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

Maseeh uz Zaman$^{1*}$, Nosheen Fatima$^{1}$, Areeba Zaman$^{2}$, Unaiza Zaman$^{3}$, Sidra Zaman$^{4}$, Rabia Tahseen$^{5}$

Abstract

**Background:** To determine progression free survival (PFS) and predictor of recurrence in patients with diffuse large B-cell lymphoma (DLBCL) with negative interim $^{18}$FDG 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 $^{18}$FDG 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, $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$FDG PET/CT) is considered as standard-of-care for reliable staging and response assessment of aggressive malignant lymphomas, including DLBCL. Currently, $^{18}$FDG-PET/CT at the end of treatment (ePET) is an accepted method for response assessment with $^{18}$FDG positivity is considered predictive of reduced survival in patients with malignant lymphoma (Cheson, 2011). There is large body of data favoring reliable role of $^{18}$FDG-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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Progression, relapse after response, or death as a result was the period from iPET diagnosis until lymphoma disease recurrence. Progression free survival (PFS) and highest SUVmax at baseline to see the impact of stage of disease, largest lesion size and highest SUVmax, revealed that the mean time of disease recurrence. Similarly, recurrence (DR). Kaplan Meier survival plot was used having remission or sustained CMR (sCMR) or disease on follow-up scan results, patients were categorized as (indeterminate) on follow-up scans were either biopsied afterward for recurrence. Patients with Deauville score –X (Boellaard et al., 2015). These patients were followed-up of Nuclear Medicine (EANM) guidelines for both studies protocol for received standard first line chemotherapy (CHOP with 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 metabolic response (CMR) using Deauville scoring 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 ±14 yr.), gender distribution (overall M:F: 63:37%), body mass index (overall: 26.47 ±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 ±34 mg%), 18FDG dose (overall: 171 ±37 MBq), uptake period (overall: 67 ±11 min) and mean hepatic uptake (overall: 1.76 ±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 ±1), largest lesion on baseline PET/CT (overall: 64 ±49 mm), highest SUVmax on baseline scan (overall: 19 ±9.27) and median follow-up (overall: 11 ±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 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 ±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 ±14 yr.), gender distribution (overall M:F: 63:37%), body mass index (overall: 26.47 ±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 ±34 mg%), 18FDG dose (overall: 171 ±37 MBq), uptake period (overall: 67 ±11 min) and mean hepatic uptake (overall: 1.76 ±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 ±1), largest lesion on baseline PET/CT (overall: 64 ±49 mm), highest SUVmax on baseline scan (overall: 19 ±9.27) and median follow-up (overall: 11 ±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
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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 2011). The 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 2011).

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     | 55 ± 15         | 55 ± 12         | 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                           | 117: 68     | 75:48:00        | 42:20:00        | 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                   | 19.00 ± 9.27| 17.95 ± 8.08    | 21.00 ± 10.99   | 0.179          | 0.858   |
| Mean ± SD (Range)                | 3.9-61.2    | 3.7-47.6        | 3.9-61.2        | -0.146         | 0.8841  |
| Largest lesion                   | 64 ± 49     | 64 ± 52         | 63 ± 50         | -0.146         | 0.8841  |
| Mean ± SD Range in mm            | (05-266) mm | (05-266) mm     | (09-237)        | -0.146         | 0.8841  |
| Median Baseline stage             | 03 ± 01     | 03 ± 01         | 03 ± 01         | 0              | 1       |
| Median follow up in months        | 11 ± 19     | 10 ± 16         | 14 ± 23         | 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

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
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).

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 |
|-------------------------------|------|-----------|-------------|-------------|-----|--------------------------|---------|
| 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 ≤ mediastinal or ≤ 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 (ΔSUVmax ≤66%) than Deauville scoring >3 on iPET for dose intensification to avoid over-treatment (Rekowski et al., 2020). However, DS ≤3 and ASUVmax ≤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 18FDG PET/CT was found an independent predictor for PFS in patients with a negative iPET. Prognostic significance of pretreatment SUVmax of 18FDG 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 18FDG 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 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.

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Author Contributions

Conceptualization: Nosheen Fatima, Maseeh uz Zaman
Data curation: Nosheen Fatima, Maseeh uz Zaman
Investigation: Nosheen Fatima, Maseeh uz Zaman, Rabia Tahseen, Sidra Zaman
Methodology: Maseeh uz Zaman, Nosheen Fatima, Areeba Zaman, Rabia Tahseen
Software: Nosheen Fatima, Maseeh uz Zaman, Unaiza Zaman
Validation: Nosheen Fatima, Maseeh uz Zaman
Writing-original draft: Maseeh uz Zaman, Nosheen Fatima, Unaiza Zaman, Areeba Zaman
Review and Approved: All authors

Competing of Interest

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

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