

Changes in Bone Scan Index and Progression-Free and Overall Survival in Patients with Bone Metastasis of Breast Cancer

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Abstract

Purpose

The bone scan index (BSI) describes the tumor burden in bones as a percent of the total skeletal mass based on reference skeletal masses by bone scintigraphies. We conducted a prospective observational study to investigate the utility of BSI for breast cancer patients with bone metastasis.

Methods

We included patients with histologically or cytologically diagnosed breast cancer, radiologically or histologically confirmed bone metastasis, and receipt of less than three lines of systemic treatments. Bone scintigraphies were performed at the period of study enrollment and 12 and 24 weeks later. BSI was evaluated centrally. The primary endpoint was progression-free survival (PFS); secondary endpoints were overall survival (OS) and skeletal-related events.

Results

A total of 167 patients were enrolled and 153 were evaluable in the analysis. All the patients had bone metastasis; 45.8 % (n = 70) had bone-only disease, 17.0 % (n = 26) had lung, and 4.6 % (n = 7) had liver metastasis. The change in BSI from baseline to 12 weeks was significantly correlated with PFS (HR 1.25, 95%CI 1.13-1.40, p<0.01) and OS (HR 1.26, 95%CI 1.08-1.47, p<0.01). The change in BSI from baseline to 24 weeks was also significantly correlated with PFS (HR 1.32, 95%CI 1.06-1.65, p = 0.01) and OS (HR 1.47, 95%CI 1.11-1.95, p<0.01). The baseline BSI was not associated with PFS or OS.

Conclusion

Among the metastatic breast cancer patients with bone metastasis, BSI changes from baseline to 12 weeks and 24 weeks were significantly related with PFS and OS.

Background

Breast cancer is one of the most common cancers worldwide [1, 2]. The bone is the most frequent site of metastasis, and occasionally, it is the only metastatic site in patients with metastatic or recurrent breast cancer. In the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guideline, bone metastasis without soft tissue masses is usually considered as “non-measurable” lesion, so it is difficult to evaluate a response of systemic treatments in patients only with bone metastasis [3]. Tumor markers such as carcinoembryonic antigen (CEA) and CA15-3 have been used to guide response evaluation in such situations. However, tumor marker levels are often within normal ranges and the clinical validity is limited, so we need more reliable marker to evaluate the response of systematic therapy for bone metastasis.

Bone scans are widely used to screen for bone metastasis from solid tumors including breast cancer. The bone scan index (BSI) is a quantitative tool for improving the interpretability and clinical relevance of

bone scans. The BSI describes the tumor burden in bone as a percent of the total skeletal mass based on reference skeletal masses. A software program for calculating the BSI using the neural network system was originally developed based on whole-body images from a Swedish database. Then, Nakajima and colleague developed new software program named BONENAVI that improved identification of bone metastasis using neural network [4].

The clinical utility of the BSI has been studied in prostate cancer. In both hormone-sensitive and castration-resistant prostate cancer, the pre-treatment BSI was significantly correlated with overall survival [5–7]. Moreover, patients with a lower BSI after endocrine therapy or chemotherapy exhibited better survival than those with a higher BSI [8, 9]. Recently BSI has been utilized as the primary endpoint of the investigatory drug trial in prostate cancer [10]. However, among patients with metastatic breast cancer, there are few retrospective studies evaluating the efficacy of the BSI. Given the promising results in prostate cancer, we plan to investigate the clinical utility of the BSI in metastatic breast cancer.

Methods

Design

This was a multi-institutional prospective cohort study evaluating BSI in patients with breast cancer bone metastasis. The current study aimed to clarify whether quantitative measurements of bone metastatic lesions are related to progression-free survival (PFS) and overall survival (OS) in breast cancer. The primary endpoint was PFS, defined as the period from the enrollment to the date of all-cause death, the date of imaging that confirmed progression, or the date of clinical diagnosis of progression, whichever occurred earlier. If death or progression was not confirmed at the time of analysis or if the date of such an event was unknown, the patients were censored at the latest outpatient or inpatient examination before being lost to follow-up. The secondary endpoints were OS defined as the period from the enrollment day to the date of all-cause death and the presence of skeletal related events (SREs) including pathologic fracture, surgery for bone lesion, radiotherapy for bone lesion, spinal cord compression, or hypercalcemia. All the participants gave written informed consent before being enrolled in the study. This study was approved by each institutional review board and conformed to the guidelines of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects [11]. The study was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000016868) on 23rd March 2015. The details are available at the following web address: <http://www.umin.ac.jp/ctr/>.

Patients

Key inclusion criteria for this study were as follows: histologically or cytologically diagnosed breast cancer, bone metastasis (confirmed by biopsy, radiograph computed tomography, or magnetic resonance imaging), indicated for zoledronate or denosumab therapy, receipt of less than three prior systemic

treatments (chemotherapy, endocrine therapy, molecular targeted therapy or both) for metastatic disease, aged 20 years or older, Eastern Cooperative Oncology Group performance status 0–2, adequate organ function, and life expectancy more than 6 months.

Treatment And Evaluation

The current study was a prospective observational study without experimental treatment intervention. We offered every participant a standard treatment according to clinical guidelines of breast cancer [12]. The target accrual was up to 200 patients with metastatic breast cancer. Since there was no prior prospective study that evaluated BSI in patients with breast cancer, we determined the target accrual number based on the study fund and consensus by investigators. A bone scan was performed periodically (before treatment and at 12 and 24 weeks after registration). All BSI values were calculated centrally and independently as a percentage of the total skeletal mass based on reference skeletal masses. Response to the systemic therapy was evaluated periodically (before treatment and at 12 and 24 weeks after registration, thereafter every 12 weeks or as indicated clinically). The hazard ratios of BSI against PFS and OS were determined by penalized spline Cox regression. A landmark Cox analysis was also performed to compare the on-treatment BSI changes in 12 and 24 weeks. SAS® Ver 9.4 (Cary, NC) and R 3.6.1 were used in statistical analysis. We considered that a two-sided p-value of <0.05 was significant.

Results

Patient Characteristics

From June 2015 to December 2017, a total of 167 patients were enrolled in the study. The full analysis set included 153 patients (14 patients were excluded for not meeting the eligibility criteria ($n = 4$), for early progression before any treatment was administered ($n = 3$), and for lacking data about bone metastasis ($n = 7$)). The median age was 63.0 [interquartile range (IQR) 54.0-70.0] years. All the patients had bone disease; 45.8% ($n = 70$) had bone-only disease, 17.0% ($n = 26$) had lung, and 4.6% ($n = 7$) had liver metastasis (Table 1). Most diseases were hormone receptor-positive and HER2-negative ($n = 125$, 81.7%), followed by hormone receptor-positive and HER2-positive ($n = 9$, 5.9%), triple negative ($n = 9$, 5.9%), and hormone receptor-negative and HER2-positive ($n = 6$, 3.9%). Among the patients, 71.2% ($n=109$) received endocrine therapy, 17.6% ($n=27$) received chemotherapy, and 11.1% ($n=17$) received anti-HER2 therapy. Bone metastases were osteogenic in 43 patients (25.7%), osteoclastic in 76 (45.5%), and mixed in 46 (27.5%) out of the 167 enrolled patients.

Table 1
Patient characteristics

Total patients	N = 153	
Age	median (range)	63.0 (54-70)
Subtype	ER+/HER2-	125 (81.7%)
	ER+/HER2+	9 (5.9%)
	ER-/HER2+	6 (3.9%)
	ER-/HER2-	9 (5.9%)
	unknown	4 (2.6)
Performance status	0	107 (69.9%)
	1	35 (22.9%)
	2	11 (7.2%)
Site of metastasis	bone	153 (100%)
	Lung	26 (17.0%)
	liver	7 (4.6%)
Prior endocrine therapy	No	75 (49.0%)
	Yes	78 (51.0%)
Prior chemotherapy	No	126 (82.9%)
	Yes	26 (17.1%)
Prior anti-HER2 therapy	No	143 (94.7%)
	Yes	8 (5.3)
Type of treatment	endocrine therapy	109 (71.2%)
	chemotherapy	27 (17.6%)
	anti-HER2 therapy	17 (11.1%)
Bone-modifying agent		153 (100%)
Zoledronate	No	123 (80.4%)
	Yes	30 (19.6%)
Denosumab	No	36 (23.5%)

Abbreviation: ER: estrogen receptor

Total patients	N = 153
Yes	117 (76.5%)
Abbreviation: ER: estrogen receptor	

Outcome analysis

There were 124 events for PFS and 51 death with a median follow up of 22.5 (IQR:16.8–29.5 months) months. The data cut-off was December 2019. Bone scan was performed for 153 patients at baseline, 124 patients at 12 weeks, and 87 patients at 24 weeks. The baseline BSI value was not associated with PFS [hazard ratio (HR), 1.01; P = 0.88] and OS (HR, 1.07; P = 0.23). However, as shown in Figure 2 and 3, the change in BSI from baseline to 12 weeks on treatment was significantly related with PFS (HR 1.25, 95% CI, 1.13 to 1.40; P<0.01) and OS (HR 1.26, 95% CI, 1.08 to 1.47; P<0.01). The change in BSI from baseline to 24 weeks during treatment was also significantly related with PFS (HR 1.32, 95% CI, 1.06 to 1.65; P = 0.01) and OS (HR 1.47, 95% CI, 1.11 to 1.95; P<0.01). This trend was also observed in a subgroup of osteogenic metastasis (data not shown).

SREs were reported in 28 patients (13 with radiotherapy for bone metastasis, 8 pathological fracture, 3 spinal cord compressions, 3 hypercalcemia, 1 surgery for bone metastasis). Because the number of SREs are limited, statistical analysis was not performed.

Discussion

This is the first prospective study evaluating the efficacy of BSI in breast cancer patients with bone metastasis. Changes in BSI from baseline to 12 and 24 weeks were predictive for both PFS and OS. Baseline BSI was not correlated with either PFS or OS, in contrast to what is seen in prostate cancer [5–7]. One possible cause of this difference between breast cancer and prostate cancer is the pattern of bone metastasis. In prostate cancer, osteogenic metastasis is the main pattern of bone metastasis [13]. In our study osteoclastic pattern was the most common pattern of metastasis observed, and this may have contributed to the different results. However, in the exploratory analysis there was no correlation between the baseline BSI and PFS even in patients with osteogenic metastasis. The number of patients with osteogenic metastasis is limited and the current study has not sufficient power to detect the impact of BSI in a small subgroup. In terms of bone metastasis manner, the current study was the only study evaluating the efficacy of BSI in patients with osteoclastic or mixed pattern bone metastasis.

In the currents study, the change in BSI significantly correlated with both PFS and OS. As almost half of the patients in our study had bone-only diseases, the impact of the results was meaningful for the decision-making process in those patients. However, it is unclear whether the treatment should be changed based on the BSI change before radiological progression or not, and this is a question for future research. Previous reports demonstrated that early treatment intervention based on circulating tumor cells

failed to demonstrate a benefit over the standard radiological response-based strategy [14]. Therefore, a prospective confirmatory study is needed to evaluate early intervention based on the change in BSI value. The current study is meaningful because the change in BSI predicted not only radiological progression but also OS. Recent systematic review demonstrated that there was no endpoint which was judged to be valid surrogate for OS in metastatic breast cancer [15]. Our study suggests that change in BSI could serve as a surrogate marker for OS and be evaluated more easily in clinical trials. Recent advances in endocrine therapy, including CDK4/6 inhibitors [16, 17] and PI3K inhibitor [18], have improved the prognoses in patients with hormone receptor-positive breast cancer. These agents will be introduced if the disease shows progression base on the RECIST criteria, and could be the most appropriate candidates for clinical trials evaluating response-guided treatment modification based on BSI change.

There are some additional limitations to our study. First the number of patients included in our study was relatively small. However, the impact of BSI on PFS and OS was sufficiently demonstrated. In a larger study, smaller benefits for PFS or OS without clinical relevance may be detected. However, in a report the sensitivity of BONENVAI is not so high [19], and the efficacy of BSI may be focused on predicting PFS and OS. Second, the subgroup of patients treated with chemotherapy or anti-HER2 therapy was small, and it was difficult to reach a definitive conclusion for this population. The settings of the current study reflected the actual status of daily practice. However, the impact of BSI for patients treated with chemotherapy or anti-HER2 therapy warrants further evaluation.

In conclusion, the current study demonstrated the clinical utility of BSI associated with PFS and OS. Change in BSI could serve as a surrogate endpoint for overall survival in breast cancer.

Declarations

Authors' contributions

YN: Designing study, writing protocol, recruitment of participants, and writing manuscript.

HA: Designing study, recruitment of participants, and reviewing manuscript.

RN: Designing study, recruitment of participants, and reviewing manuscript.

SO: Designing study, recruitment of participants, and reviewing manuscript.

YS: Designing study, recruitment of participants, and reviewing manuscript.

NK: Designing study, recruitment of participants, and reviewing manuscript.

IY: Designing study, statistical analysis, and reviewing manuscript.

HM: Designing study, recruitment of participants, and reviewing manuscript.

All authors read and approved the final version of the manuscript.

Compliance with ethical standards

Ethics approval

This study was approved by the Institutional Review Board of each institution and conformed to the guidelines of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Informed consent: Written informed consent forms for comprehensive research use were obtained from all patients involved in the study.

Acknowledgement

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Figures

Breast cancer with confirmed bone metastasis (N = 167)

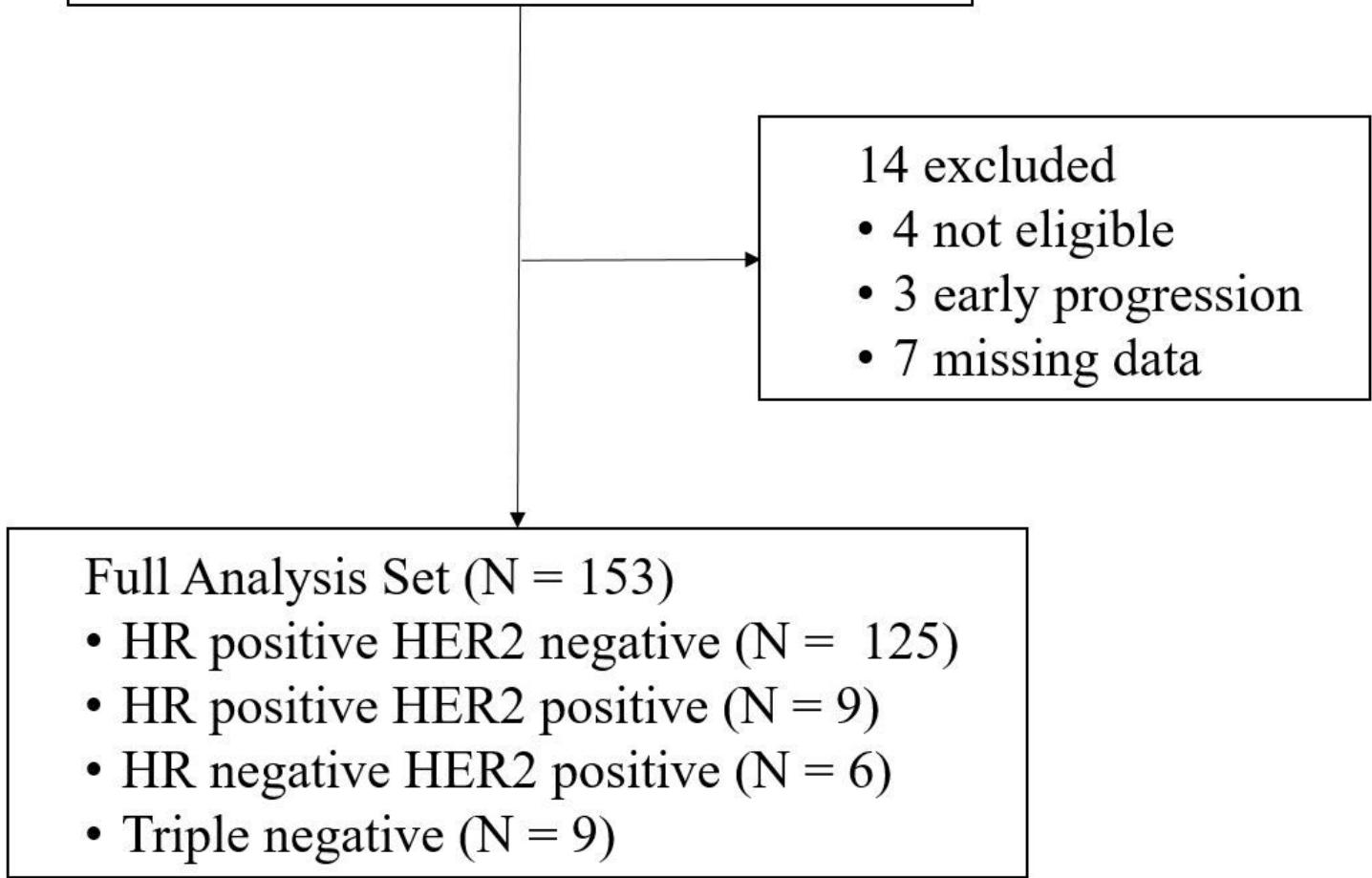


Figure 1

Patient flow

A total of 167 patients were enrolled to our study. 14 patients were excluded and 153 were analyzed as full analysis set.

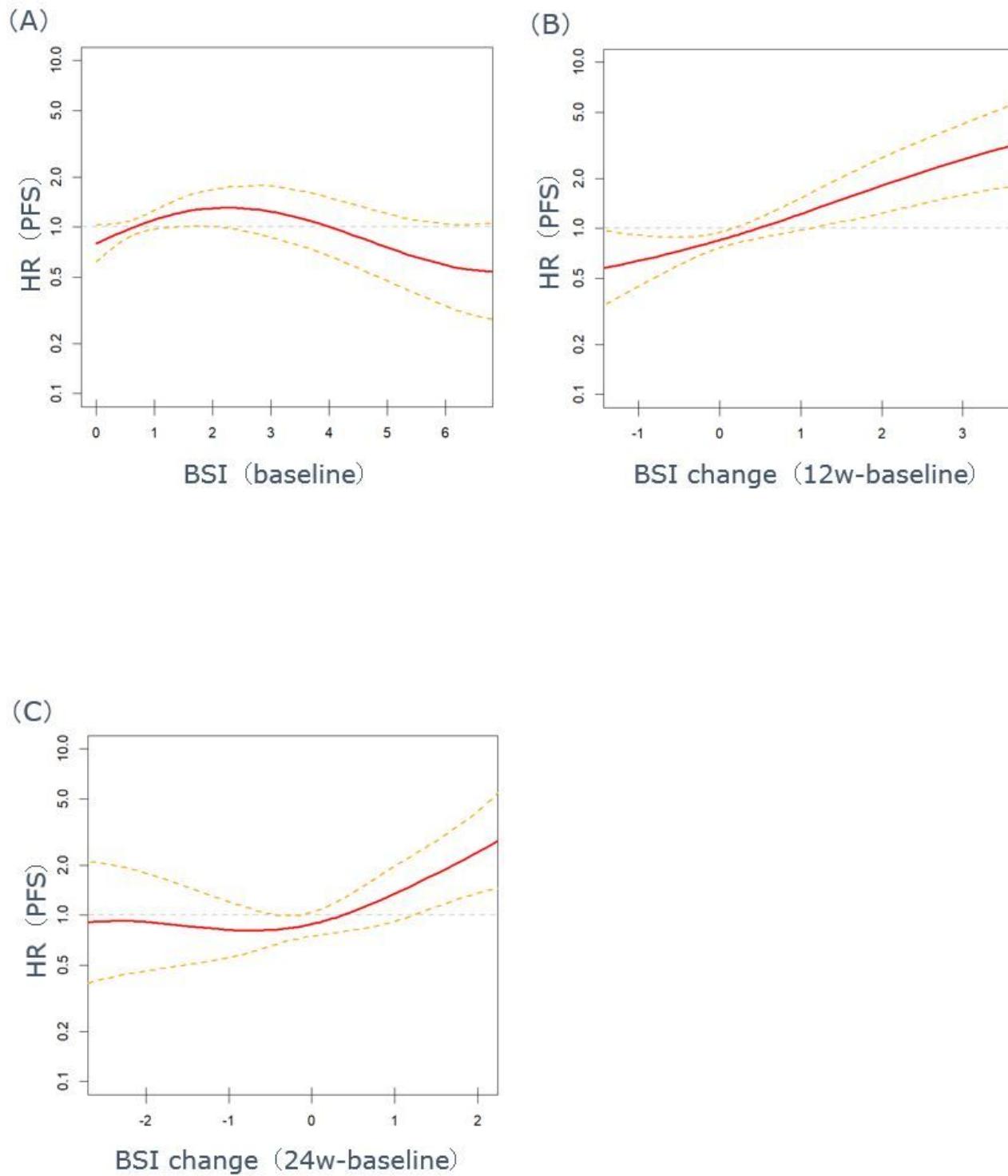


Figure 2

Estimated Cubic Spline Transformation of the Association Between BSI and PFS

Baseline BSI did not correlate with PFS. On the other hand, change in BSI from baseline to 12 weeks and 24 weeks significantly correlated with PFS.

Abbreviations: BSI: bone scan index, PFS: progression-free survival

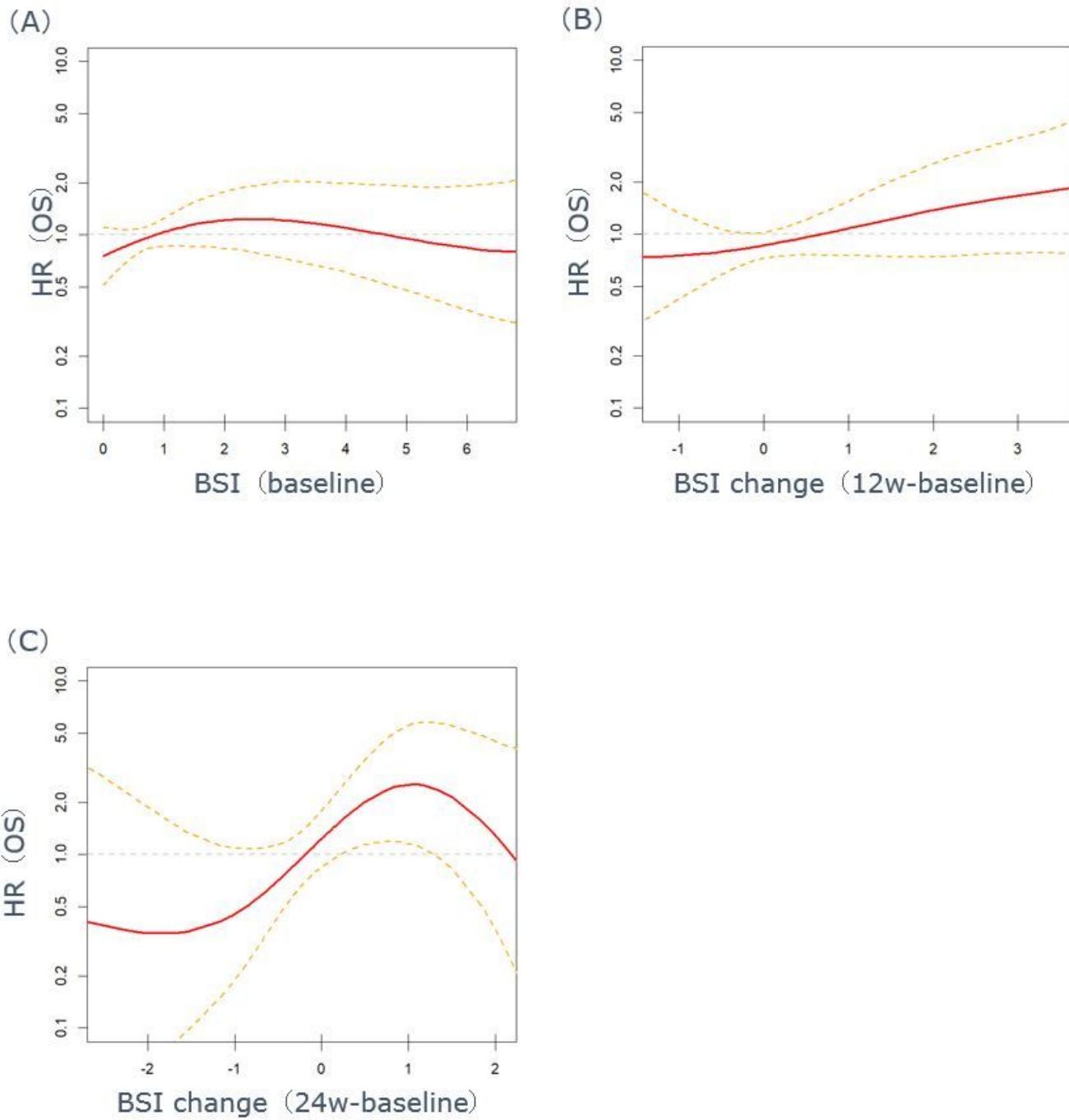


Figure 3

Estimated Cubic Spline Transformation of the Association Between BSI and OS

Baseline BSI did not correlate with PFS. On the other hand, change in BSI from baseline to 12 weeks and 24 weeks significantly correlated with OS.