ORIGINAL ARTICLE

# Interim$^{18}$ F-FLUORO-2-deoxy-d-glucose positron emission tomography scan/computed tomography scan in diffuse large B cell lymphoma-as a prognostic tool

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## Abstract

**Objective:** To assess the role of interim [18F]-Fluoro-2-deoxy-d-glucose positron emission tomography scan/computed tomography scan in the management of diffuse large B-cell lymphoma in terms of progression-free survival and overall survival prediction.

**Methods:** The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital, Lahore, and comprised data of newly diagnosed patients of diffuse large B-cell lymphoma treated between January 2010 and June 2013.Baseline characteristics of patients were documented and compared. Response on interim positron emission tomography/computed tomography and end of treatment scan was taken a look at, and .progression-free survival and overall survival for positive/negative scans were calculated. Data was also reviewed for sensitivity, specificity, positive predictive value and negative predictive value for relapse. SPSS 19 was used for statistical analysis.

**Results:** Data of 119 patients was reviewed, and 87(73%) of them were males. Overall median age was 33 years (range 18-50). Interim scan was positive for 63(53%) patients and negative for 53(47%), and showed positive predictive value, negative predictive value, sensitivity and specificity for relapse of 35%, 89%, 79% and 55% respectively. Two-years progression-free survival and overall survival for scan-positive patients was 66% and 72% compared to 88% (p=0.002) and 92% (p=0.005) for scan-negative patients. Corresponding values at 2 years for patients having positive end-of-treatment scan were 35% and 44% against 94% (p<0.001) and 96%(p<0.001) for patients with negative scan.

**Conclusion:** Interim positron emission tomography/computed tomography had high sensitivity and negative predictive value for relapse in diffuse large B-cell lymphoma. Both interim and end-of-treatment scans were predictors of progression-free survival and overall survival.

**Keywords:** Diffuse large B-cell lymphoma, Survival analysis, Positron emission tomography, Computed Tomography. (JPMA 66: 380; 2016)

## Introduction

According to World Health Organisation (WHO) classification, diffuse large B cell lymphoma (DLBCL) is an aggressive B cell non-Hodgkin's lymphoma (NHL).[1] It is the most frequently diagnosed histological subtype of NHL and accounts for approximately 25 percent of all NHL cases.[2] Addition of Rituximab (R), an anti-CD20 monoclonal antibody, to the standard doses of chemotherapy regimen Cyclophosphamide-Hydroxydoxorubicin-Oncovin-Prednisone (CHOP/R-CHOP)in recent years has considerably improved the clinical results of DLBCL patients.[3,4] Overall outcomes have improved significantly. However, relapsed/refractory disease causes great deal of morbidity and mortality.[5] It is, therefore, important to know the prognosis while dealing with this disease.

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International prognostic index (IPI) is a well-established prognostic tool for DLBCL.[6] In recent years, interim and end-of-treatment (EOT) positron emission tomography/ computed tomography (PET/CT) scan has been investigated as predictor of prognosis.[7] PET/CT provides both anatomic and functional information which leads to more accurate staging and ultimately better choice of treatment.[8] Therefore, its use is growing for tumour staging and evaluating the response to treatment in NHL.[9] On the basis of these findings, the International Working Group response criteria incorporated PET for assessment of response in aggressive NHL.[10]

A review conducted in 2009 failed to demonstrate useful role of PET/CT in predicting the outcome for DLBCL patients. This was attributed to disparity in imaging condition and interpretation criteria, lack of consistency in treatment regimens and heterogeneous study populations.[11] A recent meta-analysis showed low sensitivity (Se) and specificity (Sp) of interim scan (I-PET/CT) as predictor of outcome.[12] However, another meta-analysis concluded that interim and EOT PET/CT scans have independent prognostic value in

management of DLBCL.[13] Usefulness of PET/CT to predict survival in Hodgkin's lymphoma is well established.[14] Similarly, prognostic utility of PET/CT has been investigated in Follicular, Natural killer T(NKT) cell and Mantle cell lymphomas as well.[15-18]

The current study was planned to investigate whether or not I-PET/CT scan can provide any useful information regarding progression-free survival (PFS), overall survival (OS) and relapse risk in DLBCL patients.

## Patients and Methods

The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital (SKMCH), Lahore, and comprised data of newly diagnosed DLBCL patients treated between January 2010 and June 2013. The study was approved by the institutional review board.

All patients had I-PET/CT scan done, and had also undergone EOT PET/CT. Baseline PET/CT was performed in most but not in all patients. Patient's demographics, clinical characteristics at presentation like Ann Arbor stage, IPI, presence of bulky disease, baseline and follow-up imaging, biopsy results from residual masses, response to therapy, and survival duration were recorded.

All patients had been treated with 6 to 8 cycles of anthracyline-based CHOP chemotherapy either with or without rituximab, administered every 3 weeks. Intrathecal chemotherapy and radiotherapy had been given where clinically indicated.

All patients were studied utilising PET/CT Philips Gemini TF (Philips Healthcare, Eindhoven, Netherlands), combining a germaniumoxyorthosilicate-based PET scanner and a 16-slice CT scanner (Figure-1). Each patient had been studied utilising the same PET protocol parameters. I-PET studies had been carried out on an average of about 14 days (range 9-19 days) after the last dose of chemotherapy, while the EOT scan was done 7 weeks (range 5-9 weeks) after the last chemotherapy cycle.

All the patients had fasted for at least 6 hours before the start of the (18F)-Fluoro-2-deoxy-d-glucose (FDG) PET scan. Serum glucose level was determined at the time of 18F-FDG injection using a glucometer and all the patients had glucose level <150 mg/dl. Sixty minutes after intravenous administration of 5MBq/kg of 18F-FDG, a PET imaging study from the head to the mid-thigh was acquired. The images had been independently reviewed by a nuclear medicine physicians and a radiologist with knowledge of the clinical data. Each scan had been interpreted as being either negative or positive for disease activity. A positive PET scan had been defined as one having higher 18F-FDG uptake relative to uptake in liver or surrounding background, with no similar activity seen on the contralateral side, or increased activity at any location incompatible with normal physiological distribution. A negative scan had been defined as having no abnormally increased 18F-FDG at any site.

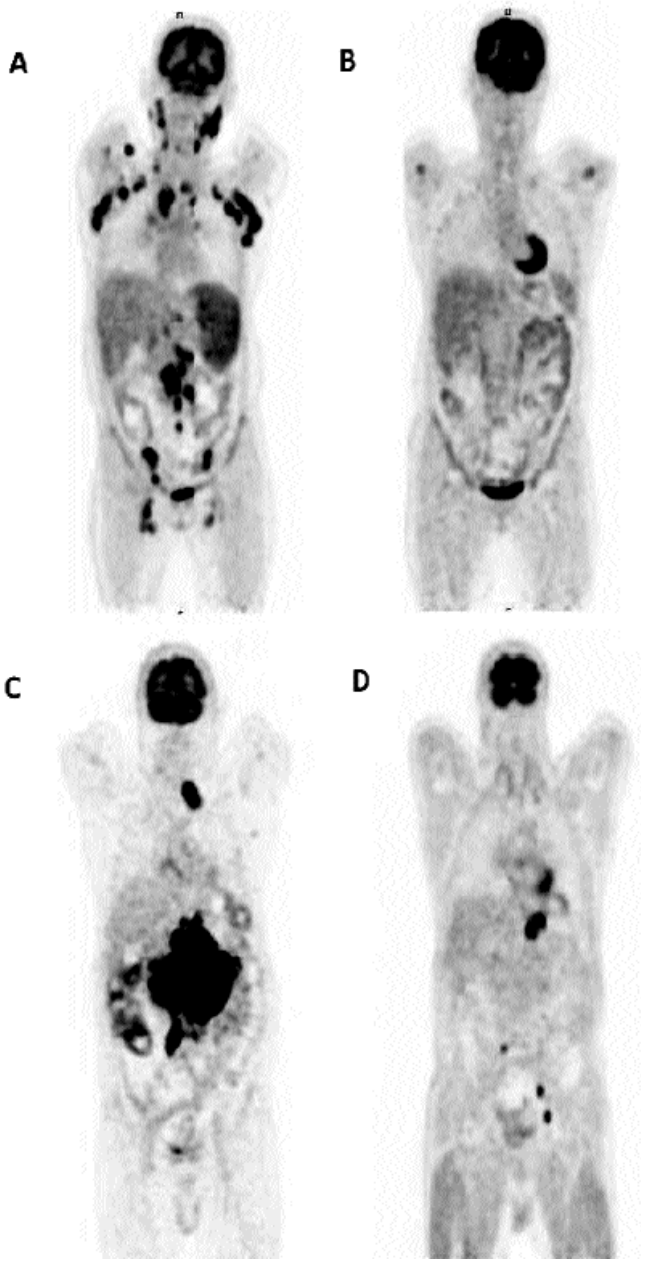


**Figure-1:** Positron emission tomography (PET) images of patients. (A) Baseline PET image of first patient showing extensive disease. (B) Interim PET image of first patient showing metabolic complete response.(C) Baseline PET image of second patient showing extensive disease.(D) Interim PET of second patient showing metabolic partial response.

PFS was defined as the time from diagnosis to the date of

death, relapse, or disease progression. OS was defined as the time from diagnosis to the date of death or last follow-up.

SPSS 19 was used for statistical analysis. Continuous variables were summarised as median and range. Categorical variables were summarised as frequencies and percentages. Patient characteristics were compared using the Fisher exact test for discrete variables. Kaplan-Meier method was used to estimate PFS and OS and the positive PET and negative PET groups were compared using the log-rank test. P<0.05 indicated statistical significance.

## Results

Data of 119 patients was studied and 87(73%) cases related to males. Overall median age was 33 years (range: 18-50 years). Median follow-up time was 26 months (range: 7-44 months).There were 10(8.6 %) patients with Ann-arbor stage I; 25(21.6%) in stage II; 18(15.5%) in stage III; and 63(54.3%) in stage IV. IPI score meant 54(46.6%) patients were low-risk, 32(27.6 %) low-intermediate, 28(24.1%) high-intermediate and 2(1.7%) high-risk. Overall, 66(55%) patients received CHOP chemotherapy and 53(45%) received R-CHOP. Baseline FDG PET had been performed in 81(68%) patients; while the rest had CT scan done at baseline. All patients had undergone I-PET/CT which was performed after 2 cycles chemotherapy in 24(20%), 3 cycles in 8(7%) and 4 cycles in 87(73 %) patients (Table).

Patients showing negative I-PET/CT had better PFS and OS compared to patients with positive I-PET/CT, with 2-year PFS and OS of 92% and 88% compared to 72% and 66%, respectively (Figure-2). Positive EOT PET/CT also led to poor PFS and OS figures compared to patients who registered metabolic complete response (CR) on EOT imaging; OS and PFS of 44% and 35% versus 96% and 94% respectively.

The positive predictive value (PPV), negative predictive value (NPV), Se, and Sp of the I-PET/CT for the prediction of relapse were 35% (95% confidence interval [CI]:23-48%), 89% (95% CI: 78-96%), 79% (95% CI: 59-92%), and 55% (95% CI: 44-65%), respectively.

I-PET/CT was positive in 63(53%) patients (Figure-3). Of these, 32(51%) patients had negative EOT imaging, while 19(30%) progressed, and 12(19%) exhibited persistent PET positivity but did not demonstrate disease progression. Out of these 12 patients, biopsy was performed in 7(58%), with negative biopsy results in 6(86%) and they remained in remission on subsequent follow-up. One (14%) patient showed persistent disease activity on biopsy and he was treated with second-line chemotherapy but ultimately progressed and died. Five (42%) patients did not undergo biopsy because of technical difficulties and they had subsequent imaging.

Among the 19 patients who progressed on EOT imaging after positive interim PET/CT, 5(26.3%) were alive: 2(40%)

**Table:** Clinical Characteristics.

| Characteristics | All patients (n=119) no.(%) of patients | I-PET negative (n=56) no.(%) of patients | I-PET positive (n=63) no.(%) of patients | p value |
|---|---|---|---|---|
| **GENDER** | | | | |
| Male | 87(73) | 40(71) | 47(75) | |
| Female | 32(27) | 16(29) | 16(25) | 0.42 |
| **STAGE** | | | | |
| I/II | 36(30) | 17(30) | 19(30) | |
| III/IV | 83(70) | 39(70) | 44(70) | 0.56 |
| **IPI** | | | | |
| 0-2 | 87(73) | 40(71) | 47(75) | |
| >3 | 32(27) | 16(29) | 16(25) | 0.42 |
| **BULKY DISEASE** | | | | |
| Present | 21(18) | 11(20) | 10(16) | |
| Absent | 98(82) | 45(80) | 53(84) | 0.38 |
| **BONE MARROW** | | | | |
| Involved | 12(10) | 9(16) | 3(05) | |
| Not involved | 107(90) | 47(84) | 60(95) | 0.04 |
| **CHEMOTHERAPY** | | | | |
| RCHOP | 53(45) | 28(50) | 25(40) | |
| CHOP | 66(55) | 28(50) | 38(60) | 0.17 |

I-PET: Interim positron emission tomography
CHOP:Cyclophosphamide-Hydroxydoxorubicin-Oncovin-Prednisone
RCHOP: Rituximab-Cyclophosphamide-Hydroxydoxorubicin-Oncovin-Prednisone

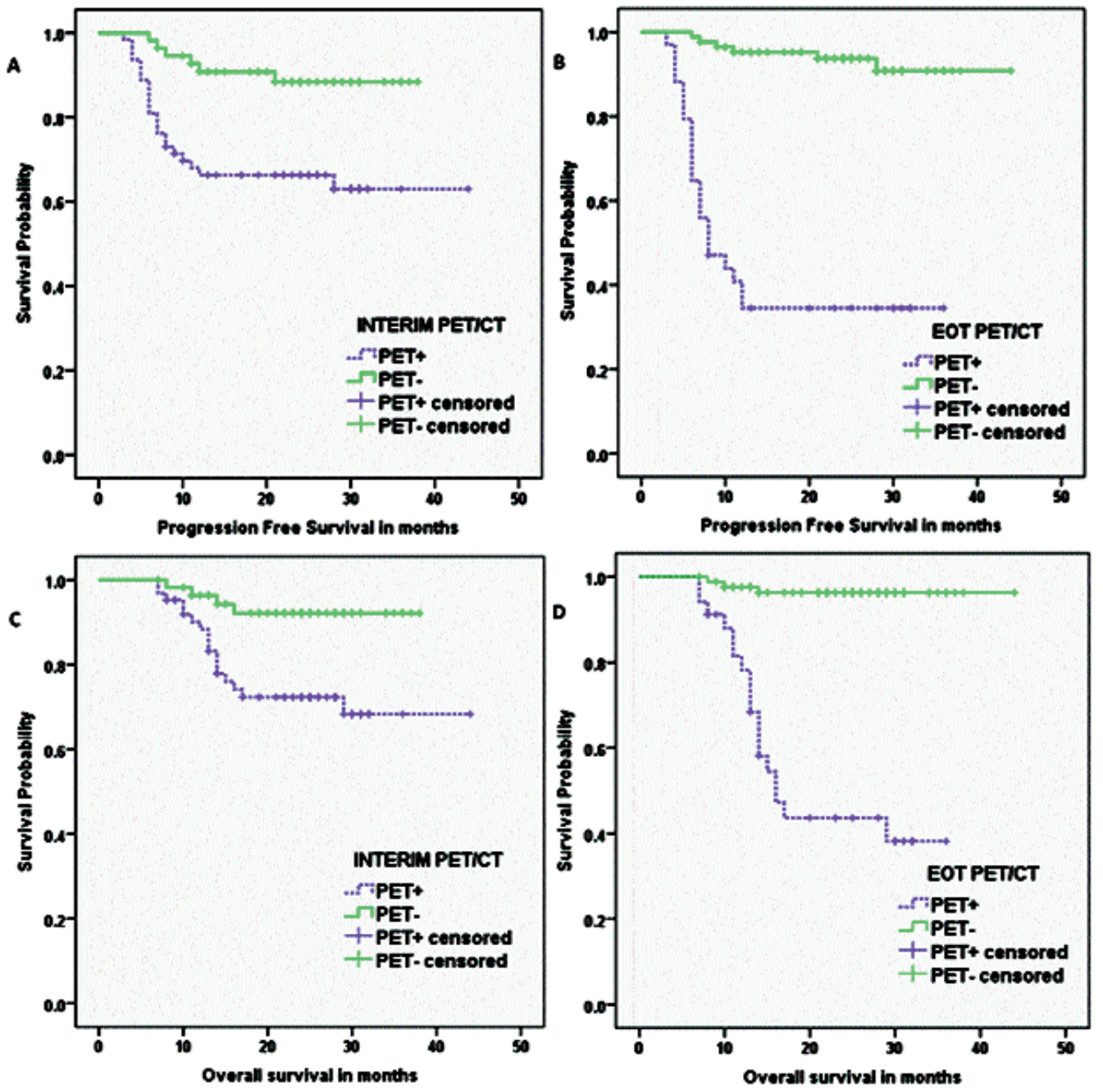


**Figure-2:** Kaplan Meier plot. (A) Progression-free survival according to interim positron emission tomography/computed tomography (PET/CT) results (p=0.002). (B) Progression-free survival according to end-of-treatment (EOT) scan results (p<0.001). (C) Overall survival according to interim scan results (p=0.005). (D) Overall survival according to EOT scan results (p<0.001).PET +, PET/CT positive; PET -, PET/CT negative.

in complete remission after second-line chemo, and 3(60%) were undergoing chemotherapy at the time of study. The remaining 14(73.7%) patients had died of disease progression. Out of these, 6(43%) patients progressed on 2 second-line chemotherapies, 6(43%) showed progression after 1 second-line chemo, and 2(14%) patients did not receive any chemotherapy.

The 32(51%) patients with negative EOT studies were followed for 6-40 months (median: 19 months). Two (6%) patients relapsed within 6 months of treatment completion. One (50%) of them is in remission after second-line chemotherapy, the other patient (50%) died due to

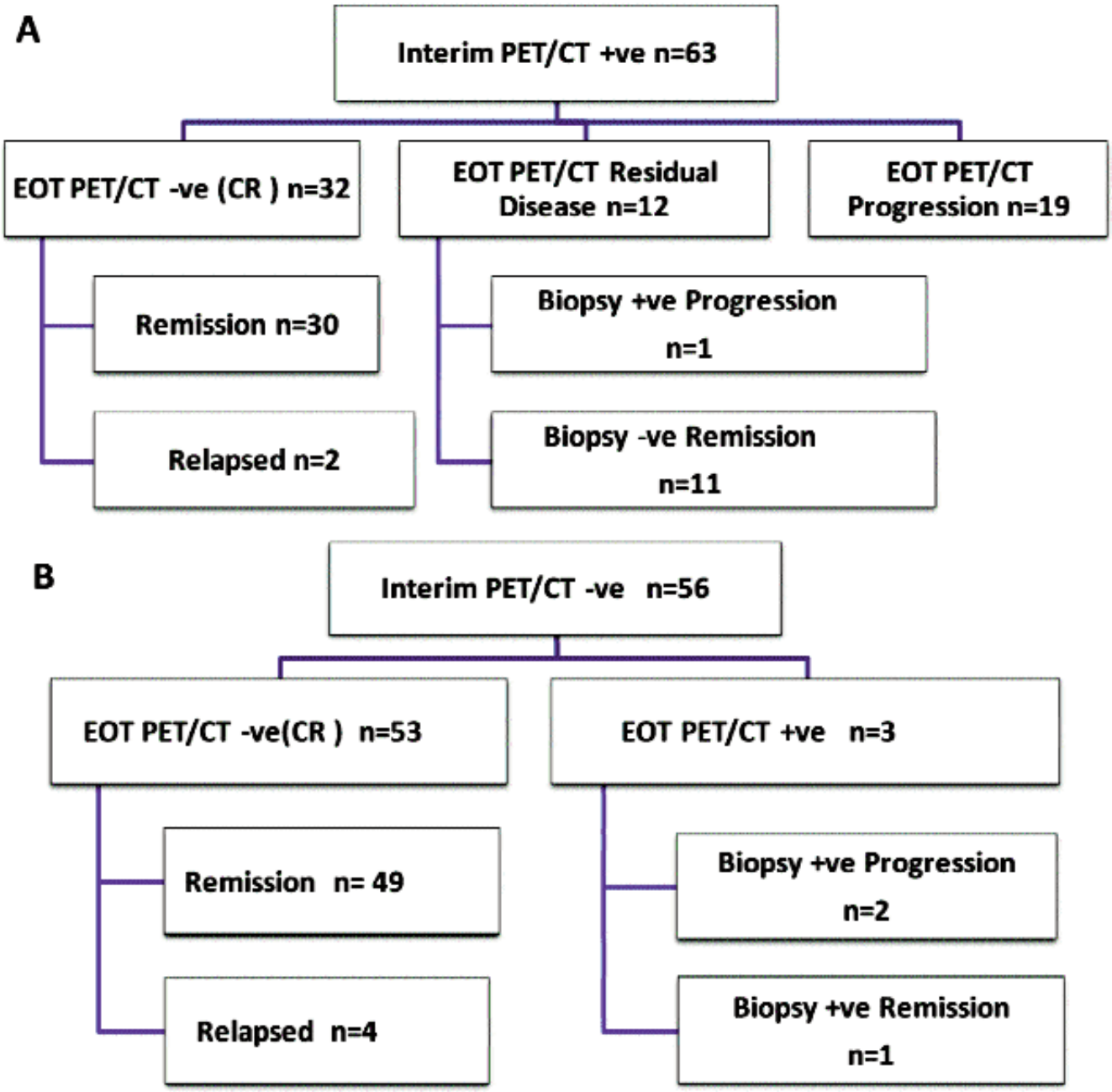


**Figure-3:** Clinical outcome of patients according to Interim positron emission tomography/computed tomography (PET/CT) results.

therapy-related complications while on chemotherapy.

Out of the 56(47%) patients who had negative I-PET, 3(6%) patients had positive EOT PET/CT. All 3(100%) patients underwent biopsy which led to disease confirmation in 2(66.6%). One (33.3%) patient had benign pathology on biopsy. The 2(66.6%) patients who received second-line chemotherapy, but ultimately showed progression after showing initial partial response, died due to disease. The other 53(94%) patients continued to be in CR on EOT imaging. Of them, 51(96%) patients were in remission after a median follow-up of 24 months (range: 8-40). Two (4%) patients relapsed and died subsequently after being refractory to second-line chemotherapy.

## Discussion

In this retrospective study of patients with DLBCL, I-

PET/CT had a low PPV (35%) but high NPV (89%) for disease relapse. Data from various other investigators showed more or less similar results.[19-22] I-PET/CT was found to have relatively high Sefor relapse (79%), but Sp was relatively low (55%).

I-PET/CT was able to segregate patients with different PFS and OS results-based PET positivity in our study. These results are in concordance with certain other studies.[23,24] Almost half of our patients (47%) had negative I-PET/CT. Most of them (94%) remained in metabolic CR on EOT imaging with less than 5% relapse rate on an average follow-up of 24 months. Significant proportion of patients with positive I-PET/CT failed to achieve metabolic CR on EOT imaging.

Our results also suggest that EOT PET/CT showed strong association with PFS as well OS which is in line with international data established by 2 reviews.[25,26] Researchers of two recent trials have found high concordance rate between interim and EOT PET/CT results and have questioned the role of EOT PET/CT after a negative I-PET/CT scan in management of DLBCL.[27,28]

Outcome of our patients who had relapsed or had refractory disease was poor even in those patients who achieved metabolic CR on PET/CT initially. Most of these patients responded poorly to second-line chemotherapy regimens and none of them had autologous stem cell transplant.

Standard anthracyline-based chemotherapy in combination with rituximab do not cure all patients with DLBCL.[29,30] Different regimen used for salvage high-dose chemotherapy followed by autologous stem cell transplantation in patients previously treated with R-CHOP offer cure rates of less than 30% to 35%.[31,32] Thus, finding reliable prognostic indicators would be very helpful in the management of NHL patients. The most commonly used factors are histopathological subtypes and the IPI.[6,33]

The important potential of I-PET/CT in aggressive lymphomas like DLBCL is to separate group of patients more likely to end up with relapse or refractory disease among patients being treated on first-line R-CHOP chemotherapy regimen. Second-line chemotherapy and autologous stem cell transplant or participation in clinical trials of new molecular targeted agents early on in the course of disease might improve long-term outcome of these patients.

There were some limitations of this study, like baseline PET/CT had not been performed in all patients which might have impaired the imaging specialist's ability to interpret the interim scans. About 50% patients had not received rituximab due to unaffordability. There was lack of uniformity in timing of I-PET/CT scan but it was performed after 4 cycles in most patients. All patients included in this analysis were below 50 years of age. Nuclear medicine physician interpreting the PET/CT scan had knowledge of clinical history of the patients.

## Conclusion

I-PET/CT had high Se and NPV for relapse in DLBCL. It was predictor of better PFS and OS. A negative Interim 18F-FDG PET/CT signified a better response to chemotherapy that translated into a better long-term survival. EOT PET/CT was also a strong predictor of PFS and OS. Large-scale prospective studies are required to validate the findings and to determine the optimal timing of I-PET/CT scan.

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