

ORIGINAL ARTICLE

Prognostic value of FDG-PET scan imaging in lymphoma patients undergoing autologous stem cell transplantation

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We conducted a retrospective analysis of 50 lymphoma patients (Hodgkin's disease and non-Hodgkin's lymphoma) who had an ¹⁸F-fluoro-deoxyglucose positron emission tomography (FDG-PET) scan after at least two cycles of salvage chemotherapy and before autologous stem cell transplantation (ASCT) at our institution. The patients were categorized into FDG-PET negative (N=32) and positive (N=18) groups. The median follow-up after ASCT was 19 months (range: 3–59). In the FDG-PET-negative group, the median progression-free survival (PFS) was 19 months (range: 2–59) with 15 (54%) patients without progression at 12 months after ASCT. The median overall survival (OS) for this group was not reached. In the FDG-PET-positive group, the median PFS was 5 months (range: 1–19) with only one (7%) patient without progression at 12 months after ASCT. The median OS was 19 months (range: 1–34). In the FDG-PET-negative group, chemotherapy-resistant patients by CT-based criteria had a comparable outcome to those with chemotherapy-sensitive disease. A positive FDG-PET scan after salvage chemotherapy and prior ASCT indicates an extremely poor chance of durable response after ASCT.

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Introduction

A significant portion of lymphoma patients are cured by primary treatment with anthracycline-containing chemotherapy regimens.^{1,2} For the majority of patients who are

primary refractory or who relapse after complete response (CR), a combination of salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) is considered the standard of care. In non-Hodgkin's lymphoma (NHL), the clinical benefit of adding high-dose chemotherapy and ASCT is limited only to those patients with disease sensitive to salvage chemotherapy.^{3,4} In Hodgkin's disease (HD), some reports showed that a small portion of patients who were resistant to salvage chemotherapy can achieve cure after high-dose chemotherapy and ASCT.^{5,6} However, these reports might be subject to selection bias and most clinicians agree that even in HD, response to salvage chemotherapy is highly predictive of outcome after ASCT.⁷

Traditionally, conventional computed tomography (CT) scans have been used as the radiographic assessment tool in standardized response criteria in patients with lymphoma.^{8,9} Clinical trials that established the benefit of ASCT in chemotherapy sensitive patients used the CT-based response criteria. Chemosensitivity to salvage therapy was defined as a reduction greater than 50% in all measurable disease for at least 1 month.^{3,10}

Functional imaging with ¹⁸F-fluoro-deoxyglucose-positron emission tomography (FDG-PET) scan provides additional information to conventional anatomic imaging by CT scan. It is superior in characterization of residual masses that are a common finding after treatment of lymphoma.¹¹ Elstrom *et al.*¹² demonstrated that most lymphoma subtypes take up FDG and can be detected by FDG-PET imaging. One hundred percent of patients with large B-cell lymphoma and 98% of patients with HD had FDG-PET-positive disease.¹²

FDG-PET scans have been used to predict outcome after initial treatment. In patients with HD undergoing initial treatment, a positive FDG-PET scan after 2 cycles of chemotherapy was superior to CT scan for prediction of poor progression-free survival (PFS).¹³ In HD and NHL patients, detection of activity by FDG-PET at the end of treatment had a higher predictive value for relapse than CT scan imaging.¹¹ Recently, it has been suggested that FDG-PET results should be incorporated in the standardized response criteria for NHL.¹⁴

To determine whether functional imaging with FDG-PET might predict the clinical outcome of patients

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undergoing ASCT, we conducted a retrospective analysis of lymphoma patients who had an FDG-PET scan after at least two cycles of salvage chemotherapy and before high-dose chemotherapy and ASCT.

Patients and methods

Patients and treatment

The study was approved by the institutional review board at the University of Pennsylvania.

We reviewed a database of 267 patients who underwent ASCT for relapsed or primary refractory HD (90 patients) or NHL (177 patients) in our institution between January 1999 and September 2005. Initially, we identified 53 non-consecutive patients who had an FDG-PET scan after at least two cycles of salvage chemotherapy, but before ASCT. Three patients were not included in the final analysis. One had a metabolically active area at the site of an obvious superficial skin infection and two patients had FDG-PET scans with minimal focal activity, which were deemed 'non-conclusive' after the review by our radiologist. Patients with FDG-PET scans more than 3 months before ASCT and those with second relapse after ASCT were excluded from the study.

Classification of risk and response

Results of radiographic studies including measurements of individual lesions on CT scans and standardized uptake values (SUV) of FDG-PET were retrieved from medical records. Before starting salvage chemotherapy, relapsed disease or progression on primary therapy was documented by conventional CT scans. FDG-PET results were categorized as negative when no evidence of lymphoma was found by the radiologist at the time of the scan. FDG-PET results were categorized as positive when the intensity of any non-physiological signal was >2.5 SUV, which is the measurement of FDG uptake often used to differentiate between benign and malignant lesions.^{12,15-17} Patients with diffuse bone marrow activity while on growth factors and with mild symmetric supraclavicular adipose tissue activity in the absence of focal lesions were categorized into the FDG-PET negative group.

Patients within each group (FDG-PET negative and positive) were also evaluated for their status of sensitivity to the salvage chemotherapy by CT scan. Traditional criteria were strictly followed (at least 50% reduction in measurable disease) to assign either chemotherapy-sensitive or -resistant disease status by CT scan. Progression or relapse after ASCT was determined by standard CT criteria. Most patients received the first response assessment at approximately 100 days after ASCT or earlier if clinical signs of progression developed.

Statistical analysis

The closing day for analysis was January 17, 2006. All survival distributions and rates were calculated according to the Kaplan-Meier method. PFS was measured from the day of stem cell infusion (day 0) until the time of disease relapse or progression, or disease-related death, with

censoring at the time of death unrelated to lymphoma or at last follow-up. Overall survival (OS) was measured from day 0 until the date of death, with censoring at the time of last follow-up. The exact 95% confidence intervals (CI) were calculated for the 1 year PFS using the binomial distribution. Univariable hazard ratios (HR) for PFS were derived from the Cox proportional hazards regression model and *P*-values were calculated for the log-rank test. All *P*-values are two-tailed. Statistical analysis was performed with the STATA software (STATA Corporation v.8, Research Park, TA, USA, 2003).

Results

We identified 50 patients who were divided into two groups based on the qualitative results of the FDG-PET scan performed after salvage chemotherapy and before transplant. The overall response rate (CR and partial response) at day 100 after ASCT for the 50 analyzed patients was not

Table 1 Patient characteristics

Patients	FDG-PET negative (%)	FDG-PET positive (%)
Number	32	18
Age		
Median	46	45
Range	19-73	23-64
Sex		
Male	17	12
Female	15	6
Diagnosis		
HD	12 (37)	7 (39)
NHL		
DLBC	14 (43)	7 (39)
FL	1 (3)	1 (6)
MCL	3 (9)	2 (11)
MZL	1 (3)	1 (6)
T-cell	1 (3)	0 (0)
Salvage chemotherapy		
ICE	24 (75)	13 (81)
ESHAP	3 (9)	2 (12)
High-dose chemotherapy		
BCV	25 (78)	15 (83)
Cy/TBI	2 (6)	1 (6)

Abbreviations: BCV = carmustine 300 mg/m²/day i.v. day -6, cyclophosphamide 1500 mg/m²/day i.v. days -5, -4, -3, and -2 (total dose 6000 mg/m²), etoposide 350 mg/m² i.v. every 12 h on days -5, -4, and -3 (total dose 2100 mg/m²); Cy/TBI = high-dose cyclophosphamide 60 mg/kg/day on days -5 and -4 (total dose 120 mg/kg), total body irradiation at 200 cGy/dose twice a day on days -3, -2, and -1 (total dose 1200 cGy); DLBC = diffuse large B-cell lymphoma; ESHAP = etoposide 40 mg/m²/day i.v. days 1, 2, 3, 4 (total dose 160 mg/m²), methylprednisolone 500 mg/days i.v. days 1, 2, 3, 4, 5 (total dose 2500 mg), cytarabine 2 gm/m²/day i.v. day 5, cisplatin 25 mg/m²/days i.v. day 1, 2, 3, 4 (total dose 100 mg/m²); FL = follicular lymphoma; HD = Hodgkin's disease; ICE = ifosfamide 2000 mg/m²/day i.v. days 1, 2, 3 (total dose 6000 mg/m²), carboplatin 300 mg/m²/day i.v. day 1, etoposide 75 mg/m²/day i.v. day 1, 2, 3 (total dose 225 mg/m²) or etoposide 100 mg/m²/day i.v. days 1, 2, 3 (total dose 300 mg/m²), ifosfamide 5000 mg/m²/day i.v. day 2, carboplatin AUC 5 i.v. day 2; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NHL = non-Hodgkin's lymphoma.

statistically different from the remaining 217 lymphoma patients in the ASCT database who did not undergo FDG-PET (74 vs 66%; $P=0.3$). There were various reasons for patients to undergo FDG-PET scanning before ASCT and included clarification of CT scan findings and physician's preference.

The FDG-PET-negative group included 32 patients (64%) and the FDG-PET-positive group included 18 patients (36%). The characteristics of each group are described in Table 1. The most commonly used salvage chemotherapy regimens were ifosfamide, carboplatin, etoposide (ICE), and etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP). Many patients with CD20-positive NHL received rituximab as part of their salvage regimens (375 mg/m² on day 1 with each cycle of salvage therapy). The most common conditioning regimens (high-dose chemotherapy) were carmustine, cyclophosphamide, etoposide (BCV) and high-dose cyclophosphamide with total body irradiation (Cy/TBI). Of note, two patients in the FDG-PET-positive group and seven patients in the FDG-PET-negative group received consolidative radiation to areas of FDG-PET positive or bulky disease after recovering from the toxicities of ASCT.

Age, lymphoma subtype, salvage treatment and conditioning regimen were well-balanced between the two groups. The median follow-up for patients without progression was 19 months after ASCT (range: 3–59). There were no early transplant-related deaths.

The median PFS was 19 months (range 2–59 months) in the FDG-PET-negative group and 5 months (range 1–19) in the FDG-PET-positive group ($P<0.001$; Figure 1a). The median OS was not reached in the FDG-PET-negative group and was 19 months in the FDG-PET-positive group ($P=0.04$; Figure 1b). Although 15 patients (54%; CI: 34–72%) in the FDG-PET-negative group remain without progression at 12 months after ASCT, only one patient (7%; CI: 0.2–32%) in the FDG-PET-positive group remains without progression ($P=0.002$). The only patient without progression at 12 months from the FDG-PET-positive group had HD and received consolidation therapy with external beam radiation to the area of the FDG-PET-positive lesion in the mediastinum. There are currently two more patients without progression in the FDG-PET-positive group, but both have a follow-up less than 1 year.

Conventional CT scans after at least two cycles of salvage chemotherapy were available for 47 of the 50 of patients in the study. In the FDG-PET-negative group, 24 (77%) patients had chemosensitive disease and seven (23%) patients had chemoresistant disease by CT-based response criteria (Table 2). In the FDG-PET-positive group, five (31%) patients had chemosensitive disease and 11 (69%) patients had chemoresistant disease by CT-based response criteria (Table 2).

Among patients with chemoresistant disease by CT scan, 10 (100%) out of 10 with positive FDG-PET progressed within 12 months after ASCT; however, only one (20%) out of five patients who had negative FDG-PET scan progressed at 12 months after ASCT ($P=0.004$). In this group of chemoresistant patients with negative FDG-PET, five patients had a diagnosis of HD with mediastinal involvement and one patient had advanced diffuse large B

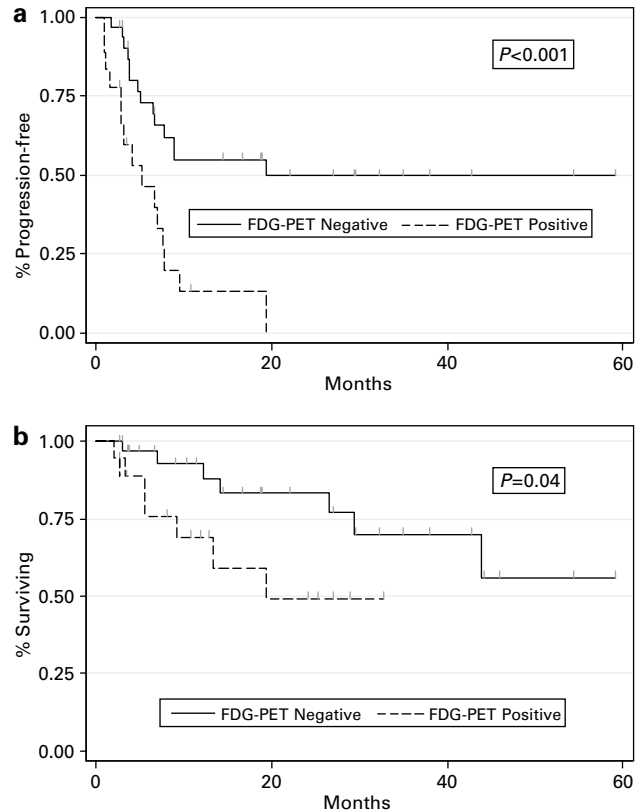


Figure 1 (a) PFS for the FDG-PET-negative group (median PFS: 19 months; range: 2–59) and-positive group (median PFS: 5 months; range: 1–19). (b) OS for the FDG-PET-negative group (median OS not reached) and-positive group (median OS: 19 months; range: 1–34).

Table 2 Correlation between CT scan-based response and FDG-PET result after at least two cycles of salvage chemotherapy for 47 patients who had both studies available for review

	FDG-PET negative (%)	FDG-PET positive (%)
Sensitive by CT	24 (77)	5 (31)
Non-sensitive by CT	7 (23)	11 (69)

Abbreviations: CT = computed tomography; FDG-PET = ¹⁸F-fluorodeoxyglucose positron emission tomography.

cell NHL. The most frequent salvage chemotherapy was ICE (four patients) and high-dose chemotherapy was BCV (three patients). The patient who experienced progression at 9 months had diagnosis of HD and died in 14 months after the ASCT. One of the four patients without progression received consolidative radiation to the area of bulky disease. Out of 22 patients with chemosensitive disease by CT who had negative FDG-PET, 10 (45%) patients remain without progression at 12 months.

For patients with chemoresistant disease by CT-based response criteria, the HR for progression after ASCT was 1.5 (CI (0.71–3.3); $P=0.3$) when compared to the chemosensitive patients. For patients in the FDG-PET-positive group, the HR for progression after ASCT was 3.4

Table 3 HR for progression after ASCT based on CT scan vs FDG-PET vs both CT and FDG-PET after at least two cycles of salvage chemotherapy

	N	HR	CI	P-Value
Non-sensitive by CT	18	1.5	(0.7–3.3)	0.3
Sensitive by CT	29	—	—	—
FDG-PET positive	18	3.4	(1.6–7.1)	<0.001
FDG-PET negative	32	—	—	—
Non-sensitive by CT and FDG-PET positive	11	4.2	(1.7–10)	<0.001
Sensitive by CT and FDG-PET negative	24	—	—	—

Abbreviations: ASCT = autologous stem cell transplantation; CT = computed tomography; CI = confidence interval; FDG-PET = ¹⁸F-fluoro-deoxyglucose positron emission tomography; HR = hazard ratios.

(CI (1.6–7.1); $P < 0.001$) when compared to the FDG-PET negative group. For the 11 patients who had both chemoresistant disease by CT and positive FDG-PET, the HR for progression after ASCT was 4.2 (CI (1.7–10); $P < 0.001$) when compared to the 24 patients with chemosensitive disease by CT and negative FDG-PET (Table 3).

Discussion

In patients with relapsed or primary refractory lymphomas, the response to salvage chemotherapy is highly predictive of outcome after ASCT.^{4,6} However, the traditional evaluation of response with CT-based response criteria may not allow as accurate a risk stratification as previously believed. Functional imaging with FDG-PET has growing prominence in the diagnosis, staging and response evaluation of patients with lymphoma.^{11,13,14} We have thus evaluated FDG-PET as a predictor of outcome for patients with relapsed or primary refractory lymphoma undergoing ASCT. In this retrospective analysis of 50 patients, we found that FDG-PET is a superior predictive tool than conventional CT scanning. In fact, an incomplete metabolic response to salvage chemotherapy as indicated by a positive FDG-PET scan defined a population of patients who have an extremely poor prognosis with standard ASCT.

Our study confirms findings from a few smaller reports on the role of FDG-PET before ASCT in patients with relapsed or primary refractory lymphoma.^{18–21} The only larger study included 60 patients with chemosensitive HD and NHL who underwent either autologous or allogeneic transplantation.²² Each of the previous reports had a different design, size, entry criteria and methodology which resulted in the wide range of values attained.

For example, median PFS after ASCT in the FDG-PET-positive groups ranged from less than 4 months in a study that included chemosensitive and chemoresistant patients to over 13 months in a study with chemosensitive patients only. However, even in the study that included only chemosensitive patients by CT, less than 15% (four out of 30 patients) in the FDG-PET-positive group remained without progression at the conclusion of the study. In our analysis, the median PFS of 5 months after ASCT in the FDG-PET-positive group agrees with results of two smaller

studies that included both chemosensitive and chemoresistant patients by CT criteria.

It had been proposed that FDG-PET scan after salvage chemotherapy might be a better predictor of clinical outcome after ASCT when compared to CT scan.^{18,20} In our analysis, the HR for progression after ASCT based on the FDG-PET result was higher when compared to the HR based on CT scan criteria. Combination of unfavorable FDG-PET and CT scan results produced an even higher HR (Table 3). Although the sample size is limited, this finding suggests that combination of anatomic and functional imaging has superior predictive ability for progression after ASCT when compared to either modality alone. This conclusion is in concordance with the findings of Juweid *et al.*¹⁴ who found that when compared to CT-based criteria only, addition of FDG-PET imaging provides a more accurate response classification in patients with NHL.

Our analysis also included a group of 18 patients with chemoresistant disease by the traditional CT-based response criteria who underwent FDG-PET prior ASCT. To our knowledge, this is the largest group of patients with these characteristics published in the literature. All had less than 50% reduction in their disease after salvage chemotherapy, but proceeded to ASCT. We noted that the small group of chemoresistant patients who had negative FDG-PET scans experienced prolonged PFS, which was comparable to those with chemosensitive disease and negative FDG-PET scan. Similar findings have been described in a different setting by Juweid *et al.*¹⁴ who recently suggested that FDG-PET might provide additional benefit to conventional CT scans in predicting clinical outcome for patients undergoing induction treatment for NHL. Their 10 patients who had only partial response by CT scan and negative FDG-PET, had comparable PFS to those in CR by CT scan and negative FDG-PET.¹⁴ It is likely that anatomic imaging with CT scan cannot distinguish between a scar and a residual tumor. Additional information from functional imaging appears important in both assessment of response to primary therapy and assessment of true sensitivity to salvage chemotherapy before ASCT.

As a retrospective analysis of all lymphoma patients undergoing ASCT in a single institution, our study has several limitations including a potential selection bias. However, there were no statistically significant differences

in overall response rate at day 100 after ASCT in patients who underwent FDG-PET and those who did not. The significance of the FDG-PET findings before ASCT could vary among the subtypes of lymphoma. But it has been shown that active disease can be detected by FDG-PET in the subtypes of lymphomas included in this study.¹² Other issues, such as optimal timing of FDG-PET scanning during salvage chemotherapy and the interpretation of non-conclusive results were beyond the scope of this analysis and will need to be addressed in future studies.

In spite of its limitations, our report provides several important conclusions. Functional imaging with FDG-PET scans after salvage chemotherapy has an important role in predicting outcome after ASCT. It confirms that a positive FDG-PET scan after salvage chemotherapy and before ASCT indicates an extremely poor chance of achieving a prolonged response after ASCT. When patients with relapsed or primary refractory lymphoma remain FDG-PET positive after optimal salvage chemotherapy, they should consider entering a clinical trial. Future clinical trials might utilize more intensive conditioning regimens before ASCT, consolidative external beam radiation after ASCT, allogeneic bone marrow transplant or novel therapeutics for these patients. For example, a recent study showed that patients with chemoresistant disease by CT scan criteria might benefit from addition of radioimmunotherapy to the conventional conditioning regimen.²³

Our finding of prolonged PFS in patients with chemoresistant disease by CT-based criteria and negative FDG-PET is based on a limited number of patients, but it appears important. This observation generates a hypothesis that patients with chemoresistant disease by CT scan who have negative FDG-PET scan might benefit from ASCT. This finding might apply especially to patients with mediastinal HD who represented the majority of patients in the group.

In the near future, new technology that combines an FDG-PET scan and a low-dose, non-contrast CT scan in a single instrument will be used more frequently in patients with lymphoma.^{24,25} At this point, it needs to be established whether the new FDG-PET/CT fusion technology is equivalent to or superior to dedicated scanners. However, we predict that some combination of anatomic and functional imaging will replace traditional CT scans in the process of selecting appropriate patients with relapsed or primary refractory lymphoma for ASCT.

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