognostic factor for prostate cancer-specific survival (Table 3).

Figure 3: Correlations between EOD and BSI or No. of hotspots

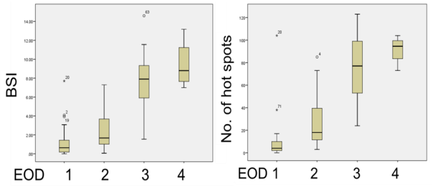


Figure 4: Kaplan-Meier curve for cancer-specific survival, stratified by BSI and No. of hotspots

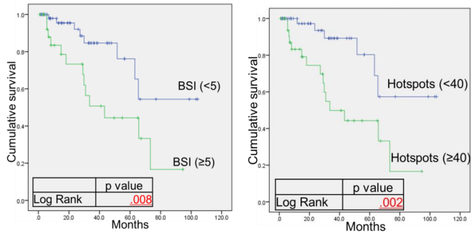


Table 3: Correlation between prostate cancer-specific survival and clinicopathological factors, BSI and No. of hot spots.

	Univariate analysis			Multivariate analysis					
	p value	Odds	95.0% CI	P value	Odds	95%CI	P value	Odds	95%CI
Age	0.719	0.990	0.938-1.045	0.819	1.008	0.943-1.077	0.711	1.013	0.947-1.082
Initial PSA	0.817	1.000	0.999-1.000	0.298	1.000	0.999-1.000	0.200	1.000	0.999-1.000
Gleason scores (≥9 vs ≤8)	0.120	2.012	0.833-4.859	0.285	1.686	0.646-4.400	0.093	2.291	0.871-6.029
T (≥T4 vs ≤T3)	0.712	0.793	0.231-2.717	0.664	1.339	0.359-4.992	0.427	1.735	0.446-6.475
N (N1 vs N0)	0.231	1.723	0.708-4.192	0.109	2.226	0.836-5.927	0.128	2.089	0.810-5.392
M (M1c vs M1b)	0.834	0.804	0.105-6.168	0.856	1.223	0.140-10.695	0.588	1.852	0.199-17.195
BSI	**0.011**	1.141	1.031-1.263	**0.003**	**1.195**	**1.064-1.342**	-	-	-
No. of hotspots	**0.003**	1.017	1.006-1.028	-	-	-	**0.000**	**1.025**	**1.012-1.039**

BSI and number of hotspots were independent prognostic factors for prostate cancer-specific survival.

Discussion

- BSI (calculated by manual) was associated with prognosis of prostate cancer with bone metastases (Sabbatini et al. JCO 17, 1999).
- Ulmer and colleagues reported that BSI was associated with the prognosis of prostate cancer with bone metastases (Eur Urol 62, 2012). This study included the patients without bone mets and only 33 (8.5%) patients have bone mets with BSI more than 1%.
- In our study, all patients had bone mets, and 57 (66.2 %) patients showed high BSI (>1 %) .

The limitation of our study

- More cases, Further follow-up, and multi-institutional analysis are warranted.
- Established prognostic factors such as metastatic sites, performance status, comorbidity index and laboratory data were not included.
- In this study, false negative of BONENAVI was shown in only one patient. For exact diagnosis of bone mets, other diagnostic modality such as CT, MR and PET/CT imaging are needed.

Conclusions

- **Bone scan index (BSI) and the number of hotspots calculated by BONENAVI were independent prognostic factors in hormone-naive prostate cancer with bone metastases.**
- **BONENAVI might be useful for risk stratification of prostate cancer patients with bone metastases.**