

RESEARCH ARTICLE

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Progression Free Survival and Predictor of Recurrence in DLBCL patients with Negative Interim ¹⁸FDG PET/CT Using Standardized Imaging and Reporting Protocols

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Abstract

Background: To determine progression free survival (PFS) and predictor of recurrence in patients with diffuse large B-cell lymphoma (DLBCL) with negative interim ¹⁸FDG PET/CT (iPET) using standardized imaging and reporting protocols. **Materials and Methods:** This prospective study was conducted at PET/CT Section of a JCIA accredited healthcare facility from December 2015 till February 2020. Patients with DLBCL having complete metabolic response (CMR; Deauville score: 1-3) on iPET were selected and followed for a median period of 11 months (4-144 months). End point response on follow-up PET/CT (either end of treatment or surveillance) was categorized as sustained CMR (sCMR) and disease recurrence. Kaplan Meier survival curve was used to measure PFS and receiver operating characteristics (ROC) was plotted for age, largest lesion size, highest standardized uptake value (SUVmax), disease stage and body mass index (BMI) on baseline scan to find their impact on recurrence. **Results:** Total 185 patients with DLBCL who had achieved CMR on iPET with a median age 55 years (19 – 88 yr.) with male predominance (63% male) were selected. On follow-up, 123 (66%) had sCMR while recurrence was found in 34% (p <0.05). No significant difference in demographics was found between two groups. Median PFS time was 34 months (22.8 – 45.1 months). On ROC analysis, only baseline highest SUVmax was found as a significant independent predictor of disease recurrence at a cut off >22.6 (highest area under curve: 0.595; SE 0.046; p <0.05). **Conclusion:** We conclude that recurrence is found in 34% of DLBCL patients with a negative interim ¹⁸FDG PET/CT using standardized imaging and reporting protocols. Despite of early response, these patients need continued intensive follow-up especially those with a baseline SUVmax > 22.6.

Keywords: Interim PET/CT- DLBCL- negative iPET- lymphoma- recurrence- progression free survival-predictor

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Introduction

Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of adult Non-Hodgkin lymphoma (NHL) cases with an aggressive clinical course (Burggraaff et al., 2019). With standard rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) cure is achieved in 60-70% cases (Gisselbrecht et al., 2010). However, treatment failure is still an important problem as the 3-year progression-free survival (PFS) is approximately 60–70% (Vitolo et al., 2017). In current era, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸FDG PET/CT) is considered as standard-of-care for reliable staging and response assessment of aggressive malignant lymphomas, including DLBCL. Currently,

¹⁸FDG-PET/ CT at the end of treatment (ePET) is an accepted method for response assessment with ¹⁸FDG positivity is considered predictive of reduced survival in patients with malignant lymphoma (Cheson, 2011). There is large body of data favoring reliable role of ¹⁸FDG-PET during therapy (Interim-PET; iPET) for successful PET-guided treatment modification in Hodgkin lymphoma (Gallamini et al., 2018). But use of iPET for early response assessment and treatment modification in DLBCL remains controversial due to inconsistency in reported results (Dührsen et al., 2018; Yuan et al., 2019). Fundamental reason is low to modest positive predictive value (PPV) of iPET for DLBCL due to significantly high false positive (FP) results as it fails to discriminate between residual viable neoplastic tissue and a nonspecific inflammatory host response (Barrington et al., 2014). According to a

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recent meta-analysis, proportion of FP results for iPET are significantly higher (83%) than ePET (31.5%) (Adams and Kwee, 2016). While, negative predictive value (NPV) of iPET has been reported >80-85% in various reports with longer overall survival (OS) and progression free survival (PFS) (Pregno et al., 2012; Gallamini and Zwarthoed, 2017). But iPET is also known to be associated with false-negative (FN) findings as it can't exclude clinically significant microscopic disease. A study reported a recurrence of 39.1% at a median follow-up of 30.8 months in DLBCL patients who had had a negative iPET (Kwon et al., 2016). Heterogeneity in results of various studies is caused by adjustable and non-modifiable factors seen in patient population of published studies. Adjustable factors include age and gender (significantly different age groups with gender predominance), non-standardized imaging protocols and interpretation criteria used in different studies. Non-modifiable factors include tumor behavior and presence of microenvironment cells like CD8+ tumor-infiltrating lymphocytes and PD1-positive lymphocytes (Fatima et al., 2019). So it is imperative to conduct studies upon patients' population with minimal impact of above mentioned adjustable factors.

Aim of this study was to find progression free survival (PFS) and predictor of recurrence on follow-up ¹⁸F PET/CT in DLBCL patients who had a negative iPET using standardized imaging and reporting protocols.

Materials and Methods

This prospective study was conducted at PET/CT Section of Department of Radiology, Aga Khan University Hospital Karachi, Pakistan from July 2017 till February 2020. Study was duly approved by ethical review committee of institute. We included patients with biopsy proven DLBCL who had ¹⁸F PET/CT studies at baseline and interim PET/CT (at least 10 days after 2nd or 4th chemotherapy) which was reported as complete metabolic response (CMR) using Deauville scoring system (score 1-3) (Meignan et al., 2017). All patients have received standard first line chemotherapy (CHOP with or without rituximab). We strictly followed a standardized protocol for ¹⁸F PET/CT as per European Association of Nuclear Medicine (EANM) guidelines for both studies (Boellaard et al., 2015). These patients were followed-up with ¹⁸F PET/CT performed at end of treatment or afterward for recurrence. Patients with Deauville score -X (indeterminate) on follow-up scans were either biopsied or followed with imaging at shorter intervals. Based on follow-up scan results, patients were categorized as having remission or sustained CMR (sCMR) or disease recurrence (DR). Kaplan Meier survival plot was used to estimate mean time of disease recurrence. Similarly, receiver operating characteristic (ROC) plot was used to see the impact of stage of disease, largest lesion size and highest SUVmax at baseline ¹⁸F PET/CT upon the disease recurrence. Progression free survival (PFS) was the period from iPET diagnosis until lymphoma progression, relapse after response, or death as a result of any cause (Cheson, 2011).

¹⁸F PET/CT Imaging: ¹⁸F PET/CT was

performed as per institutional protocol adopted from EANM guidelines (Boellaard et al., 2015). All patients had 4-6 hour fasting (only plain water was allowed) and a fasting blood sugar less than 200 mg% before receiving an intravenous ¹⁸F FDG dose of 3 MBq/Kg in the uptake room. During uptake period (55 -75 minute) patients were requested to lie comfortably and allowed to take about 500-1,000 ml of plain water. Bladder was emptied prior to call the patient for PET/CT imaging suite equipped with Celesteion, Toshiba, Japan. A low dose CT examination (mid brain to mid-thigh) from head to toe followed by acquisition of PET imaging using 3 minute/bed position from toe to head in all patients. Follow up scans were performed using same protocols, keeping ¹⁸F FDG dose, uptake time and hepatic SUVmean of baseline and follow-up studies within $\pm 10\%$, $\pm 15\%$ and 20% minutes respectively as per published recommendations (Boellaard, 2011).

Statistical Analysis: Comparisons between patient groups were performed using Student's t test for continuous variables and the χ^2 test for categorical variables. Continuous variables were described by mean \pm standard deviation (SD). Receiver operating characteristic analysis was performed to calculate the area under the curve (AUC) and cut off values for age, stage, BMI, largest lesion size and highest SUVmax on baseline PET/CT with a corresponding 95% confidence interval as predictor(s) for tumor recurrence. Kaplan-Meier survival curve was plotted for recurrence free survival. Statistical significance was defined as $P < 0.05$. Commercially available packages Microsoft excel 2010, Medcalc[®] and statistical package for social sciences (SPSS 19[®]) were used.

Results

During study period, 185 patients with biopsy proven DLBCL who have achieved CMR (Deauville score: 1-3) on iPET were included. Based on follow-up (median: 11 \pm 19 months) PET/CT findings, 123 patients (66%) remained in remission (sCMR) while 62 patients (34%) had developed metabolically active recurrence (DR) groups. No significant difference (p value > 0.05) was seen in mean age (overall: 55 \pm 14 yr.), gender distribution (overall M:F: 63:37%), body mass index (overall: 26.47 \pm 4.96) and history of diabetes (overall: 36%) between sCMR and DR groups (Table 1). Similarly, no significant difference was observed for fasting blood sugar (overall: 109 \pm 34 mg%), ¹⁸F FDG dose (overall: 171 \pm 37 MBq), uptake period (overall: 67 \pm 11 min) and mean hepatic uptake (overall: 1.76 \pm 0.47) between two groups ensuring strict adherence to standardized imaging protocol (Table 1). Furthermore, no significant difference was found for median baseline stage of disease (overall: stage 3 \pm 1), largest lesion on baseline PET/CT (overall: 64 \pm 49 mm), highest SUVmax on baseline scan (overall: 19 \pm 9.27) and median follow-up (overall: 11 \pm 19 months; range: 04-44 months) between sCMR and DR groups. The Kaplan Meier survival plot for time of recurrence revealed an overall mean PFS of 55.28 months (95% CI: 40.56 -70.0) (Figure 1). ROC analysis of various factors like age, stage of lymphoma, BMI, baseline largest lesion size and highest SUVmax, revealed that the

Table 1. Demographic Comparison of DLBCL Patients with CMR on Interim and Follow-up 18FDG PET/CT Studies

| Variables | Total N=185 | sCMR N=123 (66%) | Disease Recurrence N=62 (34%) | Test/X ² values | P-values |
|---|----------------------------|----------------------------|----------------------------------|----------------------------|----------|
| Age Median ± SD (range) | 55 ± 14 (19-88) years | 55 ± 15 (19-88) years | 55 ± 12 (28-78) years | 0 | 1 |
| BMI (Kg/m ²) (Mean ± SD) | 26.47 ± 4.96 | 26.14 ± 4.60 | 26.82 ± 5.42 | 0.893 | 0.373 |
| Gender (Male: Female) | 117: 68 (63 : 37%) | 75:48:00 (61 : 39%) | 42:20:00 (68 : 32%) | 0.865 | 0.3523 |
| Obesity (≥30Kg/m ²) | 39 (21%) | 23 (19%) | 16 (26%) | 1.197 | 0.274 |
| DM | 36 (19%) | 25 (20%) | 11 (18%) | 0.105 | 0.7457 |
| FBS (mg/dl) (Mean ± SD) | 109 ± 34 | 109 ± 33 | 111 ± 35 | 0.381 | 0.7035 |
| FDG dose (MBq) (Mean ± SD) | 171 ± 37 | 170 ± 36 | 175 ± 39 | 0.867 | 0.3871 |
| Uptake period (Mean ± SD) | 67 ± 11 | 70 ± 15 | 68 ± 10 | -0.948 | 0.3442 |
| Mean hepatic uptake (Mean ± SD) | 1.76 ± 0.47 | 1.77 ± 0.47 | 1.73 ± 0.46 | -0.55 | 0.5828 |
| Highest SUVmax Mean ± SD (Range) | 19.00 ± 9.27 (3.9-61.2) | 17.95 ± 8.08 (3.7-47.6) | 21.00 ± 10.99 (3.9-61.2) | 0.179 | 0.858 |
| Largest lesion Mean ± SD Range in mm | 64 ± 49 (05-266) mm | 64 ± 52 (05-266) mm | 63 ± 50 (09-237) | -0.146 | 0.8841 |
| Median Baseline stage | 03 ± 01 | 03 ± 01 | 03 ± 01 | 0 | 1 |
| Median follow up in months (04-144) | 11 ± 19 (04-144) | 10 ± 16 (04-82) | 14 ± 23 (05-144) | 1.379 | 0.1697 |

*p<0.05; SD, Standard Deviation; BMI, Body Mass Index; DM, Diabetes Mellitus; FDG, Fluorodeoxy glucose; FBS, Fasting Blood Sugar; SUV, Standardized Uptake Value; sCMR, sustained Complete Metabolic Response

highest SUVmax > 22.6 was the only significant predictor of disease recurrence (Figure 2 and Table 2).

Discussion

¹⁸FDG-PET/CT is a widely used hybrid imaging modality for reliable staging of malignant lymphomas and response assessment as it can differentiate between

viable tumor from post-treatment fibrosis and/or necrosis (Kitajima et al., 2019). Currently ¹⁸FDG-PET/CT performed at end of treatment (ePET) is recommended for response assessment in Hodgkin's (HL) and NHL including DLBCL as positive scan has reasonably good predictive value for OS and PFS (Cheson, 2011). Based on published results, iPET has been considered good for response adapted management in HL (Gallamini

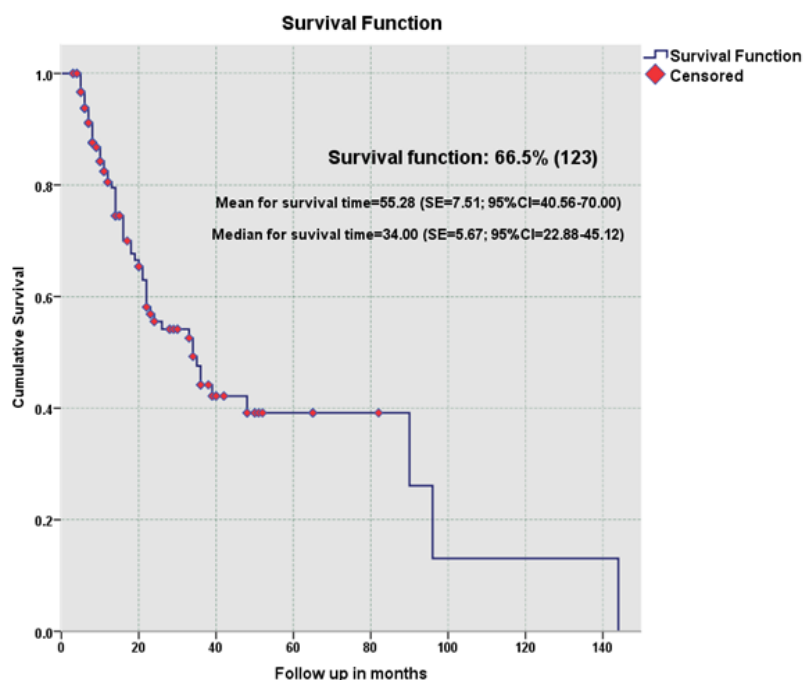


Figure 1. Kaplan Meier Survival Plot for Recurrence Free Survival of DLBCL Patients Based on Complete Metabolic Response on Follow up ¹⁸FDG PET/CT Studies. SE, Standard Error; CI, Confidence Interval

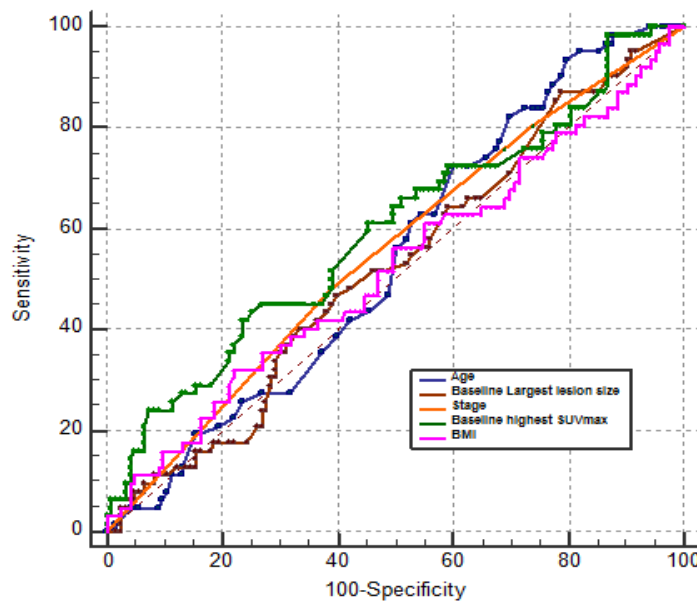


Figure 2. Receiver Operating Characteristics Plots for Predictors of Recurrence on Follow up ¹⁸FDG PET/CT Studies in DLBCL Patients with Complete Metabolic Response on iPET. SUV, Standardized uptake value; BMI, Body mass index

et., 2018; André et al., 2017). However, the predictive value of iPET for response adapted treatment in DLBCL has been questioned due to inconsistent results (Adams and Kwee., 2016; Terasawa et al., 2009; Sun., 2015). Inhomogeneity in patients’ population, therapy regimens, imaging and reporting protocols have made it hard to clarify predictive accuracy of iPET in DLBCL (Burggraaff et al., 2019). We have tried our best to mitigate the impact of above mentioned confounding factors by strictly following standardized ¹⁸FDG PET/CT imaging protocol on same scanner and using Deauville 5-point scoring for reporting all studies. Furthermore, no significant difference in factors like age, gender predisposition, BMI, history of diabetes and stage of disease seem to have successfully mitigated their impact. However, this study has limitation in addressing non-modifiable factors like tumor behavior and presence of microenvironment cells like CD8+ tumor-infiltrating lymphocytes and PD1-positive lymphocytes (Fatima et al., 2019). Regarding the treatment regimens, all of studied patients have had received CHOP or R-CHOP till iPET was done which again increases the statistical strength of our study.

As a matter of fact, most of the published studies have addressed the predictive value of positive iPET in

DLBCL with unsatisfactory sensitivity and specificity (Milana et., 2015). In this study we tried to determine how many patients would have recurrence after achieving a complete remission as documented by a negative iPET (DS ≤3). Despite of variable results, NPV of iPET in DLBCL has been reported greater than 80% (Moskowitz and Shoder., 2015). However, in our study, NPV of iPET was found to be 66% which is significantly lower. On reviewing literature, Jerusalem et al., (2000) also reported a NPV of 67% in a small study of 28 patients including 16 with DLBCL. Another study published in 2005 upon 90 DLBCL patients revealed a NPV of 70% at 24 months median follow-up (Haioun et al., 2005). Therefore plausible explanations could be a relatively homogenous patient population and use of a standardized imaging and reporting criteria compared with published studies.

The reported recurrence after completion of treatment in patients with DLBCL is around 30-40% (Pfreundschuh et al., 2011). In our study, 62/185 patients with negative iPET developed disease recurrence during a median follow-up of 11 months (false negative: 34%). This recurrence rate is significantly higher than published studies. Carr et al., (2014) reported a recurrence of 10% in a large cohort of patients with negative iPET. Similarly

Table 2. Receiver Operating Characteristics Analysis for Predictors of Recurrence on Follow up ¹⁸FDG PET/CT Studies in DLBCL Patients on Follow up

| Variables | AUC | Criterion | Sensitivity | Specificity | SE | 95% Confidence Interval | | P- value |
|------------------------------|-------|-----------|-------------|-------------|--------|-------------------------|--------------|----------|
| | | | | | | lower limits | upper Limits | |
| Age (years) | 0.541 | >36 | 93.55 | 20.33 | 0.043 | 0.456 | 0.625 | 0.3442 |
| Baseline largest lesion size | 0.523 | >23 | 87.1 | 21.14 | 0.045 | 0.436 | 0.611 | 0.6023 |
| Baseline lymphoma Stage | 0.554 | >3 | 48.39 | 60.98 | 0.042 | 0.472 | 0.637 | 0.1965 |
| Baseline highest SUVmax | 0.595 | >22.6 | 41.94 | 76.42 | 0.046 | 0.505 | 0.684 | 0.0375* |
| Baseline BMI | 0.521 | >29.675 | 32.26 | 78.05 | 0.0465 | 0.43 | 0.613 | 0.6471 |

*p<0.05; AUC, Area under Curve; SE, Standard Error; SUV, Standardized uptake value; BMI, Body mass index

study by Mamot et al., (2015) reported a recurrence of 24% in 55 patients with negative iPET. However, recurrence in our study is in concordance with the study published by Kwon et al., (2016) upon 92 DLBCL patients with negative iPET who experienced recurrence during a median follow-up of 30.8 months giving 39.1% false negative findings. These different recurrence rates in various studies are difficult to explain but warn us that a negative iPET does not guarantee no-recurrence in DLBCL patients. A possible reason for false negative iPET could be stunning of glucose metabolism by chemotherapeutic agent(s) which likely to happen in first 10 days post-treatment (Engles et al., 2006). However, the odds of metabolic stunning is less likely in our study because as per departmental protocol iPET was performed at least 10 days after recent chemotherapy. So the most plausible explanation for recurrence in negative iPET could be the presence of clinically significant viable tumor cells in non-avid residual mass(s) (less than liver SUVmax) which were beyond the spatial resolution of our scanner. This high recurrence with negative iPET indeed questions the diagnostic accuracy of Deauville scores 1-3 (no uptake or \leq mediastinal or \leq liver uptake) to interpret an iPET as CMR. Recently published results from Positron Emission Tomography-guided Therapy of Aggressive non-Hodgkin Lymphomas (PETAL Trial) found better diagnostic accuracy of delta SUVmax (Δ SUVmax \leq 66%) than Deauville scoring >3 on iPET for dose intensification to avoid over-treatment (Rekowski et al., 2020). However, DS ≤ 3 and Δ SUVmax \leq 66% were found to have comparable event free survival (EFS) in PETAL trial (Rekowski et al., 2020). Kwon et al., (2016) used DS-1 for negative iPET in homogenous population but the relapse rate is similar to our study with DS ≤ 3 as negative iPET in homogenous population with standardized imaging and reporting protocols. But they had significantly longer median follow-up (30.8 months) than current study (11 months).

In this study, only the highest SUVmax (cut-off > 22.6) in baseline ¹⁸F-DG PET/CT was found an independent predictor for PFS in patients with a negative iPET. Prognostic significance of pretreatment SUVmax of ¹⁸F-DG PET/CT has been explored by various studies with variable inferences. Study by Chihara et al., (2011) on 110 patents found 3-year PFS rates in patients with baseline SUV < 30 and those with SUV ≥ 30 were 78 and 51%, respectively. Another study published in 2016 found pretreatment SUVmax > 10.5 as a significant predictor for PFS only on univariate analysis (Kwon et al., 2016). Park et al., (2012) also reported baseline SUVmax as predictor of PFS in patients with DLBCL. However, Kim et al., (2013) found total lesion glycolysis (TLG) as a better prognostic indicator of PFS than SUVmax and international prognostic index (IPI).

This study has some limitations. Firstly, we did not mention established prognostic factors like serum lactic dehydrogenase (LDH) and IPI which will be correlated with outcome in future study. Secondly, we did not use TLG, another semiquantitative parameter, which is known to be less affected by some imaging and non-imaging parameters than SUVmax. However, it also a known

fact that SUVmax is the most common parameter use in clinical practice and estimation of TLG is time consuming in imaging systems not having a software option which was the case with our facility. Thirdly, we did not compare positive iPET with negative. However, as mentioned earlier, positive predictive value of iPET in DLBCL has extensively been studied and we find fewer studies regarding the relapse rate in negative iPET. Fourth, the standard regimen in this study was CHOP with or without rituximab. We understand this is an important limitation as rituximab is prone to induce false positive ¹⁸F-DG uptake. But this would have led to false positive iPET while our study was focused over negative iPET.

We conclude that recurrence is found in 34% of DLBCL patients with a negative interim ¹⁸F-DG PET/CT using standardized imaging and reporting protocols. Despite of early response, these patients need continued intensive follow-up especially those with a baseline SUVmax > 22.6 .

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Competing of Interest

The authors don't have any financial and/or Institutional conflict of interest to declare.

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