Original Article

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A role of interim positron emission tomography/computed tomography scan in the management of Hodgkin lymphoma: A single-center study in a developing country

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Abstract:

BACKGROUND: The Hodgkin lymphoma (HL) showed a good prognosis in Erbil city. However, a number of deaths were reported. The monitoring and treatment strategies of HL had improved in the last decade.

AIMS: The aims of this study were to evaluate the prognostic value of interim positron emission tomography/computed tomography (PET/CT) scan in HL patients and predicting the survival outcome in addition to effect on progression-free survival (PFS) of HL patients.

PATIENTS AND METHODS: A retrospective cross-sectional study was conducted in Nanakali Hospital in Erbil city, Kurdistan region, Iraq, through reviewing data of patients with HL from January 1, 2014, to December 31, 2019, on a sample of 75 HL patients. The diagnosis of HL was accomplished by the physician regarding lymph node biopsy by the World Health Organization criteria. The PET/CT scan was done after two treatment cycles. PET/CT of HL patients was done in a private center in Erbil city (Media Diagnostic Center).

RESULTS: The mean overall survival duration of HL patients was 5.39 years with an overall survival rate of 92%, and the mean PFS duration of HL patients was 5.04 years with PFS rate of 76%. The mean overall survival of HL patients with positive interim PET/CT (4 years and rate 75%) was lower than the mean overall survival of HL patients with negative interim PET/CT (7.2 years and rate of 95.2%) with a significant difference ($P < 0.001$).

CONCLUSIONS: The interim PET/CT scan is useful in prognosis of patients with HL and predicting overall survival and mortality.

Keywords:

Hodgkin lymphoma, positron emission tomography/computed tomography scan, survival

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Introduction

Hodgkin lymphoma (HL) is a rare monoclonal lymphoid neoplasm represented about 10% of all reported lymphomas, but with good long-term cure rates.[1] Biologically and clinically, this neoplasm is divided into either classical HL or nodular lymphocyte-predominant HL. Both HL categories are different in clinical features and pathological findings. The classical HL is representing about 95% of all HL cases, which, in turn, is subdivided into four subclassifications: nodular sclerosis, lymphocyte rich, mixed cellularity, and

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lymphocyte depleted. In general, the HL is characterized with a high prognosis rate with an overall survival rate reaching to 80% cure rate.[2-4]

Till now, exact etiology of HL is unknown. On other hand, many risk factors were involved in the pathogenesis of HL such as Epstein–Barr virus (EBV) infection, autoimmune disorders, and immunosuppression.[5] In addition, a genetic and familial tendency was observed in the predisposition of HL.[6]

Treatment of HL is dependable mainly on histological features, HL staging, and availability of prognostic factors. HL treatment aimed to cure the disease with control of short- and long-term complications.[7] Nowadays, the combination of chemotherapy regimen called doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is a standard treatment of HL with a complete response rate of 75% and an overall survival rate of 73%.[8] Although, the ABVD therapy failed in reaching complete remission in 20%–30% of HL which turned to salvage chemotherapy and transplantation. Another chemotherapy regimen is also used such as bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen, which reported a higher cure rate than ABVD regimen, but with higher comorbidity and mortality rates.[9-11] However, identification of high-risk patients with poor outcomes is essential to select these intensive regimens. For this purpose, many scores were developed such as International Prognostic Score (IPS7) and modified scoring system (IPS3) for assessing prognosis of HL, but they were unable to detect the high-risk HL patients who need intensive regimens.[12-14] Recently, the HL risk stratification and better prognosis with evaluating treatment outcome after two ABVD cycles were achieved through an interim positron emission tomography (PET)/computed tomography (CT) scan.[15,16]

PET is an imaging technique with molecular function in provision of qualitative and quantitative information regarding activity and localization of pathophysiological lesions. The most practiced tracer is 2-(18F) fluoro-2-deoxy-D-glucose (FDG) for the purpose of oncology. For that, it is considered the most significant nuclear medicine modality in lymphoma management in the recent years.[17]

The role of interim PET scan is important in escalation and de-escalation of therapy upon positive or negative scan. PET positivity and negativity is determined under Deauville criteria scoring from 1 to 5. In other words, PET negative has a Deauville score between 1 and 3; meanwhile, a positive PET is graded between 4 and 5. This results in dose intensification planning if positive.[18]

In Iraqi Kurdistan region, high incidence of EBV virus infection is related changing histological pattern of classical HL from mixed cellularity to nodular sclerosis.[19] However, the common histological type of HL in Erbil city is nodular sclerosis followed by mixed cellularity and the 5-year overall survival was 70%.[20] Low overall survival rate of HL patients in Kurdistan as compared to developed countries and scarcity of literatures discussing role of interim PET in raising treatment response and survival rate urged us to carry out this study that is aimed to evaluate the prognostic value of interim PET scan in HL patients and predicting the survival outcome in addition to effect on progression-free survival (PFS) of HL patients.

Patients and Methods

This was a retrospective, cross-sectional study conducted in Nanakali Hospital in Erbil city, Kurdistan region, Iraq through reviewing data of patients with HL from January 1, 2014, to December 31, 2019. The study population was achieved through the patients who are admitted in Nanakali Hospital with HL. The inclusion criteria were patients having interim PET/CT scan and received chemotherapy treatment regimen. Exclusion criteria were pediatric age, patients not subjected to PET/CT scan, missing data, not completing scheduled chemotherapy protocol, changed to other treatment protocol, and lost to follow-up. The ethical considerations were implemented according to the Helsinki Declaration regarding ethical approval of health authorities; an ethical approval was obtained from the Kurdistan Board Ethical Committee, Nanakali Hospital authority and data confidentiality. Among 226 HL patients, a convenient sample of 75 HL patients were selected after eligibility to inclusion and exclusion criteria.

The data of enrolled patients were collected from their saved records in hospital and fulfilled in a prepared questionnaire as it was designed by the researchers which included the following information: general characteristics of HL patients (age and gender), interim PET/CT scan (positive or negative), HL characteristics (stage, histopathology, IPS score, lymphopenia, bulky disease, hemoglobin (Hb), and white blood cell [WBC] count), and outcomes of HL patients (relapses, death outcome, and survival duration). The diagnosis of HL by the physician was done regarding to lymph node biopsy by the WHO criteria.[21] The PET/CT scan was achieved after two treatment cycles. PET/CT of HL patients was accomplished in a private center in Erbil city (Media Diagnostic Center). The system that is applied in Media Diagnostic Center was Siemens Biograph 64 PET/CT True Point. The IPS score was assessed by the researchers through assessing serum albumin, serum Hb, age, gender, stage, WBC, and

lymphocyte count, and IPS score was classified in our study from score 0 to 3.[12]

The overall survival rate was defined from date of staging until death from any cause, while the PFS was defined as the time from staging until progression, relapse, or death.[22] Other investigations were implemented in Nanakali Hospital. The data collected were analyzed statistically by Statistical Package for the Social Sciences software version 22 (SPSS version 22 (IBM manufacturer, Germany). The Chi-square and Fisher's exact tests were applied for analyzing categorical variables. Kaplan–Meier curve was used in measuring survival of HL patients. Level of significance (*P* value) was regarded statistically significant if it was 0.05 or less.

Results

This study included 75 HL patients with a mean age of 31.3 years and a range of 14–74 years; 14.7% of HL patients were in the age group of 45 years and more. The number of female patients in this study was more than males (60% vs. 40%). Stage II and III were predominant (42.7% and 32%, respectively). The prevalent histopathology finding of HL was classical (97.3%) and IPS scores were distributed as follows: 0 (26.7%), 1 (28%), 2 (24%), and 3 (21.3%) [Table 1].

Table 1: General characteristics of Hodgkin lymphoma patients

Variable	*n* (%)
Age (years), mean±SD	31.3±14.3
<45	64 (85.3)
≥45	11 (14.7)
Gender	
Male	30 (40)
Female	45 (60)
Stage	
I	7 (9.3)
II	32 (42.7)
III	24 (32.0)
IV	12 (16.0)
Histopathology	
Classical	73 (97.3)
NLPHL	2 (2.7)
IPS score	
Score 0	20 (26.7)
Score 1	21 (28.0)
Score 2	18 (24.0)
Score 3	16 (21.3)
Total	75 (100.0)

NLPHL=Nodular lymphocyte predominant Hodgkin lymphoma, IPS=International Prognostic Score, SD: Standard deviation

Lymphopenia was present in 13.3% of the patients. Bulky disease present in 9.3%, while low Hb level was recorded in 21.3% of the patients. In addition, high WBC count was present in 13.3% of them. Disease relapse was reported among 18.7% and death outcome was present in 6 (8%). The mean overall survival duration was 5.39 years; 42.7% of patients had more than 5 year's survival. Interim PET/CT scan was positive in 16% of patients receiving ABVD protocol, whereas 84% of them had negative scan [Table 2].

The mean overall survival duration of HL patients was 5.39 years (median = 5 years) with overall survival rate of 92% [Figure 1].

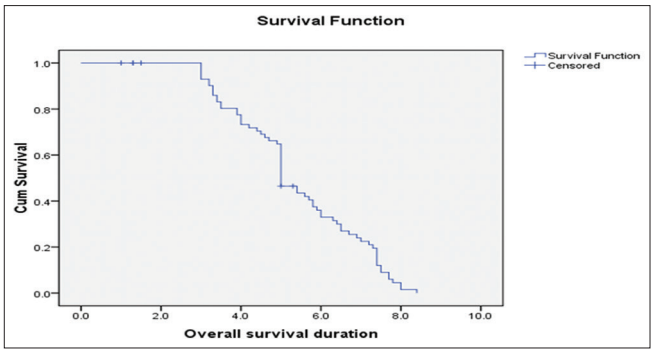

Figure 1: Kaplan-Meier curve of overall survival for HL patients. HL = Hodgkin lymphoma

The mean PFS duration of HL patients was 5.04 years (median = 4.9 years) with PFS rate of 76% [Figure 2].

No significant differences were observed between positive interim PET/CT HL patients and negative interim PET/CT HL patients regarding age ($P = 0.8$), gender ($P = 0.89$), HL stage ($P = 0.9$), and histopathology ($P = 0.53$). There was a highly significant association between increased IPI scores of HL patients and positive interim PET/CT ($P < 0.001$) [Table 3].

A significant association was observed between bulky HL disease and positive interim PET/CT ($P = 0.04$). Significant differences were not observed between PET/CT status regarding lymphopenia ($P = 0.7$), Hb ($P = 0.06$), WBC count ($P = 0.7$), and relapse ($P = 0.15$), whereas a significant association was observed between high mortality of HL patients and positive interim PET/CT ($P = 0.04$) [Table 4].

The mean overall survival of HL patients with positive interim PET/CT was 4 years and rate 75%, which was lower than mean overall survival of HL patients with negative interim PET/CT (7.2 years and rate of 95.2%), with a significant difference ($P < 0.001$) [Figure 3].

The mean PFS of HL patients with positive interim PET/CT was 5.3 years and rate of 50%, whereas the mean PFS of HL patients with negative interim PET/

Table 2: Interim positron emission tomography/computed tomography scan and outcomes of Hodgkin lymphoma patients

Variable	*n* (%)
Lymphopenia	
Yes	10 (13.3)
No	65 (86.7)
Bulky disease	
No	68 (90.7)
Yes	7 (9.3)
Hemoglobin (g/dl)	
<10.5	16 (21.3)
≥10.5	59 (78.7)
WBC count (×10^9/mcgL)	
<15	65 (86.7)
≥15	10 (13.3)
Relapse	
Yes	14 (18.7)
No	61 (81.3)
Outcome	
Alive	69 (92.0)
Dead	6 (8.0)
Overall survival duration (years), mean±SD	5.39±1.8
≤5	43 (57.3)
>5	32 (42.7)
Interim PET/CT scan	
Positive	12 (16.0)
Negative	63 (84.0)
Total	75 (100.0)

WBC=White blood cells, PET=Positron emission tomography, SD: Standard deviation, CT=Computed tomography

Table 3: Distribution of Hodgkin lymphoma patients' general characteristics according to interim positron emission tomography/computed tomography

Variable	Interim PET/CT scan		*P*
	Positive, *n* (%)	Negative *n* (%)	
Age (years)			
<45	10 (83.3)	54 (85.7)	0.8 (NS)
≥45	2 (16.7)	9 (14.3)	
Gender			
Male	5 (41.7)	25 (39.7)	0.89 (NS)
Female	7 (58.3)	38 (60.3)	
Stage			
I	1 (8.3)	6 (9.5)	0.9 (NS)
II	6 (50.0)	26 (41.3)	
III	3 (25.0)	21 (33.3)	
IV	2 (16.7)	10 (15.9)	
Histopathology			
Classical	12 (100.0)	61 (96.8)	0.53 (NS)
NLPHL	0	2 (3.2)	
IPI score			
Score 0	0	20 (31.7)	<0.001 (S)
Score 1	1 (8.3)	20 (31.7)	
Score 2	3 (25.0)	15 (23.8)	
Score 3	8 (66.7)	8 (12.7)	

S=Significant, NS=Not significant, NLPHL=Nodular lymphocyte predominant Hodgkin lymphoma, IPI=International prognostic index, PET=Positron emission tomography, CT=Computed tomography

CT was 5 years and rate of 81%, with no significant difference (P = 0.63) [Figure 4].

Discussion

In low-resource countries (like our country), the HL outcome is affected by cost of treatment, a resource-limited setting, management cost, treatment disuse, unavailability of oncologist, and absence of transplant facilities. The number of HL patients in need for salvage chemotherapy and the transplant is low, whereas the number of HL patients continued ABVD chemotherapy is high. For that, it is important to categorize HL patients after initial ABVD regimen in order to lower late toxicity and decrease number of chemotherapy cycles.[23]

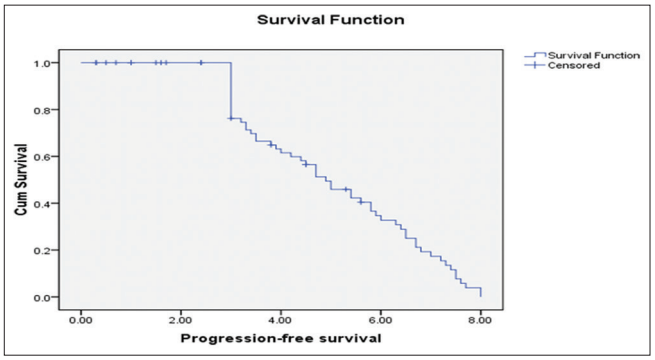

Figure 2: Kaplan-Meier curve of progression-free survival for HL patients. HL = Hodgkin lymphoma

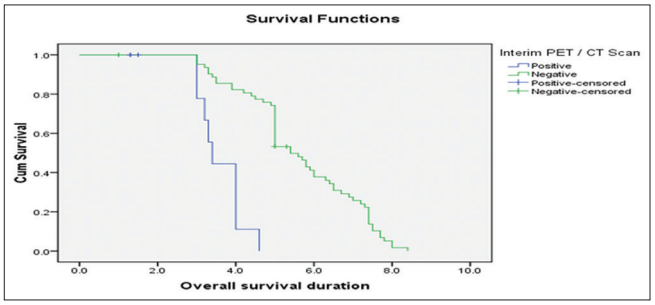

Figure 3: Kaplan-Meier curve of overall survival for HL patients (blue = positive), (green = negative). HL = Hodgkin lymphoma, PET/CT = Positron emission tomography/computed tomography

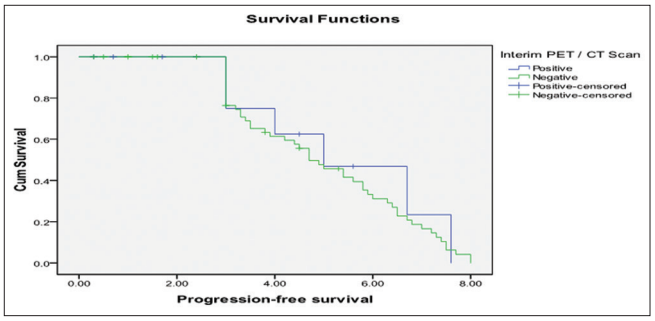

Figure 4: Kaplan-Meier curve of progression-free survival for HL patients (blue = positive), (green = negative). HL = Hodgkin lymphoma, PET/CT = Positron emission tomography/computed tomography

Table 4: Distribution of Hodgkin lymphoma characteristics and outcomes according to interim positron emission tomography/computed tomography

Variable	Interim PET/CT scan		*P*
	Positive, *n* (%)	Negative, *n* (%)	
Lymphopenia			
Yes	2 (16.7)	8 (12.7)	0.7 (NS)
No	10 (83.3)	55 (87.3)	
Bulky disease			
No	9 (75.0)	59 (93.7)	0.04 (S)
Yes	3 (25.0)	4 (6.3)	
Hemoglobin (g/dl)			
<10.5	5 (41.7)	11 (17.5)	0.06 (NS)
≥10.5	7 (58.3)	52 (82.5)	
WBC count ($\times 10^9$/mcgL)			
<15	10 (83.3)	55 (87.3)	0.7 (NS)
≥15	2 (16.7)	8 (12.7)	
Relapse			
Yes	4 (33.3)	10 (15.9)	0.15 (NS)
No	8 (66.7)	53 (84.1)	
Outcome			
Alive	9 (75.0)	60 (95.2)	0.04 (S)
Dead	3 (25.0)	3 (4.8)	

S=Significant, NS=Not significant, PET=Positron emission tomography, CT=Computed tomography, WBC=White blood cell

Patients who had positive interim PET-CT scan, chemotherapy regimen was altered to escalated BEACOPP. While the patients with negative interim PET-CT scan, Bleomycin was omitted in the ABVD protocol. Meanwhile, the relapsed patients were put under salvage chemotherapy like ifosfamide, carboplatin, and etoposide; bendamustine, gemcitabine, vinorelbine; and dexamethasone, cisplatin, and cytarabine.

FDG-PET has been increased in its use for the purpose of staging, prognosis, treatment planning, and response evaluation in patients with HL over the last few decades as well as of its acceptance widely. It is used primarily for the purpose of the pretreatment assessment for its determination of the disease stage as a result to decide upon suitable treatment regimen. Nevertheless, it is recently declared the use of PET scan during first-line chemotherapy for the patients with HL, that is interim PET following a few cycles of chemotherapy. It is believed that the interim PET scan positivity or negativity considered to be a good predictor for the patients prognosis. The purpose of achieving maximum efficacy in terms of OS and PFS was introduced following therapy adaptation upon interim PET results, after thorough exploration of the FDG-PET procedure.[24]

In the current study, the mean overall survival duration of HL patients was 5.39 years (median = 5 years) with an overall survival rate of 92%. These findings are better than results of Perez-Callejo *et al*.'s[25] study in Spain and Abbas *et al*.'s[26] study in Iraq, which reported an overall survival rate (76% and 82%, respectively) for patients with HL after 8 years of follow-up. However, our study revealed that the mean PFS duration of HL patients was 5.04 years (median = 4.9 years) with PFS rate of 76%. This finding is close to results of Khashab *et al*.'s[27] study in the USA, which reported that PFS rate of HL patients without bone marrow involvement was 72%. In general, our study findings regarding overall survival rate and PFS rate are better than results of Shamoon *et al*.'s[28] retrospective study in Erbil city (Kurdistan region/Iraq), which reported that overall survival rate and PFS rate for HL patients were 79% and 60%, respectively. This improvement in overall survival and PFS rates in our center might be attributed to availability of ABVD regimen, improvement of diagnostic and monitoring technologies, and use of interim PET in the last years.

The present study showed that the mean overall survival of HL patients with positive interim PET/CT was 4 years and rate 75%, which was lower than the mean overall survival of HL patients with negative interim PET/CT (7.2 years and rate of 95.2%), with a significant difference ($P < 0.001$). These findings are in agreement with results of many literatures such as Seshachalam *et al*.'s[8] cohort study in India and Liao *et al*.'s[29] systematic review study in China, which all found that the overall survival rate of patients with HL was significantly affected by interim PET/CT scan after two ABVD cycles. The interim PET/CT scan is also useful in prognosis, staging, and assessing treatment response in pediatric HL.[30] Our study found that the mean PFS of HL patients with positive interim PET/CT was 5.3 years and rate of 50%, while the mean PFS of HL patients with negative interim PET/CT was 5 years and rate of 81%, with no significant difference ($P = 0.63$). These findings are consistent with results of Aldin *et al*.'s[24] systematic review and meta-analysis study in Germany, which reported that interim PET/CT scan is useful in differentiation between HL patients with long and short overall survival duration, while failed in PFS rate of HL patients. This finding is inconsistent with the results of Song *et al*.'s[31] retrospective study in the Republic of Korea, which revealed that PFS was significantly longer in HL patients with negative interim PET/CT scan. This inconsistency might be due to differences in the number of relapses and discrepancy in follow-up and monitoring periods between different studies.

The current study showed a highly significant association between increased IPS scores of HL patients and positive interim PET/CT ($P < 0.001$). This finding coincides with results of El-Galaly *et al*.'s[32] study in Denmark and Naguib *et al*.'s[33] prospective study in Egypt, which stated that IPI score of patients with HL was significantly related to findings of interim PET/CT scan. Our study

also found a significant association between bulky HL disease and positive interim PET/CT (P = 0.04). This finding is similar to the results of Johnson *et al*.'s[34] study in the UK, which revealed that patients with bulky HL diseases were significantly related to positive interim PET/CT scan finding. Our study showed a significant association between high mortality of HL patients and positive interim PET/CT (P = 0.04). Consistently, Evens and Kostakoglu's[35]study in the USA reported that interim PET/CT scan is useful in prognosis of HL and prediction of poor outcomes and mortality of HL patients after two ABVD cycles.

In conclusion, interim PET/CT scan is useful in the prognosis of patients with HL and predicting overall survival and mortality. This study recommended implementation of PET/CT scan after two chemotherapy treatment cycles which help in risk stratification.

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Conflicts of interest

There are no conflicts of interest.

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