Published in final edited form as:

Leuk Lymphoma. 2010 March ; 51(3): 439–446. doi:10.3109/10428190903560198.

FDG-PET Report Interpretation as Predictor of Outcome in Diffuse Large B-Cell Lymphoma Including Analysis of “Indeterminate” Reports

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Abstract

This study evaluates the predictive value of post-therapy FDG-PET, including indeterminate studies, following curative intent therapy in Diffuse Large B-cell Lymphoma (DLBCL).

Consecutive, patients from September 2002–December 2005 were prospectively offered enrollment in an observational registry. Available FDG-PET reports after primary therapy were interpreted by hematologists-oncologists as positive, negative or indeterminate.

125 DLBCL patients had median follow-up of 35.2 months. Ninety-three percent were treated with R-CHOP-like therapy. Twenty percent of PET reports were judged indeterminate. EFS at 3 years for the negative and indeterminate groups was 85% and 71% respectively ($p=0.28$ by log-rank). OS at 3 years for negative, indeterminate, and positive groups was 89%, 88%, and 48%. Combining pre-therapy International Prognostic Index (IPI) with the post-therapy FDG-PET result added to the predictive value of the study for patients. Three-year EFS for patients with low or low-intermediate IPI risk and an indeterminate FDG-PET report was 93% while high or high-intermediate pre-therapy IPI patients had a 3 year EFS of 45% ($p<0.02$). Interpreting FDG-PET reports following curative intent chemotherapy in patients is informative but imprecise, and incorporation of pre-therapy prognosis can improve predictive utility.

Keywords

Diffuse large B-cell lymphoma; FDG-PET; prognosis

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Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Introduction

An estimated 65,980 new cases of non-Hodgkin's Lymphoma (NHL) will be diagnosed in the United States in 2009,¹ with approximately 30% of these classified as diffuse large B-Cell lymphoma (DLBCL).² Response to primary treatment in DLBCL is highly predictive of long-term outcome for this disease.

Patients achieving less than a complete remission, or with subsequent recurrence, often require salvage treatment with fewer than 30% of these patients achieving durable remissions.³ Functional imaging with 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) has improved the accuracy of restaging evaluations after primary treatment for NHL.^{4–11} Recently, FDG-PET interpretations have been incorporated into clinical trial response criteria and treatment guidelines.^{12,13} Concurrently, the radiology community published consensus guidelines to encourage more consistent scan interpretation.¹³

Research publications and guidelines to date have focused on dichotomous FDG-PET reports. In practice however, issues such as reader variability, technical limitations and confounding factors lead to a subset of scans where the result is neither definitively positive nor definitively negative. For the treating physician this circumstance can be challenging. Few published works have reported the frequency or the predictive value of equivocal FDG-PET studies in DLBCL. We analyzed data from a large prospective observation study to assess the role of FDG-PET in predicting event-free survival (EFS) and overall survival (OS) in patients with DLBCL following primary treatment given with curative intent, with particular attention to the frequency and outcomes of patients with “indeterminate” FDG-PET reports..

Materials and Methods

Study Population and Design

Patients for this analysis came from those prospectively accrued to the University of Iowa-Mayo Lymphoma SPORE Molecular Epidemiology Register (MER). Patients were enrolled at the Mayo Clinic beginning September 1, 2002 and at the University of Iowa beginning January 1, 2003. Consecutive cases of NHL who were within 9 months of the time of initial diagnosis at the time of presentation, a United States (US) resident, and age 18 years and older were offered enrollment to the MER. Exclusion criteria included HIV-positive and not competent to participate in an interview in English.

This MER is an observational database in which neither therapeutic nor diagnostic management is prescribed, and management may take place within or extramural to the enrolling institution. Baseline clinical data, pathology data, treatment data, and all follow-up data are entered into an integrated relational database. Initial data include age, stage, LDH, number of extranodal sites, and performance score at diagnosis. There are no requirements for formal staging or restaging regarding CT scans or PET scans. Data are collected on baseline assessment, the initial course of therapy as well as subsequent therapies. Responses are assessed by treating physicians, with interpretation by SPORE investigators when necessary. A central pathology review of all cases is performed, and cases are classified into the World Health Organization (WHO) Classification of Hematopoietic and Lymphoid Tissues.¹⁴ Patients are staged according to the Ann Arbor staging system.¹⁵

All patients are systematically followed every six months (± 4 weeks) for the first three years after diagnosis, and then are followed annually thereafter. At each follow-up time point, patients are either met in the clinic or contacted by phone to determine vital and disease

status. When there is disease recurrence or progression, or a new cancer, medical records are abstracted and entered into the SPORE database. For patients who report no change in their disease status and who have not been evaluated at one of our institutions in the last year, this is verified in a short letter to the local medical director. For the participants who are lost to follow-up, passive sources track the outcomes.

This study was conducted in accordance with the ethical guidelines mandated by the Declaration of Helsinki. All patients in the University of Iowa/Mayo Clinic SPORE who entered the MER signed written informed consent. The University of Iowa and the Mayo Clinic institutional boards approved this study.

Data from the SPORE MER along with individual medical records from patients with DLBCL consecutively enrolled up through December 31, 2005 were reviewed. Those with primary central nervous system lymphoma (PCNSL) and composite lymphoma histologies were excluded. Patients with an available FDG-PET report within 1–16 weeks after completion of primary therapy were analyzed. Mid-course scans were not analyzed.

De-identified FDG-PET reports issued for the medical record were separately interpreted as positive, negative or indeterminate by three hematologist-oncologists. Reviewers were blinded to other clinical information. Reports were labeled positive or negative if all three interpreters independently agreed. All others were considered indeterminate.

Statistical Analysis

Statistical analysis focused on the estimation and comparison of event-free and overall survival. Events were defined as documented DLBCL recurrence, subsequent therapy, or death, and event free survival was defined as time from diagnosis to any event. Survival estimates were obtained with the methods of Kaplan-Meier. Survival comparisons between and within positive, negative and indeterminate groupings as well as IPI groupings were performed with log-rank tests. All tests were two-sided and assessed for significance at the 5% level.

Results

Patient Cohort and Characteristics

From September 2002 to December 2005, 261 consecutive patients with newly diagnosed DLBCL were enrolled in the University of Iowa/Mayo Lymphoma SPORE registry. Of these, 90 patients were excluded as they did not have an FDG-PET within one to sixteen weeks after completion of primary treatment. Thirty-seven patients with composite lymphoma histology were excluded, as well as, nine patients with PCNSL. The remaining 125 evaluable patients had a median follow-up of 35.2 months (range of 3.9 to 66.7 months). There was no significant difference in EFS (HR = 0.84, $p=0.38$) or OS (HR = 1.09, $p=0.74$) between the 125 patients eligible for the study compared to the 136 excluded patients. One hundred and four (83%) of the post-treatment scans were performed 3–8 weeks after completion of primary chemotherapy.

Patient and disease characteristics and primary treatment regimens are outlined (Table I). The median age of this cohort was 59. Most patients had an Eastern Cooperative Group Performance Status of 0–2. The majority of patients had stage III or stage IV disease. R-CHOP was the most common primary chemotherapy regimen selected. The R-CHOP+ category included experimental agents or intrathecal methotrexate. R-EPOCH, R-ICE and R-CVP were also utilized. Other regimens included a variety of previously described second generation or ad hoc anthracycline based chemotherapy combinations. Rituximab was

administered to 118 (95%) patients and 122 (98%) of patients received an anthracycline program. Radiation therapy was included in the primary treatment for 25 (20%) patients.

FDG-PET Report Interpretation by Hematologist-Oncologists

The restaging studies utilized for analysis were FDG-PET with computerized tomography (CT) for 86 patients (69%) and FDG-PET alone for the remaining 39 patients. The distribution of FDG-PET report interpretations is shown in Figure 1. Sixty-nine reports (55%) were interpreted as negative by all three reviewers. Thirty one reports (25%) were scored positive by all three reviewers. Twenty five reports (20%) were analyzed as indeterminate, meaning there was disagreement among the reviewers or all three reviewers felt the report was indeterminate. The largest group of indeterminate reports was composed of those in which two reviewers scored the report as negative and the one reviewer interpreted the report as indeterminate. The second largest group was the one in which two reviewers found the report positive and one scored it as indeterminate. All possible scoring patterns were represented. The rate of “indeterminate” scoring was similar among the three reviewers ranging from 9 to 11%. Each reviewer disagreed with the others with similar frequency.

Eight FDG-PET studies were completed less than three weeks after completion of primary treatment. Of these studies, one was indeterminate. The indeterminate rate did not vary meaningfully between FDG-PET alone (22%) and FDG-PET/CT (18%).

Event-free Survival and Overall Survival by FDG-PET Report Interpretation

The distribution of clinical events within indeterminate scoring patterns is illustrated in Figure 1. Three of seven events occurred in patients where none of the reviewers interpreted the report as positive, and four occurred in patients where at least one reviewer interpreted the report as positive. EFS and OS by FDG-PET interpretation are shown in Figure 2. EFS is not reported for the positive group, as in many cases the FDG-PET scan led directly to the salvage treatment which was considered an event (Figure 3b). EFS at 2 years was 80% for the indeterminate group and 88% for the negative group. At three years the EFS was 71% for the indeterminate group and 85% for the negative group. OS at three years was similar for the indeterminate and negative groups at 88% and 89% respectively, while those with a positive report had 48% three year OS.

Pre-therapy International Prognostic Index and Predictive Value of the Post-therapy FDG-PET Report

For this cohort of 125 patients, EFS and OS during the follow-up period varied significantly by International Prognostic Index¹⁶. Three-year EFS was 84%, 77%, and 55% and 50% for low, low-intermediate, high-intermediate and high risk prognostic categories respectively ($p = .002$ for trend test). Three-year OS by IPI risk categories was 90%, 81%, 72% and 61% respectively ($p=.004$).

Details regarding estimates of EFS and OS by pre-therapy IPI group within each FDG-PET interpretation group are demonstrated in Table III. Three-year EFS for the 14 patients with low or low-intermediate IPI risk and an indeterminate FDG-PET report was 93% while high or high-intermediate pre-therapy IPI patients had a 3 year EFS of 45%. The IPI also further discriminated among patients with negative FDG-PET report interpretations with only one event among 24 patients with low-risk IPI, yet a 29% event rate among those with high-intermediate or high risk. In patients with indeterminate or negative PET reports, the trend in OS across IPI categories approached but did not achieve statistical significance. For patients with positive reports, 3-year OS for low, low-intermediate, high-intermediate or high risk prognosis by pre-therapy IPI was 82%, 44%, 28% and 0% respectively ($p=0.002$).

Specific Patient Outcomes

Details regarding the clinical course of 25 patients found to have indeterminate reports are depicted in Figure 3a. Three patients underwent diagnostic biopsy within three months of the FDG-PET scan and all were negative for DLBCL. The biopsy findings were sarcoid, benign thyroid tissue and cerebral spinal fluid (CSF) negative for DLBCL. One of the 25 patients died of complications related to primary treatment. Two other patients, including the one who had undergone sampling of CSF found to be negative for DLBCL, underwent immediate salvage therapy. One of these patients died. The other remains alive without evidence of disease. The remaining 22 patients were observed. During the follow-up period, there have been four DLBCL recurrences in this observed group, with 18 patients remaining event-free.

In the group of 31 patients where all three reviewers interpreted the report as positive nine patients underwent biopsy following the post-therapy FDG-PET Scan (Figure 3b). Of these biopsies, eight were positive for DLBCL. The patient with a negative biopsy remains disease free 35 months after completion of chemotherapy. Of the 22 patients who did not undergo biopsy, 17 received salvage treatment. Of these 17 patients, five remain alive without event, 12 failed the second-line therapy. Five patients were observed despite the FDG-PET findings unanimously interpreted by our reviewers as positive. One of these patients elected hospice care and died shortly thereafter. The other four (IPI low =3, low-intermediate =1) remain event-free from DLBCL, although one patient developed cutaneous follicular lymphoma four years later.

Review of post-consensus guideline studies

To assess the impact of the 2007 consensus guidelines on the rate of studies felt to be indeterminate, 29 available FDG-PET reports completed after publication of the consensus guidelines were reviewed by the same hematologist-oncologists. Using the same methodology described above, nine (31%) were judged indeterminate

Discussion

This study is the largest to date to report the negative predictive value of a restaging FDG-PET after primary treatment for DLBCL. This builds upon earlier studies involving significantly fewer patients, shorter follow-up, or heterogeneity in lymphoma subtypes.^{4–11} Previous studies found the negative predictive value of a restaging FDG-PET for two to three year progression-free survival to range from 78–87%. The 85% EFS seen at 3 years in the current study is at the higher end of this range and provides useful information for counseling patients with DLBCL who have negative restaging FDG-PET studies following primary treatment.

The current study is the first to utilize the hematologist-oncologist's interpretation of the FDG-PET report to identify indeterminate reports and to describe outcomes for this subset of patients. The methodology of having practicing hematologist-oncologists interpret scan reports reflects the variability in practice where direct interaction with the scan, radiologist, and the nuclear medicine physician may not be readily available to the treating physician. Additionally, while reviewing the actual scan with the nuclear medicine physician represents ideal practice, there remains a subset of scans where these specialists may disagree or where both feel a study is indeterminate. Neither this methodology, nor the traditionally used methodology of forcing imaging experts into a positive or negative reading is absolutely reflective of clinical practice and it is important to use varying models to test performance of this important imaging modality.

The current study and others in lymphoma, as well as in other malignancies, confirm that a subset of indeterminate studies will be a clinical issue in the FDG-PET era. Studies evaluating FDG-PET in lung cancer¹⁷ and melanoma¹⁸ patients found “indeterminate” scan rates of 19% and 18% respectively. There are two degrees of “interpretation” of any diagnostic radiology study, each of which inherently risk subjectivity and potential irreproducibility. The first is the interpretation of the images by the appropriately trained specialist and the second is the interpretation of the imaging specialist’s report by a decision-making clinician. Although expert training and reporting guidelines should minimize inconsistency in the first step, a recent report in lymphoma patients with DLBCL describe for the first time that expert nuclear medicine physicians had a 30% discordance rate when interpreting scans¹⁹. Our observations of inconsistency in the second step were also described by authors evaluating the predictive value of FDG-PET in DLBCL following 2 cycles of R-CHOP also had medical oncologists interpret the report.²⁰ In this work 40% of imaging studies were “equivocal” following 2 cycles of therapy and 29% remained “equivocal” after completion of primary therapy. Improved consistency and precision at each of these steps could be achieved by efforts of the imaging specialist to gather more clinical information and by efforts of the clinician to communicate directly with the report author. Our study methodology does not discount the possibility that the former occurred although the multi-center nature of the project precludes measuring that. Our methodology specifically eliminates the latter communication, but we believe this too often represents clinical reality.

Another series, with 183 patients with aggressive NHL, addresses a different surveillance question: what is the utility of PET/CT scanning at various intervals after documentation of remission following primary treatment for lymphoma? This work, despite three experienced readers for each study also issued a small subset of inconclusive reports, with the majority of these patients ultimately not having a relapse at the time of the equivocal study. The authors also concluded that biopsy remains essential for patients in this group²¹.

Returning to the pre-therapy IPI risk stratification significantly enhanced the predictive value of the post-therapy FDG-PET in the indeterminate group, suggesting a possible clinical tool for the potentially challenging decisions for these patients. The IPI also enhanced the predictive value of the FDG-PET report in negative and positive study groups.

Several other authors have reported on the relative or combined value of prognostic indices and FDG-PET scan in lymphoma. A recent article combined the post-therapy restaging FDG-PET with the pre-therapy IPI for 68 patients with DLBCL and reported continued predictive value of the FDG-PET in both low and high risk IPI groups.²² Other studies have evaluated the relative value of the initial IPI score compared with FDG-PET findings after early treatment for NHL and Hodgkin’s Lymphoma and found the FDG-PET results both stronger^{23,24} and independent of the IPI.²⁵ One study which included patients with recurrent NHL or recurrent Hodgkin’s lymphoma did show enhanced predictive value in combining a secondary age adjusted IPI with FDG-PET after two treatments of salvage chemotherapy.²⁶

Analysis of the specific outcomes of patients followed in this series highlights the continued importance of biopsy of any equivocal area in the treatment of DLBCL despite the apparent strength of the FDG-PET studies. A significant number of patients who underwent biopsy of indeterminate or positive sites did not have documented persistent disease. Furthermore, only five of seventeen patients with abnormal FDG-PET reports who underwent salvage treatment without biopsy remain subsequently event-free, while four of five who were observed without further therapy - likely on the basis of clinical insight not discernable from medical record abstracting - also remain free of recurrent DLBCL. This calls into question

moving forward with salvage in the absence of histologic proof of disease. Twenty-four patients in the low risk IPI group where the FDG-PET report was interpreted as negative had a 96% EFS at 3 years. These results identify a subgroup in which the value of surveillance imaging is limited if confirmed in subsequent series.

Weaknesses of this study include the retrospective evaluation of prospectively gathered data. The study is further limited by the fact that the majority of the FDG-PET scan reports reviewed came from two institutions, although many institutions from the Upper Midwest are represented. A minority of the FDG-PET scans, performed before the consensus guidelines were published, were done 1–3 or 8–16 weeks after primary therapy and current guidelines would suggest 3–8 weeks as optimal timing following chemotherapy.¹³ Reviewing the reports and not the scans, as well as being blinded to clinical data and not interacting with the nuclear medicine physicians could have altered the interpretation results. This may be most apparent in the eleven patients with positive scans in the low risk IPI group who had 82% three-year OS.

This study confirms the negative predictive value of the FDG-PET scan following primary treatment of DLBCL for three year EFS. This is the first analysis of indeterminate FDG-PET studies in DLBCL and suggests that these patients have outcomes more similar to those with negative reports than those with positive reports. This study adds to the growing body of evidence that FDG-PET cannot replace biopsy the management of patients with DLBCL. Finally, interpreting the post-therapy FDG-PET in the context of the pre-therapy IPI adds further predictive information in patients with de novo DLBCL.

Acknowledgments

Supported by *National Institute of Health* grant P50-CA97274 - Iowa/Mayo Lymphoma SPORE program

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Figure 1. FDG-PET Report Interpretation by Hematologist-oncologists
Distribution of interpretations of 125 FDG-PET reports following curative-intent therapy for newly diagnosed DLBCL. For those reports judged indeterminate, the breakdown of individual hematologist-oncologist interpretation is provided along with clinical events within each scoring pattern.

Figure 2. Kaplan Maier Estimates of Survival by FDG PET report interpretation. Kaplan Meier estimates of EFS and OS by FDG PET report interpretation.

Figure 3b

Outcome for Patients with Positive FDG-PET Report

Figure 3. Outcomes of patients with indeterminate or positive FDG-PET reports
 Schematic representation of outcomes for patients with: (a) indeterminate FDG-PET reports;
 and (b) positive FDG-PET reports.

Table I

Patient Characteristics

Characteristic	# of pts (%)
<u>Age</u>	
Median (range)	59 (20–89)
<u>Gender</u>	
Female	53 (42)
Male	72 (58)
<u>ECOG PS</u>	
0–2	98 (78)
3–4	26 (21)
<u>Stage</u>	
I	18 (14)
II	32 (26)
III	31 (25)
IV	44 (35)
<u>Primary Treatment</u>	
R-CHOP	97 (78)
R-CHOP +	7 (6)
R-EPOCH	11 (9)
R-ICE	1 (1)
R-CVP	1 (1)
Other	8 (6)

Table II

Event-free survival and Overall Survival by FDG-PET Interpretation

	FDG-PET interpretation			
	Indeterminate	Negative	Positive	
# of patients	25	69	31	
2-year EFS (95% CI)	80% (66–97%)	88% (82–96%)		
3-year EFS (95% CI)	71% (55–92%)	85% (77–94%)		p = 0.28
3-year OS (95% CI)	88% (76–100%)	89% (82–97%)	48% (34–70%)	p = <0.0001

Event-free Survival and Overall Survival by FDG-PET report interpretation and pre-therapy International Prognostic Index

Table III

		IPI Risk Category				p-value [/]
		Low	L-Int	H-Int	High	
<i>Indeterminate FDG-PET</i>	Number of Patients	9	5	8	3	
	3-year EFS Estimates (95% CI)	89% (71–100)	100%	56% (28–100)	0%	0.016
	3-year OS Estimates (95% CI)	89% (71–100)	100%	88% (67–100)	67% (30–100)	0.194
<i>Negative FDG-PET</i>	Number of Patients	24	17	17	11	
	3-year EFS Estimates (95% CI)	96% (87–100)	88% (74–100)	70% (51–96)	82% (62–100)	0.030
	3-year OS Estimates (95% CI)	96% (85–100)	94% (84–100)	82% (68–100)	82% (62–100)	0.109
<i>Positive FDG-PET</i>	Number of Patients	11	9	7	4	
	3-year OS Estimates (95% CI)	82% (62–100)	44% (21–92)	28% (5–64%)	0%	0.002

[/] for IPI within FDG-PET Result (trend test)