Original Article

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The Role of Post-treatment FDG-PET/CT Scanning after the First-line Chemotherapy in Predicting Prognosis in Patients with Hodgkin Disease and High-grade Non-Hodgkin Lymphoma: A Comparative Study with Clinical Prognostic Risk Scoring Data

Hodgkin Hastalığı ve Yüksek Dereceli Non-Hodgkin lenfomalı Hastalarda Prognozu Tahmin Etmede Birinci Basamak Kemoterapiden Sonra Yapılan FDG PET/BT Taramasının Rolü: Klinik Prognostik Risk Skorlama Verileri ile Karşılaştırmalı Bir Çalışma

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ABSTRACT

Objective: We aimed to evaluate the role of fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) performed after the first-line therapy in predicting prognosis of lymphomas and compare the results with the pre-treatment prognostic risk scoring (PRS) indices.

Methods: One hundred three patients with histopathologically confirmed Hodgkin (HD) and high-grade non-Hodgkin lymphoma (NHL) were included in the study. All patients received FDG-PET/CT imaging after the end of primary treatment. After intraveneus application of FDG, whole body PET/CT from the upper thigh to the vertex was performed.

Results: The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of post-treatment FDG-PET/CT imaging in predicting remission status were 73.6%, 91.6%, 88%, 66.6%, and 94.0%, respectively. Those values were

ÖZ

Amaç: İlk basamak tedavi sonrası yapılan florodeoksiglukoz (FDG)-pozitron emisyon tomografi/bilgisayarlı tomografinin (PET/BT) lenfomaların prognozunu öngörmedeki rolünü değerlendirmeyi ve sonuçları, tedavi öncesi yapılan prognostik risk skorlama (PRS) indeksleri ile karşılaştırmayı amaçladık.

Yöntemler: Çalışmaya histopatolojik olarak doğrulanmış Hodgkin hastalığı (HH) ve yüksek dereceli non-Hodgkin lenfoma (NHL) tanısı alan ve FDG PET/BT taraması yapılan toplam 103 hasta dahil edildi. Tüm hastalara, birinci basamak tedavinin bitiminden sonra FDG PET/BT görüntüleme yapıldı. Hastalara FDG'nin intravenöz uygulamasından sonra üst uyluktan vertekse kadar tüm vücut PET/BT yapıldı.

Bulgular: Tedavi sonrası FDG PET/BT görüntülemenin duyarlılık, özgüllük, doğruluk, pozitif öngörü değeri (PPV) ve negatif öngörü değeri (NPV), remisyon durumunu öngörmede sırasıyla; %73,6,

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63.0%, 62.0%, 62.0%, 27%, and 88.0% respectively, for pre-treatment clinical risk scoring (p<0.001). Among the patients with positive PET scans after ending of the first-line therapy, 71.4% of those with only single lymph node station involvement stayed in remission, whereas 12.5% of the patients who had involvement of multiple lymph node stations and 16.7% of the patients who had extranodal disease could sustain in remission (p<0.05).

Conclusion: We found that FDG-PET performed after first-line therapy was superior to clinical PRS systems in predicting prognosis of HD and NHL disease as conclusions. Although it was more successful to predict patients who would stay in remission with its high NPV, FDG-PET/CT imaging had a lower PPV due to false positive results. However, persistent FDG uptake in multinodal lymphatic stations and/or in extranodal sites on the post-therapy PET/CT scanning was more suggestive in predicting risk for recurrence.

Keywords: Lymphoma, positron emission tomography/computed tomography, F-18 fluorodeoxyglucose, clinical prognostic risk scores

%91,6, %88 %66,6 ve %94,0 idi. Tedavi öncesi klinik risk skorlaması için bu değerler sırasıyla %63,0, %62,0, %62,0, %27 ve %88 olarak hesaplandı (p<0,001). Birinci basamak tedavisinin bitiminden sonra PET taraması pozitif olan hastalar arasında, yalnızca tek lenf nodu istasyonu tutulumu olanların %71,4'ü remisyonda kalırken, birden fazla lenf nodu istasyonu tutulumu veya ekstranodal hastalığı olan hastalarda remisyonda kalma oranı sırasıyla %12,5 ve %16,7 olarak hesaplandı (p<0,05).

Sonuç: Sonuç olarak, birinci basamak tedaviden sonra gerçekleştirilen FDG PET'nin, HH ve NHL'nin prognozunu öngörmede klinik PRS sistemlerinden daha üstün olduğunu bulduk. Yüksek NPV nedeniyle, remisyonda kalacak hastaları tahmin etmede daha başarılı olsa da, FDG PET/BT görüntülemenin yanlış pozitif sonuçlardan dolayı PPV daha düşüktür. Bununla birlikte, tedavi sonrası PET/BT taramasında multinodal lenfatik tutulumu olan ve/veya ekstranodal tutulumu olan hastalarda, tek lenf nodu tutulumu olanlara göre rekürrens olasılığının daha yüksek olduğu görüldü.

Anahtar Sözcükler: Lenfoma, pozitron emisyon tomografisi/bilgisayarlı tomografi, F-18 florodeoksiglukoz, klinik prognostik risk skorları

Introduction

Multislice computed tomography (CT) integrated positron emission tomography/CT (PET/CT) with Flourine (F)-18 labelled fluorodeoxyglucose (FDG) has been widely used in staging and follow-up of malignant lymphomas as happens in many other solid malignancies in recent years (1,2). Malignant tissues are capable of accumulating more FDG, a radiopharmaceutical of d-glucose analogue, compared to normal tissue due to their excess energy requirement, and represent themselves as highly contrasted foci on PET/CT imaging.

In curable lymphomas, i.e Hodgkin disease (HD) and aggressive non-Hodgkin lymphomas (NHL), the use of standart doxorubicin-containing chemotherapy regimens with or without involved field radiotherapy (IF-RT) has a high success rate. These standart therapy protocols are defined mainly according to histologic subtype and stage of the disease as well as prognostic prediction based on clinical prognostic risk scoring systems (PRS) (3,4). However, a complete long-term disease control can not be achieved in a substantial portion of patients with these standart chemotherapy regimens due to either resistant disease or early relapse. In this subgroup of patients with lymphoma, it is possible to get the disease under control by applying more aggressive chemotherapy protocols (5). However, this approach is required a more serious risk-benefit ratio calculation because of undesired toxic effects of such chemotherapy protocols for the patients (6). Therefore, an effective mid- or end-treatment evaluation is desired in patients with lymphoma and this is of particular importance to discriminate the subgroup of patients either who will have a resistant disease or be at higher risk for early relapse.

In this retrospective study we aimed to determine the efficacy of FDG-PET/CT imaging performed after the first-line treatment in predicting the prognosis of patients with lymphoma and we also compared the PET/CT results with the pretreatment prognostic scores.

Methods

Patients

A total of 103 patients with a diagnosis of histologically proven lymphoma, treated in the hematology clinic of the of the İstanbul University-Cerrahpaşa Hospital, and who underwent FDG-PET/CT scan after the completion of the first-line treatment, were analyzed retrospectively. Our study project was approved by the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (16.09.2008/27584). There were 56 (54.4%) patients with HD (32 nodular sclerosing, 21 mixed type, and 3 lymphocyte rich) and 47 (45.6%) patients with high-grade NHL (43 diffuse large B-cell lymphoma, 3 anaplastic T-cell lymphoma, and 1 Burkitt's lymphoma) (Table 1). The age ranged from 16 to 81 with an average of 41.6 ±17.1 (47 females and 56 males). The PET/CT studies were performed between 10 and 90 days after completing their first-line treatment. Thereafter, all patients were followed up in haematology outpatient clinic with an interval of 3-6 months and evaluated by physical examination and laboratory parameters as well as by imaging modalities when needed. Accordingly, their disease outcome status was classified in two groups as "remission" and "non-remission". The non-remission group was including those patients with partial remission or stable disease, and relapsed or progressed disease. The median follow-up duration was 31.8±7.5 months (ranged from 24 to 55 months). The patients who did not achieve remission were treated by further chemotherapy courses and/or stem cell transplantation with high dose chemotherapy (Table 2a, 2b).

Pretreatment Prognostic Risk Scoring

All patients were staged according to Ann Arbor classification from stage I to IV in the pretreatment evaluation (7). In HD

Table 1. Histological subtypes of patients with HD and NHL diagnosis

Hodgkin lymphoma			
Total	Nodular sclerosing 21 mixed type, and 3 lymphocyte rich	Mixed type sclerosing, 21 mixed type, and 3 lymphocyte rich	Lymphocyte rich
(n=56)	32 (57.1%)	21 (37.5%)	3 (5.3%)
Non-Hodgkin lymphoma			
Total	Diffuse large B-cell	Anaplastic T-cell	Burkitt's
(n=47)	43 (91.4%)	3 (6.3%)	1 (2.1%)

HD: Hodgkin disease, NHL: Non-Hodgkin lymphoma

group, stage I-IIA patients were classified as having "early (localised) stage" and stage IIB-IV patients were classified as having "late (advanced) stage. Then, early stage patients were classified in "favorable prognostic" and "unfavorable prognostic" groups according to German Hodgkin Lymphoma study group criteria (8). In NHL group, the patients were classified into low, low-medium, medium-high and high risk groups according to IPI (International Prognostic index) and age-adjucted (aa)-IPI criteria (4). Then, they were categorized within two groups as "low risk" (for low and low-medium groups) and "high risk" (for medium-high and high groups).

First-line Treatment Protocols

According to departmental protocols, patients with early stage HD were treated with ABVD regime from 2 to 4 courses followed by consolidation IF-RT and patients with advanced stage HD were treated with 6-8 courses of ABVD (a total of 10 patients). Nine patients with NHL were essentially treated with CHOP regime with rituximab (only in 9 patients without rituximab), from 3 to 8 courses followed by IF-RT. The indications for consolidation radiotherapy included (i) initial massive mediastinal disease; (ii) individual or confluent nodal masses; and (iii) macroscopic nodules in an intact spleen as determined by CT scan.

PET/CT Imaging and Evaluation Protocol

All patients underwent a post-therapy PET/CT scan, performed 10 to 90 days (median 36.7) after completion of the first-line treatment protocol. A dedicated high-resolution LSO based PET scanner that was integrated with 6 slice CT (Siemens Biograph 6 LSO HI-REZ PET/CT, Illinois, USA) was used for PET/CT imaging. All patients were given an iodine containing contrast agent (Telebrix 30 Meglumin, Guerbet, France or Urovist-angiografin 50, Bayer Türk Kimya, İstanbul, Turkey) diluted in 1.5 L of water and asked to drink it part by part starting 4-8 hrs before their appointment time. Patients were in at least 4 hr fasting at the time of their appointment. After ensuring the peripheral blood glucose level less than 180 mg/dL, 296-703 MBq (8-19 mCi) FDG was intravenously injected into the patient via an IV catheter and thereafter the patients were rested 1-1.5 hr in a semireclining chair in the waiting room. After that, the patients were lain down in supine position on the scanner table. First, a CT topogram image was obtained from the vertex to 1/3 proximal of thighs. Then a low-dose CT imaging (60-80 mAs) without IV contrast administration was performed followed by PET emission imaging in the guidance of the CT topogram. Total PET/CT imaging was generally completed in 7-8 bed positions within 20-25 minutes. Iterative algorithms were applied to both PET and CT data reconstruction using the vendor provided software and multiplanar (axial, sagittal, coronal) slices with approximately 0.5 mm thickness of both PET and CT images as well as maximum intensity projection (MIP) views were obtained. Attenuation correction based on CT data was applied to PET images. Attenuation corrected PET slices together with identically aligned CT slices and coregistered (fused) PET/CT slices as well as MIP images were projected onto high resolution LCD monitors for reviewing and reporting.

The PET/CT images were evaluated by an experienced nuclear medicine phycisian underguidance with all clinical information available. In visual evaluation of PET/CT images, any lymph node with an increased FDG accumulation more than mediastinal blood pool and/or any focus of increased FDG uptake within an extranodal organ was considered as positive finding for residual disease. Additionally, a semi-quantitative index of FDG uptake intensity normalized to the body weight, which was called maximum standart uptake value (SUV_{max}) was calculated according to standard formula using the vendor-software by drawing a region-of-interest from the most active part of the lesion for each PET-positive region. Additionally, PET-positive patients for residual disease were categorized into 3 groups according to disease sites and extension as follows: i. Single lymphatic station involvement, ii. Multiple lymphatic stations involvement, and iii. Extranodal disease with or without nodal involvement.

Statistical Analysis

The sensitivity, specifity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of post-treatment FDG-PET/CT imaging and pre-treatment PRS in predicting of disease outcome were calculated for both whole group and subgroups (HD and NHL). Chi-square test was used to compare the diagnostic accuracy rates between the methods, as well as

Table 2 a. Characteristics of patients with Hodgkin Disease

No	Age/sex	Follow-up duration	PRS	First-line treatment	Post-therapy PET/CT (extension)	SUV_{max}	Disease outcome
1	26/F	25 months	High	4 cyc-CT	Positive	4.0	Stable
2	26/M	38 months	High	8 cyc-CT	Negative	-	Remission
3	28/F	35 months	High	8 cyc-CT	Positive	6.3	Remission
4	18/M	24 months	High	4 cyc-CT	Negative	-	Remission
5	63/F	33 months	High	8 cyc-CT	Negative	-	Remission
6	33/M	20 months	Low	4 cyc-CT	Negative	-	Remission
7	17/M	29 months	High	4 cyc-CT	Negative	-	Remission
8	38/M	34 months	High	8 cyc-CT	Negative	-	Remission
9	16/M	32 months	Low	4 cyc-CT	Positive	18.2	Exitus
10	42/M	24 months	High	4 cyc-CT+RT	Negative	-	Remission
11	34/F	28 months	Low	4 cyc-CT	Negative	-	Remission
12	37/F	29 months	Low	2 cyc-CT	Negative	-	Remission
13	17/F	29 months	Low	4 cyc-CT	Negative	-	Remission
14	55/F	55 months	Low	4 cyc-CT+RT	Negative	-	Remission
15	54/M	34 months	High	4 cyc-CT	Negative	-	Remission
16	30/F	28 months	Low	4 cyc-CT	Negative	-	Remission
17	44/M	24 months	High	4 cyc-CT	Negative	-	Remission
18	16/F	32 months	Low	2 cyc-CT	Negative	-	Remission
19	60/M	24 months	High	4 cyc-CT	Negative	-	Remission
20	18/M	29 months	High	4 cyc-CT	Positive	3.3	Remission
21	24/F	28 months	Low	6 cyc-CT	Negative	-	Remission
22	30/F	24 months	Low	3 cyc-CT	Negative	-	Remission
23	28/F	28 months	Low	4 cyc-CT	Negative	-	Remission
24	24/F	36 months	Low	8 cyc-CT+RT	Negative	-	Remission
25	21/M	35 months	High	4 cyc-CT	Positive	3.2	Remission
26	23/M	26 months	Low	4 cyc-CT	Negative	-	Remission
27	56/M	26 months	High	4 cyc-CT	Negative	-	Remission
28	65/M	32 months	High	8 cyc-CT	Negative	-	Remission
29	16/M	26 months	High	4 cyc-CT	Negative	-	Remission
30	17/F	33 months	Low	8 cyc-CT	Positive	7.4	Remission
31	23/M	34 months	High	8 cyc-CT	Positive	11.8	Exitus
32	24/M	28 months	Low	2 cyc-CT+RT	Negative	-	Remission
33	24/F	28 months	Low	4 cyc-CT	Negative	-	Remission
34	26/F	28 months	Low	4 cyc-CT	Negative	-	Remission
35	68/F	28 months	High	4 cyc-CT	Negative	-	Remission
36	66/M	27 months	High	4 cyc-CT	Negative	-	Remission
37	25/M	52 months	Low	4 cyc-CT+RT	Negative	-	Remission
38	22/F	53 months	Low	6 cyc-CT+RT	Negative	-	Remission
39	59/M	40 months	High	4 cyc-CT+RT	Negative	-	Remission
40	47/M	39 months	High	6 cyc-CT	Negative	-	Remission
41	29/M	35 months	Low	6 cyc-CT	Positive	9.0	Exitus
42	61/M	39 months	High	4 cyc-CT	Negative	-	Remission
43	22/M	28 months	Low	6 cyc-CT+RT	Negative	-	Remission
44	46/M	29 months	Low	2 cyc-CT	Negative	-	Remission
45	32/F	35 months	Low	4 cyc-CT	Negative	-	Relapse

Table 2 a. Continued

No	Age/sex	Follow-up duration	PRS	First-line treatment	Post-therapy PET/CT (extension)	SUV_{max}	Disease outcome
46	29/M	43 months	High	6 cyc-CT	Negative	-	Remission
47	56/M	34 months	High	8 cyc-CT	Negative	-	Remission
48	36/F	39 months	High	8 cyc-CT	Positive	9.6	Remission
49	58/M	37 months	High	4 cyc-CT	Negative	-	Remission
50	21/M	39 months	High	4 cyc-CT	Negative	-	Remission
51	50/F	37 months	Low	4 cyc-CT	Negative	-	Remission
52	48/M	38 months	Low	4 cyc-CT	Positive	6.6	Relapse
53	26/F	30 months	Low	4 cyc-CT+RT	Negative	-	Remission
54	31/M	35 months	High	8 cyc-CT	Positive	8.3	Relapse
55	64/F	50 months	High	3 cyc-CT	Positive	12.6	Exitus
56	18/F	48 months	Low	6 cyc-CT+RT	Positive	16.3	Relapse

PRS: Pre-treatment clinical prognostic risk scoring, LOW: Low risk group, HIGH: High risk group, CYC: Cycles, CT: Chemotherapy, F: Female, M: Male, PET/CT: Positron emission tomography/computed tomography

to find out the differences between observed frequencies in the subgroups of the patient population. Kaplan-Meier analysis was used in calculating progression free survival (PFS) curves after first-line treatment for both group and the long-rank test was used for comparison between groups. PFS was defined as the time interval from the end of chemotherapy until progression, relapse, death or date of last follow-up or endpoint of our study. The compatibility between the PET and PRS was evaluated with kappa test. Moreover, the effect of different factors on remission was assessed by Cox regression analysis. SPSS statistical analysis package software (version 15.0) was used for statistical evaluation.

Results

Of the 56 patients with HD, 27 patients had favorable prognostic criteria and remaining 29 patients had unfavorable prognostic status on pre-treatment evaluation. On the other hand, there were 32 patients in low-risk and 15 patients in high-risk categories in the group of NHL patients. Post-treatment PET/CT was negative (no residual abnormality) in 82/103 (80%) patients, and positive in the remaining 21 (20%) patients (Table 3). Of the patients with negative post-treatment PET/CT study, 52 (63%) (22 HD; 30 NHL) had favorable/low-risk PRS, while 30 of them (21 HD; 9 NHL) (37%) had unfavorable/high-risk PRS. In 7 out of 21 (33%) patients (5 HD, 2 NHL) with positive post-treatment PET/CT, there was favorable/low-risk PRS versus unfavorable/high-risk PRS in 14 (67%) patients (8 HD; 6 NHL). There was a significant difference between the favorable/low-risk group and the unfavorable/high risk group in terms of post-treatment PET/CT imaging results (p=0.013). In PET-positive patients, SUV_{max} values of the lesions ranged from 2.5 to 18.2 (average 9.1).

At the end of follow-up period, 84 of 103 patients (81.6%) stayed in remission. Among these, 52 (61.9%) patients (22 HD; 30 NHL) had favorable/low-risk PRS versus 32 (38.1%) patients (25 HD;7 NHL) with unfavorable/high-risk PRS, while a big majority of the patients (91.6%) had negative PET/CT versus a minority of the patients (8.3%) with positive PET/CT study (Table 4) (Figure 1). Nineteen of 103 (18.4%) patients were in non-remission status, of whom 12 (63.1%) (4 HD; 8 NHL) had unfavorable/high-risk PRS and 7 (36.8%) patients

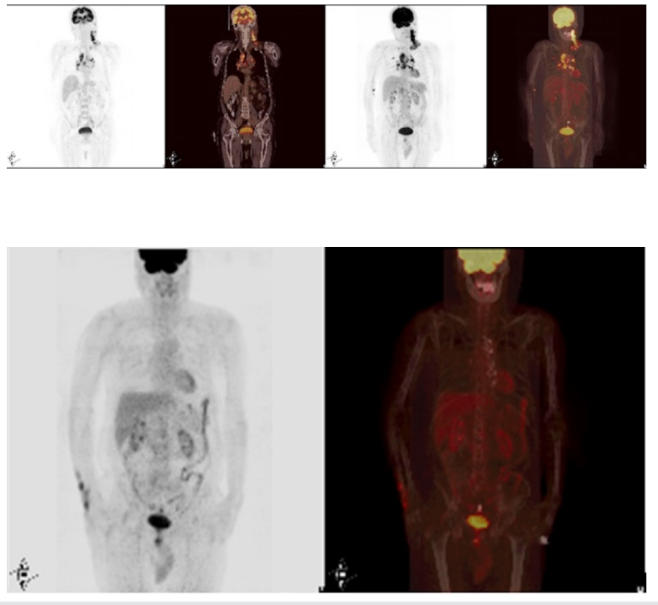

Figure 1. A) Top row: Initial (pre-treatment) FDG-PET/CT, B) Bottom row: Post-treatment FDG-PET/CT. Maximum intensity projection images of a patient with a mixed cell type of HD, who had unfavorable pre-treatment risk scoring. All hypermetabolic foci seen on the initial PET/CT study completely disappeared in the post-treatment study done after completion of chemotherapy. The patient stayed in remission during 29 months follow-up period

FDG-PET/CT: Fluorodeoxyglucose-positron emission tomography/computed tomography

Table 2b. Characteristics of patients with non-Hodgkin Lymphoma

No	Age/sex	Follow-up duration	PRS	First-line treatment	Post-therapy PET/CT (extension)	SUV_{max}	Disease outcome
1	54/F	29 months	Low	4 cyc-CT	Negative	-	Remission
2	24/M	29 months	High	8 cyc-CT	Positive	15.5	Exitus
3	70/M	28 months	Low	3 cyc-CT+RT	Negative	-	Remission
4	44/F	26 months	Low	6 cyc-CT	Positive	11.3	Remission
5	64/M	25 months	High	4 cyc-CT	Positive	3.5	Exitus
6	40/F	28 months	Low	3 cyc-CT	Negative	-	Remission
7	40/F	35 months	High	8 cyc-CT	Negative	-	Remission
8	53/M	34 months	Low	8 cyc-CT	Negative	-	Remission
9	24/M	32 months	Low	8 cyc-CT	Negative	-	Remission
10	64/M	33 months	High	8 cyc-CT	Negative	-	Exitus
11	51/M	38 months	Low	5 cyc-CT	Negative	-	Exitus
12	54/F	33 months	Low	3 cyc-CT+RT	Negative	-	Remission
13	59/F	32 months	Low	3 cyc-CT+RT	Negative	-	Remission
14	76/F	29 months	Low	5 cyc-CT	Negative	-	Remission
15	63/M	38 months	High	4 cyc-CT	Positive	7.7	Stable
16	38/M	29 months	Low	3 cyc-CT+RT	Negative	-	Remission
17	46/M	29 months	High	4 cyc-CT	Positive	8.1	Exitus
18	61/F	28 months	High	4 cyc-CT	Negative	-	Remission
19	70/F	31 months	Low	3 cyc-CT+RT	Negative	-	Remission
20	81/F	24 months	Low	8 cyc-CT	Negative	-	Remission
21	69/F	32 months	Low	3 cyc-CT+RT	Negative	-	Remission
22	24/F	48 months	Low	6 cyc-CT	Negative	-	Remission
23	50/F	24 months	Low	6 cyc-CT	Negative	-	Remission
24	57/F	36 months	Low	3 cyc-CT+RT	Negative	-	Remission
25	32/M	25 months	High	8 cyc-CT	Negative	-	Remission
26	46/M	49 months	High	8 cyc-CT	Negative	-	Remission
27	22/M	30 months	High	2 cyc-CT	Negative	-	Remission
28	62/F	24 months	High	5 cyc-CT	Negative	-	Relapse
29	72/M	24 months	Low	4 cyc-CT	Negative	-	Remission
30	47/M	24 months	Low	2 cyc-CT	Negative	-	Remission
31	35/M	24 months	Low	3 cyc-CT	Negative	-	Remission
32	45/F	24 months	Low	3 cyc-CT+RT	Negative	-	Remission
33	50/M	49 months	Low	8 cyc-CT	Negative	-	Remission
34	47/F	30 months	Low	3 cyc-CT	Negative	-	Remission
35	40/M	24 months	Low	4 cyc-CT	Negative	-	Remission
36	52/M	24 months	Low	4 cyc-CT	Negative	-	Remission
37	63/M	24 months	Low	4 cyc-CT	Positive	15.0	Stable
38	33/F	24 months	Low	8 cyc-CT	Negative	-	Remission
39	27/F	24 months	High	5 cyc-CT	Positive	2.5	Remission
40	50/F	30 months	High	8 cyc-CT	Positive	10.8	Exitus
41	30/M	40 months	High	8 cyc-CT	Negative	-	Relapse
42	62/F	48 months	Low	8 cyc-CT	Negative	-	Remission
43	55/M	25 months	High	4 cyc-CT	Negative	-	Remission
44	41/M	25 months	Low	4 cyc-CT	Negative	-	Remission
45	20/M	24 months	Low	4 cyc-CT	Negative	-	Remission
46	44/F	24 months	Low	4 cyc-CT	Negative	-	Remission
47	48/F	25 months	Low	6 cyc-CT+RT	Negative	-	Remission

PRS: Pre-treatment clinical prognostic risk scoring, LOW: Low risk group, HIGH: High risk group, CYC: Cycles, CT: Chemotherapy, F: Female, M: Male, PET/CT: Positron emission tomography/computed tomography

(5 HD; 2 NHL) had favorable/low-risk PRS. In this group, PET/CT was positive in 14 (73.7%) patients versus negative in only 5 (26.3%) patients (Figures 2, 3). Although both PRS and PET/CT imaging had statistically significant capability in terms of estimating remission status of the patients, the statistical power of PET/CT imaging was much stroger than that of PRS (p<0.001 versus p =0.046).

Post-treatment PET/CT imaging demonstrated 74% sensitivity, 92% specificity, 94% NPV, and 67% PPV and 88% accuracy in predicting remission status, whereas for PRS the same values were 63% and 62%, 88%, 27%, and 62%, respectively (p<0.001) (Tablo 5).

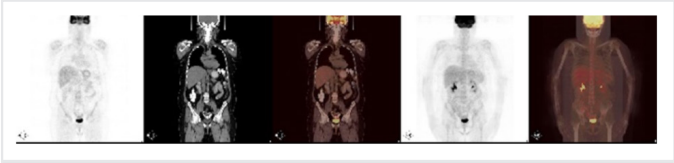

Figure 2. A patient with a diagnosis of DLBCL with a high-risk pre-treatment clinical scoring. The post-treatment PET/CT study done after 5 cycles of R-CHOP regime, revealed no residual disease. However, several trecurrences were diagnosed during 24 months follow-up period

PET/CT: Positron emission tomography/computed tomography, DLBCL: Diffuse large B-cell lymphoma

Kaplan-Meier survival analysis demonstrated a significant difference for assesment of PFS between PET positive and PET negative patients. (log-rank =2.1 p<0.05), while there was no significant difference between favorable prognostic/low-risk and unfavorable prognostic/high-risk groups for PRS (Figure 4).

There was a compatibility between PET result and remission (kappa =0.62), while no compatibility was available between PRS and remission (kappa =0.17).

On the Cox regression analysis, PET results and disease type were the most significant indices affecting final remission status. When the PET was negative, the remission more likely occurred (p<0.001). The patients with positive PET results have four times more risk to stay in non-remission status. There was also 2.3 fold less remission in the group with NHL comparing to HD group (p<0.05). Those patients with local residual disease on post-treatment PET studies had a more likelihood of staying in remission comparing to those with multifocal lymphatic and/or organ involvement (71% versus 29%; p<0.05).

Table 3. Relationships between post-treatment PET results and pre-treatment risk scoring

Hodgkin lymphoma	PET negative	PET positive	SUV_{max} (mean)
Fvr prog (n=27)	22 (81.5%)	5 (18.5%)	11.5
Unfvr prog (n=29)	21 (72.4%)	8 (27.6%)	7.4
Non-Hodgkin lymphoma			
Low-risk (n=32)	30 (93.7%)	2 (6.3%)	13.1
High-risk (n=15)	9 (60.0%)	6 (40.0%)	8.0
Overall			
Fvr prog/low-risk (n=59)	52 (88.1%)	7 (11.9%)	11.9
Unfvr prog /high-risk (n=44)	30 (68.2%)	14 (31.8%)	7.6
Total (n=103)	82	21	

Fvr prog: Favorable prognostic, Unfvr prog: Unfavorable prognostic, PET: Positron emission tomography

Table 4. Remission status related to post-treatment PET results and pre-treatment PRS

Hodgkin lymphoma	Fvr prog/low-risk	Unfvr prog/high-risk	PET positive	PET negative
Remission (n=47)	22 (46.8%)	25 (53.2%)	5 (10.6%)	42 (89.4%)
Non-remission (n=9)	5 (55.6%)	4 (44.4%)	8 (88.9%)	1 (11.1%)
Non-Hodgkin lymphoma				
Remission (n=37)	30 (81.1%)	7 (18.9%)	2 (5.4%)	35 (94.6%)
Non-remission (n=10)	2 (20.0%)	8 (80.0%)	6 (60.0%)	4 (40.0%)
Overall				
Remission (n=84)	52 (61.9%)	32 (38.1%)	7 (8.3%)	77 (91.7%)
Non-remission (n=19)	7 (36.8%)	12 (63.2%)	14 (73.7%)	5 (26.3%)
Total (n=103)	59	44	21	82

Fvr prog: Favorable prognostic, Unfvr prog: Unfavorable prognostic, PET: Positron emission tomography

Discussion

There are numerous reports available in the literature recommending the routine use of FDG-PET imaging to assess the post-therapy response in patients with HD and NHL (9-15). However, there are a considerable variation between the studies in terms of diagnostic accuracy and predictive values most probably due to heterogeneous population studied, difference of treatment protocols, and difference of PET timing etc.

Mid-treatment (interim) FDG-PET/CT scanning performed after 2-4 cycles of chemotherapy appears to have prognostic significance and may have a potential for earlier identification of chemoresistant disease in lymphomas, prior to treatment completion, leading to facilitate an individualized risk-adapted strategy. However, the importance of PET/CT at the end of the first line treatment continues (16-18).

In this retrospective study including a patient population referred from a single clinic, a new generation of hybrid PET/CT scanner was used. We found that post-treatment FDG imaging had 74% sensitivity, 92% specifity, 88% accuracy, 67% PPV and 94% NPV in predicting of long-term remission. These values were significantly better than those of obtained with the pre-treatment PRS, which were 63%, 62%, 62%, 27% and 88%, respectively (Table 5).

Despite PET's superiority comparing to PRS systems, our study revealed that the FDG-PET/CT was not excellent imaging modality for predicting disease outcome. There were 5 patients with HD and 2 patients with NHL who were were sustained in remission status at the end of follow-up period, despite positive PET results (false-postive rate =33%). This finding was most probably related to inflammatory changes occurring secondary to chemotherapy. Additionally, a sensitive reading of PET images might lead to false-positive results. We used mediastinal blood pool activity as the threshold for the lymph node uptake to define the post-therapeutical PET study as positive. There has been a great effort ongoing to find out what will be the best threshold activity, i.e mediastinum, liver or nearby background to determine positivity on the post therapeutic FDG-PET studies (19). In addition, there are reports available based on a SUVmax threshold or SUVmax difference between the initial study and post-therapeutic studies (20-22). Nevertheless, there has not been defined a well validated interpretation criteria to provide an excellent accuracy for post-treatment FDG-PET studies so far. Nevertheless, there has not been defined a well validated interpretation criteria to provide an excellent accuracy for post-treatment FDG-PET studies so far. Therefore, any ambiguous finding in FDG-PET/CT report that is not supported with clinical-laboratory data or other imaging modalities should be confirmed with biopsy if needed. Particularly, the new lesions that are not available in the pre-treatment PET/CT scan must be evaluated in caution.

On the other hand, negative post-treatment PET/CT scan could not completely predict long term remission, although it had higher NPV. In our group, there were 5 out of 82 (6%) patients

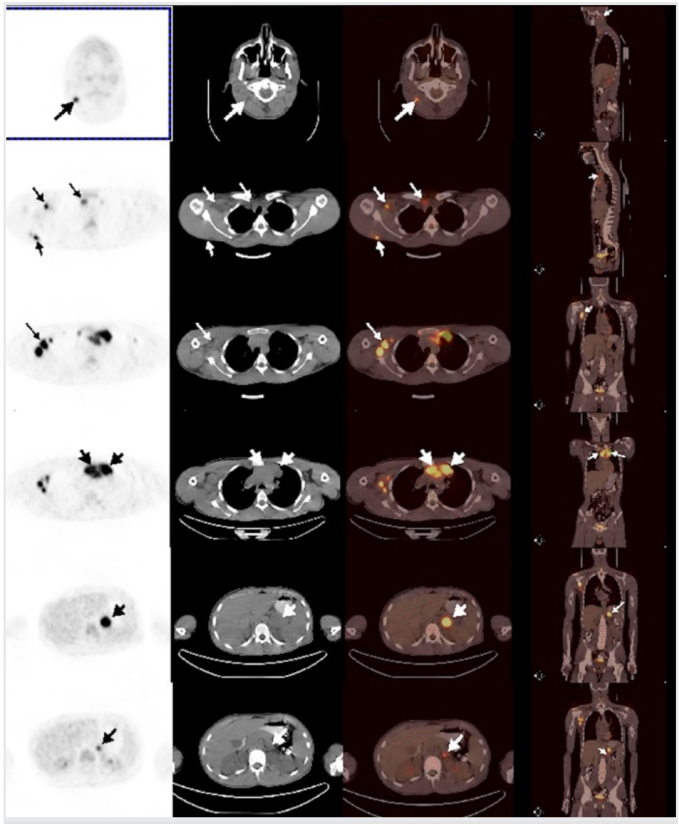

Figure 3. A 16-year-old patient with nodular sclerosing type HD with favorable prognostic factors on pre-treatment evaluation. Following 4 cycles of ABVD regime, the post-treatment PET/CT study demonstrated residive disease in multiple supradiaphragmatic and infradiaphragmatic lymphatic regions as well as in the left adrenal gland and in soft tissue of the left arm as shown on the selected slices above. Despite of further agressive chemotherapy applications, a remission status could not be managed and the patient died after 31 months

PET/CT: Positron emission tomography/computed tomography, HD: Hodgkin disease, ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine

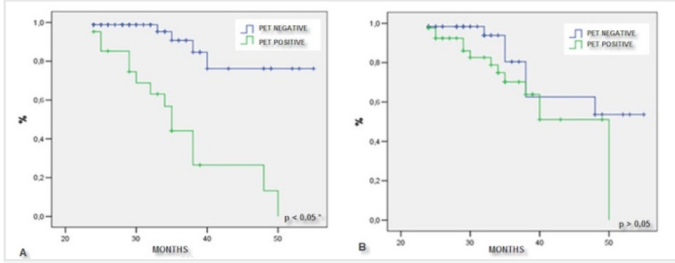

Figure 4. Kaplan-Meier plots of progression free survival in all patients: A) in relation to the post-treatment PET result; B) in relation to pre-treatment prognostic risc scoring

PET: Positron emission tomography

Table 5. Efficiacy of the post-treatment PET and pre-treatment prognostic risk scoring in assessment of remission status

	Sensitivity	Specifity	Accuracy	PPV	NPV	TP	TN	FP	FN
Hodgkin lymphoma									
PET	88.8%	89.3%	89%	61.5%	97.6%	8	42	5	1
PRS	44.4%	46.8%	46.4%	13.7%	81.4%	4	22	25	5
Non-Hodgkin lymphoma									
PET	60%	94.5%	87.2%	75%	89.7%	6	35	2	4
PRS	80%	81%	80.8%	53.3%	93.7%	8	30	7	2
Overall									
PET	73.6%	91.6%	88.0%	66.6%	94.0%	14	77	7	5
PRS	63.0%	62.0%	62.0%	27.0%	88.0%	12	52	32	7

PRS: Prognostic risk scoring, PPV: Positive predictive value, NPV: Negative predictive value, TP: True positive, TN: True negative, FP: False positive, FN: False negative, PET: Positron emission tomography

(1 HD, 4 NHL) with false-negative PET results, despitesensitive reading. This was most probably due to insufficient spatial resolution of PET imaging technology to detect microscopic residual disease. Therefore, we suggest that the patients in high risk group should be monitored closely even if their post-treatment PET/CT scans are negative.

There was a clear relationship between the disease extention on post-treatment PET scans and relaps rate in our study. The frequency of disease recurrence was significantly higher in the patients with involvement of multiple lymphatic stations or extranodal sites comparing to those with single lymphatic station involvement (Table 5).

Our results are generally compatible with the literature and the values of NPV and PPV are within the limits in published meta-analysis in this field (11,22). There is relatively few studies comparing the prognostic values between post-treatment PET and clinical risk scoring system. In Haioun study, including 90 patients with aggressive NHL, they performed PET studies before treatment, after 2 cycles of chemotherapy and at the end of treatment as well, and prospectively evaluated the predictive value of PET in the prediction of prognosis (23). In this study, 83% of post-treatment PET negative patients, and 58% of post-treatment PET positive patients stayed in complete remission. Two-year PFS was 90% in post-treatment PET negative group and 58% in post-treatment PET positive group. Accordingly, post-treatment PET was an independent prognostic marker in estimating PFS regardless the chemotherapy protocol.

Study Limitations

There are differences in treatment approaches and management of HD and NHL. The main limitation of our study was that it was not performed with a more standard patient group consisting of HD or high-grade NHL. Therefore, we presented both the general data and the data of both groups separately. In addition, the number of patients in both groups was relatively limited and the study was designed retrospectively.

Conclusion

In conclusion, our study confirmed that FDG-PET/CT scanning at the completion of the first-line therapy estimated the disease outcome of the patients with HD and aggressive NHL, better than population based pretreatment clinical risk scoring systems. However, particularly PPV of the end-treatment FDG-PET/CT imaging was still far away from the desired levels as to estimating disease recurrence, due to a relatively high false-positive rate. Nevertheless, our study demonstrated that the patients with persistent FDG uptake in multinodal lymphatic stations and in extranodal sites on the post-therapy PET/CT scanning were under more risk for recurrence. On the other hand, despite higher NPV, there might be some false-negative results with the post-treatment PET/CT imaging for estimation of permanent remission, most probably due to microscopic residual disease available at the end of therapy.

Ethics

Ethics Committee Approval: Our study project was approved by the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (16.09.2008/27584).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: E.B.E., Ş.G., K.S., Design: E.B.E., Ş.G., K.S., Data Collection or Processing: E.B.E., Ş.G., K.S., Analysis or Interpretation: E.B.E., Ş.G., K.S., Literature Search: E.B.E., Ş.G., K.S., Writing: E.B.E., Ş.G., K.S.

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