original article

FDG–PET in the assessment of patients with follicular lymphoma treated by ibritumomab tiuxetan Y 90: multicentric study

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Background: The aim of this study is the 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET) evaluation following radioimmunotherapy (RIT) with ibritumomab tiuxetan Y 90 in patients with non-Hodgkin's follicular lymphoma (FL).

Materials and methods: We retrospectively analyzed data from 59 relapsed or refractory FL patients treated with ibritumomab tiuxetan Y 90 in four different PET centers who had a PET scan carried out before and after RIT. Possible predictive factors of progression-free survival (PFS) were studied through univariate and multivariate analysis.

Results: The post-RIT PET documented 45.8% complete responders (CR), 25.4% partial responders (PR) and 28.8% nonresponders [stable disease + progressive disease], with an overall survival of 71.2% (range 59.5%–90.9%). With a median follow-up period of 23 months, the univariate analysis documented a statistically significant relation between disease extent before RIT and response to treatment with respect to PFS ($P = 0.015$), while all the other prognostic factors showed no significant correlation. When carrying out the multivariate analysis, post-RIT PET resulted as the lonely independent predictor of PFS ($P < 0.00001$).

Conclusions: RIT is an effective therapy in FL patients, as confirmed in our study too. Disease extension before treatment and response to RIT, as assessed by FDG–PET, result as main predictors of PFS, with the post-RIT PET result being the only independent predictive factor.

Key words: follicular lymphoma, non-Hodgkin's lymphoma, PET, radioimmunotherapy, ibritumomab tiuxetan Y 90

introduction

In a relatively recent period of time, significant information has been added by functional imaging with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET) for the assessment of malignant lymphoma [1, 2]. Interesting rates of sensitivity and specificity are also reported for non-Hodgkin's follicular lymphoma (FL), regardless of the grading [3–5], with consequent extension of clinical implication to the new therapeutic regimens, such as radioimmunotherapy (RIT). However, not much is reported on FDG–PET and ibritumomab tiuxetan Y 90 (Zevalin®), which is the first RIT agent introduced for clinical purpose [6]. Prevailing papers mostly concern case reports rather than limited series [7–10] or are focused on RIT carried out not exclusively with Zevalin® (Biogen IDEC Corp., Cambridge, MA), but also

with Bexxar® (Corixa Corp., Seattle, WA)[11], although the two radioimmunopharmaceuticals are not documented to show any statistical difference in therapeutic efficacy [12].

The aim of this paper concerns therefore FDG–PET in FL patients treated with Zevalin® and focuses on the correlation between PET evaluation and RIT efficacy, as measured by response to progression-free survival (PFS).

materials and methods

Our study involved four different PET Centers: S. Orsola-Malpighi Hospital, Bologna (Italy); Spedali Civili, Brescia (Italy); San Giovanni Battista Hospital, Torino (Italy); University Hospital Claude Huriez, Lille (France).

study population

A total of 59 patients (31 Bologna, 12 Brescia, 9 Torino and 7 Lille), undergoing RIT with ibritumomab tiuxetan Y 90 (Zevalin®), were considered for the analysis. All of them, 36 females and 23 males (mean age 60.5; range 27–80 years), had a histologically proven relapsed or refractory

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FL and were referred for a PET scan before and after treatment with Zevalin®. Inclusion criteria fulfilled the European Medicines Agency indications for FL patients relapsed or refractory to other therapeutic regimens, including immunotherapy with rituximab [13]. All patients at baseline were restaged according to the Ann Arbor classification [14] and subsequently divided in two groups on the basis of disease extent at relapse: stage I–II (group A) and stage III–IV (group B). They were all followed up for a median of 23 months (range 3–55) for proper assessment of progression of disease or relapse, through clinical, laboratoristic and instrumental examination every 6 months, including FDG–PET in case of suspected relapse or in patients with a positive scan after RIT.

FDG–PET scan and RIT administration

The PET study was carried out using standard procedure and all scans were acquired with PET/computed tomography (CT) instruments. Each examination was interpreted by at least two nuclear physicians with experience on PET studies and final report was set after complete agreement. Findings were classified as positive or negative on the basis of visual analysis, with liver metabolism considered as referring uptake for scan interpretation: negative, when no pathological tracer uptake was shown by FDG–PET or in case of increased uptake in keeping with physiological distribution such as kidneys, ureters or bladder, thymus, brown fat, muscles, bone marrow, etc, rather than benign processes such as inflammation; positive, when they were located at sites of previous disease (residual disease or relapse) or when they were described within asymmetrical lymph nodes or within lymph nodes unlikely to be affected by inflammation. Every suspicious increased uptake was evaluated keeping into account other data (previous scans, clinical follow-up or other instrumental reports).

Semiquantitative evaluation was also carried out at baseline PET with the estimation of standardized uptake value maximal (SUVmax) body weight (SUVbw max).

The radiopharmaceutical was prepared and administered according to the European Association of Nuclear Medicine guidelines [13].

response assessment

Response to treatment was assessed at 3 months after RIT (range 9–18 weeks) with a second FDG–PET scan. Patients were categorized on the basis of the revised response criteria [revised International Workshop Criteria (IWC)] [15] and classified as follows: complete responders (CR; PET negative for any size at CT and/or CT regression to normal size for lesions with variable FDG-avid/PET negative before treatment and/or negative bone marrow biopsy), partial responders (PR; regression of measurable disease on PET and/or ≥50% decrease in the sum of the product of the diameters on CT and no new sites), stable disease [SD; failure to obtain CR/PR or progressive disease (PD)], and PD (appearance of new lesions PET positive or >1.5 cm of diameter at CT and/or increase by ≥50% of previously involved sites from nadir).

statistical analysis

The relation between individual prognostic factors (age, gender, time from diagnosis to RIT, number of previous treatments, disease extent before Zevalin®, SUVbw max at baseline, and response to treatment) and PFS, defined as the time from RIT to either progression or relapse, was evaluated by means of Pearson correlation.

Differences between the groups were evaluated using the chi-square (χ^2) test for the dichotomic variables and the Student's t-test for independent samples for the quantitative variables. Analysis of variance (ANOVA) and a Bonferroni *post hoc* test were used in order to compare the mean values of the different groups of response to treatment with respect to PFS.

Univariate analyses of PFS were carried out either by the Kaplan–Meier method, evaluating differences between groups by the log-rank test, or by

the Cox regression model [16, 17]. Multivariate analysis was carried out using the Cox regression model.

P value <0.05 was considered statistically significant. All analyses were carried out using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL).

results

Response to treatment, assessed at 3 months after RIT according to the revised IWC, documented 27 CR patients (45.8%), 15 PR patients (25.4%), and 17 SD or PD patients (28.8%). In all cases, PET results at the 3-month evaluation were consistent with the true outcome of the patients. Table 1 encloses the principal characteristics of our study population, with respect to the two groups evaluated and statistically compared between main factors.

Kaplan–Meier analysis

The Kaplan–Meier analysis was elaborated with respect to PFS, both on the basis of disease extent before RIT (Figure 1) as well as on the basis of response to treatment and post-RIT PET result (Figure 2).

The survival curves demonstrated a significant difference (log-rank *P* = 0.0053) in the trend of PFS between limited disease (group A) and advanced disease (group B).

Significant differences in trend were demonstrated with respect to PFS also on the basis of response to treatment. The response to RIT was evaluated both as responders (CR + PR) versus nonresponders (SD + PD) (Figure 2A), depicting a log-rank *P* < 0.0001, as well as CR versus PR versus SD + PD (Figure 2B). In the second analysis, main difference was demonstrated between CR and the other two categories, both PR and SD + PD (log-rank *P* = 0.0053). The trend results between PR and SD + PD show a nonsignificant value (log-rank *P* = 0.055). While a significant difference in trend (*P* < 0.0001) is maintained when distinguishing patients with respect to PET results at 3 months (Figure 2C): PET negative (*n* = 27) versus PET positive (*n* = 32).

Pearson correlation

The correlation analysis of age, gender, number of previous treatments, and SUVbw max at baseline, with respect to PFS, showed no significant difference between group A and B.

We documented a significant difference in progression/relapse time (t_{57} = 2.51; *P* = 0.015) between group A patients, who tend to progress/relapse significantly later (mean 15.3 months) than group B patients (mean 10.1 months).

The relation between disease extent and response to RIT, as analyzed by the χ^2 test, revealed a significant difference both when comparing responders (CR + PR) versus nonresponders (SD + PD) (χ^2 = 6.65, *df* = 1, *P* = 0.016), as well as when considering separately each type of response (CR versus PR versus SD + PD) (χ^2 = 6.65, *df* = 2 *P* = 0.004).

A one-way between-group ANOVA was carried out to explore the impact of RIT on time to progression. A group effect was found ($F_{2,56}$ = 18.57; *P* < 0.0001). The *post hoc* analysis carried out by means of Bonferroni method indicated that the mean score for group CR (M = 17.07 months; SD = 7.35) was significantly different from group PR

Table 1. Patients' characteristics

Characteristics	All patients	Group A (stage I–II)	Group B (stage III–IV)	P
Gender				
Male/female	23/36	12/10	11/26	n.s.[a]
Total	59	22	37	
Age, years				
Mean (min–max)	60.58 (27–80)	60.18 (27–73)	60.8 (40–80)	n.s.[b]
Time from diagnosis to RIT, months				
Mean (range)	56.42 (5–144)	49.7 (8–119)	60.4 (5–144)	n.s.[b]
No. of previous treatments				
Mean (range)	2.66 (1–6)	2.6 (1–5)	2.7 (1–6)	n.s.[b]
Response to RIT (%)				
CR	45.8	72.7	29.7	0.004[a]
PR	25.4	18.2	29.7	
SD + PD	28.8	9.1	40.5	
OR (CR + PR) (%)	71.2	90.9	59.5	0.016[a]
Nonresponders (SD + PD) (%)	28.8	9.1	40.5	
SUVbw max				
Mean (min–max)	10.00 (2.50–29.00)	7.79 (2.60–15.00)	11.31(2.50–29.00)	n.s.[b]
PFS, months				
Mean (range)	12.03 (3–32)	15.3 (3–32)	10.1 (3–30)	0.015[b]

RIT, radioimmunotherapy; CR, complete responders; PR, partial responders; SD, stable disease; PFS, progression-free survival; PD, progression disease.
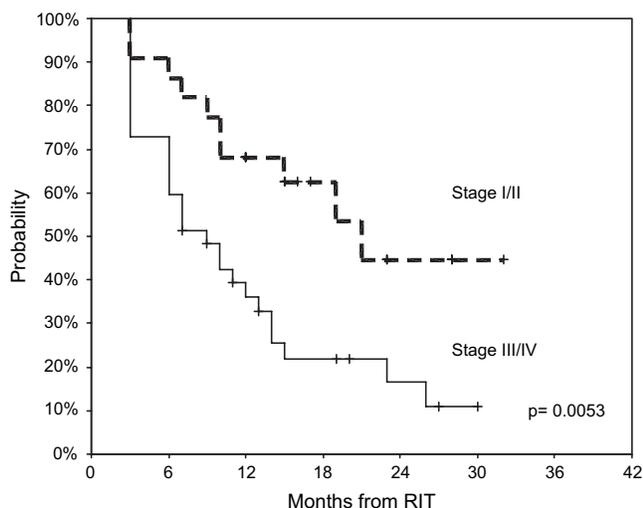[a]Chi-square analysis.
[b]Two-tailed unpaired *t*-test.

Figure 1. Kaplan–Meier survival curves depicting PFS with respect to disease extent before RIT—group A (stage I–II) in 'discontinuous line plot' versus group B (stage III–IV) in 'continuous line plot'. PFS, progression-free survival; RIT, radioimmunotherapy.

(M = 10.53 months; SD = 7.7) and nonresponder group (SD + PD) (M = 5.35 months; SD = 4.8). Groups PR and SD + PD did not differ from each other.

univariate analysis

The univariate analysis for PFS is shown in supplemental Table S1 (available at *Annals of Oncology* online). Considering disease extent, as assessed at the pre-RIT PET, with respect to PFS, group A showed a significantly longer PFS than group B, with a projected 3-year PFS of 40% versus 13%, respectively ($P = 0.01$).

According to the semiquantitative evaluation at baseline PET, we identified as cut-off a SUVbw max = 6. The patients with SUVmax < 6 ($n = 14$) at the pre-RIT PET had a significantly longer PFS when compared with the patients with SUVmax ≥ 6 ($n = 45$), with a projected 3-year PFS of 49% versus 13%, respectively ($P = 0.038$) (Figure 3).

There were no differences ($P = 0.3$) in PFS between heavily pretreated patients (i.e. number of previous lines of therapy more than two) ($n = 26$) and patients who had had two or less previous treatments ($n = 33$).

Finally, CR (post-RIT PET negative) ($n = 27$) had a significantly higher PFS, compared with PET-positive (PR, SD or PD) patients ($n = 32$), with a projected 3-year PFS of 40% versus 10%, respectively ($P < 0.00001$).

multivariate analysis

The multivariate analysis is shown in supplemental Tables S2 and S3 (available at *Annals of Oncology* online). The aim was to address the factors found to be significantly related to PFS in the univariate analysis. The multivariate setting disclosed significant independent association only with post-RIT PET ($P < 0.001$). Pre-RIT disease extent and SUVmax lost significance in the multivariate framework (supplemental Table S2, available at *Annals of Oncology* online).

discussion

Since its initial use in the 1990s [18] and, subsequently in further reported series [12, 19, 20], ibritumomab tiuxetan Y 90 has shown good results in lymphoma treatment. In average, the
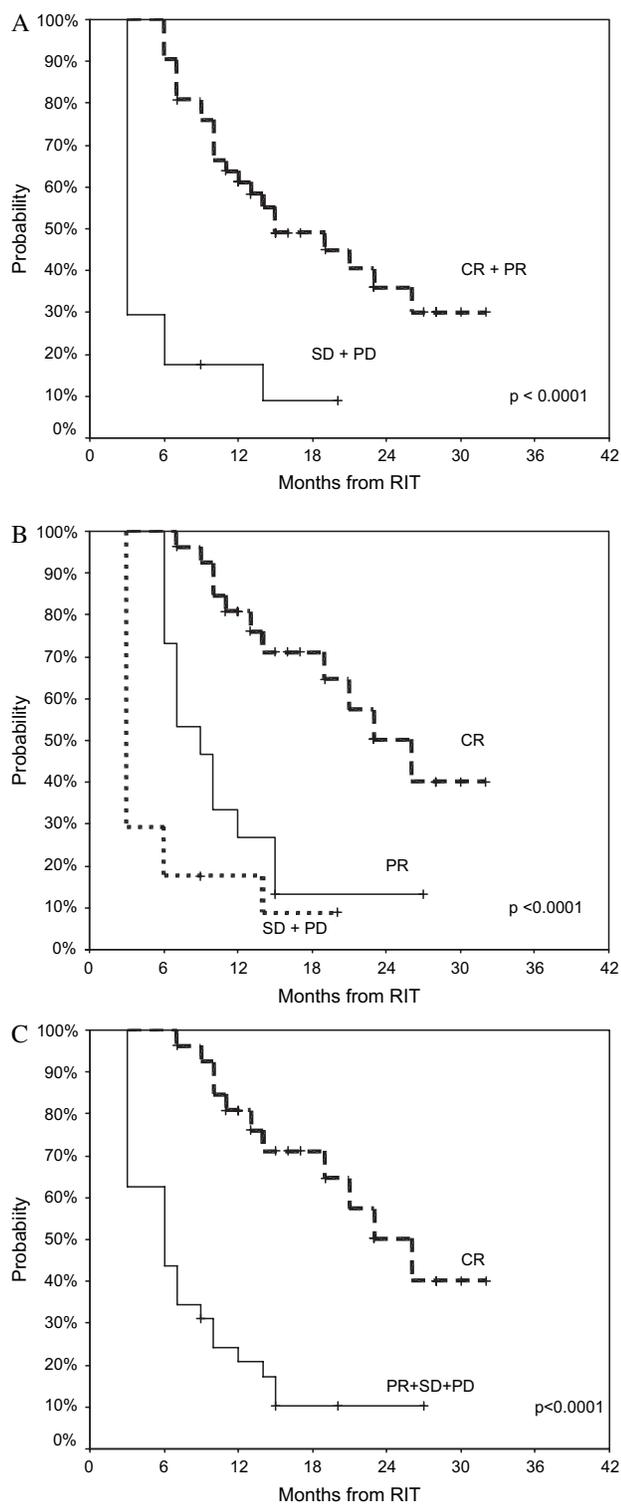
Figure 2. Kaplan–Meier survival curves depicting PFS with respect to response to RIT or PET result; (A) responders (CR + PR) in 'discontinuous line plot' versus nonresponders (SD + PD) in 'continuous line plot'; (B) three categories of response: CR (discontinuous line plot) versus PR (continuous line plot) versus SD + PD (dotted line plot); (C) PET negative (CR) in continuous line plot versus PET positive (PR + SD + PD) in continuous line plot. PFS, progression-free survival; RIT, radioimmunotherapy; PET, positron emission tomography; CR, complete responders; PR, partial responders; SD, stable disease.
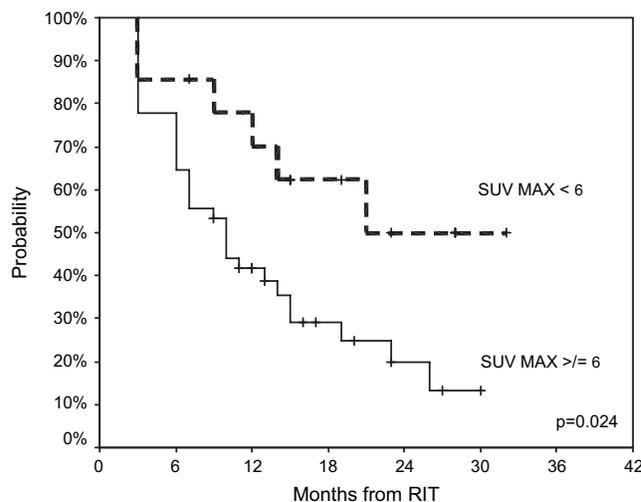

Figure 3. Kaplan–Meier survival curves depicting PFS with respect to SUVbw max before RIT; SUVmax < 6 (discontinuous line plot) versus SUVmax ≥ 6 (continuous line plot). PFS, progression-free survival; RIT, radioimmunotherapy.

response rates range from 73% to 83%, with a disease-free period of 12 months, or longer, in 37% of the patients [21, 22]. Moreover, ibritumomab tiuxetan Y 90 either alone, as primary therapy, or as consolidation treatment after chemotherapy achieves high response rates in FL by giving a complete remission in 62%–80% of cases and a 2-year PFS up to 77% [22–24].

In our study, RIT with Zevalin® documented an overall survival (OR) rate of 71.2%, including 45.8% CR, and a median PFS for all the 59 patients of 12 months, which appears in line with the already reported data [7, 9, 20, 21, 24].

When considering disease extent at baseline (group A versus group B), we noticed a large gap in CR rates between patients with limited disease (stage I–II) (72.7%) and advanced disease (stage III–IV) (29.7%), as assessed by FDG–PET before RIT, with the following OR rates, 90.9% and 59.5%, respectively (Figure 4). These data lead to the predictable conclusion that the earlier the diagnosis, while the disease is still limited, the earlier the RIT onset and the better the response to therapy and outcome of the patients.

The difference between the groups (Table 1) results statistically significant even with respect to nonresponder rate, 9.1% versus 40.5%, respectively, in group A and group B. This is not the case for PR patients, with an overall rate of 25.4%, almost concordant with the reported values [18, 25], who do not show any significant difference between the groups. However, an interesting fact came out during the evaluation of PR when considered separately from the other types of response to RIT (Figure 2B). Both on the univariate analysis and on the Pearson correlation, PR patients tended to behave more similarly to nonresponders rather than CR patients. This is confirmed by the statistically significant difference documented with respect to PFS between PR and CR, which instead is not present between PR and nonresponders. This point gives way to another observation regarding the proper incorporation of PR in responder patients, which needs an in-depth study.
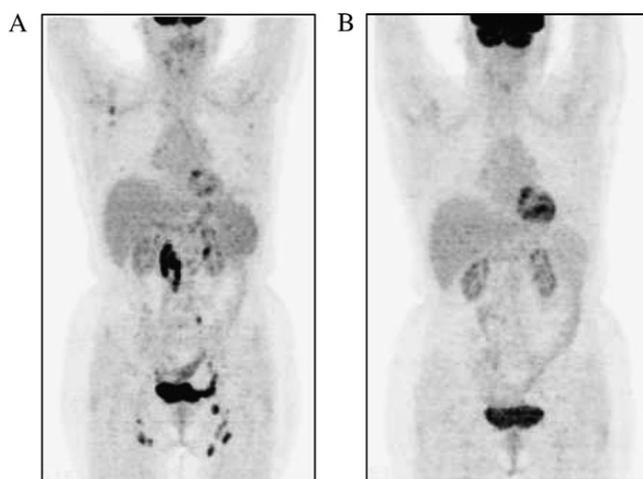
Figure 4. MIP image in CR patient after RIT: 70-year-old female, stage IV FL at presentation, treated with combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (resulting in PR) followed by rituximab (resulting in CR); relapse documented by PET during follow-up (image A) showing disease at axillary, para-aortic and inguinal lymph nodes (stage III: group B); RIT administered 4 months later, resulting in CR at PET after treatment (image B). MIP, maximum intensity projection; CR, complete responders; FL, follicular lymphoma; RIT, radioimmunotherapy; PR, partial responders; PET, positron emission tomography.

The possible predictive value of disease extent at baseline with respect to response to treatment seems to be extended also to PFS, when considering the univariate analysis. Group A patients in fact tend to progress/relapse significantly later (15.3 months) than group B patients (10.1 months), with a projected 3-year PFS of 40% and 13%, respectively. However, disease extent before RIT loses its prognostic value when included in the multivariate analysis, which instead reveals as the lonely predictor of PFS the response to treatment assessed at 3 months after RIT. CR patients in fact tend to progress/relapse in average after 17.07 months, while nonresponders in average after 5.35 months.

When considering PET findings at 3 months after RIT simply as negative (CR) or positive (PR, SD and/or PD), it results evident that a negative scan predicts a greater probability of longer PFS, with a projected 3-year PFS of 40%, while a positive PET a significantly lower one, with a 3-year projected PFS of 10%. A complete response at 12 weeks after RIT in fact is already reported to correlate with a longer progression-free period and a better overall survival [10, 12].

Reported results on RIT with tositumomab I 131 [26] have demonstrated that there is a statistically significant correlation between response to treatment and long-term duration of response, with respect to the number of previous treatments before RIT. There seems to exist in fact a significant decline in response rates after RIT, while the number of previous lines of chemotherapy increases. In our study, we compared the entity of previous treatments and PFS; more precisely, we considered separately patients with two or less lines of chemotherapy and heavily treated patients (more than two previous treatments),

by noticing however no statistically significant difference between them.

SUVbw max at enrollment, before RIT, was also evaluated as a possible predictor, showing no significant correlation with response to treatment rather than with PFS. In the univariate analysis, however, we observed that patients with relatively low FDG uptake (SUVmax < 6) at baseline PET had a significantly longer PFS when compared with the patients with SUVmax ≥ 6, with a projected 3-year PFS of 49% versus 13%, respectively. But the results were not confirmed in the multivariate analysis. In combined studies of Bexxar® and Zevalin® [10], it is already documented no predictivity of baseline SUVmax to the further response to treatment, with wide ranges of metabolic response after RIT. However, large declines in FDG uptake tended to characterize patients with the longest PFS, with a potential further response occurring in responders or PR even beyond 3 months after RIT [10, 12].

Although, for a proper assessment of the true outcome, a long period of follow-up is needed (>24 months), it seems deducible that an early treatment tends to give better responses to the RIT, leading therefore to longer periods free of progression.

In published series [11], with a longer follow-up (>88 months), limited disease (stage I–II) as well as nonbulky masses (<5 cm) were reported as possible predictive characteristics for long-term response to RIT. Age, prior radiation, extranodal disease and Follicular Lymphoma International Prognostic Index score have instead failed to correlate with RIT outcome [27]. Our study partially confirms these data and depicts as lonely independent predictive factor of PFS response to treatment, as assessed at 3 months after RIT.

The optimal time to assess treatment response in RIT, however, is not fully clarified. FDG–PET is usually recommended at least 3 weeks (6–8 weeks) after chemotherapy and 8–12 weeks after radiotherapy [28, 29]. We decided to carry out the study at 3 months after RIT (range 11–13 weeks) on the basis of our personal experience but also according to results in other published reports [20]. When the post-RIT evaluation is carried out earlier (<8–9 weeks), there seems to be a higher possibility of false-positive cases, which can simply belong to delayed responding sites (Figure 5). Delayed responses to RIT are already reported [10] even beyond 12 weeks, up to 6 months, with a progressive decline of FDG uptake without additional therapy. This may figure out the necessity to carry out further PET examinations with later checkpoints. However, in our study PET findings at 3 months after RIT were consistent with the final outcome in all cases, therefore we can conclude that 12 weeks can be a sufficient time for the malignant cells to respond to the treatment and apparently, a PET study at that point is highly reliable.

conclusions

Our data reflect the expected good results concerning the efficacy of RIT in FL. Functional imaging results an accurate method in assessing FL patients, with elevated predictive values. Disease extent before therapy and response to RIT, as assessed by FDG–PET, result as main predictors of longer periods free of progression of disease, with the post-RIT PET result being the only independent predictive factor of PFS.
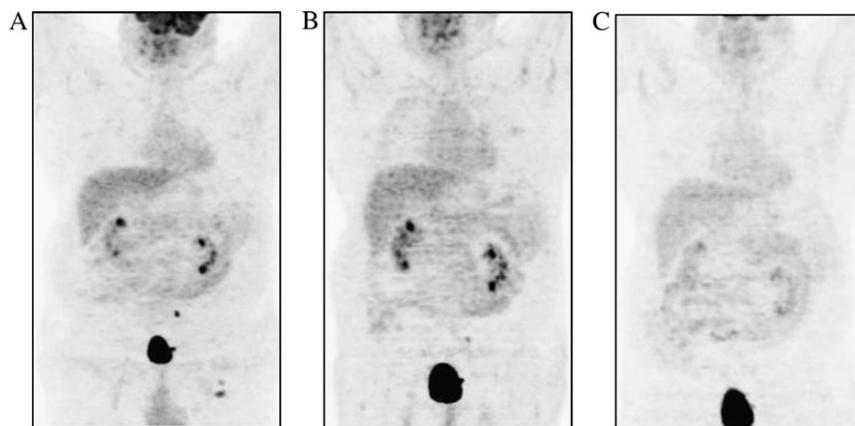
Figure 5. MIP image in a 74-year-old male with stage IV FL at presentation: CR after rituximab + FN in 2004. Relapse in September 2005 (image A) with disease set under the diaphragm (stage II: group A): iliac (SUVmax 7) and inguinal lymph nodes. RIT was administered in October 2005. A first PET scan carried out 9 weeks after RIT showed a PR (image B) with normalization of inguinal FDG uptake but persistent even though decreased uptake at iliac lymph node (SUVmax 4.3). A following reevaluation PET scan carried out 18 weeks after RIT showed the normalization of FDG uptake of the iliac lymph node. PET scan carried out too early after RIT (<3 months) can lead to false-positive findings in terms of response to therapy evaluation. MIP, maximum intensity projection; FL, follicular lymphoma; CR, complete responders; RIT, radioimmunotherapy; PET, positron emission tomography; PR, partial responders; FDG, 2-[fluorine-18]fluoro-2-deoxy-D-glucose; FN, fludarabine and mitoxantrone.

disclosure

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