

# Radiological Evaluation of Response and Resistance of Ibritumomab



Takayoshi Ishimori and Koya Nakatani

**Abstract** Radiolabeled anti-CD20 monoclonal antibody,  $^{90}\text{Y}$ -ibritumomab tiuxetan became available for the treatment of refractory or relapsed low-grade B-cell non-Hodgkin's lymphoma (NHL). Although FDG-PET is widely used for monitoring the response to chemotherapy and radiotherapy, there are limited data for monitoring the response of NHL to radioimmunotherapy (RIT) with FDG-PET.

**Experience in our institute** We retrospectively evaluated our experience using FDG-PET/CT for monitoring the response of NHL to RIT. **Methods** A total of 34 patients received  $^{90}\text{Y}$ -ibritumomab tiuxetan and underwent FDG-PET/CT scans before and at 3 months after RIT. Subsequent scans were performed at 7–12 months and at 12–24 months after RIT. PET/CT scans after additional treatment with clinical evidence of relapse after RIT was excluded from analysis; all patients did not receive additional treatment during the evaluating period. Tumor metabolic activity was assessed before and after RIT visually on PET/CT images and compared with the treatment effect and clinical course. **Results** According to the revised IWC criteria, the maximal response was CR in 22 patients, PR in 5 patients, and PD in 1 patient (1 patient not evaluable). FDG-PET was positive in 10 patients before RIT, 5 patients at 3 months, 5 patients at 7–12 months, and 1 patient at 13 months after RIT. Among 18 patients with negative PET results at 3 months after RIT, only one patient relapsed later. In 2 patients, although PET was positive at 3 months after RIT, abnormal accumulation diminished at 7–9 months after RIT without further treatment.

**Conclusions** FDG-PET/CT is a useful noninvasive imaging modality for monitoring the response of NHL to RIT. Negative PET finding at 3 months after RIT predicts the treatment effects with high probability. However, positive PET results at 3 months after RIT does not warrant immediate additional therapy because the metabolic response to RIT can be gradual, with continued declines of FDG uptake occurring between 7 and 9 months after RIT without additional therapy.

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**Keywords** B-cell non-Hodgkin's lymphoma · Follicular lymphoma · Mantle cell lymphoma ·  $^{90}\text{Y}$ -ibritumomab tiuxetan ·  $^{111}\text{In}$ -ibritumomab tiuxetan · Revised IWC criteria · FDG · PET · Metabolic response · Expected biodistribution · Altered biodistribution

## Abbreviations

$^{111}\text{In}$	Indium-111
FDG	18F-fluorodeoxyglucose
MALT	Mucosa-associated lymphoid tissue
PET	Positron emission tomography
RIT	Radioimmunotherapy

## 1 Introduction

Many therapeutic regimens for B-cell lymphomas include the chimeric anti-CD20 monoclonal antibody rituximab, in combination with chemotherapy or alone. Radiolabeled anti-CD20 monoclonal antibody,  $^{90}\text{Y}$ -ibritumomab tiuxetan, as well as  $^{131}\text{I}$ -tositumomab, became available for the treatment of refractory or relapsed low-grade B-cell non-Hodgkin's lymphoma (NHL) as shown in the previous chapters.

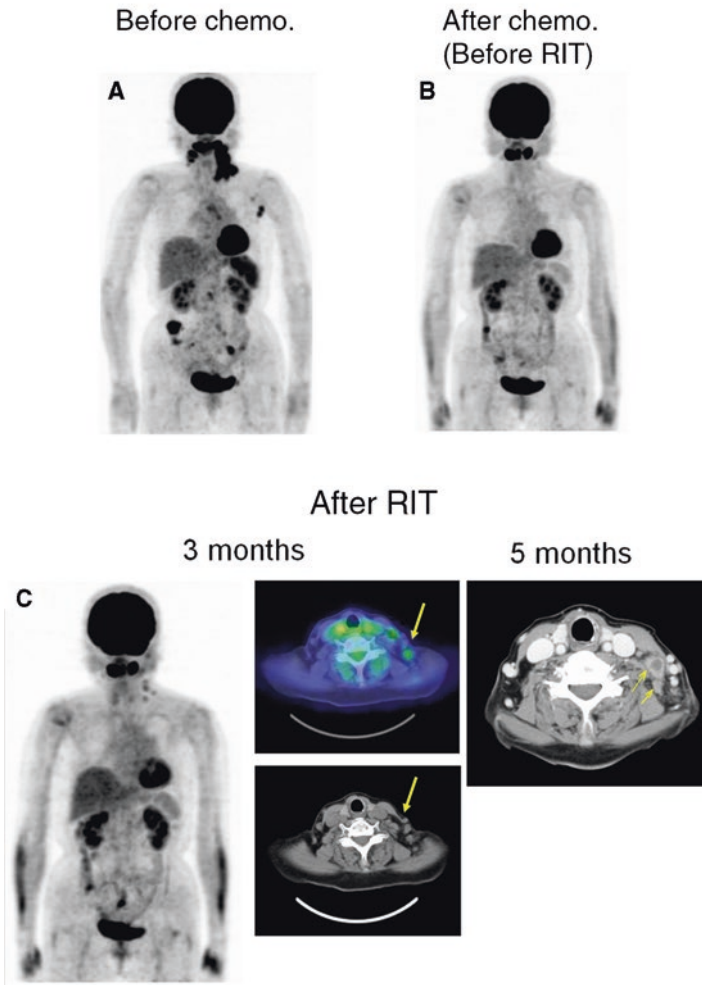
FDG-PET is known as a noninvasive imaging modality for disease staging, restaging, and monitoring response of lymphoma to chemotherapy and radiotherapy. Multiple studies have shown that FDG-PET is superior to anatomic imaging for detecting active disease after therapy [1–3].

Although FDG-PET is widely used for monitoring the response to chemotherapy and radiotherapy, there are limited data for monitoring the response of NHL to radioimmunotherapy (RIT) with FDG-PET.

## 2 Evaluation of FDG-PET/CT for Monitoring the Response to RIT

Here we present our experience (in Kurashiki Central Hospital, Kurashiki, Japan) of the evaluation of FDG-PET/CT for monitoring the response of NHL to RIT retrospectively.

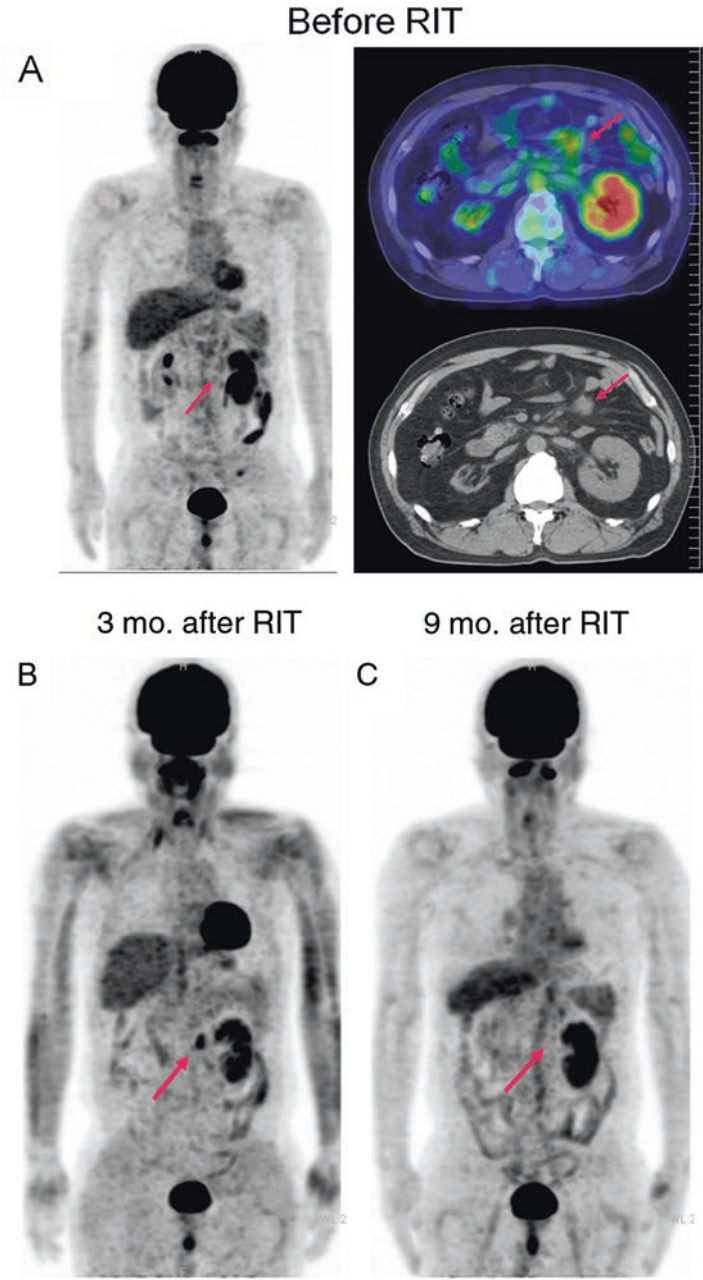
A total of 34 clinical patients with relapsed or refractory low-grade B-cell lymphoma who underwent RIT using Y-90-labeled antibody were enrolled in our study (Figs. 1 and 2).



**Fig. 1** (Relapsed case). A 72-year-old female patient with history of follicular lymphoma (grade 3a). She underwent chemotherapy of eight courses of R-THP-COP prior to RIT. FDG-PET images before chemotherapy (a) showed multiple FDG-avid nodules in the neck, axilla, spleen, and abdomen before chemotherapy. After chemotherapy (b), most of FDG-avid lesions disappeared, while some uptake was still seen in the neck and in the abdomen. At 3 months after RIT (c), increased FDG uptake was seen in the neck. At 5 months after RIT, the lymph nodes enlarged and biopsy showed relapse of lymphoma. Afterward she received additional chemotherapy

The patient characteristics are shown in Table 1. Twenty-four patients had follicular lymphoma, while four patients had MALT lymphoma and mantle cell lymphoma. One patient had marginal zone B-cell lymphoma and low-grade B-cell lymphoma not otherwise specified.

All patients received three regimens of chemotherapy before RIT on average (range 1–6).



**Fig. 2** (Late responder). A 63-year-old male patient with follicular lymphoma (grade 3). He underwent chemotherapy of R-CHOPx5, DeVICx5, and THP-COPx1 prior to RIT. FDG-PET images before RIT (**a**) (**d**) showed weak FDG accumulation in the mesenteric lymph nodes suggestive of residual lymphoma. At 3 months after RIT (**b**) (**e**), FDG uptake in the abdominal lesion increased. However, the uptake disappeared without additional treatment at 9 months after RIT (**c**) (**f**). The patient achieved CR and did not relapse during the follow-up period, suggestive of transient increase of FDG uptake at 3 months after RIT

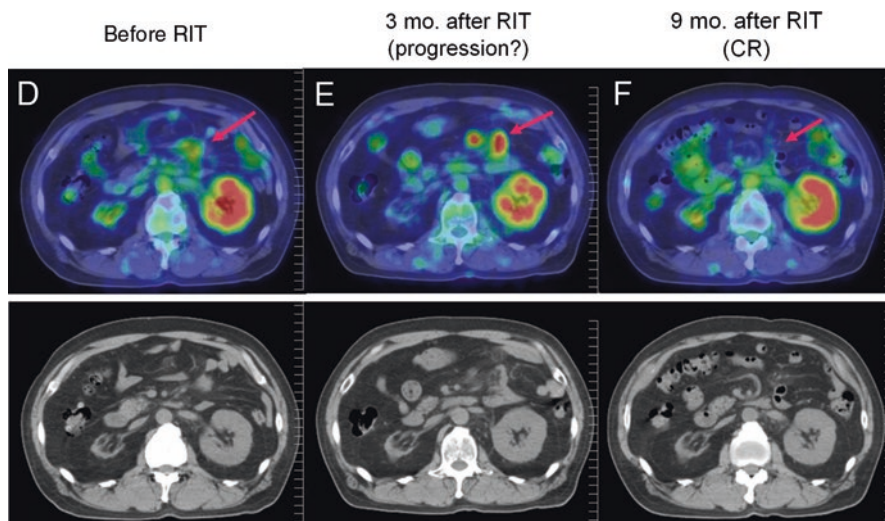


Fig. 2 (continued)

The dose of yttrium-90-labeled antibody for RIT was defined based on the platelet count as follows:

Plt $\geq$ 150,000/ $\mu$ l:	14.8(MBq/kg)	22 patients
Plt 100,000–150,000/ $\mu$ l:	11.1(MBq/kg)	12 patients

Whole-body imaging using indium-labeled antibody was routinely performed 1 week before therapy in all patients to exclude patients with improper distribution of antibody from RIT. However, no patient was excluded from RIT based on the imaging findings.

Yttrium-90-labeled antibody was injected shortly (approx. 1 h) after rituximab pretreatment.

## 2.1 FDG-PET/CT Imaging

A dedicated PET/CT scanner (Aquiduo, Toshiba Medical Systems, Otawara, Japan) was used. After fasting for at least 5 h, each patient received an IV injection of FDG (FDGscan inj., Nihon-Medipysics, Tokyo, Japan). A whole-body PET emission scan was performed 60 min after administration of FDG with our routine protocol. CT images were acquired immediately before the PET scan without the use of contrast media.

**Table 1** Patient characteristics

Total	34 patients
Male	19
Female	15
Age	64.1 ± 10.2 years old (range 43–80 years old)
Histology	
FL <sup>a</sup>	24
MALT <sup>a</sup>	4
Mantle cell	4
MZBCL <sup>a</sup>	1
Others <sup>b</sup>	1
Chemotherapy regimens prior to RIT, 1–6 (mean 3.0)	
Dose of <sup>90</sup> Y-ibritumomab tiuxetan	
14.8(MBq/kg) (Plt ≥ 150,000/μl)	22 pts
11.1(MBq/kg) (Plt 100,000–150,000/μl)	12 pts

<sup>a</sup>*FL* follicular lymphoma, *MALT* mucosa-associated lymphoid tissue lymphoma, *MZBCL* marginal zone B-cell lymphoma

<sup>b</sup>Low-grade B-cell lymphoma not otherwise specified

Tumor metabolic activity was assessed before and after RIT visually on PET/CT images as positive, negative, or inconclusive. PET/CT findings were compared with the treatment effect and clinical course. The maximal treatment response was assessed based on the revised IWC criteria and classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [4].

PET/CT scans after additional treatment with clinical evidence of relapse after RIT were excluded from analysis; all patients did not receive additional treatment during the evaluating period.

### 3 Summary of the Results

The maximal response in all 34 patients during the follow-up period of 91–796 days (median, 420 days) was shown in Table 2. No assessment was available in 1 patient. Four patients relapsed in the study group during the follow-up period.

The overall PET findings before and after RIT are summarized in Table 3. Before RIT, 11 patients were PET positive, while 17 patients were PET negative. After RIT, the number of PET-positive patients decreased by time.

The results of patient subgroups based on PET findings are shown in Tables 4, 5, 6, and 7.

**Table 2** Maximal response

CR	25
PR	7
PD	1
N/A	1
Total	34
Relapsed	4

Follow-up period: 91–796 days (median, 420 days)

**Table 3** Summary of FDG-PET findings before and after RIT

FDG-PET	Before RIT	After RIT		
		3 months	6–12 months	12–24 months
Positive	11	6	5	2
Inconclusive	3	5	3	1
Negative	17	20	8	8
Total	31	31	16	11

**Table 4** PET-positive patients before RIT

FDG-PET	Before RIT			
		3 months	6–12 months	12–24 months
Positive	<b>11</b>	5	3	2
Inconclusive		3	1	1
Negative		3	1	1
N/A			6	7

CR, 5 pts; PR, 5 pts; PD, 1 pt  
Relapsed, 3 pts

Table 4 shows PET-positive results in 11 patients before RIT. After RIT, FDG-PET became negative in three patients, while the other patients became inconclusive or remained PET positive. Although the response rate was high, three patients relapsed during the follow-up period.

Table 5 shows PET-negative results in 17 patients before RIT. Although almost all patients had PET-positive disease initially, these patients became PET-negative after chemotherapy before RIT. After RIT, FDG-PET remained negative in the majority of patients. Sixteen patients achieved CR and no patient relapsed.

Table 6 shows the results of the 6 patients with PET-positive findings at 3 months after RIT. FDG-PET became negative in some patients at subsequent PET scans after 6 months, while some other patients remained PET positive, including 3 relapsed patients.

Table 7 shows PET-negative results in 20 patients at 3 months after RIT. All patients achieved CR and no patient relapsed in this subgroup. In the follow-up PET scans, FDG-PET remained negative in the majority of patients.

**Table 5** PET-negative patients before RIT

FDG-PET	Before RIT	After RIT		
		3 months	6–12 months	12–24 months
Positive		0	0	0
Inconclusive		0	2	0
Negative	<b>17</b>	15	5	5
N/A		2	10	12

CR, 16 pts; N/A, 1 pt

Relapsed, 0 pt

**Table 6** PET-positive patients at 3 months after RIT

FDG-PET	Before RIT	After RIT		
		3 months	6–12 months	12–24 months
Positive	5	<b>6</b>	3	1
Inconclusive				
Negative			2	1
N/A	1		1	4

CR, 2 pts; PR, 3 pts; PD, 1 pt

Relapsed, 3 pts

**Table 7** PET-negative patients 3 months after RIT

FDG-PET	Before RIT	After RIT		
		3 months	6–12 months	12–24 months
Positive	3		0	0
Inconclusive	2		2	0
Negative	15	<b>20</b>	5	7
N/A	0		13	13

CR, 20 pts

Relapsed, 0 pt

## 4 Discussion

FDG-PET/CT is a useful noninvasive imaging technique for monitoring the response of lymphoma to therapy. The response of a tumor to treatment was conventionally evaluated by measuring the tumor size using morphological imaging modalities such as CT and MRI. The determination of treatment response in patients with non-Hodgkin's lymphoma is complicated, and criteria proposed by a National Cancer Institute–sponsored international workshop have been used as a standard system of classification [5]. This system defines categories of complete response, complete response–unconfirmed, partial response, stable disease, and progressive disease. Complete response requires disappearance of all disease at physical examination, normalization of lactate dehydrogenase levels, and CT findings that show that all lymph nodes and nodal masses have regressed to normal size. Partial response requires a greater than 50% decrease in mass size.



However, distinguishing viable residual tumors from fibrotic scars after irradiation is difficult. It is known that FDG-PET can distinguish viable lymphoma from fibrotic change after treatment because most non-Hodgkin's lymphomas are FDG-avid [6–10], and FDG-PET is superior to CT for the assessment of recurrent lymphoma after chemotherapy [11]. Recently, revised criteria for the assessment of lymphoma treatment response were published [4, 12]. We used these criteria for assessment of treatment response of RIT in the present study.

After radioimmunotherapy, Jacene et al. reported FDG uptake in tumors typically dropped significantly and a continued decline in tumor SUVlean max between 12 and 24 weeks without additional therapy can occur, suggesting a need for delayed-response assessment. The information provided by combined 18F-FDG-PET/CT is informative for monitoring the response of lymphoma to radioimmunotherapy [13].

Ulaner et al. reported on 10 patients with refractory or relapsed NHL who underwent 18F-FDG-PET/CT for restaging 4–6 months after <sup>90</sup>Y-ibritumomab tiuxetan, and the results were similar [10]. The use of combined FDG-PET/CT may enable superior assessment of response to <sup>90</sup>Y-ibritumomab tiuxetan treatment than the use of CT alone, at which one may underestimate <sup>90</sup>Y-ibritumomab tiuxetan response by considering inactive residual CT masses to be residual disease.

In another previous report, early assessment of response to RIT by using PET/CT (at 2 months after RIT) might be useful in the identification of patients needing additional therapeutic strategies [14].

Hanaoka et al. reported that a significant difference in pretherapeutic FDG SUVmax was observed between responders and nonresponders and pretherapeutic FDG accumulation was predictive of the tumor response in <sup>90</sup>Y-ibritumomab tiuxetan therapy. The results were consistent with our experience [15].

Quantitative analyses with SUV are not considered necessary to determine PET positivity. We applied IWC-PET criteria in our study to assess response to therapy, although prospective validation of quantitative criteria for determining response may prove helpful in the future, particularly in the setting of residual masses on CT.

The optimal timing to obtain a PET scan after radioimmunotherapy has not been defined. The initial studies evaluating 18F-FDG-PET for monitoring the response of lymphoma were primarily obtained after cytotoxic chemotherapy or radiotherapy. The optimal time to obtain a posttherapy PET is not completely resolved, but a minimum of 10 days after chemotherapy has been recommended, to avoid false-negative and false-positive scan findings due to early treatment effects of stunning and inflammation. Longer and more variable times after external-beam radiation have been suggested. According to our results and literatures, a longer delay to initial response assessment might allow more accurate assessment of a slow responder. Although long delay might not be acceptable in nonresponding patients, the potential benefit from earlier detection of disease and further treatment might not always be critical because the progression of most indolent lymphoma for RIT indication is gradual.

The mechanism of transient increase of FDG accumulation after RIT in our study is not clarified. FDG is not a cancer-specific agent and is known to accumulate in cases of acute inflammation, in granulomatous diseases, and in autoimmune

diseases. Under such conditions, the suggestion is that 18F-FDG is taken up by infiltrating cells such as macrophages, lymphocytes, and granulocytes [16]. In a report of lung cancer patients, FDG is accumulated in the inflammatory tissue of radiation induced pneumonitis and a temporal increase in FDG uptake at 1–2 weeks after stereotactic radiotherapy appeared to reflect the acute reaction of the tumor [17]. The exact mechanism of death of lymphoma cells after RIT is unknown, but it is possible that a combination of a mitotic lymphoma cell death and delayed immunologic effects may contribute to the observed temporal changes of FDG accumulation.

Prior to  $^{90}\text{Y}$ -ibritumomab tiuxetan therapy, imaging with  $^{111}\text{In}$ -ibritumomab tiuxetan may be performed to verify the expected biodistribution and exclude patients who show an altered biodistribution, such as the rapid clearance of  $^{111}\text{In}$ -ibritumomab tiuxetan from the blood pool, with prominent liver, spleen, or marrow uptakes [15]. However, a high rate of a complete response after  $^{90}\text{Y}$ -ibritumomab tiuxetan therapy has often been observed in patients with negative  $^{111}\text{In}$ -ibritumomab tiuxetan accumulation in lesions, and accumulation of  $^{111}\text{In}$ -ibritumomab tiuxetan does not predict treatment effect.

## 5 Conclusions

In conclusion, FDG-PET/CT is a useful noninvasive imaging modality for monitoring the response of NHL to RIT. In our experience, negative PET findings before and at 3 months after RIT predict the treatment effects with high probability. However, positive PET results at 3 months after RIT do not warrant immediate additional therapy because metabolic response to RIT can be gradual, with continued declines of FDG uptake occurring between 7 and 9 months after RIT without additional therapy. The optimal condition of imaging, especially the time interval between the therapy and the FDG-PET/CT scan, is to be established by further prospective studies with a large number of patients.

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