

Original Article

# The standardized uptake value calculated from $^{111}\text{In}$ -ibritumomab tiuxetan single-photon emission computed tomography/computed tomography is a useful predictor of the clinical response in patients treated by $^{90}\text{Y}$ -ibritumomab tiuxetan therapy

Ayaka Kume,<sup>1)</sup> Akira Toriihara,<sup>2)</sup> Ryo Shimizu,<sup>1)</sup> Naoki Harata,<sup>3)</sup> Jun Isogai,<sup>3)</sup> Hiroaki Tanaka<sup>1)</sup>

$^{90}\text{Y}$ -Ibritumomab tiuxetan (IT) therapy is a radioimmunotherapy for indolent B-cell lymphoma. Several predictors of insufficient therapeutic effects have been reported. We performed a retrospective study at a single institute to investigate whether  $^{111}\text{In}$  SPECT/CT can predict the therapeutic effects and grade of cytopenia due to  $^{90}\text{Y}$ -IT therapy. We enrolled 16 consecutive patients who underwent  $^{90}\text{Y}$ -IT therapy, including 15 who underwent  $^{111}\text{In}$ -IT SPECT/CT. After  $^{90}\text{Y}$ -IT therapy, there were 4 patients in complete remission in whom the lesion  $\text{SUV}_{\text{max}}$  on  $^{111}\text{In}$ -IT SPECT/CT and soluble IL-2 receptor were significantly lower than those of the other patients ( $P < 0.05$  and  $P < 0.05$ , respectively). Based on the log-rank test of factors associated with the progression-free survival (PFS),  $\geq 2$  previous treatment regimens was significantly associated with a poor prognosis ( $P < 0.05$ ). The SUV on  $^{111}\text{In}$ -IT SPECT/CT may be a good predictor of the clinical response to  $^{90}\text{Y}$ -IT therapy.

**Keywords:** Indolent B-cell lymphoma, ibritumomab tiuxetan, standardized uptake value, single-photon emission computed tomography/computed tomography

## INTRODUCTION

$^{90}\text{Y}$ -Ibritumomab tiuxetan (IT) therapy is a radioimmunotherapy for indolent B-cell lymphoma.<sup>1-3</sup> Although  $^{90}\text{Y}$ -IT therapy can be safely applied to the elderly or patients with severe complications, there are some cases in which the therapeutic effects are insufficient. Several predictors of insufficient therapeutic effects have been reported,<sup>4-6</sup> including tumor diameter and number, clinical stage, number of previous treatment regimens, and maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ) calculated from 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) positron emission tomography-computed tomography (PET/CT).  $^{111}\text{In}$ -IT scintigraphy is performed to exclude patients who are not eligible for  $^{90}\text{Y}$ -IT treatment in whom a higher bone marrow accumulation of  $^{90}\text{Y}$ -IT can be expected, followed by severe pancytopenia. On the other hand, the uptake of  $^{111}\text{In}$ -IT is also observed in lymphoma lesions; therefore,  $^{111}\text{In}$ -IT scintigraphy may be a biomarker to predict the therapeutic effects of  $^{90}\text{Y}$ -IT.

At our hospital, whole-body and single-photon emission

computed tomography (SPECT)/CT are included in the routine protocol for  $^{111}\text{In}$ -IT scintigraphy. SPECT/CT is useful to identify each site with higher radiotracer uptake. In addition, according to previous studies,<sup>7,8</sup> SPECT/CT enables the calculation of the SUV, a semiquantitative value that reflects the degree of radiotracer uptake, which is a robust parameter used to compare visual scores and is not influenced by patient factors or the evaluator. Thus, we performed a retrospective study to investigate whether  $^{111}\text{In}$  SPECT/CT can be a predictor of the therapeutic effects and grade of cytopenia due to  $^{90}\text{Y}$ -IT therapy at a single institute.

## PATIENTS AND METHODS

### Study design


This retrospective study was approved by the Asahi General Hospital ethics committee and the in-hospital ethical review board prior to its initiation.

Received: October 28, 2020. Accepted: December 21, 2020. J-STAGE Advance Published: February 6, 2021 DOI:10.3960/jslrt.20055

<sup>1)</sup>Department of Hematology, Asahi General Hospital, Chiba, Japan, <sup>2)</sup>PET Imaging Center, Asahi General Hospital, Chiba, Japan, <sup>3)</sup>Department of Radiology, Asahi General Hospital, Chiba, Japan

**Corresponding author:** Hiroaki Tanaka, MD, PhD, Department of Hematology, Asahi General Hospital, I-1326, Asahi-city, Chiba 289-2511, Japan. E-mail: htanaka@hospital.asahi.chiba.jp

Copyright © 2021 The Japanese Society for Lymphoreticular Tissue Research

 This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

## Patients

We enrolled 16 consecutive patients who underwent  $^{90}\text{Y}$ -IT therapy between January 2017 and October 2019. At our institution, patients who were unable to receive conventional chemotherapy because of their age or complications, or those who refused to receive conventional chemotherapy were indicated for  $^{90}\text{Y}$ -IT therapy. The initiation of salvage therapy for indolent B-cell lymphoma was determined by each attending physician.

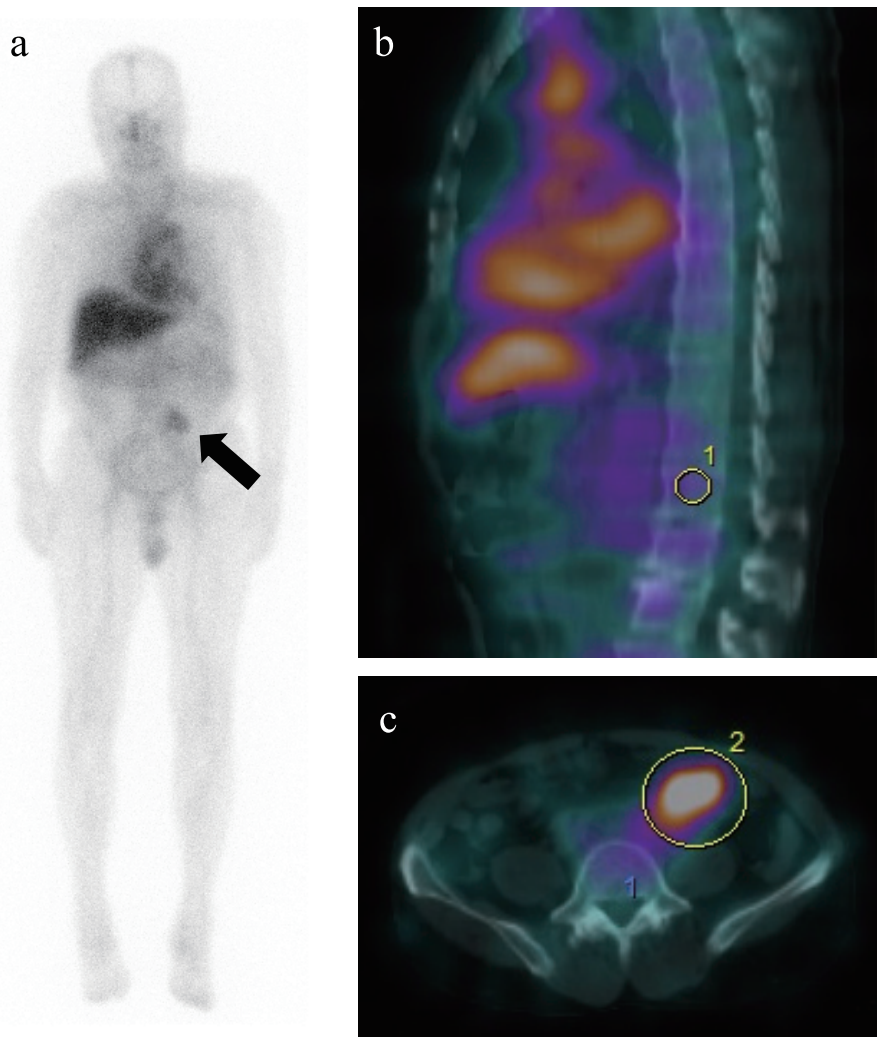
## $^{111}\text{In}$ -IT SPECT/CT protocol and image analyses

SPECT/CT images in the thoracic and abdominopelvic region were obtained 48 h following  $^{111}\text{In}$ -IT injection (130 MBq) for all patients. Prior to this retrospective study, we performed a phantom study to validate the accuracy of the calculated SUV following a similar method in a previous report.<sup>7</sup> Based on these SPECT/CT images, we calculated the  $\text{SUV}_{\text{max}}$  in the lesion with the highest  $^{111}\text{In}$ -IT uptake and

the mean SUV ( $\text{SUV}_{\text{mean}}$ ) in the BM by placing a globular volume of interest (diameter, 3 cm) in the L1 vertebral body.<sup>7</sup> An example image is shown in Figure 1. For patients who underwent  $^{18}\text{F}$ -FDG PET/CT before  $^{90}\text{Y}$ -IT therapy, we also calculated the  $\text{SUV}_{\text{max}}$  in the lesion with the highest  $^{18}\text{F}$ -FDG uptake. We defined the calculated  $\text{SUV}_{\text{max}}$  in the lesion with the highest  $^{111}\text{In}$ -IT uptake and  $^{18}\text{F}$ -FDG uptake as the IT- $\text{SUV}_{\text{max}}$  and FDG- $\text{SUV}_{\text{max}}$ , respectively.

## Statistics

The response after  $^{90}\text{Y}$ -IT therapy was assessed based on the Lugano Classification.<sup>9</sup> Pearson's correlation test was used to assess the significance of the correlation between IT- $\text{SUV}_{\text{max}}$  and other values. Welch's test was used to compare the IT- $\text{SUV}_{\text{max}}$  between patients with a tumor diameter of  $>50$  mm and other patients, the lesion  $\text{SUV}_{\text{max}}$  and soluble IL-2 receptor (sIL-2R) between good responders and other patients, and the BM  $\text{SUV}_{\text{mean}}$  between patients with or without severe cytopenia due to  $^{90}\text{Y}$ -IT therapy. Using the



**Fig. 1.**  $^{111}\text{In}$ -Ibritumomab tiuxetan SPECT/CT images of a 73-year-old man with recurrent diffuse large B cell lymphoma. An anterior scintigraphic image (**a**) showing high radiotracer uptake in the left pelvic nodal lesion (black arrow). There was no high uptake in the bone marrow. By placing volumes of interest on fused SPECT/CT images (**b** and **c**), the bone marrow  $\text{SUV}_{\text{mean}}$  and lesion  $\text{SUV}_{\text{max}}$  were calculated as 3.21 and 11.37, respectively.

Kaplan–Meier method, we created progression-free survival (PFS) curves for patients who achieved stable disease or higher. To identify the optimal cut-off values of the lesion SUV<sub>max</sub> for PFS, ROC analyses were performed. The cut-off value of IT-SUV<sub>max</sub> for PFS was 5.98 (area under curve [AUC] 0.604, 95% confidence interval [CI] 0.245-0.963) and that of FDG-SUV<sub>max</sub> was 9.52 (AUC 0.857, 95%CI 0.604-1). The following prognostic factors were included in the analysis: previous treatment regimen,  $\geq 2$ ; hemoglobin,  $< 12$  g/dl; lactate dehydrogenase (LDH),  $>$  normal range; sIL-2R,  $>$  normal range; number of lymph node lesions,  $> 3$ ; tumor diameter  $> 50$  mm; clinical stage, III or IV; Follicular Lymphoma International Prognostic Index (FLIPI),<sup>10</sup> high; complete metabolic response (CMR) achievement; CMR/partial metabolic response (PMR) achievement; IT-SUV<sub>max</sub>,  $> 6$ ; and FDG-SUV<sub>max</sub>,  $> 9.5$ . The log-rank test was used to compare differences between the survival curves. *P*-values of  $< 0.05$  were considered significant. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Japan; <http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html>; Kanda, 2012), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0).<sup>11</sup>

## RESULTS

### Patient characteristics

Table 1. summarizes the patients characteristics. The study population included 16 patients (male,  $n=8$ ; female,  $n=8$ ), with 15 who underwent <sup>111</sup>In-IT SPECT/CT. The median age was 69.5 (range, 56–90) years. Fourteen of 16 patients were diagnosed with follicular lymphoma. The median number of prior regimens was 1 (range, 1–3). The prior regimens of the patients included: rituximab monotherapy ( $n=6$ ); R-CHOP ( $n=14$ ), which consists of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; RB ( $n=2$ ), which consists of rituximab and bendamustine; EPOCH-R ( $n=1$ ), which consists of etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab; CHOP ( $n=1$ ); and CVP ( $n=1$ ), which consists of cyclophosphamide, vincristine, and prednisolone. There were only two patients in whom the diagnosis was confirmed by re-biopsy prior to <sup>90</sup>Y-IT therapy. On the evaluation of bone marrow infiltration prior to <sup>90</sup>Y-IT therapy, flow cytometry and bone marrow biopsy were performed in all patients, and there were no patients with bone marrow infiltration before <sup>90</sup>Y-IT therapy. The reasons why conventional chemotherapy was not available were age over 80 ( $n=3$ ), low performance status ( $n=2$ ), and complication of ischemic heart disease ( $n=1$ ) and collagen disease ( $n=1$ ). The median FDG-SUV<sub>max</sub> and IT-SUV<sub>max</sub> were 8.225 (range, 2.75–30.49) and 4.35 (range, 0–22.28), respectively. The median BM SUV<sub>mean</sub> calculated from <sup>111</sup>In-SPECT/CT was 2.81 (range, 1.33–4.46). The median observation period was 344.5 (range, 63–954) days. During this period, 5 patients died; 4

patients died of lymphoma progression and one patient with complete remission of lymphoma died of pneumonia.

### Correlation between IT-SUV<sub>max</sub> and other values

There was no significant correlation between IT-SUV<sub>max</sub> and FDG-SUV<sub>max</sub> ( $R = 0.196$ , 95%CI -0.37 to 0.658,  $P = 0.501$ ), LDH ( $R = 0.176$ , 95%CI -0.369 to 0.632,  $P = 0.53$ ), or sIL-2R ( $R = 0.238$ , 95% CI -0.312 to 0.669,  $P = 0.393$ ). In patients with a tumor diameter of  $> 50$  mm, the IT-SUV<sub>max</sub> was significantly higher than that of the other patients ( $p < 0.05$ ).

### Clinical response of <sup>90</sup>Y-IT therapy

After <sup>90</sup>Y-IT therapy, there were 4 patients with a complete metabolic response (CMR), 5 patients with a partial metabolic response (PMR), 3 patients with no metabolic response (NMR), and 4 patients with progressive metabolic disease (PMD). Thus, the overall response rate (ORR) and complete response rate (CRR) were 50.0% and 25.0%, respectively.

In patients who achieved CMR, the IT-SUV<sub>max</sub> and sIL-2R were significantly lower than those of the other patients ( $P < 0.05$  and  $P < 0.05$ , respectively) (Fig. 2); however, the

**Table 1.** Patient characteristics ( $n=16$ )

	Median (range)
Age at <sup>90</sup> Y-IT therapy (years old)	69.5 (56-90)
Male/female	8/8
Performance status (0/1/2)	10/4/2
The diagnosis at the first onset	
Follicular lymphoma	14
MALT lymphoma	1
Low grade B-cell, unclassified	1
Number of previous regimens	1 (1-3)
Hemoglobin ( $< 12$ mg/dl/other)	7/9
Lactate dehydrogenase ( $>$ normal range/other)	7/9
Soluble IL-2 receptor ( $>$ normal range/other)	6/10
Clinical stage (I/II/III/IV)	7/5/3/1
Number of lymph node areas ( $\leq 3$ / $> 3$ )	9/7
Tumor diameter ( $\leq 50$ mm/ $> 50$ mm)	10/6
FLIPI (low/intermediate/high)	2/6/8
Lesion SUV <sub>max</sub> on <sup>18</sup> F-FDG PET/CT	8.225 (2.75-30.49)
Lesion SUV <sub>max</sub> on <sup>111</sup> In-IT SPECT/CT	4.35 (0-22.28)
Bone marrow SUV <sub>mean</sub> on <sup>111</sup> In-IT SPECT/CT	2.81 (1.33-4.46)
Therapeutic effects evaluated by PET	
Complete metabolic response	4
Partial metabolic response	5
No metabolic response	3
Progressive metabolic disease	4
Minimum neutrophil count after <sup>90</sup> Y-IT therapy ( $\mu$ L)	603 (57-2526)
Minimum platelet count after <sup>90</sup> Y-IT therapy ( $\times 10^4/\mu$ L)	5.65 (1.7-22.5)

IT, ibritumomab tiuxetan; MALT, mucosa-associated lymphoid tissue; FLIPI, Follicular Lymphoma International Prognostic Index; SUV, standardized uptake value; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; SPECT, single-photon emission computed tomography

FDG-SUV<sub>max</sub> was not significantly lower (P=0.126).

**The prognostic effects of <sup>90</sup>Y-IT therapy**

The median PFS was 275 (range, 76-510) days. In the log-rank test, having ≥2 previous treatment regimens was associated with a poor prognosis (P<0.05) (Fig. 3). Patients with an IT-SUV<sub>max</sub> >6 had no significant difference in PFS from the other patients (P=0.103). There were two patients in whom the tumor diameter was >50 mm and the IT-SUV<sub>max</sub> was <6. One patient was in CMR with <sup>90</sup>Y-IT therapy and is alive without recurrence at day 667. The other patient was in PMR and was diagnosed with recurrence at day 563.

**Toxicities of <sup>90</sup>Y-IT therapy**

The median lowest neutrophil and platelet counts after <sup>90</sup>Y-IT therapy were 603/μL (range, 57–2526/μL) and 5.65 × 10<sup>4</sup>/μL (range, 1.7–22.5 × 10<sup>4</sup>/μL), respectively. There were 5 patients with a neutrophil count of <500/μL, 7 patients with a platelet count of <5 × 10<sup>4</sup>/μL, and 2 patients with a platelet count of <2.5 × 10<sup>4</sup>/μL. In 2 of the 3 patients older than 80 years of age, the platelet count decreased to <2.5 × 10<sup>4</sup>/μL after <sup>90</sup>Y-IT therapy. Granulocyte-colony stimulating factor (G-CSF) was administered to 8 patients, but none underwent platelet transfusion. One patient developed febrile neutropenia and influenza virus infection 21 days after <sup>90</sup>Y-IT therapy. In one patient, the number of blood cells decreased again 56 days after <sup>90</sup>Y-IT therapy and he was diagnosed with myelodysplastic syndrome. One patient developed pneumonia and died 120 days after <sup>90</sup>Y-IT therapy.

In patients with a neutrophil count of <500 μL, the BM SUV<sub>mean</sub> calculated from <sup>111</sup>In-IT SPECT/CT was higher than that of other patients, but not significantly (P=0.189). Moreover, there was no significant difference in the BM SUV<sub>mean</sub> between patients with a platelet count of <5 × 10<sup>4</sup>/

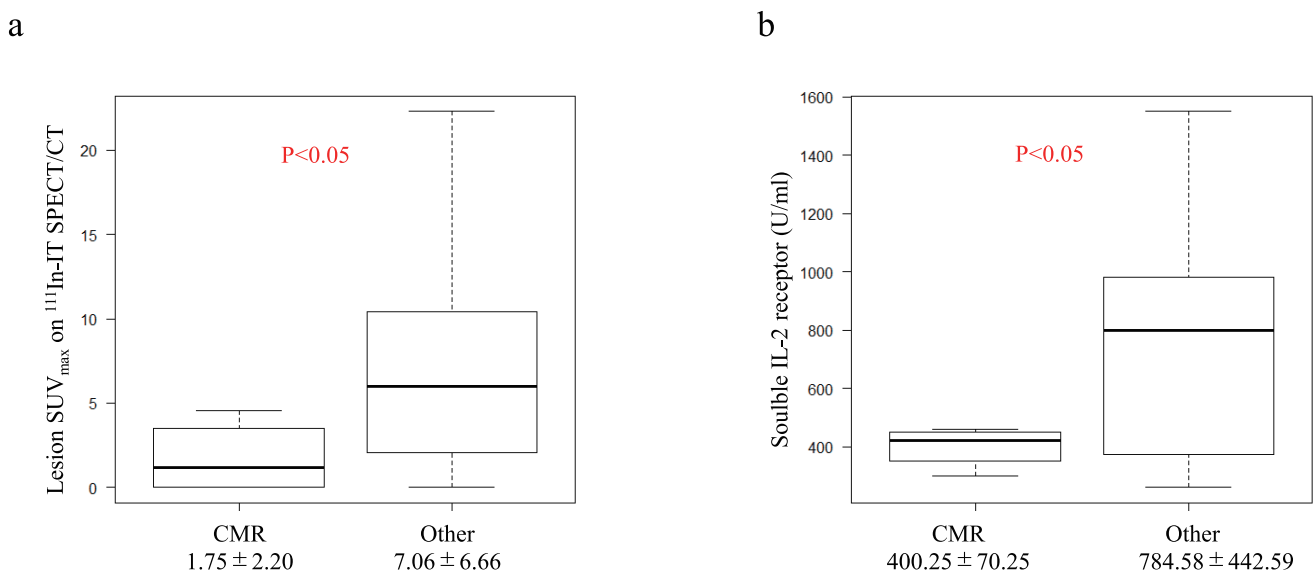
μL and other patients (P=0.289).

**DISCUSSION**

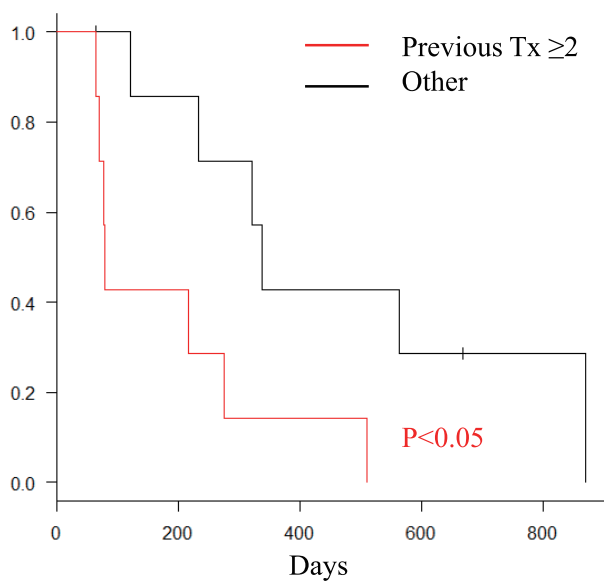
In our study, the IT-SUV<sub>max</sub> was significantly lower in patients who achieved CMR. Of note, a lower IT-SUV<sub>max</sub> was associated with a better response. In a previous study, Hanaoka *et al.* reported that the IT-SUV<sub>max</sub> in responders and non-responders did not significantly differ.<sup>12</sup> However, similar to our study, the IT-SUV<sub>max</sub> of responders was slightly lower than that of non-responders. The accumulation of <sup>111</sup>In-IT may be associated with the tumor cell density and <sup>18</sup>F-FDG,<sup>13</sup> thus fewer viable cells in lymphoma lesions may have led to better therapeutic effects. Although it is unknown whether such a phenomenon occurs with other types of radioimmunotherapy, our study may be valuable for predicting the therapeutic effects of radioimmunotherapy.

In our study, there was no significant difference in the FDG-SUV<sub>max</sub> between patients who achieved CMR and those who did not. Tsukamoto *et al.* reported that the FDG-SUV<sub>max</sub> was an independent prognostic factor.<sup>6</sup> In comparison, our study enrolled a smaller number of patients and their observation period was short. In addition, we were unable to unify the interval between <sup>18</sup>F-FDG PET/CT and <sup>90</sup>Y-IT therapy due to the retrospective nature of our study. Rituximab therapy was performed between <sup>18</sup>F-FDG PET/CT and <sup>111</sup>In-IT SPECT/CT for many patients. Rituximab after <sup>18</sup>F-FDG PET/CT may have negatively affected the power of PET/CT to predict therapeutic effects.

In previous studies of relapsed refractory low-grade B-cell lymphoma, the ORR and CRR of <sup>90</sup>Y-IT therapy were 73–91% and 30–82%, respectively,<sup>2-6</sup> whereas in our study, the ORR and CRR were 56% and 25%, respectively. As a reason for the low response, our study included more patients



**Fig. 2.** Comparison between patients who achieved CMR after <sup>90</sup>Y-IT therapy and other patients. **a** The lesion SUV<sub>max</sub> on <sup>111</sup>In-IT SPECT/CT (n=15). **b** Soluble IL-2 receptor (n=16). The numbers below the figure are the mean ± standard deviation. CMR, complete metabolic response; SUV<sub>max</sub>, maximum of standardized uptake value; IT, ibritumomab tiuxetan; SPECT, single-photon emission computed tomography; CT, computed tomography.



**Fig. 3.** Progression-free survival curves for  $\geq 2$  previous treatment regimens and others (n=16). Previous Tx, previous treatment regimen.

with a poor prognosis than previous studies because the median age of the patients was higher, the number of patients with a high LDH was higher, and half of the patients had a high FLIPI. Furthermore, some patients with transformation of follicular lymphoma may have been included in our study because most patients did not undergo repeated tissue biopsy at the time of lymphoma recurrence to confirm the diagnosis.

In our study, although the high  $SUV_{mean}$  in the BM calculated from <sup>111</sup>In-IT SPECT/CT was associated with a high grade of neutropenia, there was no significant difference. One possible reason for this is that the exact lowest neutrophil count was unable to be plotted due to G-CSF intervention in half of the enrolled patients. Regarding thrombocytopenia, two of the three patients aged  $>80$  years developed grade 4 thrombocytopenia after <sup>90</sup>Y-IT therapy. Furthermore, 5 of 16 patients had grade 4 neutropenia even though none had bone marrow infiltration before <sup>90</sup>Y-IT therapy. In some European countries, <sup>111</sup>In-IT scintigraphy is omitted. However, as <sup>90</sup>Y-IT therapy is often used for the elderly and patients with complications, it is necessary to discuss whether <sup>111</sup>In-IT scintigraphy can be omitted.

The present study has several limitations. First, we were unable to measure the size of each tumor precisely because patients had not undergone contrast-enhanced CT near the time of <sup>111</sup>In-IT SPECT/CT. Previous studies reported the tumor diameter as a prognostic factor.<sup>4,6</sup> To evaluate the prognostic power of IT- $SUV_{max}$ , the tumor diameter should be incorporated into the analysis in combination with the IT- $SUV_{max}$  data. In our study, there were two patients with a large tumor diameter and low IT- $SUV_{max}$ , and they had the most favorable course among our patients; however, no further analysis was possible. Furthermore, we should perform multivariate analysis including LDH, sIL-2R, and the number of previous treatment regimens to confirm whether IT- $SUV_{max}$  is an independent prognostic factor. However, due to the

small number of patients, only univariate analysis was performed. The second limitation is that we only analyzed the  $SUV_{max}$  as a SPECT/CT or PET/CT parameter in this study. The  $SUV_{max}$  only reflects the voxel with the highest radio-tracer uptake in the tumor. Thus, it cannot reflect the characteristics in whole lesions or tumor volumes. However, the use of volumetric parameters, such as the metabolic tumor burden, on <sup>18</sup>F-FDG PET/CT is not well-established in the field of SPECT/CT, at least <sup>111</sup>In-IT studies. The third limitation is that the study population was relatively small. A larger study that simultaneously analyzes the accurate tumor size and In- $SUV_{max}$  is required to validate our findings.

In conclusion, the SUV calculated on <sup>111</sup>In-IT SPECT/CT may be a good predictor of the clinical response to <sup>90</sup>Y-IT therapy. Our study demonstrated that a lower IT- $SUV_{max}$  is associated with a better response. Although it is unknown whether this phenomenon is only observed with <sup>90</sup>Y-IT therapy, our study may provide valuable information regarding the therapeutic effects of radioimmunotherapy.

## FUNDING

This study was not funded.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest in association with the present study.

## REFERENCES

- 1 Knox SJ, Goris ML, Trisler K, *et al.* Yttrium-90-labeled anti-CD20 monoclonal antibody therapy of recurrent B-cell lymphoma. *Clin Cancer Res.* 1996; 2 : 457-470.
- 2 Witzig TE, Gordon LI, Cabanillas F, *et al.* Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol.* 2002; 20 : 2453-2463.
- 3 Tobinai K, Watanabe T, Ogura M, *et al.* Japanese phase II study of <sup>90</sup>Y-ibritumomab tiuxetan in patients with relapsed or refractory indolent B-cell lymphoma. *Cancer Sci.* 2009; 100 : 158-164.
- 4 Witzig TE, Molina A, Gordon LI, *et al.* Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. *Cancer.* 2007; 109 : 1804-1810.
- 5 Uike N, Choi I, Tsuda M, *et al.* Factors associated with effects of <sup>90</sup>Y-ibritumomab tiuxetan in patients with relapsed or refractory low-grade B cell non-Hodgkin lymphoma: single-institution experience with 94 Japanese patients in rituximab era. *Int J Hematol.* 2014; 100 : 386-392.
- 6 Tsukamoto N, Yokohama A, Higuchi T, *et al.* Tumor long-axis diameter and  $SUV_{max}$  predict long-term responders in <sup>90</sup>Y-ibritumomab tiuxetan monotherapy. *Int J Hematol.* 2019; 109 : 91-97.

- 7 Toriihara A, Daisaki H, Yamaguchi A, *et al.* Applying standardized uptake values in gallium-67-citrate single-photon emission computed tomography/computed tomography studies and their correlation with blood test results in representative organs. *Nucl Med Commun.* 2018; 39 : 720-724.
- 8 Kaneta T, Ogawa M, Daisaki H, *et al.* SUV measurement of normal vertebrae using SPECT/CT with Tc-99m methylene diphosphonate. *Am J Nucl Med Mol Imaging.* 2016; 6 : 262-268.
- 9 Cheson BD, Fisher RI, Barrington SF, *et al.* Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014; 32 : 3059-3068.
- 10 Solal-Céligny P, Roy P, Colombat P, *et al.* Follicular lymphoma international prognostic index. *Blood.* 2004; 104 : 1258-1265.
- 11 Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant.* 2013; 48 : 452-458.
- 12 Hanaoka K, Hosono M, Tatsumi Y, *et al.* Heterogeneity of intratumoral <sup>111</sup>In-ibritumomab tiuxetan and <sup>18</sup>F-FDG distribution in association with therapeutic response in radioimmunotherapy for B-cell non-Hodgkin's lymphoma. *EJNMMI Res.* 2015; 5 : 10.
- 13 Giraud C, Karanikas G, Weber M, *et al.* Correlation between glycolytic activity on [18F]-FDG-PET and cell density on diffusion-weighted MRI in lymphoma at staging. *J Magn Reson Imaging.* 2018; 47 : 1217-1226.