Bone Marrow Transplantation (2009) 43, 941–948

www.nature.com/bmt

ORIGINAL ARTICLE

The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma

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We examined the role of fluorodeoxyglucose-positron emission tomography (FDG-PET) and the addition of involved field radiotherapy (IFRT) as potential modifiers of salvage therapy. From January 2000 to June 2007, 83 patients with chemosensitive relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL) underwent FDG-PET scans following second-line chemotherapy before high-dose therapy with autologous stem cell rescue (HDT/ASCR). We evaluated the prognostic value of having a negative FDG-PET scan before HDT/ASCR and whether IFRT improved the outcomes. Median follow-up was 45 months, and the 3-year PFS, disease-specific survival (DSS) and OS were 72, 80 and 78%, respectively. Multivariate analysis revealed that a positive FDG-PET scan had worse PFS (hazard ratio = (HR) 3.4; $P = 0.014$), DSS (HR = 7.7; $P = 0.001$) and OS (HR = 5.4; $P = 0.001$), and that patients not receiving IFRT had worse PFS (HR = 2.7; $P = 0.03$) and DSS (HR = 2.8, $P = 0.059$). Patients who received IFRT had better local control with fewer relapses within prior involved sites compared with those that did not receive IFRT ($P = 0.006$). These outcomes confirm the important prognostic value of FDG-PET scans before undergoing HDT/ASCR. It also suggests that the role of IFRT should be evaluated further.

Bone Marrow Transplantation (2009) **43,** 941–948; doi:10.1038/bmt.2008.408; published online 12 January 2009
Keywords: diffuse large B-cell lymphoma; radiation; radiotherapy; PET; non-Hodgkin lymphoma

Introduction

Over the last decade, researchers have explored the role of fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging in initial staging, response and prognosis assessment, as well as the detection of relapse in patients with diffuse large B-cell lymphoma (DLBCL).[1–5] Recent studies have shown that residual FDG-PET activity following the second-line chemotherapy is associated with poor outcome in patients who then proceed to high-dose therapy with autologous stem cell rescue (HDT/ASCR). These studies were relatively small, and some included patients from the entire spectrum of lymphoma histologies.[6–14]

For almost two decades at the Memorial Sloan Kettering Cancer Center (MSKCC), we have treated relapsed and primary refractory DLBCL with second-line chemotherapy in the context of an intent-to-transplant program for chemosensitive patients.[15] We recently reported that patients who received involved field radiotherapy (IFRT) before HDT/ASCR, according to the above criteria, had only a small risk for in-field relapse and a low IFRT-related risk of short- or long-term toxicity.[16]

In this study, we assessed the prognostic value of FDG-PET following the second-line chemotherapy for DLBCL and before HDT/ASCR, as well as the impact of adding IFRT in patients with and without residual FDG-PET activity.

Patients and methods

Patients

Between January 2000 and June 2007, 83 patients at MSKCC were treated with comprehensive HDT and ASCR for primary refractory (biopsy-proven disease within 30 days of finishing first-line therapy ($n = 22$, 27%)), relapsed (evidence of disease >30 days after finishing first-line therapy ($n = 56$, 67%)), or transformed (low-grade lymphoma at initial diagnosis with DLBCL at relapse ($n = 5$, 6%)) DLBCL. Ten other patients, treated early on in the study period (2000–2001), when FDG-PET was investigational, were excluded as they underwent gallium scans instead of an FDG-PET scan following salvage

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Presented at the American Society for Hematology (ASH) 2007 meeting in Atlanta, GA and American Society for Therapeutic Radiology and Oncology (ASTRO) 2008 meeting in Boston, MA, USA.
Received 25 July 2008; revised 1 October 2008; accepted 3 October 2008; published online 12 January 2009

chemotherapy. This retrospective study was approved by the institutional review board at MSKCC and includes all remaining patients ($N = 83$).

Histologic review of original and pre-transplant biopsy specimens was performed by MSKCC hematopathologists. All patients were restaged according to the Ann Arbor system before starting second-line therapy, and second-line age-adjusted international prognostic index (IPI) scores (sAAIPI) before second-line chemotherapy (based on eastern cooperative group (ECOG) performance status $\geqslant 2$, lactate dehydrogenase > 200 U/l, and stage III or IV disease) were calculated for all patients with the information available ($n = 80$). Patient- and disease-specific characteristics are listed in Table 1 along with subgroup classifications based on receipt of IFRT. The median age was 50 years (range = 16–72); 88% of patients were Caucasian.

Patients received ICE-based chemotherapy (ifosfamide, carboplatin and etoposide; $n = 77$, 93%), DHAP (dexamethasone, cisplatin and cytarabine) ($n = 3$, 4%), EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone; $n = 2$, 2%) or others ($n = 1$, 1%) as part of second-line therapy and for stem cell immobilization. Rituximab was part of second-line therapy in 67 patients (81%) and was given after transplant in 43 patients (52%). Response was assessed typically within 2 weeks of completing second-line therapy (median 9 days) with computed tomography (CT) and FDG-PET scans before HDT/ASCR. All patients had chemosensitive disease based on CT size (at least 50% reduction in the largest nodal masses). FDG-PET scans were retrospectively re-evaluated, and as a number of the scans were performed at outside facilities using various 2D or 3D techniques and because not every patient had a pre-treatment FDG-PET scan to compare with, a cutoff value of a maximum standard uptake value (SUV) of 3.0 was used for a positive scan result.[17–19] Sixty-five patients (78%) had an FDG-PET scan with SUV < 3.0, whereas the rest had an FDG-PET scan with SUV $\geqslant 3.0$ ($n = 18$, 22%).

Table 1 Patient characteristics and disease factors[a] ($N = 83$)

Characteristics/factors	*No IFRT* (n = *36*)		*IFRT* (n = *47*)		χ^2 (P-*value*)
	Number	*%*	*Number*	*%*	
Sex: male	19	53	26	55	0.82
Status: refractory	7	19	15	32	0.20
Bulky disease > 5 cm	12	33	27	57	0.03
Age > 60 years	8	22	13	28	0.57
Stage III or IV	29	81	18	38	0.0001
LDH > 200[b]	23	66	18	40	0.02
PS $\geqslant 2$	9	25	3	6	0.02
EN > 2 sites	13	36	7	15	0.03
sAAIPI factors[b]					
0	5	14	17	38	0.001
1	8	23	18	40	—
2	14	40	9	20	—
3	8	23	1	2	—
FDG-PET: SUV $\geqslant 3$	5	14	13	28	0.13
HDT with TBI	6	17	11	23	0.45

Abbreviations: DLBCL = diffuse large B-cell lymphoma; EN = extranodal sites; FDG-PET = fluorodeoxyglucose-positron emission tomography; HDT = high-dose therapy; IFRT = involved-field radiotherapy; LDH-lactate dehydrogenase; PS = ECOG performance status; sAAIPI = age-adjusted international prognostic index before second-line therapy; SUV = standard uptake value.
[a]Patients with primary refractory, relapsed or transformed DLBCL.
[b]$n = 35$ for non-IFRT group; $n = 45$ for IFRT group.

Methods

Involved field radiotherapy was given before HDT to eligible patients with disease limited to $\leqslant 2$ anatomical regions, to sites of disease measuring $\geqslant 5$ cm before second-line therapy or to sites with residual nodal masses $\geqslant 2$ cm after second-line therapy. IFRT was delivered to 47 patients (57%) following their post-second-line chemotherapy FDG-PET scan, with 1.5 Gy fractions given twice daily at a total dose of 30 Gy over 10 days if given alone ($n = 36$), or with 1.5 Gy fractions twice daily at a dose of 18 Gy over 6 days if followed by TBI. In these cases, the TBI dose was 12 Gy in 1.5 Gy fractions delivered twice daily as part of an HDT conditioning regimen ($n = 11$). Sites that were irradiated included the abdomen or pelvis ($n = 24$), mediastinum ($n = 17$), neck ($n = 2$), lower extremity and groin ($n = 2$) or the breast ($n = 2$).

High-dose therapy regimens depended on the protocol at that time, and included 17 patients (20%) who received TBI and 66 patients (80%) who received chemotherapy only. ASCR was performed using PBSCT (with a minimum of 2×10^6 CD34+ cells per kg body weight infused), mobilized and collected by leukapheresis following second-line chemotherapy. The median time from the completion of second-line therapy until ASCR was 40 days (range = 29–86) for patients not receiving IFRT and 51 days for those that received IFRT (range = 35–120).

Toxicity

Acute (< 100 days following ASCR) and late ($\geqslant 100$ days following ASCR) toxicities were recorded according to the National Cancer Institute (NCI) common toxicity criteria (NCI-CTC v.2. 0).

Follow-up

Median follow-up for all surviving patients was 45 months (range = 4–89), and for all patients, it was 32 months (range = 3–89). All patients had restaging CT scans 90–100 days after ASCR. Follow-up CT scans were performed every 6 months for 3 years. Patients suspected to have relapsed underwent confirmatory biopsy.

Statistical analysis

Differences in disease characteristics and local control between patients receiving IFRT, and those who did not receive IFRT were evaluated by χ^2-test. Survival analyses were performed using the Kaplan–Meier method.[20] OS, disease-specific survival (DSS) and PFS were defined as the time from ASCR until last follow-up if no event occurred, or until death (OS), until death from disease (DSS), or until time of disease progression (PFS), respectively. A log-rank test was used for univariate analysis of characteristics,[21] including pre second-line therapy stage (III/IV vs I/II), lactate dehydrogenase (> 200 vs $\leqslant 200$), performance status (ECOG $\geqslant 2$ vs < 2), number of extranodal disease

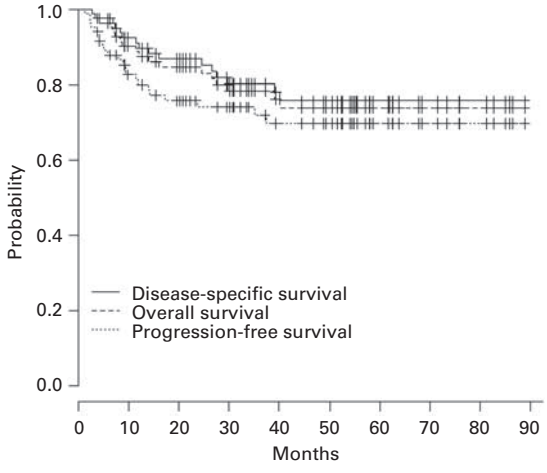
sites (>2 sites vs ⩽2 sites), age (>60 vs ⩽60), sAAIPI (2 or 3 vs 0 or 1), FDG-PET response to second-line chemotherapy (SUV ⩾3.0 vs SUV <3.0), HDT regimen (TBI-containing vs non-TBI-containing) and IFRT (no vs yes). Factors were entered into a multivariate analysis using a forward stepwise Cox proportional hazards regression model.[22]

Results

Twenty-two patients developed disease progression with a median time to relapse of 8 months (range = 1–37). The 2- and 3-year PFS, DSS and OS were 74 and 72, 87 and 80, 85 and 78%, respectively (Figure 1). At last follow-up, 18 patients had died, including 16 from disease progression, one from sepsis with pulmonary embolism 4 months following ASCR without evidence of disease progression (patient received IFRT to the stomach) and one of unknown cause 6 months following ASCR without evidence of disease (patient received TBI with IFRT to the spleen).

The effect of FDG-PET imaging on outcomes after second-line chemotherapy

Eighteen patients had a positive FDG-PET scan (SUV ⩾3.0), and seven relapsed. Patients with a negative FDG-PET scan had improved PFS (log-rank, $P=0.049$ (Figure 2a)), DSS (log-rank, $P=0.0006$ (Figure 2b)) and OS (log-rank, $P=0.0004$). Five patients with positive FDG-PET scans did not receive IFRT, and three of these patients relapsed within the prior FDG-PET-positive site(s). Thirteen patients with positive FDG-PET scans received IFRT (which included the FDG-PET-positive site(s) in all cases) and only four patients relapsed, all outside the irradiated site(s). Sixty-five patients had a negative FDG-PET scan (SUV<3.0) and 15 relapsed, including four who received IFRT and 11 who did not. Three of the four patients who received IFRT had widespread relapses both inside and outside the irradiated site(s), and one patient had a widespread relapse completely outside the irradiated site. Those who did not receive IFRT relapsed completely within an involved lymph node site ($n=5$), widespread both inside and outside prior involved nodal sites ($n=3$), outside the nodal site ($n=2$) or at an unknown site ($n=1$).



	Months				
Survival	0	20	40	60	80
			Number at risk		
DSS	83	59	34	16	6
OS	83	59	34	16	6
PFS	83	52	31	15	6

Figure 1 Kaplan–Meier survival curves showing overall, disease-specific and progression-free survival in patients with relapsed or primary refractory DLBCL who underwent high-dose therapy. Abbreviations: DLBCL = diffuse large B-cell lymphoma; DSS = disease-specific survival.

The effect of IFRT on outcomes after second-line chemotherapy

Forty-seven patients received IFRT before HDT/ASCR and only eight relapsed. Patients selected to receive IFRT had significantly improved PFS (log-rank, $P=0.02$, (Figure 2c)) and improved DSS (log-rank, $P=0.077$, (Figure 2d)) compared with those who did not receive IFRT. Patients who received IFRT did not have a significantly improved OS (log-rank, $P=0.21$). Sites of relapse in patients who received IFRT included five completely outside the irradiated region, three both inside and outside the irradiated region and none in the irradiated site(s) only. Fourteen of thirty-six patients who did not receive IFRT relapsed, including five within a prior involved lymph node region, six both within the involved lymph node region and outside the region, two completely outside the involved region and one in an unknown site. Crude local control rates showing fewer relapses within previously involved lymph node regions were better in the group that received IFRT compared with those that did not receive IFRT (94 vs 69%, $P=0.006$).

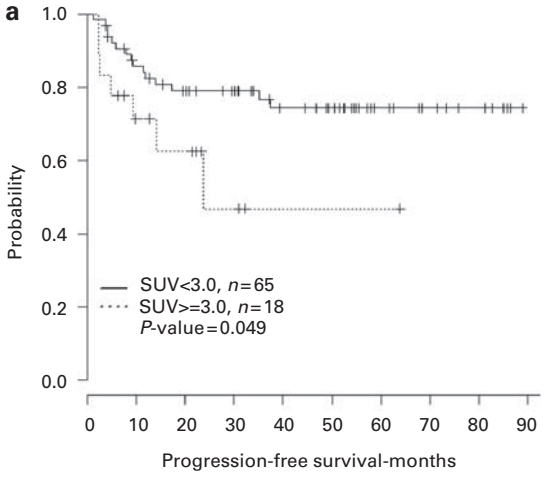
Figures 3a and b depict the PFS and DSS by group according to FDG-PET status and receipt of IFRT.

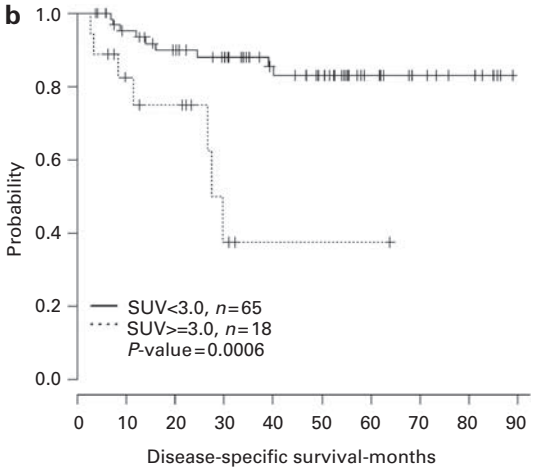
Other prognostic factors

Univariate analysis was also performed on other factors thought to influence PFS, DSS and OS (Table 2). Results of a multivariate analysis for PFS, DSS and OS are also listed in Table 2.

Toxicity

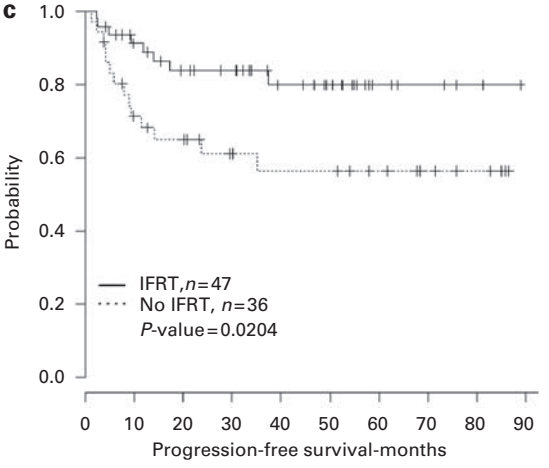
No treatment-related deaths occurred within 100 days after ASCR. One patient who received IFRT to the spleen with TBI developed bilateral pulmonary infiltrates shortly after ASCR, but recovered following intensive pulmonary care. Two patients developed transient radiation enteritis. Three patients (none of whom received IFRT) developed a transient supraventricular tachycardia syndrome during HDT. One of these patients subsequently developed grade 3 congestive heart failure that improved with standard measures. Two patients, both in the non-IFRT group, developed mild transient pericardial effusions. Ten patients developed a late infectious/inflammatory disorder affecting the lungs, which resolved with antibiotics, antifungals and/

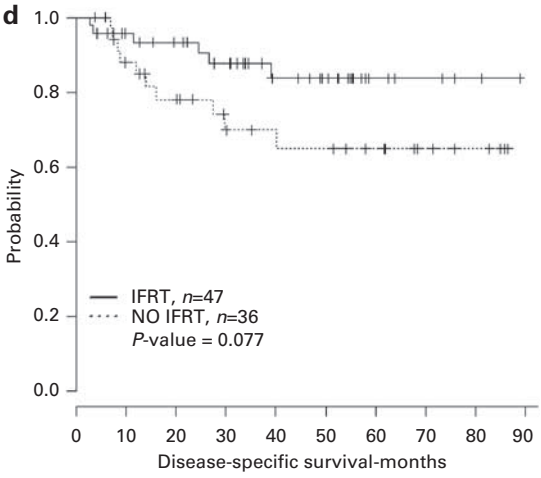




	Months				
SUV	0	20	40	60	80
			Number at risk		
< 3.0	65	45	30	14	6
≥ 3.0	18	7	1	1	0

	Months				
SUV	0	20	40	60	80
			Number at risk		
< 3.0	65	50	33	15	6
≥ 3.0	18	9	1	1	0





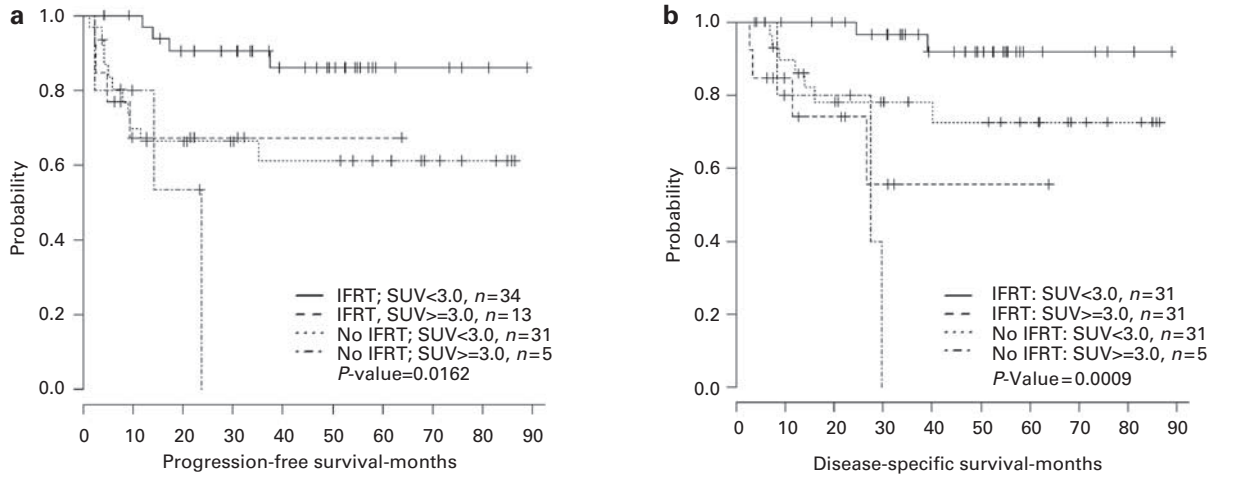
	Months				
Radiotherapy	0	20	40	60	80
			Number at risk		
IFRT	47	32	19	6	2
No IFRT	36	20	12	9	4

	Months				
Radiotherapy	0	20	40	60	80
			Number at risk		
IFRT	47	36	20	6	2
No IFRT	36	23	14	10	4

Figure 2 Kaplan–Meier survival curves based on (**a**) residual FDG-PET activity for PFS or (**b**) disease-specific survival, and also based on the receipt of involved-field radiotherapy for (**c**) PFS or (**d**) disease-specific survival. Abbreviations: IFRT = involved-field radiotherapy; SUV = standard uptake value.

or steroids. Only two of these could in part be related to IFRT. One patient who did not receive IFRT developed grade 3 chronic renal failure.

Two patients in the non-IFRT group developed second malignancies, including one with myelodysplastic syndrome and another with metastatic carcinoma to the lung and liver of unknown primary. In the IFRT group, there were three second malignancies in two patients, all completely outside the irradiated field, including a patient who developed lymphocyte-predominant



Radiotherapy;FDG-PET Activity	Months 0	20	40	60	80
			Number at risk		
IFRT; SUV<3	34	27	18	5	2
IFRT; SUV≥3	13	5	1	1	0
No IFRT; SUV<3	31	18	12	9	4
No IFRT; SUV≥3	5	2	0	0	0

Radiotherapy;FDG-PET Activity	Months 0	20	40	60	80
			Number at risk		
IFRT; SUV<3	34	30	19	5	2
No IFRT; SUV<3	31	20	14	10	4
IFRT; SUV≥3	13	6	1	1	0
No IFRT; SUV≥3	5	3	0	0	0

Figure 3 Kaplan–Meier survival curves of PFS (**a**) or disease-specific survival (**b**) based on whether patients received involved-field radiotherapy and on residual FDG-PET activity. Abbreviations: IFRT = involved-field radiotherapy; SUV = standard uptake value.

Hodgkin's lymphoma and a second patient who developed superficial bladder cancer and then prostate cancer several years later. None of these four patients has died from a second malignancy.

Discussion

Decisions regarding the benefit of treating relapsed or refractory DLBCL with HDT/ASCR are governed by response to second-line, standard-dose chemotherapy. Many treating physicians proceed to HDT/ASCR only if a patient is considered chemosensitive by CT scan.[23,24] Recently, FDG-PET response has also been considered following second-line chemotherapy, but its prognostic relevance has not been fully explored. To our knowledge, this study is the largest to evaluate the prognostic value of FDG-PET following second-line chemotherapy in chemosensitive patients with relapsed or primary refractory DLBCL who underwent HDT/ASCR. Our results confirm the findings of other groups showing that patients who failed to achieve a negative FDG-PET scan before HDT/ASCR have a significantly worse outcome.[6–14] Our earlier study on the safety of incorporating IFRT before HDT suggested also that irradiating sites of original bulky or residual disease may enhance disease control.[16] In this study, we further show that local control was improved in patients who were selected to receive IFRT, which could have translated into an improvement in PFS and into a trend toward improvement in DSS, independent of FDG-PET response (Table 2; Figures 3a and b).

Table 3 summarizes studies evaluating the prognostic value of FDG-PET in patients with relapsed or refractory lymphoma. In each study, the definition of a negative FDG-PET scan varied, ranging from a maximum SUV threshold to a more complicated definition including evaluation by two nuclear radiologists assessing the degree of change between pre- and post-treatment scans. Although consensus guidelines emphasize the use of comparison between pre- and post-treatment scans instead of a threshold dose for evaluating treatment response,[25] in our study, we chose a simple definition for a positive FDG-PET: maximum SUV was $\geqslant 3.0$, a commonly used cutoff to indicate nonmalignant pathology[17–19] because of the limited information we had (several patients did not have pre-treatment FDG-PET scans to compare with and further, because the scans were performed at a number of different institutions over a period of 7 years using both 2D and 3D techniques). Despite the differences among how the studies described FDG-PET response, all the other studies support our results of improved outcomes when patients had a negative FDG-PET scan before HDT/ASCR.

Early experiences with second-line chemotherapy and HDT/ASCR in the 1990s showed the predominant site of relapse to be within previously bulky disease.[26,27] In this study, those patients who did not receive IFRT primarily relapsed within the involved field region, especially within FDG-avid regions. Interestingly, IFRT

Table 2 Adverse prognostic factors influencing OS, DSS and PFS (by univariate and multivariate analyses)

Variable	*Unadjusted HR (95% CI)*	P-*value*	*Adjusted*[a] *HR (95% CI)*	P-*value*
PFS estimates				
FDG-PET	2.44 (0.98–6.10)	0.056	3.38 (1.28–8.91)	0.014
EN	2.86 (1.22–6.70)	0.016	2.59 (1.08–6.23)	0.033
IFRT	2.69 (1.13–6.41)	0.026	2.72 (1.10–6.72)	0.030
Gender	1.26 (0.54–2.95)	0.59		
TBI	1.73 (0.67–4.42)	0.26		
Stage	2.34 (0.92–5.98)	0.076		
sAAIPI	1.78 (1.03–3.07)	0.038		
Age	1.29 (0.53–3.16)	0.58		
LDH	1.59 (0.65–3.88)	0.31		
PS	1.46 (0.49–4.33)	0.49		
Refractory	0.71 (0.24–2.11)	0.54		
Disease-specific survival estimates				
FDG-PET	5.14 (1.84–14.38)	0.002	7.65 (2.33–25.17)	0.001
EN	2.92 (1.09–7.85)	0.03	5.16 (1.54–17.24)	0.008
Gender	2.69 (0.87–8.34)	0.09	3.26 (1.00–10.64)	0.051
TBI	2.84 (1.03–7.83)	0.04	4.10 (1.30–12.95)	0.016
IFRT	2.42 (0.88–6.68)	0.09	2.82 (0.96–8.26)	0.059
Stage	2.58 (0.83–8.01)	0.10		
sAAIPI	1.80 (0.96–3.40)	0.068		
Age	1.13 (0.39–3.25)	0.82		
LDH	1.59 (0.57–4.47)	0.38		
PS	2.39 (0.77–7.44)	0.13		
Refractory	1.17 (0.38–3.65)	0.78		
OS estimates				
FDG-PET	4.98 (1.89–13.08)	0.001	5.39 (1.97–14.75)	0.001
EN	2.37 (0.92–6.12)	0.07	4.73 (1.57–14.24)	0.006
Gender	3.10 (1.02–9.43)	0.05	3.74 (1.16–12.13)	0.028
TBI	3.76 (1.48–9.56)	0.005	4.36 (1.59–11.96)	0.004
IFRT	1.79 (0.71–4.55)	0.22		
Stage	1.70 (0.64–4.53)	0.29		
sAAIPI	1.44 (0.80–2.57)	0.22		
Age	0.97 (0.34–2.71)	0.95		
LDH	1.19 (0.46–3.08)	0.73		
PS	1.98 (0.65–6.05)	0.23		
Refractory	1.34 (0.48–3.76)	0.58		

Abbreviations: DSS = disease-specific survival; EN = extranodal sites; FDG-PET = fluorodeoxyglucose-positron emission tomography; HR = hazard radio; IFRT = involved-field radiotherapy; LDH = lactate dehydrogenase; PS = ECOG performance status; sAAIPI = age-adjusted international prognostic index before second-line therapy.
[a]Only those included in final model from stepwise Cox regression have an estimate.

Table 3 Summary of studies evaluating prognostic value of FDG-PET following second-line chemotherapy in patients with relapsed or primary refractory lymphoma

Study author	*No. patients*	*Median F/U, months*	*Lymphoma types*	*OS, % (FDG-PET: + vs −)*	*PFS/EFS, % (FDG-PET: + vs −)*
Becherer *et al.*[6]	16	13	HD + NHL	18 vs 100	55 vs 100
Spaepen *et al.*[13]	60	NA	HD + NHL	55 vs 100	23 vs 96
Filmont *et al.*[9]	60	15	HD + NHL	NA	43 vs 80
Cremerius *et al.*[7]	24	30	NHL	33 vs 87	0 vs 60
Schot *et al.*[12]	77	22	HD + NHL	NA	20 vs 72
Svodboda *et al.*[14]	50	19	HD + NHL	0 vs 50	50 vs 75

Abbreviations: FDG-PET = fluorodeoxyglucose-positron emission tomography; HD = Hodgkin disease; NA = not applicable; NHL = non-Hodgkin's lymphoma.

significantly improved local control in the involved region, even when the site was FDG avid following second-line chemotherapy. Local control was 94% compared with 69% in the group that did not receive IFRT. This improvement in local control may have contributed to the significant improvement in PFS, and trend toward improvement in DSS seen on multivariate analysis in patients selected to receive IFRT. OS was not found to be improved with IFRT, and this may be due in part to a short length of follow-up and improvement in other salvage chemotherapy options. A longer follow-up might prove beneficial for examining overall and DSS more appropriately.

Other groups have also shown improvements with IFRT added to HDT/ASCR.[28–32] Rodriguez *et al.*[31] reported 5-year OS of 82 vs 31% ($P = 0.01$) when IFRT was given to

patients with bulky relapsed or refractory NHL undergoing HDT/ASCR. Rapoport *et al*.[30] reported an improvement in EFS (35 vs16%, $P=0.04$) in a similar group of patients with the addition of IFRT to HDT/ASCR. Kahn *et al*.[28] and Vose *et al*.[32] reported a higher risk of death if patients with relapsed or refractory lymphoma did not receive IFRT with HDT/ASCR (hazard ratio (HR) 2.1, $P=0.066$ and HR 1.6, $P=0.05$, respectively).

This study is subject to the limitations of a retrospective analysis. Yet, in the absence of a prospectively designed study on the role of FDG-PET in this context, it presents several enhancements to currently available data. Unlike other similar FDG-PET studies, ours is limited to patients with a single histology (DLBCL), and it includes the largest number of patients and the longest reported follow-up in this setting. We believe that our findings provide sound support to the important prognostic value of FDG-PET before HDT/ASCR and may thus affect clinical decisions.

Although there was an improvement in outcome in the group that received IFRT in our series, we recognize a caveat in making firm conclusions because patients were not randomly assigned to receive IFRT, but were chosen according to specific criteria described earlier. As a result, the disease-specific characteristics are different between those patients who received IFRT and those who did not. This includes the observation that those who received IFRT were more likely to have positive FDG-PET scans following second-line chemotherapy and/or bulky disease (both poor risk factors), whereas the non-IFRT group included more patients with stage III/IV disease, abnormal lactate dehydrogenase, poor performance status and higher sAAIPI (other factors also associated with worse outcomes). Therefore, we remain cautious when drawing our conclusions. Only a phase III randomized trial will adequately address whether IFRT clearly adds an improvement to the outcome, and whereas a prospective study was initiated by the National Cancer Institute of Canada Clinical Trials Group (LY 8), it closed because of poor accrual (Dr Richard Tsang, personal communication, June 2007). We do feel that the improvement seen in this study in local control and PFS, with a minimal increase in toxicity in those patients who received IFRT, supports further investigation of radiation in combination with HDT/ASCR. In fact, as radiation fields shrink with our growing knowledge of relapse patterns, and our treatment techniques improve with the use of intensity-modulated radiation therapy, the toxicity profiles from radiation should only improve, making radiation a good choice to reduce the relapse rate in sites at high risk.

In conclusion, FDG-PET scans following second-line chemotherapy and before HDT/ASCR have significant prognostic value and have been incorporated into our treatment algorithm. Those patients with positive FDG-PET scans should go on to receive further chemotherapy until their scans become negative or, at the very least, consider IFRT (to cover the FDG-avid sites of disease) before undergoing HDT/ASCR. Furthermore, we consider using IFRT only for patients with disease that is still limited to a small number of sites that are at high risk of local recurrence (bulky or FDG avid following second-line therapy), which is supported by the improvements seen in local control. Future studies should be aimed at clearly defining whether the improvements seen in local control, PFS and DSS in our study are due to the addition of IFRT or are strictly due to selection bias.

Acknowledgements

This study was supported from the Lymphoma Foundation and the Sports Foundation against Cancer. BSH, MD, was a Dr Mortimer Lacher 2007 Lymphoma Fellow at the Memorial Sloan-Kettering Cancer Center. We thank Carol Pearce, MFA, writer/editor with the MSKCC Department of Medicine Editorial Unit, for reviewing this manuscript.

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