FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma

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Background: Less than 50% of all high-grade non-Hodgkin lymphoma (NHL) patients experience lasting disease-free survival. Risk-adapted treatment strategies require better tools for prediction of outcome. This investigation aimed to assess the value of positron emission tomography with 2-[18F]fluoro-2-deoxy-D-glucose (FDG-PET) after two to three cycles of chemotherapy for prediction of progression-free survival (PFS) and overall survival (OS).

Patients and methods: One hundred and twenty-one patients with high-grade NHL underwent FDG-PET. The therapy response on FDG-PET was correlated to PFS and OS using Kaplan–Meier survival analysis. Cox regression analyses were employed to test for independence of known pretreatment prognostic factors.

Results: Fifty FDG-PET scans were negative, 19 scans showed minimal residual uptake (MRU), and 52 scans were positive. The estimated 5 year PFS was 88.8% for the PET-negative group, 59.3% for the MRU group, and 16.2% for the PET-positive group. Kaplan–Meier analyses showed strong associations between FDG-PET results and PFS (P<0.0001) and OS (P<0.01). Early interim FDG-PET was independent of the other prognostic factors.

Conclusions: Early interim FDG-PET is an accurate and independent predictor of PFS and OS. An early assessment of chemotherapy response with FDG-PET could provide the basis for selection of patients for alternative therapeutic strategies.

Key words: fluorodeoxyglucose F18, non-Hodgkin lymphoma, positron emission tomography, prognosis

Introduction

Despite attempts to increase the efficacy of conventional chemotherapy, less than 50% of patients diagnosed with high-grade non-Hodgkin lymphoma (HG-NHL) will experience prolonged disease-free survival with the current treatment regimens [1]. The paradigm of treatment is moving towards a more risk-adapted therapy, where the treatment is tailored to the individual patient’s prognosis. Some patients might benefit from an early change to alternative, more intensive treatment whereas other patients could be cured with less intensive therapy, thus lowering their risk of treatment-related morbidity and mortality [2].

The prognosis in HG-NHL is most commonly established on the basis of histopathological subtype and the clinical characteristics in the International Prognostic Index (IPI); clinical disease stage, age, performance status, number of affected extranodal sites, and serum lactate dehydrogenase concentration [3]. IPI is a well-established predictor of treatment outcome but there is considerable variation between the outcomes of individual patients within the same IPI prognostic group. Response to treatment is another predictor of outcome, which has the advantage of guiding the management decision for the individual patient. The monitoring of treatment efficacy is generally performed with sequential evaluations of tumour size using anatomical imaging modalities, most commonly computerised tomography (CT). CT cannot distinguish between a viable tumour mass and residual scar tissue. Equally important, assessment of response is not reliable early on during treatment since tumour volume reduction takes time.

Positron emission tomography with 2-[18F]fluoro-2-deoxy-D-glucose (FDG-PET) performed early during the course of chemotherapy has in recent years been recognised as a strong predictor of outcome. Published data suggest that complete response (CR) is readily evident on FDG-PET after two to three cycles and that such early CR on FDG-PET confers a favourable prognosis. However, the studies published so far...
are all based on relatively small numbers of patients, and some include patients with Hodgkin’s lymphoma (HL), which has a much higher response rate and better overall prognosis [4–8]. This study aims to investigate the prognostic value of an early interim FDG-PET scan in a large cohort of HG-NHL patients.

Patients and methods

Patients

One hundred and twenty-one consecutive patients with histologically verified HG-NHL who had early interim FDG-PET scans were included in this study (for histological subtypes and patient characteristics see Table 1). The patients were referred to the lymphoma clinic at Guy’s and St. Thomas’ Hospital, London, between February 1996 and April 2004. They underwent initial staging FDG-PET along with standard staging procedures and early interim FDG-PET after two to three cycles of chemotherapy. Not all patients with HG-NHL in the inclusion period had early interim FDG-PET. There was, however, no deliberate selection of patients for this investigation. Follow-up data were recorded at regular visits. Four patients were lost to follow-up earlier than 2 years from first presentation.

Treatment

Treatment was given according to the departmental protocol. Depending on the stage and site of presentation, patients were given either

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Follow-up of patients still alive (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median 55.0</td>
<td>Male 65</td>
<td>Median 28.5</td>
</tr>
<tr>
<td></td>
<td>Mean 54.9</td>
<td>Female 56</td>
<td>Mean 38.2</td>
</tr>
<tr>
<td></td>
<td>Range 20–84</td>
<td></td>
<td>Range 2.5–101</td>
</tr>
</tbody>
</table>

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Histological types with stage distribution</th>
<th>Frequency (%)</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse, large B-cell lymphoma</td>
<td>63 (52.1%)</td>
<td>21</td>
<td>16</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Mediastinal large B-cell lymphoma</td>
<td>12 (9.9%)</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>High-grade B-cell, not otherwise specified</td>
<td>20 (16.5%)</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>High-grade T-cell lymphoma</td>
<td>13 (10.7%)</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Post-transpl. lymphoproliferative disease</td>
<td>5 (4.1%)</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>4 (3.3%)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>4 (3.3%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other features with stage distribution</th>
<th>Frequency (%)</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-symptoms</td>
<td>26 (21.5%)</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td>69 (57.0%)</td>
<td>26</td>
<td>12</td>
<td>7</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment regimen with stage distribution</th>
<th>Frequency (%)</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP or CHOP-R</td>
<td>90 (74.4%)</td>
<td>35</td>
<td>23</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>PMitCEBO</td>
<td>16 (13.2%)</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>DHAP or DHAP-R</td>
<td>8 (6.6%)</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>7 (5.8%)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Additional radiotherapy</td>
<td>47 (38.8%)</td>
<td>27</td>
<td>13</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall stage distribution</th>
<th>Frequency</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>121 (100%)</td>
<td>44</td>
<td>32</td>
<td>21</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>
chemotherapy alone or a combination of chemotherapy and radiotherapy. The majority of patients received CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in standard doses every 3 weeks with dose modification or delays depending on blood counts. Sixteen patients received PMitCEBO (mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine and prednisone), in which case 4 weeks of treatment were regarded as one cycle. Eight patients received DHAP (cytarabine, cisplatin, dexamethasone). Some patients received rituximab in addition to CHOP or DHAP. Radiotherapy was given with megavoltage energies using an involved field technique to tumour doses of 30–36 Gy in 1.8 Gy daily fractions.

PET scans

18F-FDG was produced from an onsite cyclotron and chemistry facility. All PET scans were performed as half-body scans (mid-brain to upper thigh) after a 6 h fast. Emission data were acquired for 5 min per bed position starting approximately 60 min after intravenous injection of 350 MBq 18F-FDG, using an ECAT 951R dedicated PET scanner (Siemens/CTI, Knoxville, TN). Diazepam was given orally to some patients before FDG-administration to avoid muscle/brown fat uptake of the tracer. Images were displayed as whole body projections and as transaxial, coronal and sagittal tomographic sections. When indicated, localised images were produced with attenuation correction. Two experienced nuclear medicine physicians read all scans, and differences were decided by consensus. Interim FDG-PET results were scored as either negative, minimal residual uptake (MRU), or positive [7]. Negative was defined as the disappearance of all abnormal disease-related uptake. MRU was defined as low-grade uptake of FDG in a focus within an area of previously noted disease, reported by the nuclear medicine physicians as likely to represent inflammation but where small volume malignancy could not be excluded. Positive was defined as the persistence or appearance of new areas of increased uptake, thought to be lymphoma-related. PET data were scored with no knowledge of the clinical outcome of treatment.

Statistical analysis

Progression-free survival (PFS) and overall survival (OS) were chosen as end points. PFS was defined as the time from diagnosis to first evidence of progression or relapse, or to disease-related death. OS was defined as the time from diagnosis to death from any cause. Data was censored at other causes of death or if the patients were free of progression/relapse at last follow-up. Survival was depicted using Kaplan–Meier plots. Differences between groups were analysed using the log-rank test. Proportional survival at certain times was determined using life-table statistics. Multivariate proportional hazards (Cox) regression analysis was applied to assess the effects of the relevant prognostic factors on the survival times and the independency of these variables (Backward Wald stepwise procedure). Schoenfeld and Martingale residuals plots were employed to check for assumptions of proportional hazards and linearity. The plots were evaluated visually with the help of locally weighted regression fits. Confidence intervals were given as 1.96 × standard error of the mean. Tests were two-sided with 5% as the level of significance. All data analyses were performed using the statistical software package SPSS 12.0 (SPSS Inc., Chicago, IL) [9, 10].

Results

The study included 121 patients with a median follow-up of 24.4 months for the whole group and 28.5 months for the patients still alive. PFS at 2 and 5 years was 59.2% and 50.7%; OS at 2 and 5 years was 85.1% and 77.7%, respectively. This was compared with the survival of all other HG-NHL registered in the clinic in the inclusion period. For this group of patients, PFS was 63.0% at 2 years and 54.7% at 5 years, and OS was 86.2% at 2 years and 79.3% at 5 years. No significant differences in survival times were found between the patients who received early interim FDG-PET and the rest of all HG-NHL (log rank; PFS, P = 0.51 and OS, P = 0.78) (Figure 1). Eighty-five patients had interim FDG-PET after two cycles and 36 after three cycles of chemotherapy. Fifty-two of these scans were positive, 50 scans were negative and 19 scans showed MRU. During the variable follow-up periods, 49 patients experienced progression and 20 of these patients died. Of the 49 patients with progression, nine failed to reach satisfactory remission during initial chemotherapy. Three of those patients were identified during primary chemotherapy and changed to alternative therapy. Six patients had an incomplete remission after end of treatment.
Of the nine patients with primary refractory disease, eight had positive early interim FDG-PET and one had MRU. Forty patients with initial response to therapy later relapsed. Fifteen of the patients who died came from the FDG-PET positive group. Only two patients from the PET-negative group died. In the 49 patients with progression, 37 were from the FDG-PET positive group, seven had MRU and five had been FDG-PET negative. These distributions are shown in Figure 2.

The mean time from the interim FDG-PET scan to the recognition of progression with conventional methods was 9.6 months (range 0.2–69 months) for the FDG-PET-positive patients, 7.2 months (range 4–18 months) for the MRU patients and 23.6 months (range 4–68 months) for the FDG-PET-negative patients.

Figure 3 shows the survival plots depicting PFS and OS, respectively. Log-rank tests with \( P < 0.0001 \) for PFS and \( P < 0.01 \) for OS demonstrated that the differences between the curves of response groups according to FDG-PET are statistically highly significant. A multivariate Cox regression analysis of PFS was performed, including the following variables: presence of B symptoms, extranodal disease, bulky disease, clinical disease stage, age at diagnosis and early interim PET. The model showed that the value of FDG-PET for prediction of PFS was independent of the other factors \( (\chi^2, P < 10^{-6}) \). The model showed that early response on FDG-PET was by far the most influential of the independent variables. Clinical stage also showed significant independent contributions to the model \( (\chi^2, P < 0.01) \). In a different model, clinical stage was included as a stratifying variable rather than as an independent covariate. This is arguably more appropriate, since the clinical stage is the most important determinant of treatment. In this model, the interim FDG-PET result proved to be the only independent predictor of PFS \( (\chi^2, P < 10^{-5}) \). A Cox regression model with the same variables was fitted for OS (Table 2); similar conclusions were reached. Response on interim FDG-PET and clinical stage proved to be the strongest variables with independent prognostic value, and again FDG-PET was by far the stronger of the two \( (\chi^2, P < 0.05 \text{ for PET and } P < 0.1 \text{ for stage}) \). With clinical stage as a stratifying variable, interim PET was the only variable with independent predictive value \( (\chi^2, P < 0.05) \). An overview of the results of the regression models is given in Tables 2 and 3.

To display the prognostic independence of early interim FDG-PET from the clinical staging, Figure 4 displays survival curves for stages 1–2 and 3–4 separately. A clear separation of the positive and negative curves is seen both for early and advanced stages. It is noteworthy that in the early stages (Figure 4A, C), the MRU curve lies very close to the PET-negative curve, while in the advanced stages (Figure 4B, D), the MRU curve is almost identical to the PET-positive curve.

The results of life table statistics given in Table 4 show the significant differences in 2- and 5-year survival between the FDG-PET-positive and FDG-PET-negative groups.

Seventy-five patients were diagnosed with diffuse or mediastinal large B-cell lymphoma (DLBCL). Being the largest of the histological subgroups in this lymphoma, this group of patients was analysed separately. The results are shown in Figure 5. The survival plots show very little difference from the plots in Figure 3.

**Discussion**

Current standard chemotherapy regimens for HG-NHL (e.g. CHOP) result in less than 50% prolonged disease-free survival [1, 11]. More intensive multidrug combinations failed to improve outcome over CHOP in randomised controlled studies [12]. More recently, the addition of anti-CD20 monoclonal antibody rituximab to CHOP (CHOP-R) has improved outcome modestly [13]. Salvage high-dose chemotherapy with
haematopoietic stem cell support improves outcome of primary refractory or relapsed disease [14]. However, the routine upfront use of high-dose chemotherapy in poor prognosis patients is controversial, as a proportion of these patients are potentially curable with CHOP or CHOP-R alone, and this approach has not yet been proven in randomised controlled studies [15, 16]. This may be partly due to the selection of patients for these trials on the basis of pretreatment prognostic factors, regardless of response to treatment and partly due to the successful early salvage of patients not achieving CR on conventional chemotherapy, with subsequent high-dose treatment.

Therefore, in order for treatment intensification to improve outcome, reliable prognostic indicators are required, to identify those patients who would benefit from intensive treatment strategies and those who could be cured with less intensive and less toxic treatment [17]. At present, the risk stratification is usually based on a number of prognostic factors included in the IPI [3]. The IPI takes into account pretreatment characteristics only, although, for the individual patient, the response to treatment is probably the single most important determinant of outcome. Armitage et al. [18], showed that patients with an early response to induction therapy are more likely to enter a lasting remission. Response is usually assessed by CT. Since CT does not differentiate between a viable tumour mass and residual scar tissue, it has limited value in assessing the degree of response [19].

Molecular imaging reflects the metabolic activity rather than the size of tissue masses. Furthermore, metabolic changes during therapy tend to precede the anatomical changes and this allows for earlier and perhaps more effective changes of therapy. It is well recognised that an early

![Figure 3. Kaplan–Meier plots depicting (A) the progression-free survival and (B) overall survival according to the outcome of early interim FDG-PET.](image)

Table 2. Multivariate analyses of progression-free survival

<table>
<thead>
<tr>
<th>A. Multivariate Cox regression—clinical stage as an independent covariate</th>
<th>Wald</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Step 5</td>
<td>Interim PET, overall</td>
<td>29.000</td>
<td>0.000</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>PET, MRU versus negative</td>
<td>6.484</td>
<td>0.011</td>
<td>4.732</td>
</tr>
<tr>
<td></td>
<td>PET, positive versus negative</td>
<td>26.923</td>
<td>0.000</td>
<td>12.588</td>
</tr>
<tr>
<td></td>
<td>Clinical stage (I–IV)</td>
<td>7.600</td>
<td>0.006</td>
<td>1.420</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Multivariate Cox regression—clinical stage as a stratifying variable</th>
<th>Wald</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Step 5</td>
<td>Interim PET, overall</td>
<td>26.235</td>
<td>0.000</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>PET, MRU versus negative</td>
<td>6.470</td>
<td>0.011</td>
<td>5.308</td>
</tr>
<tr>
<td></td>
<td>PET, positive versus negative</td>
<td>24.025</td>
<td>0.000</td>
<td>13.436</td>
</tr>
</tbody>
</table>

Excluded in previous steps: Age, B-symptoms, extranodal disease, and bulky disease.

Sig., level of significance; Exp(B), Hazard ratio; CI, confidence interval; MRU, minimal residual disease; NA, not applicable.
treatment change in patients who fail to respond to treatment is beneficial [20]. The concept of molecular imaging for prediction of treatment response in NHL is not a new one. There is good evidence that a gallium-67 scan after one to two cycles of chemotherapy has high specificity and is a much better predictor of treatment failure than CT. However, the sensitivity is rather low since the method fails to identify a large number of non-responders. Furthermore, gallium scans are laborious procedures for both the patient and the clinic, with a high radiation burden for the patient [21–24].

The value of an interim FDG-PET performed early during treatment in NHL has been addressed in a number of smaller studies. Hoekstra et al. [4] presented the first report suggesting a role for FDG in the early monitoring of lymphoma therapy in 1993. Thirteen NHL patients were examined after two courses of chemotherapy with a planar gamma camera. Negative scans preceded complete remission in seven of 13 patients and abnormal uptake preceded treatment failure or death in four patients. A previous investigation by our group demonstrated the prognostic properties of an early interim FDG-PET after two to three cycles of chemotherapy has high specificity and is a much better predictor of treatment failure than CT. However, the sensitivity is rather low since the method fails to identify a large number of non-responders. Furthermore, gallium scans are laborious procedures for both the patient and the clinic, with a high radiation burden for the patient [21–24].

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The optimal timing of the interim scan is not clear. It is obviously desirable to assess response and predict prognosis as early as possible. Kostakoglu et al. [6] found FDG-PET after just one cycle of chemotherapy to be a strong predictor of relapse, but follow-up was quite short and the 17 HG-NHL patients were not analysed separately from the 13 HL patients in the study. Römer et al. [8] examined 11 NHL patients at baseline and at days 7 and 42 after initiation of chemotherapy. They found quantitative measures of FDG uptake reduced at day 7 (after one cycle) and further reduced at day 42 (after two cycles), but only the scan after two cycles had significant predictive value. With current chemotherapy schedules, we consider the highest value of an interim FDG-PET is achieved after two cycles of chemotherapy. Due to practical reasons, however, a fraction of the patients included in this study could not be scanned until after the third cycle of chemotherapy.

As in earlier investigations from our group, we chose not to score PET results exclusively as either positive or negative, but as either clearly positive or negative, or belonging to

<table>
<thead>
<tr>
<th>Step 5</th>
<th>Interim PET, overall</th>
<th>Wald</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PET, MRU versus negative</td>
<td>1.334</td>
<td>0.248</td>
<td>3.175</td>
<td>0.447  22.558</td>
</tr>
<tr>
<td></td>
<td>PET, positive versus negative</td>
<td>7.872</td>
<td>0.005</td>
<td>8.277</td>
<td>1.891  36.229</td>
</tr>
<tr>
<td></td>
<td>Clinical stage (I–IV)</td>
<td>3.332</td>
<td>0.068</td>
<td>1.444</td>
<td>0.973  2.142</td>
</tr>
</tbody>
</table>

Excluded in previous steps: Age, B-symptoms, extranodal disease, and bulky disease.

Sig., level of significance; Exp(B), Hazard ratio; CI, confidence interval; MRU, minimal residual disease; NA, not applicable.

In the current study, with 121 patients and a median follow-up of 28.5 months (range 3–101), Kaplan–Meier analyses showed highly significant associations between the early interim FDG-PET results and PFS (P<0.0001) and OS (P<0.01). The multivariate survival analyses proved FDG-PET to be independent of the other prognostic factors and to have stronger predictive value than any of these. In 37 out of 52 PET-positive patients who had disease progression within the follow-up period, the average time from the early interim FDG-PET to first objective sign of progression with conventional methods was 9.6 months. The very high relapse rate in the interim FDG-PET-positive group has a significant clinical implication and suggests that an early change in therapy is indicated in these patients. It is worth noting that the high relapse rate was consistent in early and advanced stages (Figure 4). However, the benefit of early treatment intensification needs to be assessed in randomised controlled trials.
a group with MRU. The reason for this approach was to reflect the daily life in the lymphoma clinic where a certain number of FDG-PET scans are reported to the clinicians as neither clearly positive nor negative. Interestingly, the survival curves in Figure 4 where early and advanced stage patients are displayed separately show that regarding PFS and OS, MRU patients behave like PET-negative patients in the early stages and like PET-positive patients in the advanced stages. One

Table 4. Life table statistics of progression-free and overall survival

<table>
<thead>
<tr>
<th></th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interim PET positive</td>
<td>Minimal residual uptake</td>
</tr>
<tr>
<td></td>
<td>2-year survival</td>
<td>5-year survival</td>
</tr>
<tr>
<td>Interim PET positive</td>
<td>30.3% (CI 16.6–44.1)</td>
<td>59.3% (CI 35.5–82.9)</td>
</tr>
<tr>
<td>Minimal residual uptake</td>
<td>59.3% (CI 35.5–82.9)</td>
<td>88.8% (CI 77.9–99.7)</td>
</tr>
<tr>
<td>Interim PET negative</td>
<td>93.0% (CI 85.4–100)</td>
<td>88.8% (CI 77.9–99.7)</td>
</tr>
</tbody>
</table>
possible explanation is the routine use of involved-field radio-
therapy in stage 1 and 2 patients, which might have eradicated
small-volume residual disease represented by a low-grade
FDG uptake on the interim scan.

The flow charts in Figure 6 indicate that an end-of-
treatment FDG-PET does not provide more prognostic infor-
mation to an early interim FDG-PET that is either clearly
positive or negative. On the other hand, where interim
FDG-PET results were uncertain (MRU), end-treatment PET
seemed a valid predictor of the prognosis, although the
numbers were too small for any firm conclusions to be
drawn.

Our series clearly did not include all high-grade NHL
patients in our clinic during the 8-year period described. As
mentioned before, there has been no deliberate selection of
patients. The clinical characteristics and the survival data of
the included patients were compared with the survival of all
HG-NHL patients recorded in the lymphoma clinic within the
inclusion period (Figure 1). No relevant differences were
found between the patients who had interim FDG-PET and the
background HG-NHL population. However, compared with
the literature, our survival rates seem slightly higher. Some
possible explanations for this are the higher percentage of
stage 1 patients in our clinic and the relatively young median
age. These characteristics are probably due to the referral
pattern, as our clinic is the only clinic in the region with a
radiotherapy facility.

However, our results represent the most substantial body of
evidence so far of the value of an early interim FDG-PET
scan for prediction of PFS and OS in HG-NHL patients. The
Cox regression analyses displayed in Table 2 show early
interim FDG-PET to be correlated stronger with PFS and OS
than any of the important pretreatment prognostic factors, and
independent of all these.

The relatively high number of patients in our study allowed
for a subgroup analysis of the 75 patients with diffuse large
B-cell lymphoma. Within this more homogenous subgroup,
FDG-PET still had a significant value for prediction of PFS
and OS (Figure 5) and survival curves are almost identical to
those of the whole group (Figure 3).

Despite the strong prognostic value of early interim FDG-
PET, there are still a few PET-negative patients who experi-
ence progression, especially with advanced stage. As our data
showed that the prognostic value of early response on interim
PET was independent from other prognostic factors, a logical
extension of the use of interim PET would be to combine it
with the IPI to see if together they enhance the estimation of
long-term prognosis. Unfortunately, this was not possible in
our retrospective cohort, as the IPI score was not always
recorded. On the other hand, there is a range of biological
factors, measurable with immunohistochemistry, polymerase
chain reaction or microarrays, that are increasingly proving to
be predictive of outcome in high-grade lymphoma including
BCL2, BCL6 and CD10 [26–28]. It is possible that one or
more of these factors, in conjunction with FDG-PET as an
early measure of therapy response, could provide a basis for
the selection of patients for treatment adaptation. Other deve-
lopments in functional imaging may also prove to be useful.
The introduction of PET/CT scanners may further improve the
evaluation of treatment response. New tracer developments
may provide a means of monitoring proliferation, using F-18
fluorothymidine, or chemotherapy-induced apoptosis with
\(^{99m}\)Tc-labelled Annexin V, which in early investigations has
proved to be a predictor of tumour response to therapy as
early as 1 day after administration of the first cycle of
chemotherapy [29].

In conclusion, early interim FDG-PET offers a unique tool
for early prediction of long-lasting CR and PFS as well as
OS in patients with HG-NHL. The predictive value of early interim FDG-PET is stronger than many of the known pretreatment prognostic factors and is independent of these. If new therapy regimens include early treatment intensification for selected high-risk patients, who are unlikely to be cured with conventional chemotherapy, early interim FDG-PET could play an important role in the selection of these patients.

Figure 6. Flow charts showing the frequencies of progression after end-treatment according to results of both early interim FDG-PET and end-treatment FDG-PET.
References

2. Canellos GP. CHOP may have been part of the beginning but certainly not the end: issues in risk-related therapy of large-cell lymphoma. J Clin Oncol 1997; 15: 1713–1716.