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NUCLEAR MEDICINE

Early evaluation of tumor response to ^{90}Y-ibritumomab radioimmunotherapy in relapsed/refractory B cell non-Hodgkin lymphoma: what is the optimal timing for FDG-PET/CT?

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Abstract

Purpose To determine the earliest optimal timing for assessment of early response following radioimmunotherapy in non-Hodgkin lymphoma patients using FDG-PET/CT.

Methods FDG-PET/CT was performed prior to treatment (PET1), at 2 (PET2) weeks, and at 6 (PET3) weeks after ^{90}Y-ibritumomab radioimmunotherapy in 55 patients. Response was evaluated based on the Deauville 5-point scale and Lugano criteria as well as semiquantitative analysis and compared with progression-free survival (PFS).

Results PET 2 showed complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), and progressive metabolic disease (PMD) in 33, 13, 6, and 3 patients, respectively, while PET 3 in 41, 8, 3, and 3 patients, respectively. Mean SUV_{max} of 168 target lesions decreased over time (PET1, 2, 3; 5.58 ± 2.58, 1.87 ± 1.78, 1.75 ± 2.25, respectively). Progression or recurrence after a median of 12.6 months (range 2.6–72.0 months) was seen in 44 patients. Patients with CMR or metabolic response (CMR + PMR) on PET2 showed significantly longer PFS as compared to those who did not ($p = 0.00028$ and $p = 0.029$, respectively). A similar significant difference was observed based on PET3 ($p = 0.00013$ and $p = 0.017$, respectively). The same trend was observed when analyzing only the subgroup of patients with follicular lymphoma ($N = 43/55$) ($p < 0.0001$).

Conclusion Use of FDG-PET/CT findings with Lugano criteria for assessing early response to radioimmunotherapy after 6 weeks allowed for accurate evaluation and prognostic stratification, though scanning after 2 weeks was too soon to precisely evaluate response.

Key Points

- *The optimal timing of FDG-PET/CT to obtain a suitable tool for assessment of response after ^{90}Y-ibritumomab radioimmunotherapy of lymphoma has not yet been defined.*
- *Assessment after 6 weeks by FDG-PET/CT using the Lugano criteria accurately evaluates treatment response and prognosis.*
- *FDG-PET/CT performed 2 weeks after radioimmunotherapy is too early as it significantly misses objective responses.*

Keywords Non-Hodgkin lymphoma · Radioimmunotherapy · PET-CT · Progression-free survival

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Abbreviations

CMR	Complete metabolic response
FDG	^{18}F-fluorodeoxyglucose
FOV	Field of view
MALT	Mucosa-associated lymphoid tissue
PET/CT	Positron emission tomography/computed tomography
PFS	Progression-free survival
PMD	Progressive metabolic disease
PMR	Partial metabolic response
SMD	Stable metabolic disease
SUV_{max}	Maximum standardized uptake value
VOI	Volume of interest

Introduction

Radioimmunotherapy was recently introduced as a targeted therapy method, in which radiation from radionuclides is delivered to the tumor more selectively by the use of antibodies directed towards tumor-associated antigens. ^{131}I-tositumomab (Bexxar®, GlaxoSmithKline,) is approved for clinical use in the USA, while ^{90}Y-ibritumomab tiuxetan (Zevalin™, Biogen IDEC Pharmaceuticals) has been approved in Europe and Japan, as well as the USA, for patients with relapsed or refractory B cell non-Hodgkin lymphoma [1–5].

^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) is considered to be suitable for assessment of therapy response in patients with malignant lymphoma, though the optimal timing for FDG-PET scanning after radioimmunotherapy needs to be clarified. On the one hand, slow responders should be allocated with a relevant delay to reliably evaluate the response. On the other hand, non-responders would likely benefit from the earliest detection and treatment re-orientation. This is a crucial issue.

FDG-PET images obtained at 6 weeks or earlier after radioimmunotherapy have been suggested to provide important prognostic information that is useful for response prediction [6–8]. Bodet-Milin et al [6] and Jacene et al [7] evaluated FDG-PET results obtained at 6 weeks after radioimmunotherapy, and found that timing was useful for accurate response evaluation and prognostic stratification in 27 and 12 patients, respectively. Lim et al [8] evaluated treatment response at 4 weeks after radioimmunotherapy in 24 patients using FDG-PET/CT. Torizuka et al [9] performed FDG-PET scanning twice, at 1 week and then again 4–8 weeks after immunotherapy, in 14 patients and reported that results from the later examination were well correlated with response, while changes in FDG uptake shown after only 1 week were less well correlated. Based on these studies, with a limited number of patients, it is difficult to decide for the optimal timing.

To solve this question, we examined the timing of early assessment of metabolic response in a larger cohort of patients with non-Hodgkin lymphoma, using FDG-PET/CT at 2 and 6 weeks after ^{90}Y-ibritumomab radioimmunotherapy.

Materials and methods

Patients

This prospective study was approved by the ethics committee of our institution. Informed consent was obtained from each patient after the procedure details were fully explained. Fifty-five patients (24 males, 31 females; mean 62.9 years old, range 31–84 years,) with histologically confirmed relapsed or refractory B cell non-Hodgkin lymphoma underwent ^{90}Y-ibritumomab radioimmunotherapy at the PET Center of Hyogo College of Medicine Hospital between June 2009 and December 2012. For study inclusion, they were required to have undergone three FDG-PET/CT examinations, including before (baseline, PET1), and then again at 2 (PET2) and 6 (PET3) weeks after radioimmunotherapy, for assessment of lymphoma lesions. No treatment other than radioimmunotherapy was given during the time period of the 3 FDG-PET/CT examinations. Clinical characteristics are presented in Table 1. The 55 patients were affected by follicular lymphoma ($n = 43$), mucosa-

Table 1 Patient characteristics

Characteristics	Value
Age (years)	
Mean	62.9 ± 10.0
Range	31~84
Sex	
Male	24 (43.6%)
Female	31 (56.4%)
Histological subtype	
Follicular lymphoma	43 (78.2%)
Mucosa-associated lymphoid tissue (MALT) lymphoma	3 (5.5%)
Mantle cell lymphoma	3 (5.5%)
Small lymphocytic lymphoma	3 (5.5%)
Lymphoplasmacytic lymphoma	2 (3.6%)
Marginal zone lymphoma	1 (1.8%)
Stage at radioimmunotherapy	
I	3 (5.5%)
II	12 (21.8%)
III	26 (47.3%)
IV	14 (25.5%)
Previous treatment	
Chemotherapy+rituximab	40 (72.7%)
Chemotherapy+rituximab+radiotherapy	6 (10.9%)
Chemotherapy	5 (9.1%)
Chemotherapy+rituximab+stem cell support	4 (7.3%)

associated lymphoid tissue (MALT) lymphoma ($n = 3$), mantle cell lymphoma ($n = 3$), small lymphocytic lymphoma ($n = 3$), lymphoplasmacytic lymphoma ($n = 2$), and marginal zone lymphoma ($n = 1$), and enrolled after failing 1 or more prior treatments (chemotherapy, $n = 55$; rituximab, $n = 50$; external beam radiation therapy, $n = 6$; stem cell support, $n = 4$).

^{111}In-ibritumomab imaging and ^{90}Y-ibritumomab radioimmunotherapy

Pre-treatment imaging with ^{111}In-ibritumomab tiuxetan (i.e., ^{111}In-ibritumomab scanning) is routinely performed in Japan to assess biodistribution using reported interpretation criteria [10]. All of the present patients underwent a standard ^{90}Y-ibritumomab radioimmunotherapy regimen, which began with an initial dose of rituximab (250 mg/m^2) infused on day 0 prior to administration of ^{111}In-ibritumomab. Next, ^{111}In-ibritumomab tiuxetan was given at a diagnostic dose (185 MBq), and whole-body anterior and posterior gamma camera nuclear medicine examinations were performed at 48 and/or 72 h after administration using a dual-head gamma camera (FORTE, HITACHI,). A second infusion of rituximab (250 mg/m^2) was given on day 7, followed by a weight-based dose of ^{90}Y-ibritumomab tiuxetan, e.g., 11.1 MBq/kg (platelet count 100× to 149 × 10^9/L) or 14.8 MBq/kg (platelet count 150 × 10^9/L or higher). The maximum dose was 1184 MBq.

FDG-PET/CT examinations

FDG-PET/CT scans (PET1, 2, 3) were performed using a Gemini GXL16 PET/CT scanner (Philips Medical Systems,) with gadolinium oxyorthosilicate detectors. Each patient fasted for 5 h prior to the scan, with blood glucose measured immediately before injection of FDG at 4.0 MBq/kg body weight. No patient had a blood glucose level greater than 150 mg/dL. Static emission images were obtained approximately 60 min after the injection. Helical CT scans for attenuation correction and anatomic localization were performed from the top of the head to the bottom of the feet using the following parameters: tube voltage, 120 kV; effective tube current auto-mA (up to 120 mA); gantry rotation speed, 0.5 s; detector configuration, 16 × 1.5 mm; slice thickness, 2 mm; and transverse field of view (FOV), 600 mm. Immediately after CT completion, PET imaging of the region extending from the head to the mid-thigh level was performed for 90 s/bed position (13–14 bed positions) and the mid-thigh to the tips of the toes for 30 s/bed position (6 bed positions), using a variable sampling method. Instructions to breathe normally during the PET acquisitions were given. For PET images reconstructed for fusion, the transaxial field of view was 576 mm and matrix size was 144 × 144 mm. Reconstruction of attenuation-corrected PET images was done with a line-of-response row-action maximum likelihood algorithm (n/a subsets, 2 iterations).

Image interpretation

All PET/CT images were interpreted by a single board-certified nuclear medicine physician, who had 11 years of experience with oncologic FDG-PET/CT. The visual Deauville 5-point scale in accordance with the Lugano criteria was used for determination of objective response [11]. Two different evaluation methods, one using results of the first 2 scans (PET1 and 2) and the other using results of the first and third scans (PET1 and 3) were utilized to classify patients as showing complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), or progressive metabolic disease (PMD). For determining mediastinal blood pool and liver uptake as reference settings, a 5-point scale was used. According to the Lugano classification, achievement of CMR was defined as a completely PET-negative scan, or a scan with minimal residual uptake that was less than or equal to liver activity (Deauville score ≤ 3). For cases with a Deauville score of 4 or 5, PMR, SMD, or PMD was defined using visual comparison with a previous PET scan.

Semiquantitative analysis of abnormal radiotracer uptake for each lesion was performed using maximum standardized uptake value (SUV_{max}), calculated as follows: SUV = volume of interest (VOI) radioactivity concentration (Bq/mL)/(injected dose (Bq)/patient weight (g)). We determined the SUV_{max} value, defined as the highest SUV value for pixels with the highest count within the VOI, and recorded that for focal areas of uptake. Using baseline PET/CT scanning results (PET1), all lymph nodes and extranodal masses were evaluated systematically according to topographic criteria, with up to 5 representative lesions with the highest levels of uptake (> 1 cm in size) identified as target lesions in each patient.

Statistical analysis

Analysis of progression-free survival (PFS) was done using Kaplan-Meier plots and a log-rank test, and defined as the time from radioimmunotherapy to tumor progression or recurrence, as determined by histologic or follow-up findings including imaging. We also determined the existence of a significant difference for mean SUV_{max} of target lesions between 2 PET/CT scans using a paired t test. Statistical analysis was performed with SAS, version 9.3 (SAS Institute Inc.), with p values < 0.05 considered to indicate significance.

Results

Objective treatment response

Evaluating PET2 as compared with baseline PET1, CMR, PMR, SMD, and PMD were seen in 33 (60%), 13 (23.6%), 6

(10.9%), and 3 (5.5%) patients, respectively. Evaluating PET3 as compared with PET1 showed 41 (74.5%), 8 (14.5%), 3 (5.5%), and 3 (5.5%) patients, respectively (Table 2).

Table 3 presents findings showing metabolic changes from PET2 to PET3. Initially, 33 (60%) of the 55 patients showed CMR at PET2 and then CMR was maintained at PET3, while 8 (14.5%) who were without CMR at PET2 (5 PMR, 2 NMR, 1 PMD) showed no metabolic activity at PET3. In 5 patients (9.1%) who showed PMR ($n = 3$), SMD ($n = 1$), or PMD ($n = 1$) at PET2, the objective response was intensified at PET3. Among 7 who showed initial improvement to PMR at PET2, 3 patients demonstrated progression and 4 stable metabolic activity at PET3. Of 3 patients judged initially to be SMD at PET2, 1 showed progression at PET3 and 2 had sequential stable metabolic activity at PET3. Representative cases are presented in Figs. 1, 2, 3, and 4.

Semiquantitative analysis

The 168 target lesions were lymph nodes ($n = 146$), tonsils ($n = 5$), spleen ($n = 4$), pleura ($n = 3$), bone marrow ($n = 3$), adrenal gland ($n = 2$), liver ($n = 1$), lung ($n = 1$), skin ($n = 1$), nerve ($n = 1$), and muscle ($n = 1$). The mean SUV_{max} of all target lesions showed a decrease from PET1 to PET2 and then again to PET3 (5.58 ± 2.58, 1.87 ± 1.78, 1.75 ± 2.25, respectively), with the difference between PET1 and 2, and also between PET1 and 3 significant (both $p < 0.0001$), whereas the difference between PET2 and 3 was not significant ($p = 0.098$).

Survival analysis

Recurrent or progressive disease occurred in 44 (80.0%) of the 55 patients, with a median period of 12.6 months (2.6–72.0 months). The overall median duration of follow-up was 11.4 months (2.6–72.0 months) for those 44 with recurrence or progression, and 18.0 months (3.3–63.1 months) for the 11 without recurrence or progression during the follow-up period. The 1- and 2-year PFS rates were 52.7% (29/55) and 18.2% (10/55), respectively.

Twenty-three (69.7%) of 33 patients with CMR on PET2 showed recurrence or progression, whereas 21/ 22 (95.4%) with non-CMR patients (PMR, SMD, PMD) did. Patients who achieved CMR had a significantly longer PFS as compared to the non-CMR group ($p = 0.00028$) (Table 2, Fig. 5a). Furthermore, 35 (69.7%) of 46 patients with metabolic response (CMR, PMR) on PET2 developed recurrence or progression, whereas all 9 (100%) patients with no metabolic response (SMD, PMD) demonstrated recurrence or progression. Patients with metabolic response had a significantly longer PFS as compared to the non-metabolic responders ($p = 0.029$) (Table 2, Fig. 5b).

Thirty (73.2%) out of 41 patients with CMR on PET3 developed later recurrence or progression, whereas all 14 non-CMR patients (100%) did. Patients who achieved CMR had a significantly longer PFS as compared to those who did not ($p = 0.00013$) (Table 2, Fig. 5c). Of the 49 metabolic responders, 38 (77.6%) developed recurrence or progression, whereas all 6 (100%) non-metabolic responders demonstrated recurrence or progression. As compared with non-metabolic responder patients, those who achieved metabolic response had significantly longer PFS ($p = 0.017$) (Table 2, Fig. 5d).

Survival analysis in 43 patients with follicular lymphoma

Recurrent or progressive disease occurred in 35 (81.4%) of the subgroup of 43 patients with follicular type of lymphoma, with a median period of 11.9 months (2.6–72.0 months). The overall median duration of follow-up was 11.1 months (2.6–72.0 months) for those 35 with recurrence or progression and 18.3 months (3.3–63.1 months) for the 8 without recurrence or progression during the follow-up period. The 1- and 2-year PFS rates were 55.8% (29/43) and 18.6% (10/43), respectively.

Patients who achieved CMR and metabolic response (CMR, PMR) on PET2 had a significantly longer PFS as compared to the non-CMR and non-metabolic responders group ($p < 0.00001$ and $p < 0.00001$), respectively (Figs. 6a, b).

Patients who achieved CMR and metabolic response (CMR, PMR) on PET3 had a significantly longer PFS as compared to the non-CMR and non-metabolic responders group ($p < 0.00001$ and $p < 0.00001$), respectively (Figs. 6c, d).

Table 2 Treatment response of three evaluation methods

	PET1,2	PET1,3
CMR	33	41
PMR	13	8
SMD	6	3
PMD	3	3
The difference predicting PFS between CMR and non-CMR	$p = 0.00028$	$p = 0.00013$
The difference predicting PFS between responders and non-responders	$p = 0.029$	$p = 0.017$

CMR, complete metabolic response; *PMR*, partial metabolic response; *SMD*, stable metabolic disease; *PMD*, progressive metabolic disease; *PFS*, progression-free survival

Discussion

We analyzed 55 patients with relapsed or refractory B cell non-Hodgkin lymphoma who underwent FDG-PET/CT

Table 3 Metabolic change from PET2 to PET3

PET2 (2 weeks)	PET3 (6 weeks)
CMR (n=33)	No metabolic activity (n=33)
PMR (n=13)	No metabolic activity (n=5)
	Decreasing metabolic activity (n=1)
	Stable metabolic activity (n=4)
	Progressed metabolic activity (n=3)
SMD (n=6)	No metabolic activity (n=2)
	Decreasing metabolic activity (n=1)
	Stable metabolic activity (n=2)
	Progressed metabolic activity (n=1)
PMD (n=3)	No metabolic activity (n=1)
	Decreasing metabolic activity (n=0)
	Stable metabolic activity (n=1)
	Progressed metabolic activity (n=1)

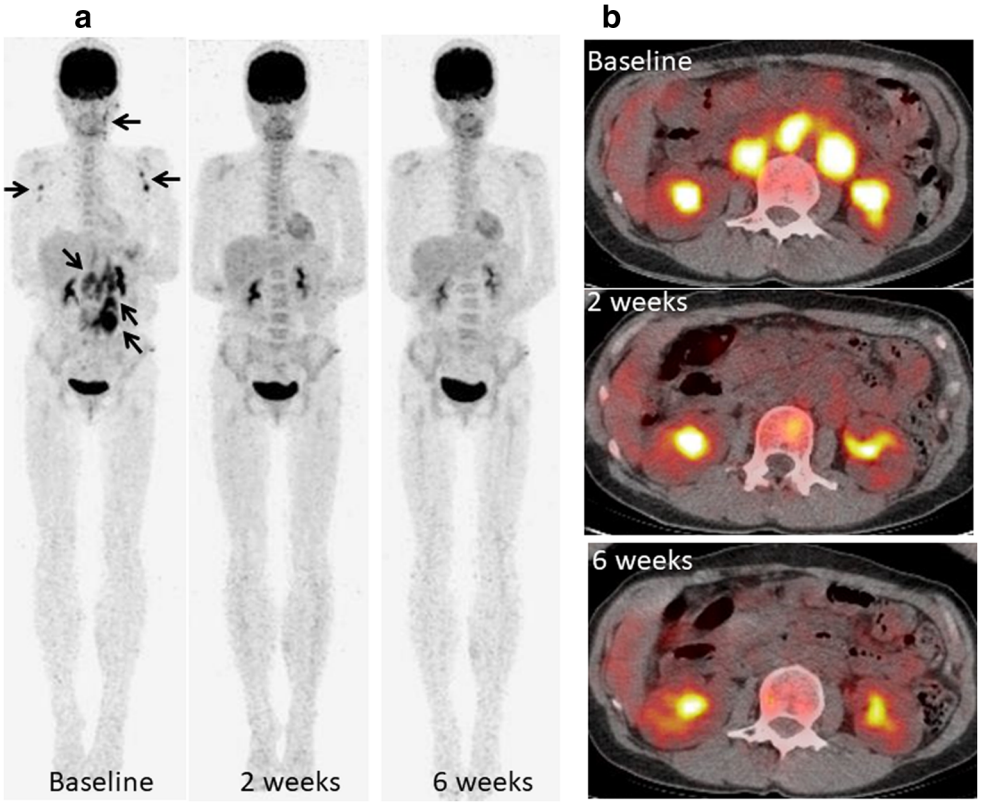

Fig. 1 Female, 43 years old, with a follicular lymphoma received ^{90}Y-ibritumomab radioimmunotherapy. **a** Maximum intensity projection (MIP) of baseline FDG-PET showing several areas of intense FDG uptake in the left neck, bilateral axilla, and abdominal and pelvic regions (arrows). FDG-PET scanning performed at 2 weeks showed complete resolution of abnormal metabolic activity with an objective response of CMR, while that at 6 weeks showed a continuance of no abnormal uptake, with an objective response of CMR. **b** Baseline FDG-PET/CT showing multiple swollen para-aortic lymph nodes with intense FDG uptake (SUV_{max} 9.44). Scanning at 2 weeks showed a decreased number of nodes with vanishing FDG uptake and at 6 weeks a continuance of no abnormal uptake.

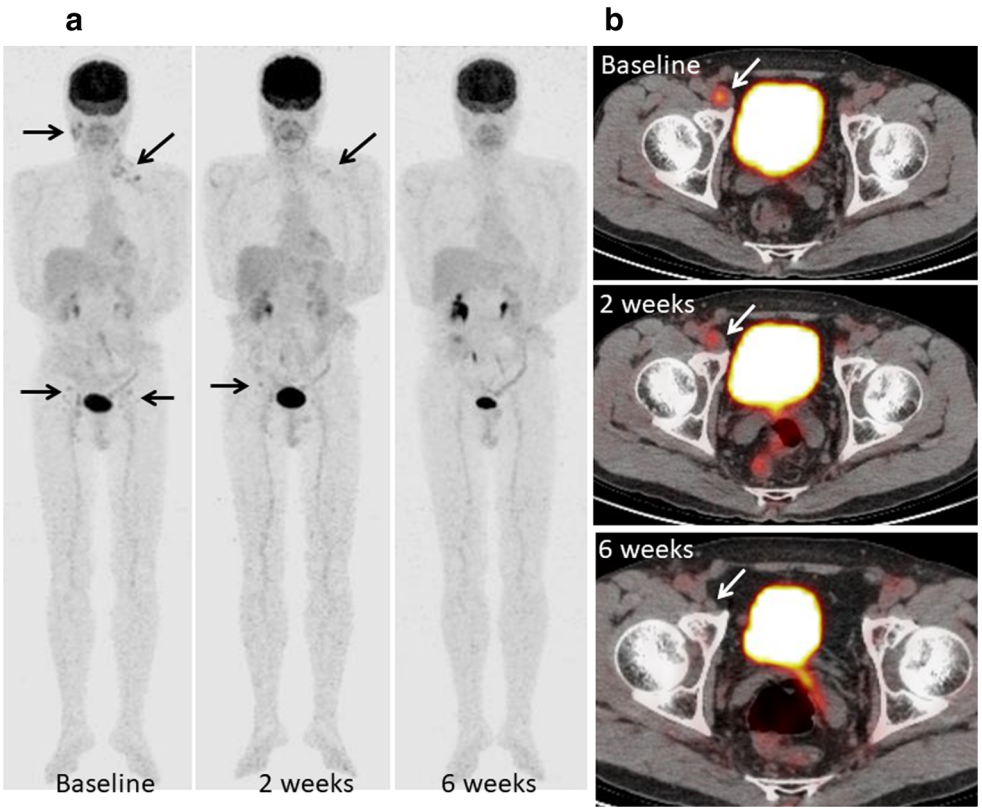

Fig. 2 Male, 60 years old, with follicular lymphoma received ^{90}Y-ibritumomab radioimmunotherapy. **a** MIP of baseline FDG-PET showing several areas of abnormal FDG uptake in right neck, left axilla, and bilateral inguinal regions (arrows). FDG-PET scanning performed at 2 weeks showed decreased FDG activity in same areas (arrows) with an objective response of PMR. and at 6 weeks showed complete resolution of abnormal metabolic activity in those areas, with an objective response of CMR. **b** Baseline PET/CT showing a swollen right inguinal lymph node with moderate FDG uptake (SUV_{max} 4.01) (arrow). Scanning at 2 weeks showed a transient decline in metabolic activity (SUV_{max} 2.56) in that node (arrow). Scanning at 6 weeks after therapy revealed that the lesion was decreased and no abnormal FDG uptake

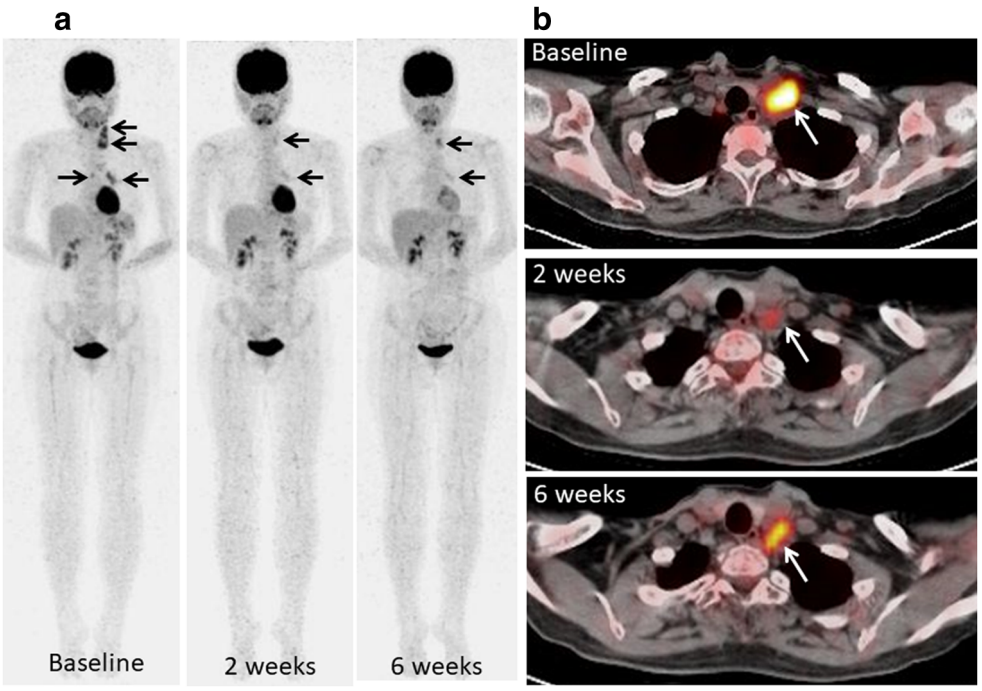

Fig. 3 Female, 50 years old, with follicular lymphoma received ^{90}Y-ibritumomab radioimmunotherapy. **a** MIP of baseline FDG-PET showing several areas of abnormal FDG uptake in the left neck, left inferior clavicular, and mediastinal/hilar regions (arrows). FDG-PET scanning performed at 2 weeks showed decreased FDG activity in those areas (arrows), with an objective response of PMR and at 6 weeks showed slightly increased FDG activity in those areas, though the level of FDG uptake was lower in comparison with baseline findings, with an objective response of PMR. **b** Baseline PET/CT showing a swollen left inferior clavicular lymph node with high FDG uptake (SUV_{max} 7.71) (arrow). Scanning at 2 weeks showed a transient decline in metabolic activity (SUV_{max} 2.73) in that node (arrow) and at 6 weeks revealed that the metabolic activity of the lesion had progressed (SUV_{max} 4.87) (arrow).

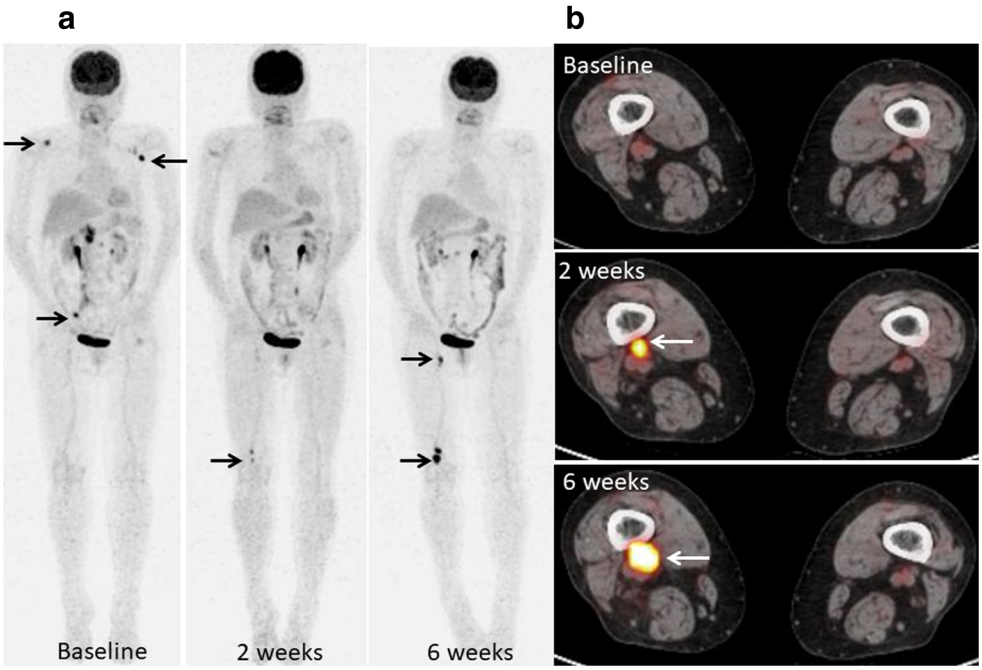

Fig. 4 Female, 78 years old, with a follicular lymphoma received ^{90}Y-ibritumomab radioimmunotherapy. **a** MIP of baseline FDG-PET showing several areas of abnormal FDG uptake in bilateral axilla and right pelvic regions (arrows). FDG-PET scanning performed at 2 weeks showed complete resolution of abnormal metabolic activity in those nodes, but new abnormal FDG uptake in the right popliteal fossa (arrow), with an objective response of PMD. Scanning at 6 weeks showed increased FDG activity in the right popliteal fossa region and a new lesion in the right inguinal region (arrow), with an objective response of PMD. **b** Baseline PET/CT showing no abnormal uptake in right popliteal fossa region. Scanning at 2 weeks revealed new abnormal FDG uptake (SUV_{max} 6.17) in the right popliteal fossa node (arrow), while 6 weeks progression of metabolic activity of the lesion was shown (SUV_{max} 22.64) (arrow).

scanning at 3 different time points: baseline (PET1) and then 2 (PET2) and 6 (PET3) weeks after undergoing ^{90}Y-ibritumomab radioimmunotherapy. The results demonstrated the usefulness of early PET; however, the optimal timing was rather 6 weeks than 2 weeks.

There were three important findings in this study. First, in PET2 results, CMR, PMR, SMD, and PMD were seen in 33 (60%), 13 (23.6%), 6 (10.9%), and 3 (5.5%) of the patients, respectively, while in PET3 imaging those were seen in 41 (74.5%), 8 (14.5%), 3 (5.5%), and 3 (5.5%), respectively. Second, we noticed a change in objective response in every patient, as 14.5% who initially showed non-CMR resolved to CMR in PET3 imaging. On the other hand, 12.7% of those who demonstrated initial improvement in PET2 findings showed no progression or no change in PET3. Third, we consider that both PET2 and PET3 findings were useful for prediction of recurrence or progression in these cases, though PET3 was slightly superior.

As for the optimal timing for FDG-PET/CT scanning for treatment monitoring following radioimmunotherapy in patients with malignant lymphoma, there is no consensus. Several studies have noted that FDG-PET/CT performed approximately 3 months after radioimmunotherapy may be appropriate for evaluating treatment response and predicting prognosis [5, 12–16]. In examinations of earlier evaluation timing, a few studies found that FDG-PET scanning performed earlier than or equal to 6 weeks after radioimmunotherapy provided important prognostic information and were useful for response prediction [6–8]. Similar to the present findings, Bodet-Milin et al [6] reported that positive FDG-PET findings obtained at 6 weeks after ^{90}Y-epratuzumab radioimmunotherapy had an association with shorter time to progression as compared to negative FDG-PET findings (5.4 vs. 15.6 months). They concluded that metabolic response could be determined as early as 6 weeks after radioimmunotherapy in more than 90% of their cases, while radiation-induced inflammation effects on FDG-PET results are probably not an important consideration because of the low level of irradiation used with that therapy. In another study, Torizuka et al [9] examined FDG-PET scans performed at 1 and again 4–8 weeks after radioimmunotherapy. They found a more gradual decline in FDG uptake, indicating metabolic response as a result of chemotherapy, as compared to previously reported, which may be related to the mechanism of cell death induced by radioimmunotherapy. In addition, they concluded that FDG-PET imaging performed at 1 week after radioimmunotherapy was too early and failed to reliably assess long-term effects, which was confirmed by the PET2 findings in our study (imaging performed 2 weeks after radioimmunotherapy).

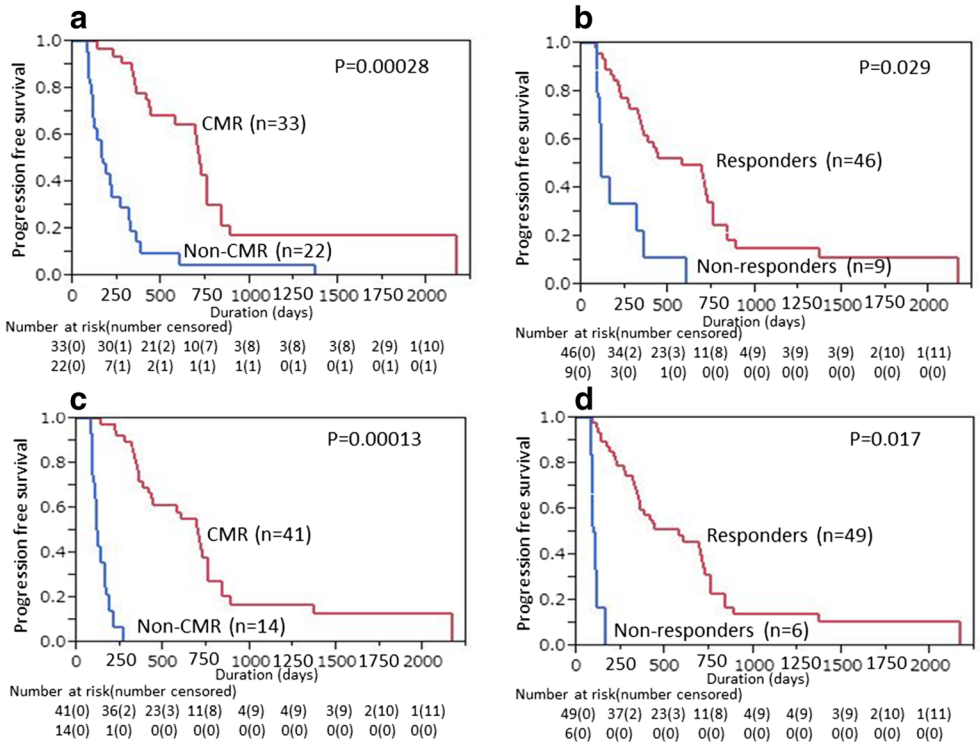

Fig. 5 All patients ($n = 55$). **a** Kaplan-Meier curves showing progression-free survival (PFS) based on PET1 and 2. As compared to 22 non-CMR patients (PMR, SMD, PMD), 33 patients who achieved CMR had significantly longer PFS ($p = 0.00028$). **b** Kaplan-Meier curves showing progression-free survival (PFS) based on PET1 and 2. As compared to 9 metabolic non-response patients (SMD + PMD), 46 patients who achieved metabolic response (CMR + PMR) had significantly longer PFS ($p = 0.029$). **c** Kaplan-Meier curves showing progression-free survival (PFS) based on PET1 and 3. As compared to 14 non-CMR patients, 41 patients who achieved CMR had significantly longer PFS ($p = 0.00013$). **d** Kaplan-Meier curves showing progression-free survival (PFS) based on PET1 and 3. As compared to 6 metabolic non-response patients (NMR + PMD), 49 patients who achieved metabolic response (CMR + PMR) had significantly longer PFS ($p = 0.017$).

Several groups have evaluated the usefulness of FDG-PET for early assessment if treatment response in a pre-clinical mouse model of human cancers [17–19]. De Saint-Hubert et al [17] evaluated FDG-PET imaging of treatment response to cyclophosphamide or temsirolimus in human Burkitt B cell lymphoma xenograft tumors in mice. They demonstrated that FDG-PET uptake decreased immediately after cyclophosphamide compared to baseline −38% on day 2 and −52% on day 4 and SUV_{mean} decreased immediately following temsirolimus compared to baseline −38% on day 2 and −46% on day 4. Brepoels et al [18] evaluated FDG-PET imaging of treatment response to cyclophosphamide in human B cell lymphoma xenograft tumors in mice and reported that a significant decrease of SUV_{mean} was observed on day 2 (reduction rate of $-31 \pm 4\%$). Moreover, Song et al [19] evaluated FDG-PET imaging for monitoring cyclophosphamide effect in human malignant lymphoma xenograft tumors in mice and demonstrated that FDG uptake at 1 day after treatment significantly decreased with a reduction rate of $-67.4 \pm 17.5\%$.

The present study has limitations. First, this study was retrospective in design and still had a relatively small sample size, which limits generalization and possibly introduced statistical errors. Second, assessment of overall survival was not possible because the follow-up period was insufficient. Third, 90 s per bed position from the head to the mid-thigh level for PET acquisition was short. Two to 3 min per bed position is considered ideal. Forth, a single reader could theoretically introduce a systematic bias into image interpretation. Independent reading by multiple readers is considered ideal. Fifth, follow-up was only partially available for few patients from another institution.

In conclusion, early response to ^{90}Y-ibritumomab radioimmunotherapy can be optimally assessed after 6 weeks using FDG-PET/CT findings in patients with relapsed or refractory B cell non-Hodgkin lymphoma. The Lugano criteria used for the evaluation were consistent with progression-free survival and therefore helpful for prognostic stratification. In contrast, such assessment performed at 2 weeks after radioimmunotherapy is probably too early and inadequate for accurate treatment response evaluation.

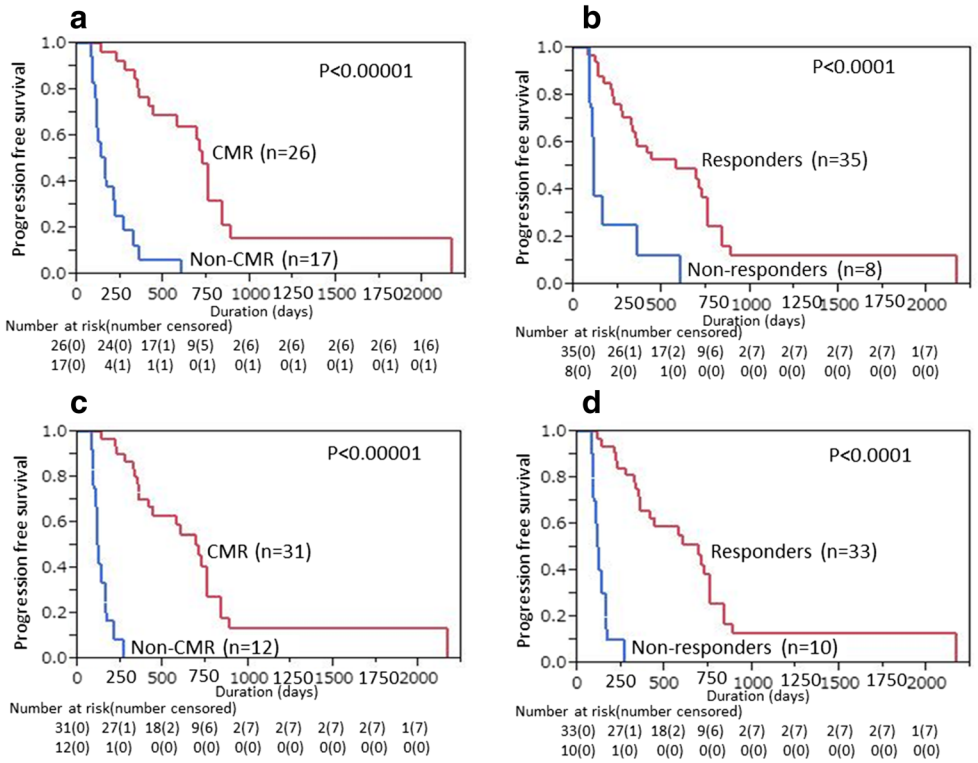

Fig. 6 Patients with follicular lymphoma ($n = 43$). **a** Kaplan-Meier curves showing progression-free survival (PFS) based on PET1 and 2. As compared to 17 non-CMR patients (PMR, SMD, PMD), 26 patients who achieved CMR had significantly longer PFS ($p < 0.00001$). **b** Kaplan-Meier curves showing progression-free survival (PFS) based on PET1 and 2. As compared to 12 metabolic non-response patients (SMD + PMD), 31 patients who achieved metabolic response (CMR + PMR) had significantly longer PFS ($p < 0.0001$). **c** Kaplan-Meier curves showing progression-free survival (PFS) based on PET1 and 3. As compared to 8 non-CMR patients, 35 patients who achieved CMR had significantly longer PFS ($p < 0.00001$). **d** Kaplan-Meier curves showing progression-free survival (PFS) based on PET1 and 3. As compared to 10 metabolic non-response patients (SMD + PMD), 33 patients who achieved metabolic response (CMR + PMR) had significantly longer PFS ($p < 0.0001$).

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Koichiro Yamakado.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Informed consent was obtained from each patient after the procedure details were fully explained.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- diagnostic or prognostic study
- performed at one institution

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