Use of FDG-PET to monitor response to chemotherapy and radiotherapy in patients with lymphomas

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Abstract. Lymphoma is a heterogeneous group of diseases with many curable subtypes. Primary treatment cures a significant proportion of, but not all, patients. Patients not achieving a complete remission with primary treatment, or those who relapse later, have a second chance of cure with high-dose chemotherapy and haematopoietic stem cell transplantation. Response assessment is therefore crucial in the management of lymphomas. FDG-PET has an emerging role in assessing response, both at the end of and during treatment. This article will review the current published evidence and offer some suggestions on future directions from a clinician's viewpoint.

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Importance of response monitoring

Lymphoma is generally a curable disease, but its treatment is associated with significant short- and long-term toxicity. In the treatment of curable lymphomas [e.g. Hodgkin's lymphoma (HL) and aggressive, i.e. high-grade non-Hodgkin's lymphoma (HG-NHL)], the goal of treatment is to achieve a complete response (CR), which is a prerequisite for cure. Patients who do not achieve a CR by the end of treatment are offered extra or salvage treatment. Accurate remission assessment after the completion of a planned course of treatment is therefore essential, to improve the prognosis of patients with less than CR and to avoid unnecessary treatment, with its associated morbidity, for those achieving a CR. The above will be referred to as "post-treatment remission assessment". Another equally interesting, and potentially more important, form of assessment is "early response assessment". The main appeal of this is the potential to tailor the intensity and type of treatment to the individual patient's prognosis. Response to treatment is arguably the most important single factor determining the prognosis of the individual patient. Response-adapted treatment aims to optimise the balance between cure and toxicity for the individual patient (i.e. to achieve cure with the least possible toxicity). Early response assessment enables this strategy by minimising treatment for good prognosis patients and intensifying treatment for patients with a poor prognosis. This article will address the role of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in (a) post-treatment remission assessment and (b) early response assessment.

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Post-treatment remission assessment

Remission status is usually assessed by repeating the positive pre-treatment staging investigations to ensure normalisation of all abnormal findings. This commonly involves clinical examination, blood tests, CT scanning and, in some cases, histopathological examination of bone marrow and other imaging modalities. Criteria for response assessment and response categories have been established for lymphomas and are commonly known as the "International Workshop Classification" (IWC) [1]. This system relies heavily on anatomical imaging modalities, primarily CT scanning. However, it has long been recognised that lymphoma masses, especially when bulky on presentation, may not disappear completely even if the disease has been eradicated completely. These "residual masses" are formed of mainly necrotic or fibrotic tissue and may continue to shrink during follow-up [2, 3]. Only a small proportion harbour residual viable malignant cells and therefore offering more treatment to all patients with residual masses would involve overtreating many unnecessarily. Follow-up of these masses to treat only the progressing ones may waste valuable time and compromise the chances of cure.

Against this background, the introduction of functional metabolic imaging using FDG-PET has proven to be helpful in accurate assessment of remission post-treatment and

in characterising residual masses. In particular, the role of FDG-PET in assessing residual masses has been widely accepted.

There are more than 20 published studies in the literature on the value of FDG-PET in post-treatment remission assessment [4–30]. Although there are a number of limitations (including variability in patient population, treatment given, duration of follow-up, timing of PET scanning and reporting of outcome as crude relapse rate versus actuarial progression-free survival), some general conclusions can be drawn. Firstly, FDG-PET appears to be more accurate than CT. Secondly, the accuracy of PET is high enough for it to be used as a standard method of remission assessment, either supplementing CT or, as will become quite likely with the increasing use of PET/CT, replacing CT.

Jerusalem et al. reviewed 17 selected studies (eight with mixed HL and NHL, seven HL and two HG-NHL) with a total of 752 patients [31] (Table 1). The overall accuracy of PET was 88–91%. It is of note that PET had a better positive predictive value (PPV) for NHL (100%) than for HL (74%) and a better negative predictive value (NPV) for HL (93%) than for NHL (83%). Stated differently, a positive PET after NHL treatment is strongly predictive of residual disease, but less so in HL. A negative PET after HL treatment is predictive of freedom from residual disease, but slightly less so in HL. This possibly reflects the presence of inflammatory cellular infiltrate in HL and the higher relapse rate of NHL. It is important to remember that within the same disease, the NPV and PPV will vary with the pre-treatment prognosis (e.g. staging and prognostic scoring).

Juweid et al. [19] retrospectively compared the response classification based on the integration of FDG-PET into the IWC (IWC+PET) with IWC alone in 54 patients with aggressive NHL who underwent PET and CT 1–16 weeks (median 4) after four to eight cycles of chemotherapy. Overall, 33 patients had concordant designations and 21 had discordant designations. The CR rate was doubled by IWC+PET compared with IWC (35 versus 17 patients, respectively). More importantly, the progression-free survival (PFS) was more accurately predicted by IWC+PET designation. Four of 17 (24%) patients with CR by IWC alone experienced progression (median 17 months), while 6/35 (17%) patients with CR by IWC+PET had progression (median 17 months). The estimated 3-year PFS for the two groups was 74% and 80%, respectively. For patients designated as having a "partial response" (PR) (19 by IWC and 12 by IWC+PET), 3-year PFS was 62% and 42%, respectively. In general, this study confirms that addition of PET to IWC increases the accuracy of remission assessment; however, the exact figures have to be interpreted with caution owing to the small number of patients, the retrospective design and the fact that the patient population was slightly skewed towards patients with residual abnormalities on CT (69% of patients), which may have magnified the additional value of PET. Validation in larger prospective trials is highly desirable. On the other hand, international efforts are currently underway to incorporate PET/CT into the IWC.

Early response assessment

About 30–40% of aggressive (high-grade) NHL patients fail to achieve CR to initial standard chemotherapy [32], which is a prerequisite for cure. Overall long-term remission is achieved in only 50–60%. This means that a substantial proportion of patients may not be responding to their initial treatment, and an early assessment of response is usually performed using a CT scan after three to four cycles of chemotherapy. PET has been investigated in this role and a number of studies have been published [10, 33–41]. Again, despite the limitations of these studies, some general conclusions can be drawn: (1) CR is readily evident on a repeat PET after one to three cycles of chemotherapy (much earlier than on CT). (2) Such an early CR on PET (presumably reflecting high chemosensitivity) correlates with better prognosis. (3) Early PET is a more accurate predictor of outcome than post-treatment PET.

In aggressive NHL, three large studies are particularly interesting. In a Belgian series [34], 70 patients with aggressive NHL underwent PET at midtreatment. Thirty-three patients were not in CR and none of them achieved a durable CR, whereas 31 of 37 patients with negative scans remained in CR with a median follow-up of 110 days. PET was a stronger prognostic predictor for PFS and overall survival (OS) than an "international prognostic index". A French study [38] on 90 patients with aggressive NHL who had PET after two cycles showed similar results. PET was negative in 54 patients and positive in 36 patients, with 2-year PFS of 82% and 43% ($p<0.0001$) and 2-year OS of 90% and 60% ($p<0.006$), respectively. The largest series is from the UK [39], comprising 121 patients with aggressive NHL with a median follow-up of 28.5 months (range 3–101). The results in this series confirm that response on PET after two to three cycles strongly predicts PFS and OS. 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

Table 1. Predictive value of FDG-PET for post-treatment remission assessment (modified from Jerusalem et al. [31])

	No. of studies	No. of patients	Sensitivity	Specificity	PPV	NPV	Accuracy
Mixed	8	357	79%	94%	82%	93%	91%
HL	7	257	80%	91%	74%	93%	88%
NHL	2	138	67%	100%	100%	83%	88%

associations between FDG-PET results and PFS ($p<0.0001$) and OS ($p<0.01$).

Taken together, the above evidence suggests that an early repeat FDG-PET during treatment is an accurate predictor of PFS and OS and is stronger than other known prognostic factors. FDG-PET offers a more individualised prognostic tool (based on response to treatment), allowing early identification of high-risk patients who are unlikely to be cured by conventional therapy and in whom more intensive treatment is warranted. The clinical utility of this information (apart from its prognostic value) is yet to be evaluated, as there is no firm evidence to date to suggest that early change in therapy in poorly responding patients improves survival. This evidence will need to be obtained from a well-designed randomised controlled trial. However, before such a trial can be conducted, several questions need to be answered. What is the optimal timing of repeat PET (see below)? What is the exact prognosis of patients with PET-positive and PET-negative disease after a few cycles of chemotherapy? In the French study, the PET-positive patients had a 2-year PFS of 43% and a 2-year OS of 60%, which may not be considered by many clinicians to be low enough to change therapy. On the other hand, the PET-positive patients in the British study had a 30% and 16% 2- and 5-year PFS, respectively. This may have been due to the use of the "minimal residual uptake" (MRU) category, which has an intermediate prognosis between the PET-positive and -negative groups and helps in further separating the two groups. Although it is logically plausible, this three-group system suffers from the limitation of the subjectivity of the MRU designation, which needs a more reproducible definition. An ideal future study would involve prospective study of the prognostic value of early repeat PET at a fixed point in time during treatment, in a uniformly treated homogeneous population, without a change of therapy on the basis of PET, and with some way of quantitatively assessing response and accurately defining a three-group system. The accurate information obtained could then be used to inform the design and sample size calculation of a prospective randomised trial to test the value of early change in therapy on the basis of PET. The National Cancer Research Institute (NCRI) in the UK is currently developing a study to address this issue [42].

Similar data are available on the value of early repeat PET in assessing early response and prognosis in HL. The largest series is from the UK [40] and includes 85 patients who had a repeat PET after two to three cycles of chemotherapy and were followed up for a median of 3.3 years. Sixty-three patients had negative FDG-PET scans, nine had MRU and 13 had positive scans. Three patients from the PET-negative group and one patient from the MRU group relapsed. In the PET-positive group, nine patients had disease progression and two died. Survival analyses (with MRU patients analysed with the PET-negative group) showed highly significant associations between early interim FDG-PET and PFS ($p<0.0001$) and OS ($p<0.03$). The estimated 5-year PFS was 91.5% and 38.5% for PET-negative and PET-positive groups, respectively. The predictive value of FDG-PET was independent of clinical stage. It is also worth noting in this study that all advanced-stage patients with positive interim FDG-PET relapsed within 2 years. In another prospective series from Denmark [41], 77 consecutive new patients with HL underwent a PET scan at staging, after two and four cycles of chemotherapy and at the end of treatment. Median follow-up was 23 months. After two cycles of chemotherapy, 61 patients had a negative PET and only three of this group had disease progression. In the remaining 16 patients with positive PET, 11 had disease progression and two died. Survival analysis showed a strong association between PET after two cycles and PFS ($p<0.001$) and OS ($p<0.01$). PET was as accurate after two cycles as later during treatment and was superior to CT at all times.

The clinical utility of these data needs to be tested in well-designed prospective trials. In early stage HL, where cure rates are high and the main concern is to minimise long-term toxicity of treatment, PET may help in achieving this goal while maintaining cure rates. An example is the UK's NCRI trial [42], where patients with non-bulky stage 1–2A HL receive three cycles of chemotherapy and a PET scan. Patients with positive PET receive involved-field radiotherapy (IFRT). Patients with negative PET are randomised to receive IFRT versus not. The goal is to assess whether omitting radiotherapy in PET-negative patients will be possible without reducing cure rates. In advanced disease, where the prognosis is worse, PET may be used to select suboptimally responding patients for more intensive treatment. Again, this needs to be tested in randomised trials.

Timing of early response assessment

Few studies have addressed the issue of timing of repeat PET for early response assessment. Romer et al. [43] compared repeat PET at day 7 and day 42 from start of chemotherapy and calculated metabolic rates for FDG in 11 NHL patients. FDG uptake at 42 days after therapy was superior to day 7 parameters in predicting long-term outcome. Kostakoglu et al. [44] performed dual-head coincidence camera PET on 30 patients (17 NHL and 13 HL) after one cycle of chemotherapy. Of the 30 patients, 23 had a repeat PET after completion of treatment. Post-cycle-1 PET was predictive of outcome and was superior to end of treatment PET. Hutchings et al. [41] compared post-cycle-2, post-cycle-4 and end of treatment PET and found that PET after two cycles is as predictive as PET performed later during treatment. In centres using PET for early response assessment, including ours, post-cycle-2 PET seems to be the preferred choice at present. It probably presents a balance between giving enough chemotherapy to meaningfully assess CR and performing the assessment early enough to show chemosensitivity and good prognosis (i.e. separate early from late CR, which is prognostically important).

Response to treatment of relapsed disease

Very few studies have addressed the value of PET in relapsed disease in the context of high-dose chemotherapy and haematopoietic stem cell transplantation. Some studies were done post-reinduction chemotherapy and pre-transplantation [45, 46] while others were done after transplantation [47, 48]. Although PET generally seems to be helpful, it is difficult to draw firm conclusions on the exact prognostic value or optimal timing from the current data. More homogeneous studies are required in this respect.

In conclusion, FDG-PET is a very valuable tool in response monitoring of lymphoma treatment. It is likely to be incorporated in "response classification systems" and be used in clinical trials. Early response assessment may be used in the future to modify treatment, but more studies are needed for this role to evolve.

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