High incidence of false-positive PET scans in patients with aggressive non-Hodgkin’s lymphoma treated with rituximab-containing regimens

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Background: Positron emission tomography (PET) is a powerful predictor of relapse and survival in non-Hodgkin’s lymphomas (NHLs) based on studies carried out in the prerituximab era. Little is known about the predictive power of PET in rituximab-treated patients.

Patients and methods: Patients with aggressive B-cell NHL with baseline and follow-up PET studies were included. Clinical characteristics, PET and computed tomography scans, biopsy results, and outcomes were reviewed. PET was defined as positive if higher than mediastinal or background activity was observed.

Results: In all, 51 patients (diffuse large B cell—38; mantle cell lymphoma—13) treated with rituximab-containing regimens were included. For 13 of 40 patients (32.5%), mid-therapy PET studies were positive and 9 of 48 patients (18.7%) had positive posttherapy PET. The positive predictive value (PPV), negative predictive value (NPV), sensitivity (Se), and specificity (Sp) of the mid-therapy PET for predicting relapse were 33% [95% confidence interval (CI) 19% to 49%], 68% (95% CI 51% to 81%), 33% (95% CI 6% to 76%), and 68% (95% CI 49% to 82%), respectively. For posttherapy PET, the relapse PPV, NPV, Se and Sp were 19% (95% CI 9% to 33%), 81% (95% CI 67% to 91%), 13% (95% CI 0.6% to 53%), and 80% (95% CI 64% to 90%), respectively.

Conclusions: Compared with previous reports in prerituximab era, addition of rituximab resulted in reduced PPV and sensitivity of mid- and posttherapy PET in patients with aggressive B-cell NHL.

Key words: lymphoma, PET scan, rituximab

introduction

The accurate documentation of anatomic extent of disease and the response to therapy are of paramount importance in the management of lymphoma patients. Computed tomography (CT) is the most commonly used imaging modality for staging and response assessment of lymphoma patients. However, there has been compelling evidence that CT has limitations in identifying the presence of disease in normal size lymph nodes and in differentiating between viable tumor, necrosis and fibrosis in residual masses. By contrast, functional nuclear imaging techniques using ¹⁸F-fluorodeoxyglucose (FDG) can provide metabolic tissue characterization which may be useful for demonstration of disease activity in anatomically normal organs and in determining the etiology of posttherapy residual masses in patients with non-Hodgkin’s lymphomas (NHLs). Therefore, FDG–positron emission tomography (PET) scanning is increasingly used in the initial staging, posttherapy restaging, and treatment planning of patients with aggressive NHL.

Multiple, mostly retrospective, studies have suggested the superiority of adding PET to conventional scanning techniques. For staging, PET scans have often demonstrated more extensive disease than conventional imaging study with CT. End of therapy response evaluations with PET scans for aggressive NHL have been shown to have high sensitivity and specificity. Furthermore, early interim PET results were shown to predict outcomes by differentiating which patients will do well and which will do poorly. On the basis of these findings, the International Working Group response criteria were recently revised to incorporate PET for assessment of response in aggressive NHL [1].

Although PET is now widely used in the management of patients with aggressive NHL, the data available assessing its usefulness were derived from patients who were not treated with rituximab. Arguably, the current gold standard therapy has evolved and comprises a combination of chemotherapy with rituximab. Rituximab is a chimeric human/murine immunoglobulin G1 mAb that binds specifically to the B-cell surface antigen, CD20. The antibody induces lymphoma cell
lysis through different immunologic or direct mechanisms, such as apoptosis, complement-mediated cytolysis, and antibody-dependent cell cytotoxicity. Consequently, it is possible that addition of rituximab to chemotherapies used in the treatment of aggressive NHL might result in an inflammatory response that could lead to false-positive PET scan interpretation. The impact of rituximab on PET scan interpretation, predictive value for continuous remission or relapse is unknown.

To examine the usefulness of PET scan for early interim and end of therapy evaluation of response in patients with aggressive NHL treated with combination of chemotherapy regimens with rituximab, we carried out a retrospective analysis of 51 patients treated in our institution. Our data demonstrate that compared with previous reports in the prerituximab era, addition of rituximab resulted in a reduced positive predictive value and sensitivity of mid- and posttherapy PET in patients with aggressive B-cell NHL.

patients and methods

patients

From September 2002 to March 2007, 51 consecutive patients with newly diagnosed aggressive NHL that were treated with rituximab-containing chemotherapy regimens at the University of Miami Sylvester Comprehensive Cancer Center were entered into this retrospective analysis. Thirty-eight patients had diffuse large B-cell lymphoma (DLBCL) and 13 patients were diagnosed with mantle cell lymphoma (MCL). All patients had a positive PET scan at the time of diagnosis and underwent follow-up PET studies. All patients were followed until death or for at least 1 year posttherapy initiation. Treatment regimens and schedules, as well as imaging frequency, were at the discretion of the treating physician. Patient demographics, clinical characteristics at presentation [Ann Arbor stage, international prognostic index, baseline lactate dehydrogenase, chemotherapy regimens, baseline, and follow-up imaging (PET and CT scan)], biopsy results from residual masses, response to therapy, and survival duration were reviewed retrospectively. The study was approved by the University of Miami Institutional Review Board.

treatment

All patients were treated with rituximab containing anthracycline-based chemotherapy regimens. Patients with DLBCL were treated with six to eight cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) administered every 3 weeks while all MCL patients received treatment according to the phase II study protocol with R-MACLO-IVAM-T [2]. Therapy consisted of R-MACLO; rituximab 375 mg/m² on day 1, adriamycin 45 mg/m² i.v. on day 1, cyclophosphamide 800 mg/m² i.v. on day 1 and 200 mg/m²/day on days 2–5, vincristine 1.5 mg/m² on days 1 and 8, methotrexate 1.2 g/m² i.v. on day 10 over 1 h followed by 5.52 g/m² over 23 h, then leucovorin 36 h later, granulocyte colony-stimulating factor was begun on day 13, and R-IVAM including rituximab 375 mg/m² i.v. day 1, cytarabine 2.0 g/m² i.v. every 12 h on days 1 and 2, ifosfamide 1.5 g/m² days 1–5 with mesna and etoposide 60 mg/m² days 1–5 which begun when absolute neutrophil count was >1.5 × 10⁹/L. This was repeated 14 days after hospital discharge. At the completion of chemotherapy, thalidomide 200 mg/day was started in patients achieving complete remission (CR) and was continued until lymphoma recurrence or toxicity.

imaging and interpretation

All patients studied from 2002 to March 2005 were studied utilizing a C-Pet Philips System and from 3 March 2005 to the end of the study in 2007 were studied using a Gemini Philips System. Each patient was studied utilizing the same PET protocol parameters for each individual PET scan carried out on that patient.

All patients underwent a baseline whole-body FDG–PET study before starting therapy, an early interim scan carried out either two to four cycles after therapy (mid-PET, 40 patients) and/or a restaging FDG–PET study after completion of therapy (post-PET, 48 patients). The mid-PET was carried out after two cycles in all the patients with MCL, while in DLBCL patients it was carried out after second (four patients), third (two patients), and fourth (23 patients) cycles of chemotherapy. The mid-PET studies were carried out at least 2 weeks after the last dose of chemotherapy while the end of therapy studies were carried out at least 1 month after last chemotherapy cycle. All the patients fasted for at least 6 h before the start of the FDG–PET study. Serum glucose level was determined at the time of ¹⁸F-FDG injection using a glucometer and all the patients had glucose level <130 mg/dl. Sixty minutes after i.v. administration of 150–450 MBq of ¹⁸F-FDG, a PET imaging study from the skull base to the upper thigh was acquired.

The PET scan images were independently reviewed by two separate nuclear medicine physicians without any knowledge of the clinical data. Each scan was interpreted as being either negative or positive for disease activity. A positive PET scan was defined as one having higher ¹⁸F-FDG uptake relative to uptake in mediastinum or surrounding background, with no similar activity seen on the contralateral side, or increased activity at any location incompatible with normal physiological distribution. A negative scan was defined as having no abnormally increased ¹⁸F-FDG at any site.

clinical outcomes

Response to induction chemotherapy was based on conventional diagnostic methods that included physical examination, laboratory tests, CT of the chest, abdomen and pelvis (neck was included if it was initially involved), and bone marrow biopsy if bone marrow was involved at baseline. The International Workshop Criteria (IWC) were used for response assessment [3]. A CR was defined as complete disappearance of all detectable clinical and radiological evidence of disease and negative bone marrow biopsy (if the patient exhibited bone marrow involvement at presentation). An unconfirmed complete remission (CRu) is defined as complete disappearance of all detectable clinical evidence of disease but a residual mass >1.5 cm in greatest transverse diameter seen on anatomical imaging that has regressed by >75% or indeterminate bone marrow. Partial response (PR) is defined as at least a 50% reduction in the sum of the product of the greatest diameters (SPD) of the six largest dominant nodes or nodal masses. Progressive disease (PD) is ≥50% increase in the SPD from nadir of any previously identified abnormal node for PRs and nonresponders or appearance of any new lesion during or at the end of therapy. Relapsed disease (for patients with a CR or CRu) is the appearance of any new lesion or ≥50% increase in the greatest diameter of any previously identified node >1 cm in short axis or in the SPD of more than one node.

Progression-free survival (PFS) was defined as the time from diagnosis to the date of death, relapse, or disease progression. Overall survival (OS) was defined as the time from diagnosis to the date of death or last follow-up.

statistical analysis

Continuous variables are summarized as the median and range. Categorical variables are summarized as frequency counts and percentages. The Kaplan–Meier method was used to estimate PFS and OS and the positive PET and negative PET groups were compared using the log-rank test. Analyses were done using SAS software (SAS Institute, Inc., Cary, NC). All statistical tests were two sided and P < 0.05 was used to indicate statistical significance.
results

patient characteristics

Fifty-one patients with newly diagnosed B-cell aggressive NHL had the following histologies: DLBCL (38 patients) and MCL (13). The median age was 59 years (range 21–92) and 29 were males (56.8%). All patients were treated with anthracycline-containing chemotherapy with rituximab. Patient characteristics are summarized in Table 1. All patients had positive PET scans at diagnosis. Following initial treatment, 35 (68%) patients achieved a CR (including all patients with MCL), 14 (27%) had CRu, one had a PR (2%), and one patient had PD (2%). Nine (18%) patients experienced a relapse and received salvage chemotherapy including autologous stem-cell transplantation in three patients. After a median follow-up of 24 months (range 6–60 months), six (12%) patients had died.

mid-therapy PET

patients with a positive mid-therapy PET. Mid-therapy PET study was carried out in 40 patients (11 with MCL and 29 with DLBCL). Thirteen (33%) mid-therapy PET studies were positive and 12 of these had an additional PET study at the end of the therapy (Figure 1A). Four of these 12 patients with positive mid-therapy PET exhibited persistent PET positivity at the end of treatment but did not demonstrate disease progression or recurrence during subsequent follow-up ranging from 19 to 65 months (median 20). Among the remaining eight patients with negative studies after chemotherapy completion that were followed for 6–40 months (median 19), one patient relapsed 6 months after treatment completion and one died while being in continuous CR from lymphoma-unrelated cause. The remaining six patients are alive with no evidence of disease with a median follow-up of 24 months (range 13–40).

patients with a negative mid-therapy PET. Twenty-seven patients had negative mid-therapy PET studies (Figure 1A). Four of these patients relapsed during median follow-up of 13 months (range 8–17). Two of these patients died following relapse.

accuracy of mid-therapy PET. The positive predictive value (PPV), negative predictive value (NPV), sensitivity (Se), and specificity (Sp) of the mid-therapy PET for the prediction of relapse were 33% (95% confidence interval [CI] 19% to 49%), 68% (95% CI 51% to 81%), 33% (95% CI 6% to 76%), and 68% (95% CI 49% to 82%), respectively. There was no difference in PFS and OS of mid-therapy PET-positive and -negative patients (Figures 2 and 3), thus suggesting that the mid-therapy PET is not predictive of survival outcomes in our aggressive NHL patient population treated with rituximab-based regimens.

posttherapy PET

patients with a positive posttherapy PET. Forty-eight (94%) patients included in this study had posttherapy PET scans. In nine (19%), the posttherapy PET scans were positive (Figure 1B). One patient had a PR and received second-line chemotherapy followed by autologous stem-cell transplantation with no subsequent evidence of disease. Two patients with positive posttherapy PET without any residual masses had subsequent follow-up PET scans which all became negative within 1–5 months and remained in CR. Six patients had residual masses on CT scans and in three patients, mid-therapy PET scan was positive. In one of these patients, biopsy from the PET-positive site mandible was carried out based on the PET findings and demonstrated inflammation and necrosis without evidence of lymphoma. One patient with stage IV MCL exhibited a persistent FDG-avid right perinephric mass both in the immediate posttherapy and in 3-month follow-up PET scan with disappearance of disease at other initially involved organs and lymph nodes. Right nephrectomy revealed the presence of renal cell carcinoma without evidence of residual lymphoma. The other four patients were followed up without post-PET biopsies and did not demonstrate evidence of progressive lymphoma with median follow-up of 24 months (range 16–65 months). Of note, in all four patients subsequent follow-up PET scans became negative without evidence of pathological uptake. In one patient who originally had stage II AE DLBCL with extranodal lung involvement, follow-up CT scans revealed a new left upper lobe lung nodule that was FDG avid on the PET scan 5 years after diagnosis of DLBCL. Wedge resection of the lung showed evidence of adenocarcinoma.

patients with a negative posttherapy PET without residual masses. Negative posttherapy PET scans were observed in 39 patients (Figure 1B). Thirty patients had no residual masses by CT scan criteria. Of these, 24 patients are in continuous CR without evidence of lymphoma recurrence and an additional two patients died of unrelated causes while being in continuous CR. In 22 of these patients, subsequent follow-up PET scans continued to be negative. In two patients, subsequent follow-up PET scans carried out 5 and 4 months after posttherapy PET scans were negative. In the remaining 15 patients, posttherapy PET scans were positive in four (27%) patients, only two of whom were relapsing. Of note, in one of these two patients, multiple imaging studies, including positron emission tomography/computed tomography (PET/CT), revealed the presence of renal cell carcinoma. In the remaining 11 (73%) patients, posttherapy PET scans were negative.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range)</td>
<td>59 (21–92)</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>29/22</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>38</td>
</tr>
<tr>
<td>MCL</td>
<td>13</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>25</td>
</tr>
<tr>
<td>IPI</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
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<tr>
<td>1</td>
<td>15</td>
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<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
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</tbody>
</table>

DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; IPI, international prognostic index.
Figure 1. Clinical outcome of aggressive non-Hodgkin’s lymphoma patients according to the results of the 18F-fluorodeoxyglucose PET carried out at mid- (A) and post (B) therapy. PET, positron emission tomography; NED, no evidence of disease; CR, complete remission; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma.
became positive with FDG uptake in the kidney and posterior neck lymph node, respectively. Biopsy was carried out in these two patients and revealed renal cell carcinoma and lymph node with nonspecific inflammation, respectively. These two patients are alive without evidence of disease. Four of 30 patients with negative posttherapy PET and no residual mass based on CT scan had subsequently relapsed.

Nine patients with a negative posttherapy PET demonstrated residual masses by CT scan. Two of these patients relapsed while the remaining seven are in continuous CR for 8–52 months (median 30 months). Follow-up PET scan was noted to be positive in one of these seven patients in a follow-up study carried out 4 months after posttherapy PET scan. However, biopsy revealed inflammatory changes with no evidence of lymphoma (Figure 4).

**Figure 2.** Kaplan–Meier plot showing progression-free survival (PFS) according to mid-therapy positron emission tomography (PET). PET results did not correlate with PFS ($P = 0.47$).

**Figure 3.** Kaplan–Meier plot showing overall survival (OS) according to mid-therapy positron emission tomography (PET). PET results did not correlate with OS ($P = 0.18$).

patients with a negative posttherapy PET with residual masses. Nine patients with a negative posttherapy PET demonstrated residual masses by CT scan. Two of these patients relapsed while the remaining seven are in continuous CR for 8–52 months (median 30 months). Follow-up PET scan was noted to be positive in one of these seven patients in a follow-up study carried out 4 months after posttherapy PET scan. However, biopsy revealed inflammatory changes with no evidence of lymphoma (Figure 4).

**Figure 4.** Illustrative case of a false-positive positron emission tomography (PET) scan. A 26-year-old male with diffuse large B-cell lymphoma, stage IIA who achieved unconfirmed complete remission with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone but had a positive PET after the completion of the therapy. Biopsy was negative for lymphoma and showed necrosis and inflammation. Patient is well and alive for 2 years since last treatment.

accuracy of posttherapy PET. For the posttherapy PET: PPV, NPV, Se, and Sp were 19% (95% CI 9% to 33%), 81% (95% CI 67% to 91%), 13% (95% CI 0.6% to 53%), and 80% (95% CI 64% to 90%), respectively (Table 3). Patients with positive posttherapy PET exhibited similar PFS or OS as patients with negative posttherapy PET (Figures 5 and 6).

**posttherapy surveillance PET.** Routine surveillance PET scans for detection of lymphoma relapse are not currently recommended after end of therapy scan. Forty-four patients included in this study (31 with DLBCL and 13 with MCL) underwent surveillance follow-up PET scans. Follow-up PET scans were positive in seven of eight patients at the time of lymphoma relapse. The patient with the negative PET scan at the time of relapse presented with mental status changes. CT and PET scan studies were negative but lumbar puncture demonstrated evidence of leptomeningeal lymphoma. Among the seven patients with positive PET scans at the time of the relapse, preceding new symptoms or findings on physical examination were present in four patients and in two relapse was initially diagnosed by follow-up CT scan. PET scan was the initial modality to diagnose relapse in only one asymptomatic patient with nondiagnostic CT scan.

There were eight false-positive follow-up PET scans for detection of lymphoma. In two patients, PET findings led to biopsy of residual mediastinal mass and neck lymph node that showed nonspecific inflammatory changes, while in
In recent revised response criteria by the International Working Group (IWC) incorporated PET scans as part of therapy response assessment of aggressive NHLs [1]. The rationale for integrating PET into previous IWC criteria was based on several retrospective studies carried out mostly in the prerituximab era that demonstrated improved diagnostic accuracy of PET scans compared with the previous gold standard CT scans (Tables 2 and 3). These studies demonstrated that mid-therapy PET scans in nonrituximab-treated patients exhibit PPV of 71%–100%, NPV of 67%–100%, Se of 42%–100%, and Sp of 75%–100% for prediction of lymphoma relapse or progression. Similarly, posttherapy PET scans in the same patient population exhibited PPV of 79%–100%, NPV of 65%–100%, Se of 43%–100%, and Sp of 81%–100%. Furthermore, Juweid et al. reported that in 54 patients with aggressive NHL (47 DLBCL) treated with an anthracycline-based regimen (only 29 patients received rituximab), posttherapy PET increased the number of CR patients, eliminated the CRu category, and enhanced the ability to discern the difference in PFS between patients with CR and PR [16].

There are several limitations of these previously reported studies including the use of now outdated chemotherapy and the retrospective nature of the studies. The current gold standard therapy has evolved to include rituximab with chemotherapy. This therapeutic evolution might result in a change in the predictive value of PET scans, as was previously reported for biological markers, requiring reevaluation of PET accuracy in patients treated with rituximab–chemotherapy combination. This is especially important since the mechanism of action of rituximab may involve inflammatory changes associated with recruitment of immune cells to the tumor which might lead to false-positive PET results. Similar findings were previously reported in animal models [17].

In comparison to previous reports in nonrituximab-treated patients, our study demonstrates lower PPV and Se of mid- and posttherapy PET for prediction of lymphoma relapse. Of note, similarly low PPV for mid-therapy PET scans was recently reported by Haioun et al. in a group of 90 patients with B- and T-cell NHL, 37 of which were treated with rituximab-containing therapies [9]. In our study, nonspecific inflammation and necrosis were the most common pathological changes in patients with false-positive PET scan that underwent biopsies. In a recent prospective study of dose-dense R-CHOP followed by risk-adapted consolidation therapy presented by Moskowitz et al. [18] in an abstract at the American Society of Hematology annual meeting in 2006, mid-therapy PET scan was positive in 31 of 81 patients (36%) of which only four (13%) had evidence of lymphoma. Similar to our findings, nonspecific inflammatory changes and necrosis were accounted for false-positive PET scans in the remaining patients. There was no difference in PFS and OS between PET-positive and PET-negative patients, as was also observed in our study. Overall, these initial observations suggest that in rituximab-treated patients, mid- and/or posttherapy PET positivity does not necessarily imply persistence of lymphoma and requires biopsy to confirm presence of lymphoma and to rule nonspecific inflammatory changes and necrosis. In patients with dissociated response (persistence of FDG uptake in one locus and disappearance of uptake in other previously avid sites) or appearance of FDG uptake in a previously nonavid site, biopsy should be carried out to rule out unrelated secondary neoplasm, as was shown in three of our patients.

Although incorporation of rituximab into the therapeutic regimen likely accounts for the discrepancy in PET predictive
Table 2. The role of mid-therapy PET during first-line therapy of aggressive NHL

<table>
<thead>
<tr>
<th>Study</th>
<th>Ni</th>
<th>Median follow-up (months)</th>
<th>Rituximab</th>
<th>No. of cycles before PET</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PFS: PET+ (%)</th>
<th>PFS: PET− (%)</th>
<th>OS: PET+ (%)</th>
<th>OS: PET− (%)</th>
<th>PFS: PET+ versus PET−</th>
<th>OS: PET+ versus PET−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerusalem et al. [4]</td>
<td>28 NHL&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>17.5</td>
<td>No</td>
<td>2–5</td>
<td>100</td>
<td>67</td>
<td>42</td>
<td>100</td>
<td>2-year: 0%</td>
<td>2-year: 62%</td>
<td>2-year: 0%</td>
<td>2-year: 68%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Mikhaeel et al. [5]</td>
<td>23 NHL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30</td>
<td>No</td>
<td>2–4</td>
<td>88</td>
<td>100</td>
<td>100</td>
<td>92</td>
<td>1-year: 12%</td>
<td>1-year: 100%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Kostakoglu et al. [6]</td>
<td>30 (17 NHL&lt;sup&gt;d&lt;/sup&gt;; 13 HL&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>19</td>
<td>No</td>
<td>1</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>18-month: 10%</td>
<td>18-month: 75%</td>
<td>NR</td>
<td>NR</td>
<td>Median PFS: 5 months versus not reached</td>
<td></td>
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<tr>
<td>Spaepen et al. [7]</td>
<td>70 NHL&lt;sup&gt;e&lt;/sup&gt;</td>
<td>36</td>
<td>No</td>
<td>3–4</td>
<td>100</td>
<td>84</td>
<td>85</td>
<td>100</td>
<td>2-year: 4%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2-year: 85%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2-year: 40%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2-year: 90%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Median PFS: 1.5 months versus 35.3 months</td>
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<tr>
<td>Mikhaeel et al. [8]</td>
<td>121 NHL&lt;sup&gt;f&lt;/sup&gt;</td>
<td>24.4</td>
<td>Some NR</td>
<td>2–3</td>
<td>71</td>
<td>90</td>
<td>88</td>
<td>75</td>
<td>2-year: 30%; 5-year: 16%</td>
<td>2-year: 93%; 5-year: 89%</td>
<td>2-year: 100%; 5-year: 90%</td>
<td>2-year: 90%</td>
<td>Mean PFS: 9.6 months versus 23.6 months</td>
<td></td>
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<tr>
<td>Hainoun et al. [9]</td>
<td>90 NHL&lt;sup&gt;e&lt;/sup&gt;</td>
<td>24</td>
<td>Yes in 37</td>
<td>2</td>
<td>44</td>
<td>90</td>
<td>76</td>
<td>70</td>
<td>2-year: 43%</td>
<td>2-year: 82%</td>
<td>2-year: 61%</td>
<td>2-year: 90%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Querellou et al. [10]</td>
<td>48 (24 NHL&lt;sup&gt;g&lt;/sup&gt;; 24 HL&lt;sup&gt;h&lt;/sup&gt;)</td>
<td>15.5 for NHL; 17 for HL</td>
<td>Yes in 28 NHL</td>
<td>2–4</td>
<td>83</td>
<td>83</td>
<td>63</td>
<td>94</td>
<td>2-year: 20%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2-year: 80%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2-year: 75%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2-year: 100%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Median EFS: 7.7 months versus 15.5 months</td>
<td></td>
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<tr>
<td>Present study</td>
<td>40 NHL&lt;sup&gt;e&lt;/sup&gt;</td>
<td>24</td>
<td>Yes</td>
<td>2–4</td>
<td>33</td>
<td>68</td>
<td>33</td>
<td>68</td>
<td>2-year: 77%</td>
<td>2-year: 83%</td>
<td>2-year: 84%</td>
<td>2-year: 90%</td>
<td></td>
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</tbody>
</table>

Values in bold, calculated from data.

<sup>a</sup>B- and T-cell NHL.

<sup>b</sup>Few relapsed patients included.

<sup>c</sup>Four patients with MRU were not included in this analysis.

<sup>d</sup>B-cell NHL included.

<sup>e</sup>Nineteen patient with MRU were not included in this analysis.

<sup>f</sup>Estimation of data.

<sup>g</sup>Twenty-four NHL patients were included for the analysis.

PET, positron emission tomography; NHL, non-Hodgkin’s lymphoma; PPV, positive predictive value; NPV, negative predictive value; Se, sensitivity; Sp, specificity; PFS, progression-free survival; OS, overall survival; NR, not reported; MRU, minimal residual uptake, defined as low grade uptake of FDG in a focus within an area of previously noted disease.
Table 3. The role of posttherapy PET of aggressive NHL

<table>
<thead>
<tr>
<th>Study, Authors (Year)</th>
<th>n</th>
<th>Median follow-up (months)</th>
<th>Rituximab</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PFS: PET+ (%)</th>
<th>PFS: PET− (%)</th>
<th>OS: PET+ (%)</th>
<th>OS: PET− (%)</th>
<th>Median/Mean PFS or EFS of PET+ versus PET−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerusalem et al. [11]</td>
<td>35 NHL; 19 HL</td>
<td>9–23</td>
<td>No</td>
<td>100</td>
<td>83</td>
<td>43</td>
<td>100</td>
<td>1-year: 0%</td>
<td>1-year: 86 ± 5%</td>
<td>1-year: 50 ± 20%</td>
<td>1-year: 92 ± 4%</td>
<td>NR</td>
</tr>
<tr>
<td>Mikhaeel et al. [5]</td>
<td>45 NHL</td>
<td>30</td>
<td>No</td>
<td>100</td>
<td>83</td>
<td>60</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Spaepen et al. [12]</td>
<td>93 NHLa</td>
<td>22</td>
<td>No</td>
<td>100</td>
<td>84</td>
<td>70</td>
<td>100</td>
<td>2-year: 4%</td>
<td>2-year: 85%</td>
<td>NR</td>
<td>NR</td>
<td>Median PFS: 73 days versus 404 days</td>
</tr>
<tr>
<td>Kostakoglu et al. [6]</td>
<td>17 NHL; 13 HL</td>
<td>19</td>
<td>No</td>
<td>83</td>
<td>65</td>
<td>45</td>
<td>92</td>
<td>18 months: 17%</td>
<td>18 months: 65%</td>
<td>NR</td>
<td>NR</td>
<td>Median PFS: 0 months versus not reached</td>
</tr>
<tr>
<td>Mikosch et al. [13]</td>
<td>49 NHL; 44 HL</td>
<td>NR</td>
<td>No</td>
<td>79</td>
<td>92</td>
<td>91</td>
<td>81</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Zinzani et al. [14]</td>
<td>34 NHL; 41 HL</td>
<td>9 PET+; 12–14 PET−</td>
<td>No</td>
<td>87</td>
<td>100</td>
<td>100</td>
<td>97</td>
<td>1-year: 9%</td>
<td>1-year: 100%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Reinhardt et al. [15]</td>
<td>61 NHLb; 40 HL</td>
<td>32</td>
<td>No</td>
<td>83</td>
<td>90</td>
<td>71</td>
<td>95</td>
<td>3-year: 17%</td>
<td>3-year: 90%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Juweid et al. [16]</td>
<td>54 NHL</td>
<td>35</td>
<td>Yes in 29</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2-year: 17%–42%; 3-year: 17%–42%</td>
<td>2-year: 91%; 3-year: 80%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Present study</td>
<td>48 NHL</td>
<td>24</td>
<td>Yes</td>
<td>19</td>
<td>81</td>
<td>13</td>
<td>80</td>
<td>2-year: 89%</td>
<td>2-year: 83%</td>
<td>2-year: 100%</td>
<td>2-year: 91%</td>
<td></td>
</tr>
</tbody>
</table>

Values in bold, calculated from data
aFourteen low-grade lymphoma included.
bSeventeen low-grade NHL included.

PET, positron emission tomography; NHL, non-Hodgkin’s lymphoma; PPV, positive predictive value; NPV, negative predictive value; Se, sensitivity; Sp, specificity; PFS, progression-free survival; OS, overall survival; NR, not reported.
value between our study and historical studies, other causes might contribute to the observed differences. In contrast to our study that included only patients with aggressive B-cell NHL (DLBCL and MCL), other studies frequently also included patients with Hodgkin’s lymphoma, T-cell lymphomas, and different B-cell lymphoma subtypes. In addition, the reported studies differ in the definition of positive PET imaging, in the timing of PET imaging relative to chemotherapy, and in the chemotherapeutic regimen used. In our study, mid-therapy PET was carried out 2 weeks postchemotherapy and posttherapy PET scan was carried out at least 1 month after the last cycle of chemotherapy. Performance of mid-therapy PET scan 2 weeks after preceding therapy might contribute to higher incidence of false-positive scans.

In the present study, we also examined the clinical potential of surveillance PET scans for detection of lymphoma relapse postcompletion of chemotherapy. Follow-up PET scans were usually carried out at 3–6 month intervals postchemotherapy completion. Our results demonstrate that in majority of patients, lymphoma relapse could be diagnosed based on new patients complain, clinical examination findings, and/or findings on CT scans. Furthermore, false-positive surveillance PET scans were common. Consequently, our findings suggest that routine postend of therapy surveillance PET scans should not be carried out for detection of lymphoma relapse.

Although a major strength of this study is that it is one of the first that has evaluated the value of PET scans in assessing patients with B-cell NHL uniformly treated with rituximab–chemotherapy combination, it harbors several potential limitations. The study was retrospective and included only patients who had pretreatment and treatment evaluation PET scans, thus potentially introducing bias in patient inclusion. Furthermore, not every patient with a positive PET scan underwent diagnostic biopsy. However, our findings are consistent with preliminary results of a prospective study reported by Moskowitz et al. in which all patients with mid-therapy PET had biopsies that in majority of cases demonstrated inflammatory changes without evidence of lymphoma. Another limitation of our study is nonhomogeneous diagnosis and incorporation of patients with both DLBCL and MCL. MCL is currently considered a noncurable disease and majority of patients relapse following standard therapy. MCL patients included in this study were treated on phase II investigational protocol that resulted in 100% CR rate with only one relapse during the follow-up period. Five of these patients had positive mid-therapy PET scan results and two of these five patients also had a positive posttherapy PET that became negative during further follow-up. These findings might contribute to the lower PPV stemming from a higher false-positive rate. However, separate analysis limited only to DLBCL patients still demonstrated lower PPV and Se compared with reported studies in nonrituximab-treated patients (data not shown).

In conclusion, our findings suggest that mid- and end of therapy PET positivity may have a limited prognostic implication in the treatment of patient with aggressive B-cell NHL in the era of rituximab. Given this low PPV, positive PET imaging in residual masses of patients with aggressive B-cell NHL treated with rituximab-based chemotherapy requires histological confirmation of lymphoma persistence before a change in therapeutic plan and institution of salvage chemotherapy. Similar to prerituximab era, mid- and end of therapy negative PET scans are associated with prolonged PFS of patients with aggressive B-cell NHL. Large prospective clinical trials of NHL patients with homogeneous histological subtype treated with a uniform rituximab–chemotherapy regimen and evaluated based on standardized criteria are warranted to validate our data.

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references