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Predictors of metabolic response in propensity-matched lymphoma patients on interim ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography using standardized imaging and reporting protocol: Do we really have one?

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Abstract

The purpose of this prospective study was to determine metabolic response predictor(s) in propensity-matched patients having lymphomas who had baseline and interim ^{18}fluorodeoxyglucose (FDG) positron-emission tomography/computed tomography (PET/CT) using strict standardized imaging and reporting protocols. This prospective study was conducted at PET/CT section of a JCI-accredited healthcare facility from April 2017 to February 2018. Patients with baseline and interim ^{18}FDG PET/CT scans using standardized protocol were selected. Interim scans were performed not earlier than 2nd or later than 4th chemotherapy. During the study period, 97 of 112 consecutive patients with lymphomas (Hodgkin-HL: 32/97 and Non-Hodgkin-NHL: 65/97) were included in the study. Mean age of cohort was 45 ± 19 years (71% male and 29% female) having a mean body mass index (BMI) of 25.57 ± 5.54 Kg/m^2 having Stage I (21%), Stage II (18%), Stage III (16%), and Stage IV (45%) disease. Bulky disease was found in 14% and ^{18}FDG-avid marrow deposits in 33%. Standardized PET/CT imaging protocol as per EANM guidelines was strictly adopted for baseline and interim studies. %Δ changes in fasting blood sugar, ^{18}FDG dose, uptake time, and liver SUV mean were 3.96%, 2.83%, 2.49%, and 12.15%, respectively. Based on Deauville's scoring, cohort was divided into responders having Score 1–3 (49/97) and nonresponders having Score 4–5 (48/97). The demographic analysis found no significant difference between responders and nonresponders for age, gender, BMI, staging, bulky disease or marrow involvement, and study protocol. No significant coefficient or odd ratios were found on multivariate analysis for age, gender, maximum standardized uptake value (SUV_{max}), size, BMI, NHL, and advance disease (Stage III and IV) in both groups (χ^2: 5.12; receiver operating characteristic [95% confidence interval]: 0.616 [0.51–0.713]; P =0.528). Among responders, baseline SUV_{max} and tumor size had a direct correlation with a metabolic

response on iPET, more pronounced in NHL than HL groups (SUV_{max}: 13.4 vs. 19.5 and size: 52 vs. 87 mm; $P < 0.0001$). We conclude that no significant predictor was found for response in propensity-matched patients with lymphomas (both HL and NHL) who had baseline and interim PET/CTs acquired with a standardized protocol. However, NHL responders were found to have higher baseline median SUV_{max} and larger lesion size as compared to HL responders. Although, these data are not in concordance with published findings but need to be validated with larger studies using standardized imaging and reporting protocols in propensity-matched patients with lymphomas.

Keywords: Interim positron-emission tomography/computed tomography, lymphoma, metabolic response, predictors, standardization

INTRODUCTION

In the Western world, lymphoma is the 6th most common malignancy which accounts for 4.8% of all malignancies.[1] Lymphomas are treated with chemotherapy, immune-chemotherapy, or radiation therapy, either as monotherapy or as combined modality treatment. In current practice, ^{18}F-FlouroDeoxyglucose positron-emission tomography/computed tomography (^{18}FDG PET/CT) is considered as the standard of care due to its high diagnostic accuracy in staging and response evaluation at the end of treatment (ePET).[2] Interim PET/CT (iPET) performed during chemotherapy is being widely investigated in Hodgkin's lymphoma (HL), diffuse large B-Cell lymphomas, and other subsets of non-HL (NHL) for response-adapted therapy.[3] However, results are quite variable as a negative iPET has high negative predictive value (>80%) but a positive iPET has significantly low positive predictive value (around 15%) for progression-free survival (PFS).[3] This is because iPET cannot discriminate between the presence of residual viable neoplastic tissue and a nonspecific inflammatory host response.[3,4] This heterogeneity is caused by adjustable and nonmodifiable factors seen in patient population of published studies. Adjustable factors include age and gender (significantly different age groups with gender predominance), nonstandardized imaging protocols, and interpretation criteria used in different studies. Nonmodifiable factors include tumor behavior and presence of microenvironment cells such as CD8+ tumor-infiltrating lymphocytes and PD1-positive lymphocytes.[5] Hence, it is imperative to conduct studies on patients' population with minimal impact of above-mentioned adjustable factors.

The purpose of this study was to determine metabolic response predictor(s) in propensity-matched patients having lymphomas who had baseline and interim ^{18}FDG PET/CT using a standardized imaging and interpretation protocols.

MATERIAL AND METHODS

This prospective study was conducted at PET/CT Section of Department of Radiology, Aga Khan University Hospital Karachi, Pakistan from July 2017 to February 2018. We included patients with biopsy-proven lymphomas which were referred for ^{18}FDG PET/CT studies at baseline and midtreatment scan performed not earlier than 2nd or later than 4th chemotherapy (iPET) for response evaluation. We strictly followed a standardized protocol for ^{18}FDG PET/CT as per European Association of Nuclear Medicine (EANM) guidelines for both studies.[6] Response evaluation was assessed on visual assessment using Deauville's 5-point scoring system[7] and patients with Score 1–3 were considered as responders (complete metabolic response) while those with Scores 4 and 5 as nonresponders (partial metabolic response).

^{18}Fluorodeoxyglucose positron-emission tomography/computed tomography imaging

^{18}FDG PET/CT was performed as per the institutional protocol adopted from EANM guidelines.[6] All patients had 4–6 h fasting (only plain water was allowed) and a fasting blood sugar <200 mg% before receiving an intravenous ^{18}FDG dose of 3 MBq/Kg in the uptake room. During uptake period, (55–75 min) patients were requested to lie comfortably and allowed to take about 500–1000 ml of plain water. Bladder was emptied before call the patient for PET/CT imaging suite equipped with Celesteion, Toshiba, Japan. A low-dose CT examination (midbrain to midthigh) from head to toe followed by acquisition of PET imaging using 3 min/bed position from toe to head in all patients. Follow-up scans were performed with the same protocols, keeping ^{18}FDG dose, uptake time, and hepatic SUV mean of baseline and follow-up studies within ±10%, ±15%, and 20% minutes, respectively, as per published recommendations.[8] Nodal mass ≥10 cm was considered as a bulky disease and splenomegaly when ≥13 cm.[9] SUV_{max} were measured over the hottest tumor deposits in both scans and % change in the highest SUV_{max} of baseline and iPET studies (%△SUV_{max}) were also measured. Similarly, % change in size of the largest lesion (%△ size) in baseline and iPET scans were also measured.

Statistical analysis

Comparisons between patient groups were performed using Student's *t*-test for continuous variables and the Chi-square test for categorical variables. Continuous variables were described by mean ± standard deviation. Multiple regression analysis was performed to calculate the area under the curve and odd ratios for age, gender, body mass index (BMI), baseline SUV_{max}, bulky disease, and baseline lesion size in lymphoma responders. Kaplan–Meier cumulative response for HL and NHL responders was performed, and curves were compared using the log-rank test. The median response for age, BMI, baseline SUV_{max}, and baseline largest lesion size was expressed with a corresponding 95% of confidence interval [CI]. Statistical significance was defined as a value of $P < 0.05$. Commercially, available packages Microsoft excel 2010, Medcalc,® and statistical package for social sciences (SPSS 19 (IBM Company, SPSS, Inc, USA)®) were used.

RESULTS

During the study period, 97 of 112 consecutive patients (15 patients who did not have iPET were excluded) with lymphomas. Thirty-two patients (32/97) had HL while 65/97 had NHL. Mean age of total cohort was 45 ± 19 years (71% male and 29% female) having a mean BMI of 25.57 ± 5.54 Kg/m^2 [Table 1]. Patients were categorized to have Stage I (21%), Stage II (18%), Stage III (16%), and Stage IV (45%) disease [Table 2]. Bulky disease was found in 14%, splenic involvement in 30%, hepatic in 09%, extralymphatic in 37%, and 33% had ^{18}FDG-avid marrow deposits [Table 2]. Pulmonary nodules (both ^{18}FDG avid and nonavid) were seen in 29% while pleural effusion and ascites were seen in 9% and 4%, respectively [Table 2]. %Δ changes in fasting blood sugar, ^{18}FDG dose, uptake time, and liver SUVmean were 3.96%, 2.83%, 2.49%, and 12.15%, respectively [Table 1]. Based on Deauville's scoring, cohort was divided into responders having Score 1–3 (49/97); [Figure 1] and nonresponders having Score 4 and 5 (48/97; [Figure 2 and Table 1]. Demographic analysis found no significant difference between responders and nonresponders for age, gender, BMI, staging, the presence of bulky disease or marrow involvement, and study protocol (baseline and iPET) [Tables 1 and 2]. No significant coefficient or odd ratios were found on multivariate analysis for age, gender, SUV_{max}, size, BMI, NHL, and advance disease (stage III and IV) in both groups (χ^2: 5.12; receiver operating characteristic [95% CI]: 0.616 (0.51–0.713); P =0.528) [Table 3]. Among the responders, 18/49 had HL and 31/49 had NHL. HL responders were found to be significantly younger with significant fall in BMI on iPET as compared to NHL responders. Rest of the variables was found to be nonsignificant Table 4. Among the responders, median SUV_{max} and size were significantly lower in HL as compared to NHL (SUV_{max}: 13.4 vs. 19.5 and size: 52 vs. 87 mm; $P <$ 0.0001) [Figures 3 and 4].

DISCUSSION

^{18}FDG PET/CT has revolutionized the management of lymphomas and considered as gold standard for accurate staging and response evaluation at the end of treatment.[10] However, the role of interim ^{18}FDG PET/CT (iPET) in response adaptation in lymphomas (especially in NHL) is under evaluation due to variable results observed in various trials.[9] The basic reason is high false-positive rate ranging from 57% [11] to 94%[12] due to ^{18}FDG uptake by posttherapy inflammatory tissue rather than viable tumor.[13] Other possible reasons for variable results are heterogeneity in patients' population (age and gender predominance), nonstandardized imaging, and interpretation criteria used in different studies. In the present study, we studied the factors predicting the metabolic response on iPET scan.

In this study, age was not found to have significant relation in responders and nonresponders which is in contradiction to published facts that age is considered as a negative predictor of response.[14] BMI is considered as a better predictor of response and overall survival (OS) in patients with lymphoma.[15] Our data did not show any impact of BMI in responders and nonresponders. This is in concordance with another published study which also failed to show the impact of BMI on metabolic response.[16] Response rate (Deauville score 1–3 on iPET) was >50% in HL while <50% in NHL, but these were not statistically significant which could be attributed to small sample size. However, this response rate is almost similar to a recently published study having a response rate of 53%[12] but significantly lower than another study having a response rate as high as 72%.[11] Importantly, SUV_{max} and size of the largest lesion on baseline PET/CT did not show any significant difference between responders and nonresponders on iPET. Our findings are in concordance with another published study which did not find any significant correlation of baseline SUV_{max} with response on iPET.[17] Univariate and multivariate analyses also failed to show any significant impact of age, gender, BMI, baseline SUV_{max} and lesion size, NHL, and advance disease on the metabolic response on iPET. These observations are surprising as most of the published studies did find the impact of these factors on PFS. However, we have investigated the impact of these factors on the metabolic response on iPET and not PFS or OS as data are being collected in studied cohort until writing this manuscript. We feel that large sample size studies with propensity-matched patients having ^{18}FDG PET/CTs with standardized imaging and reporting protocols are deemed necessary to further explore this observation.

We did not observe any significant difference of staging, extranodal involvement, bulky disease, and marrow involvement between responders and nonresponders. These observations are in contradiction to published findings revealing the poor impact of bulky disease, staging, and extranodal involvement on PFS.[14] HL responders were found to be significantly younger with a higher decline in BMI as compared to NHL responders. This could be secondary to wider range of BMI at baseline in HL patients. This was also confirmed by no statistically significant difference on cumulative response by median BMI in both HL and NHL groups ($P = 0.546$).

Another important observation in our study is that baseline SUV_{max} and tumor size among total cohort (more pronounced in NHL than HL) had a direct correlation with a metabolic response on iPET. This is in contradiction to the study by Mikhaeel *et al*.,[18] revealing negative impact of SUV_{max} and metabolically active tumor burden on PFS. However, in current study, we have studied the impact of metabolic response on iPET and we need longer follow-up to validate these findings for PFS.

Our study has some limitations which need to be addressed in the future studies. First, the sample size is small which was due to strict inclusion criteria. We did not include those patients who had baseline PET/CT performed outside for the sake of maintaining standardization. Second, we did not validate nonresponders on iPET by biopsy to ascertain false-positive results. Third, we did not subgroup HL and

NHL responders to see the response in early and advanced disease as it would further attenuate the sample size. Fourth, end point of our study is metabolic response on iPET rather than PFS which needs follow-up which is currently underway.

CONCLUSION

We conclude that no significant predictor was found for response in propensity-matched patients with lymphomas (both HL and NHL) who had baseline and interim PET/CT acquired with a standardized protocol. However, NHL responders were found to have higher baseline median SUV_{max} and larger lesion size as compared to HL responders. Although, these data are not in concordance with published findings but need to be validated with larger studies using standardized imaging and reporting protocols in propensity-matched patients with lymphomas.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Table 1

Patients' demographics in Hodgkin and Non-Hodgkin lymphomas labeled as a responder and nonresponder on interim ^{18}fluorodeoxyglucose positron-emission tomography/computed tomography study

Variables	Total (*n*=97)	Responder (*n*=49)	Non-responder (*n*=48)	Test values	*P*
Age mean±SD (range)	45±19 (06-77) years	42±18 (06-77) years	47±19 (08-77) years	1.331	0.187
Gender (male:female)	69:28 (71%:29%)	32:17 (65%:35%)	37:11 (77%:23%)	1.676	0.195
BMI (kg/m^2) (mean±SD)	25.57±5.54	26.18±5.58	24.95±5.48	−1.095	0.276
%Δ BMI (mean±SD)	0.44%±7.44%	0.81%±7.09%	0.07%±7.83%	−0.488	0.627
%Δ FBS (mean±SD)	3.96%±23.75%	6.83%±28.76%	1.91%±21.42%	−0.954	0.343
%Δ FDG dose (mean±SD)	2.83%±27.61%	0.04%±34.11%	5.76%±18.73%	1.021	0.310
%Δ Uptake period (mean±SD)	2.49%±20.55%	1.38%±18.78%	3.63%±22.35%	0.537	0.592
%Δ Mean hepatic uptake (mean±SD)	12.15%±34.60%	16.52%±34.94%	7.95±34.10	−1.222	0.225
%Δ CTDI (mean±SD)	9.77%±24.32%	10.90%±26.18%	8.61±22.47	−0.462	0.645
%Δ DLP (mean±SD)	8.59%±23.24%	7.51%±23.54%	9.68%±23.14%	0.458	0.648
Hodgkin lymphoma (%)	32 (33)	18 (56)	14 (44)	1.382	0.239
Non-Hodgkin lymphoma (%)	65 (67)	31 (48)	34 (52)	0.154	0.695
Highest SUV, (mean±SD)	13.7±8.3	14.0±8.25	13.29±8.49	−0.418	0.677
Largest lesion (mm), (mean±SD)	58±47	62±49	55±46	−0.725	0.470
%Δ in highest SUV_{max}, (mean±SD)	58%±41%	81%±21%	34%±41%	−7.127	<0.0001*
%Δ lesion size, Mean±SD	58%±42%	68%±24%	47%±53%	−2.522	0.0133*

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*P<0.05. BMI: Body mass index; SD: Standard deviation; FBS: Fasting blood sugar; CTDI: Computed tomography dose index; DLP: Dose-length product; SUV_{max}: Maximum standardized uptake value; FDG: Fluorodeoxyglucose

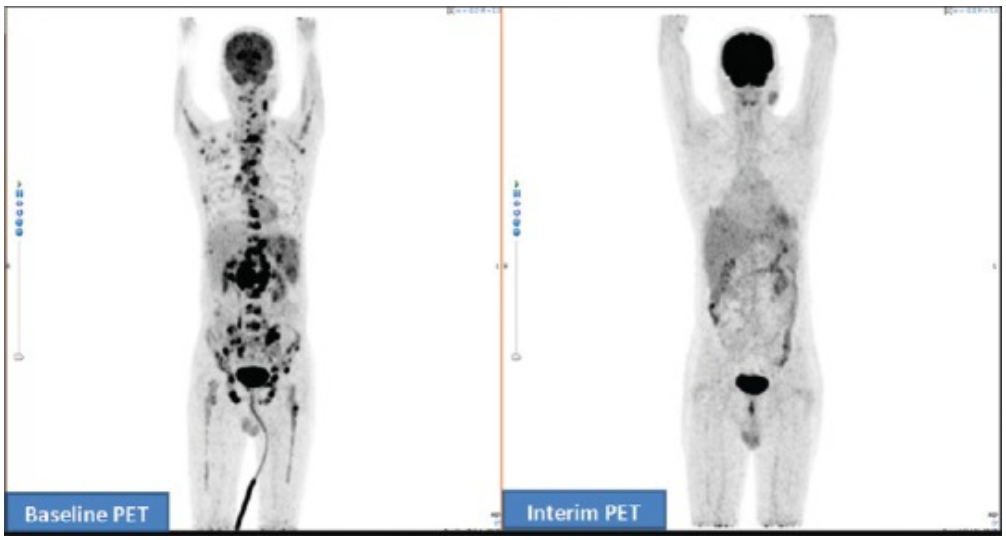
Table 2

Tumor demographics

Variables	Total (*n*=97), *n* (%)	Responder (*n*=49), *n* (%)	Nonresponder (*n*=48), *n* (%)	Test values	*P*
Stage I	20 (21)	11 (22)	9 (19)	0.132	0.716
Stage II	17 (18)	8 (16)	9 (19)	0.150	0.699
Stage III	16 (16)	8 (16)	8 (17)	0.017	0.895
Stage IV	44 (45)	22 (45)	22 (45)	0.000	1.000
Spleen involvement	29 (30)	13 (27)	16 (33)	0.412	0.521
Liver involvement	9 (9)	3 (6)	6 (12)	1.058	0.304
Bulky disease ≥100 mm	14 (14)	7 (14)	7 (15)	0.019	0.889
Marrow involvement	32 (33)	16 (33)	16 (33)	0.000	1.000
Extra lymphoid organ involvement	36 (37)	17 (35)	19 (40)	0.256	0.613
Lung nodules	28 (29)	15 (31)	13 (27)	0.186	0.666
Pleural effusion	9 (09)	5 (10)	4 (08)	0.117	0.732
Ascites	4 (04)	2 (04)	2 (04)	0.000	1.000
Incidental findings	25 (26)	10 (20)	15 (31)	1.531	0.216

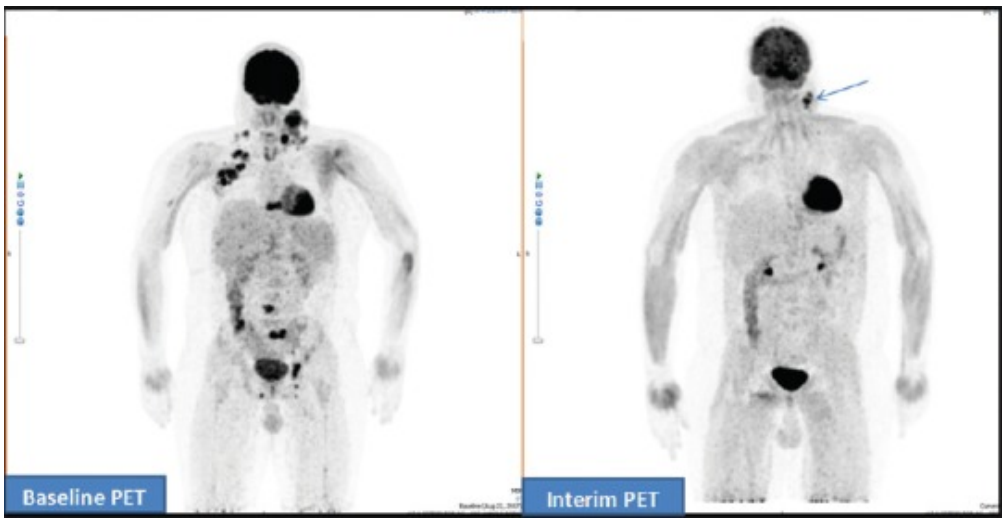
*$P<0.05$

Figure 1



Six-year-old male with a known case of classical Hodgkin's lymphoma, ^{18}fluorodeoxyglucose positron-emission tomography/computed tomography revealed Stage IV disease on baseline and complete metabolic response (score 01 on Deauville 5PS) on interim scan after receiving 4th cycle of chemotherapy

Figure 2



Twenty-three-year-old male with a known case of classical Hodgkin's lymphoma, ^{18}fluorodeoxyglucose positron-emission tomography/computed tomography revealed Stage IV disease on baseline and partial metabolic response (score 05 on Deauville 5PS) on interim scan after receiving 2nd cycle of chemotherapy

Table 3

Lymphoma response on interim ^{18}fluorodeoxyglucose positron-emission tomography/computed tomography in correlation with age, baseline maximum standardized uptake value, baseline largest lesion, and baseline body mass index

Lymphoma response versus variables	**Logistic regression χ^2**	**Area under the ROC Curve (95% CI)**	***P***
Age + gender + SUV_{max} + size+ BMI + NHL + advanced disease	5.122	0.616 (0.512-0.713)	0.528
Lymphoma response versus variables	**Coefficient (SE)**	**OR (95% CI)**	***P***
Age (years)	−0.015 (0.014)	0.985 (0.958-1.012)	0.270
Male gender	−0.504 (0.472)	0.604 (0.239-1.523)	0.286
Baseline SUV_{max}	0.008 (0.028)	1.008 (0.954-1.065)	0.781
Baseline largest lesion (mm)	0.008 (0.05)	1.003 (0.993-1.013)	0.590
Baseline BMI (kg/m^2)	0.054 (0.040)	1.056 (0.975-1.144)	0.183
NHL	−0.135 (0.543)	0.873 (0.301-2.532)	0.803
Advance disease (Stage III, IV and Bulky disease)	0.064 (0.048)	1.066 (0.413-2.751)	0.895

*P<0.05. SUV_{max}: Maximum standardized uptake value; BMI: Body mass index; CI: Confidence interval; SE: Standard error; NHL: Non-Hodgkin lymphoma

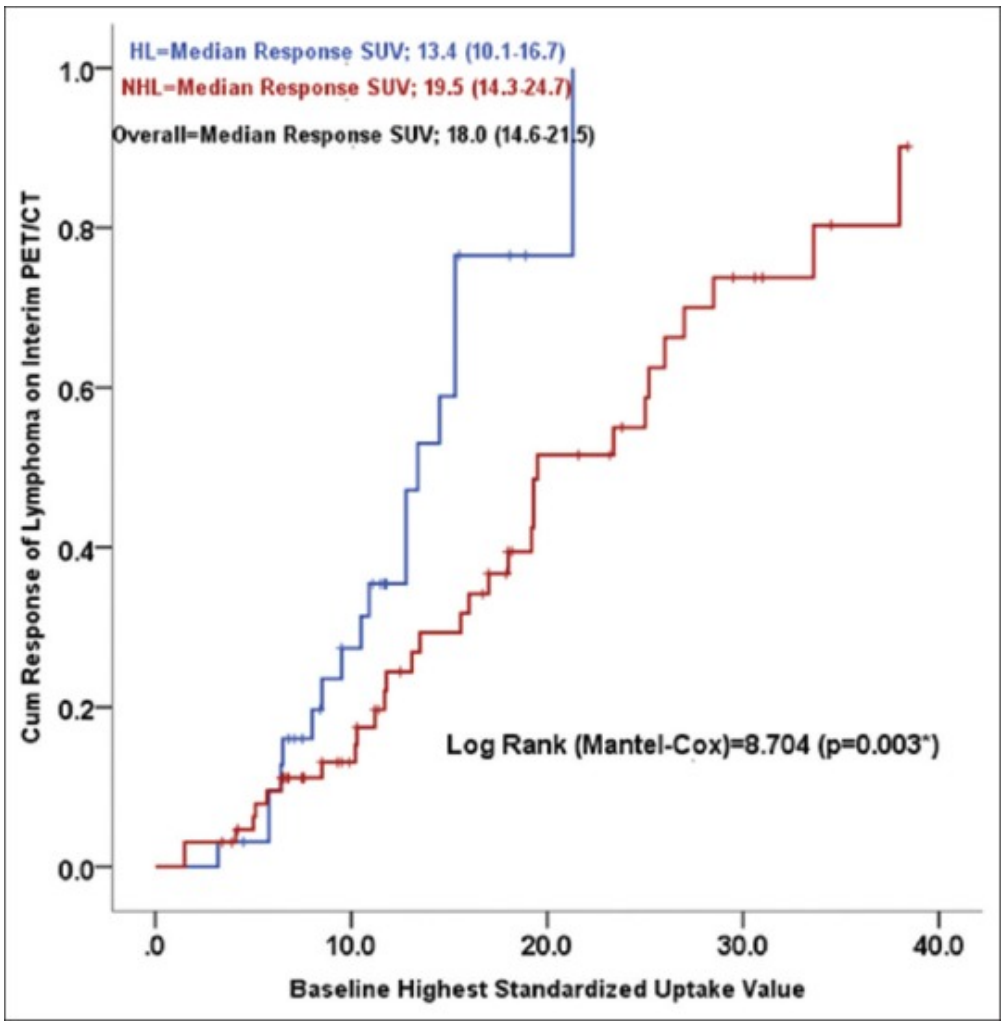
Table 4

Demographic comparisons in Hodgkin and non-Hodgkin lymphomas labeled as responders on interim ^{18}fluorodeoxyglucose positron-emission tomography/computed tomography study

Variables	Responders (*n*=49)	HL (*n*=18)	NHL (*n*=31)	Test values	*P*
Age mean±SD (range)	42±18 (06-77) years	30±17 (06-77) years	52±15 (21-77) years	4.713	<0.0001*
Gender (male:female)	32:17 (65%:35%)	11:07 (61%:39%)	21:10 (68%:32%)	1.676	0.195
BMI (kg/m^2), (mean±SD)	26.18%±5.58%	24.38%±7.33%	26.15%±4.35%	1.064	0.293
%Δ BMI, (mean±SD)	0.81%±7.09%	−3.42%±5.67%	1.02%±7.69%	2.076	0.043*
%Δ FBS, (mean±SD)	6.83%±28.76%	−0.54%±15.00%	5.64%±26.34%	−0.911	0.367
%Δ FDG dose, (mean±SD)	−1.00%±15.00%	1.13%±21.0%	3.67%±30.53%	0.312	0.756
%Δ Uptake period, (mean±SD)	1.38%±18.78%	0.62%±20.93%	−4.03%±20.34%	−0.763	0.449
%Δ Mean hepatic uptake, (mean±SD)	16.52±%34.94%	−9.25%±23.80%	−3.58±38.93	0.585	0.561
%Δ CTDI, (mean±SD)	10.90%±26.18%	−12.5%±24.28%	−8.41±24.41	0.567	0.574
%Δ DLP (mean±SD)	7.51%±23.54%	−10.56% ±24.79%	−7.62%±22.58%	0.424	0.674
Highest SUV_{max}, mean±SD (range)	14.0±8.3 (1.5-38)	10.9±4.4 (3.2-21.3)	15.0±9.5 (1.5-38)	1.721	0.091
Largest lesion (mm), mean±SD (range)	62±49 (12-266)	45±28 (12-95)	53±46 (14-266)	0.668	0.507
%Δ in highest SUV_{max}, Mean±SD (range)	81%±21% (+26% + 95%)	68%±25% (44%-94%)	52%±46% (07%-95%)	−1.360	0.180
%Δ lesion size, Mean±SD (range)	68%±24% (00%-97%)	62%±28% (33% -92%)	55%±48% (00-97%)	−0.564	0.575

*P<0.05. SD: Standard deviation; BMI: Body mass index; FBS: Fasting blood sugar; CTDI: Computed tomography dose index; DLP: Dose-length product; SUV_{max}: Maximum standardized uptake value; HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma

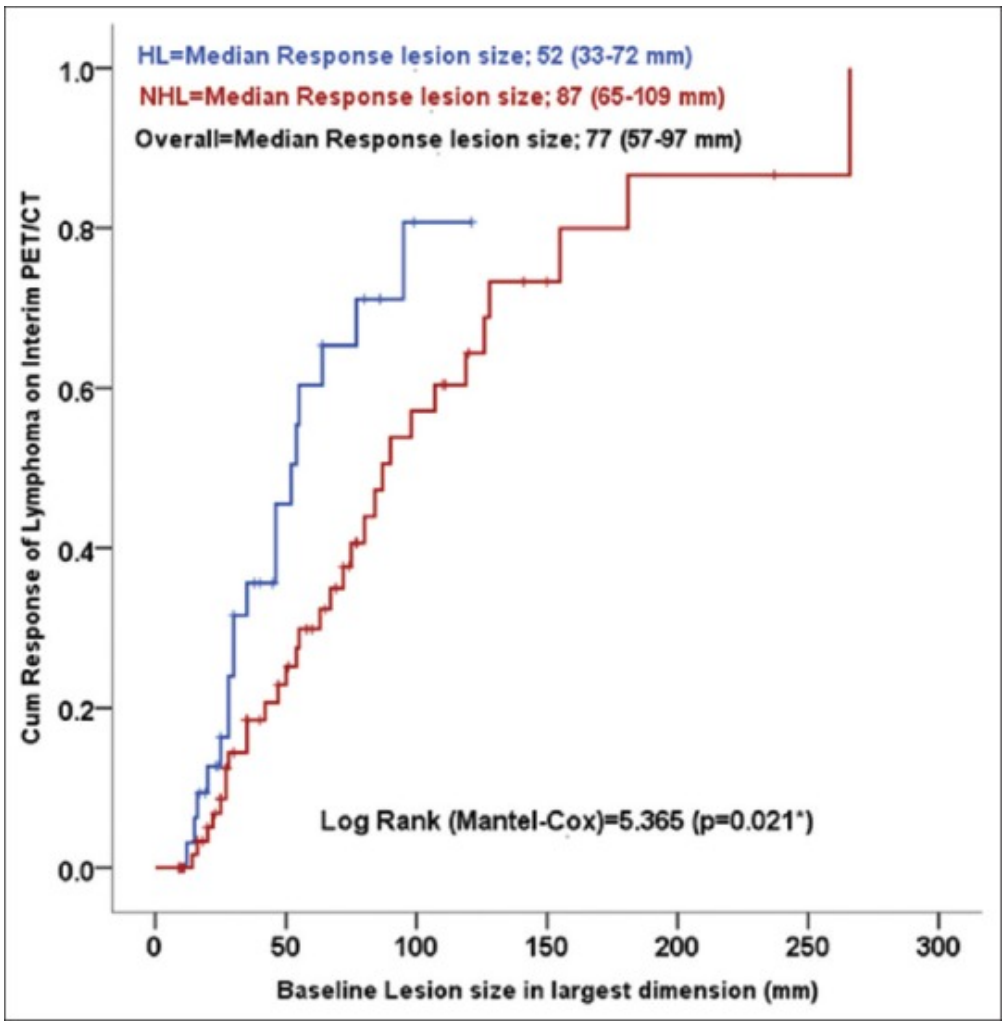
Figure 3



Open in a separate window

Kaplan–Meier plot for cumulative response on first interim positron-emission tomography/computed tomography in Hodgkin and non-Hodgkin lymphomas against the highest median baseline maximum standardized uptake value. HL = Hodgkin lymphoma, NHL = Non-Hodgkin lymphoma

Figure 4



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Kaplan–Meier plot for cumulative response on first interim positron–emission tomography/computed tomography in Hodgkin and non-Hodgkin lymphomas against median baseline lesion size in the largest dimension. HL = Hodgkin lymphoma, NHL = Non-Hodgkin lymphoma