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Original

Productivity of ^{18}F-FDG-PET/CT Diagnostic Tool in the Management of Pediatric Lymphoblastic Lymphoma

Ahmed Elhussein[1], Mohamed Fawzy[2], Hany Abdel Rahman[2], Walid Omar[3], Elshaymaa Mohamed Hussein[4]

[1] Children's Cancer Hospital Egypt (CCHE [57357]), Cairo, Egypt
[2] National Cancer Institute (NCI), Cairo University, Cairo, Egypt; Children's Cancer Hospital Egypt (CCHE/[57357]), Cairo, Egypt
[3] National Cancer Institute (NCI), Cairo University, Cairo, Egypt
[4] Department of Nuclear Medicine and Radiation Oncology, Faculty of Medicine, Cairo University, Cairo, Egypt

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Abstract

BACKGROUND: Lymphoblastic lymphoma (LL) comprises approximately 20% of childhood non-Hodgkin lymphoma (NHL); however, few studies had investigated the role of ^{18}F-FDG-PET/CT in pediatric LL patients. We aim in this study to assess the role of ^{18}F-FDG-PET/CT in the initial staging of newly diagnosed pediatric patients with LL as well as in the assessment of response after induction chemotherapy.

PATIENTS AND METHODS: A prospective study enrolled biopsy proven newly diagnosed pediatric LL patients presenting in the Children Cancer Hospital Egypt (CCHE) during the period from October 2014 to October 2016. ^{18}F-FDG-PET/CT was done initially before therapy and after induction chemotherapy in all patients. The patients were followed until the end of April 2018 (mean 23.5 months).

RESULTS: All lymphoma involvement lesions (n = 43) were FDG avid and the intensity of nodal FDG uptake was variable. Two patients (11%) had bone marrow (BM) involvement by < 25% blast cells with corresponding positive BM focal uptake in ^{18}F-FDG-PET/CT (SUVmax = 4 and 4.5). Evaluation post induction phase; CT detected 8 residual lesions in 8 patients (44.4%), while ^{18}F-FDG-PET/CT detected only 3 Deauville-positive residual lesions in 3 patients (16.6%). No intensification of therapy was done in all post-induction positive patients. Repeated ^{18}F-FDG-PET/CT at week 18 for post-induction patients revealed cleared all Deauville-positive residual lesions. On the other hand, repeated CT at week 18 detected regression but still residual in 4/8 (50%) post-induction CT lesions with clearance of the rest (50%).

CONCLUSION: In initial staging, ^{18}F-FDG-PET/CT is a useful tool for disease extent evaluation of pediatric LL. Moreover, it could provide a diagnostic hint for BM involvement. ^{18}F-FDG-PET/CT done after induction therapy has a good negative predictive value with higher specificity than CT alone, but is not an indication for treatment intensification due to false positive results. However, larger sample size is required for better conclusion.

KEY words: pediatric lymphoblastic lymphoma, ^{18}F-FDG-PET/CT, CCHE

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Background

Lymphoblastic lymphoma (LL) comprises approximately 20% of childhood non-Hodgkin lymphoma (NHL) [1]. Precursor T-lymphoblastic (T-LL) subtype constitutes 75% of LL cases, with the remainder being precursor B-cell LL (B-LL) [2].

Clinical presentation of LL varies according to immune-phenotype. T-cell lymphoblastic lymphomas most commonly involve the supra-diaphragmatic lymph nodes, especially the anterior mediastinum [3]. On the other hand, B-LL are usually localized in peripheral lymph nodes and extra-nodal sites such as soft tissues, skin and bone [4].

^{18}F-FDG-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is emerging as a potential non-invasive diagnostic modality for initial staging as well as assessment of response to therapy and follow-up in pediatric oncology [5]. However, few studies had investigated its role in LL separately, especially in children [6].

The aim of this study was to explore the potential role of ^{18}F-FDG-PET/CT in the initial staging of newly diagnosed pediatric patients with lymphoblastic lymphoma (LL) as well as in the assessment of response to therapy after induction chemotherapy.

Correspondence to: Elshaymaa Mohamed Hussein, Consultant of nuclear medicine, Department of Nuclear Medicine Andradiation Oncology, Faculty of Medicine, Cairo University, Cairo, Egypt;
e-mail: elshaymaahussein@cu.edu.eg

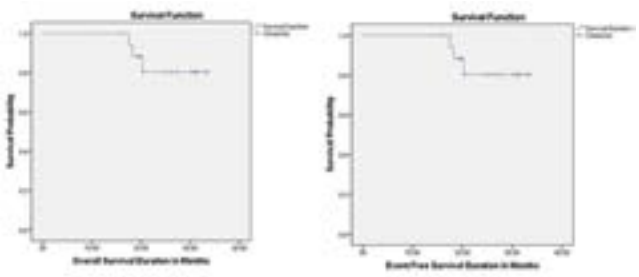

Figure 1. Correlation between results of post-induction ^{18}F-FDG-PET compared to CT and the outcome at last time of follow up

Patients and methods

This prospective study included 18 pediatric patients (14 males and 4 females; median age, 13 years) who were diagnosed and treated for histopathologically confirmed LL at the CCHE during the period from October 2014 to October 2016 and followed until April 2018.

All Patients were treated according to St. Jude Children Research Hospital ALL Total Therapy XV protocol, standard risk arm [7]. Staging was done following Murphy's classification [8] highlighting natural history, management, and end results, emphasizing dissimilarities from lymphomas occurring in adult years. Childhood will arbitrarily be defined as the period from infancy to adulthood, encompassing adolescence, rougly up until the fifteenth to eighteenth years of life. The lymphomas typical of childhood naturally do not vanish at an arbitrary upper threshold in maturity but rather decline in frequency. A separate emphasis on childhood NHL is warranted for numerous reasons, not the least being that a better insight into ontogeny may be gained. Children experience a different spectrum of malignant disease than adults do, the common sites of origin typically being embryonal tissues of the hematopoietic system, central and sympathetic nervous system (including the eye and the adrenal.

As part of the baseline staging work-up, all patients underwent whole-body ^{18}F-FDG-PET/CT scanning; contrast-enhanced CT of the chest, abdomen, and pelvis; and bone marrow aspiration (BMA) and biopsy (BMB), cerebrospinal fluid examination (CSF) and serum lactate dehydrogenase (LDH) level measurement. Evaluation post-induction therapy was done by ^{18}F-FDG-PET/CT, (+/- BMA and BMB which were repeated for initially positive patients only). ^{18}F-FDG-PET/CT was also repeated at week 18 maintenance for positive post-induction patients.

Evaluation of treatment response post induction was done according to CT and BMB, ^{18}F-FDG-PET/CT according to the International Pediatric NHL Response Criteria (IRC) [9].

^{18}F-FDG-PET/CT procedure

Whole body ^{18}F-FDG-PET/CT studies were conducted according to the European Association of Nuclear Medicine (EANM)

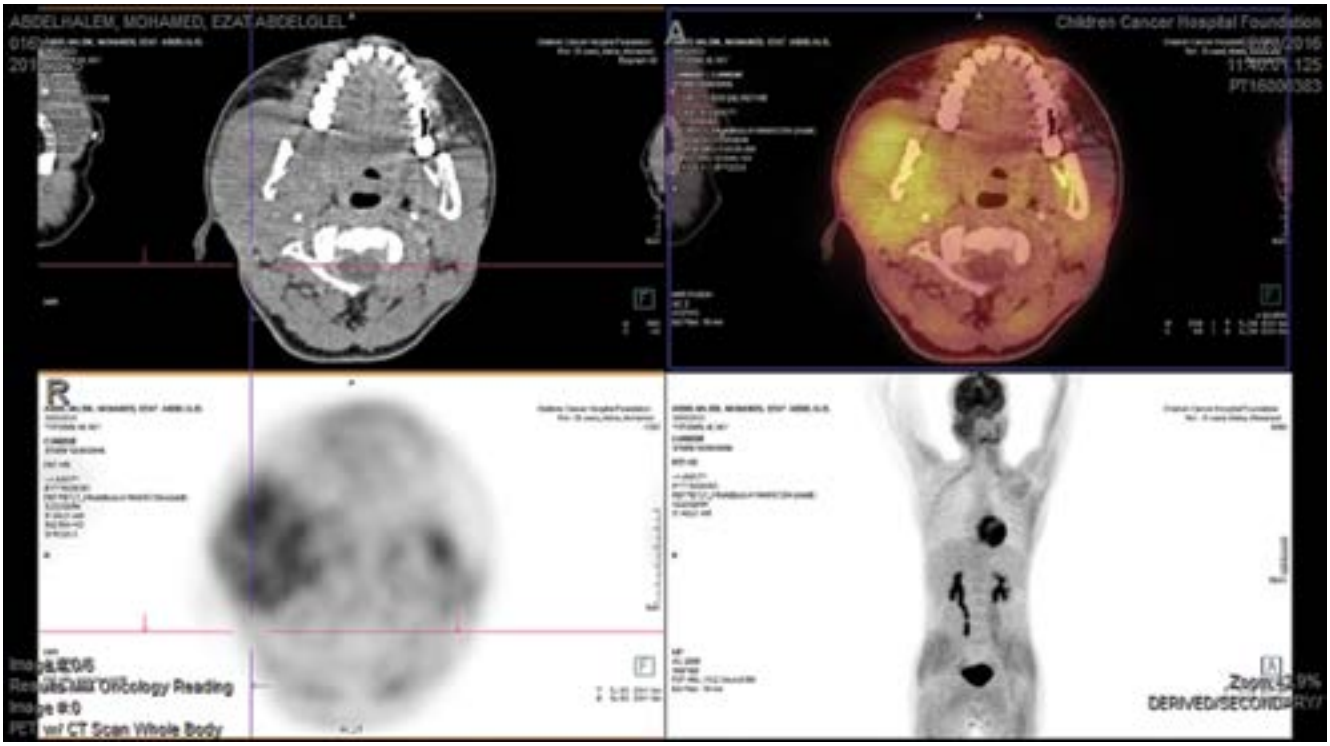

Figure 2. Axial and MIP images of PET/CT and fused18F-FDG-PET/CT images of patient number 2 at initial staging showing: right mandibular mass lesion with SUVmax 4 associated with enlarged right cervical LNs with low grade FDG uptake

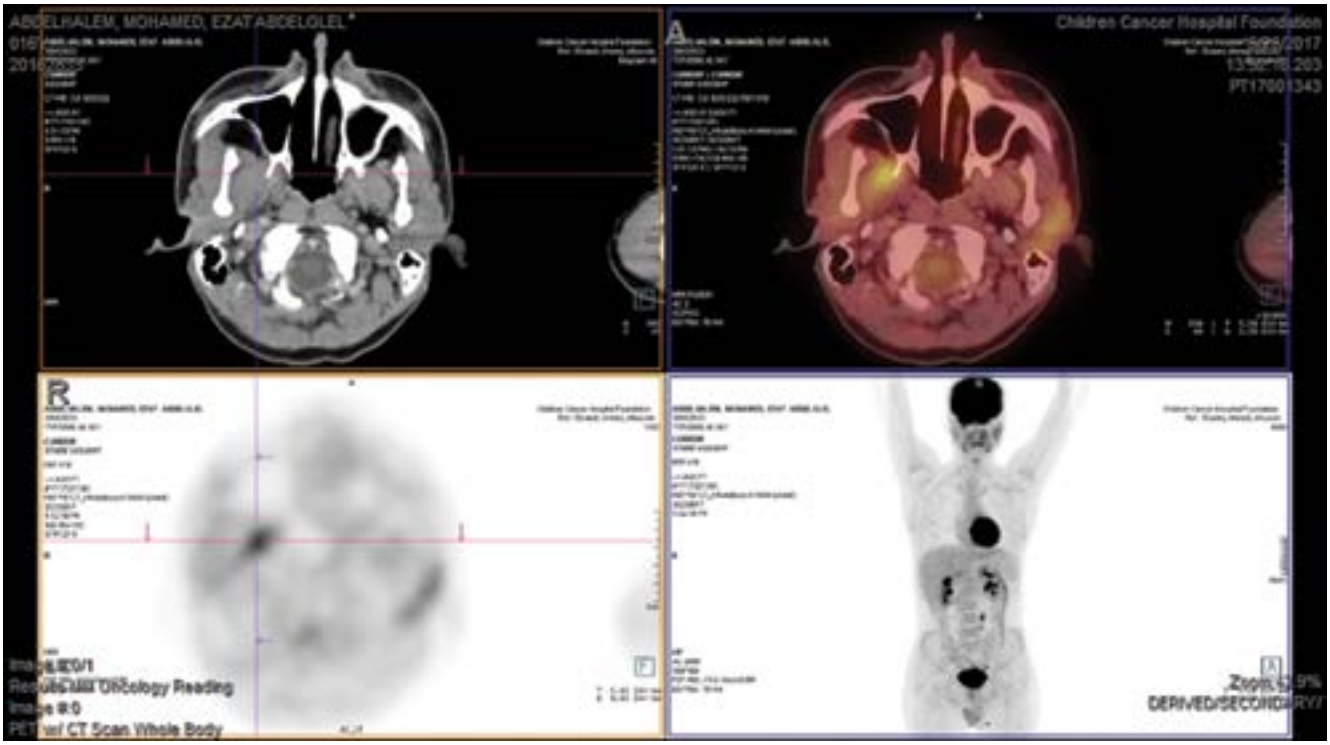

Figure 3. Axial and MIP images of PET/CT and fused18F-FDG-PET/CT images of the same patient's post induction phase showing partial response of the mandibular lesion SUVmax 4 , the patient was scored according to 5-ps as score 4

procedure guidelines for FDG-PET/CT tumor imaging: version 2.0 [10].

Children fasted no less than 4 hours before ^{18}FDG injection dose and blood glucose level was controlled prior to the injection

The study was acquired on a Discovery LS PET/CT imaging system (GE Medical Systems) after intravenous administration of 5–7 MBq/kg of ^{18}FDG or on a mCT Biograph imaging system (Siemens) following intravenous injection of 3 MBq/kg of ^{18}FDG. The images were acquired from the skull to the mid-thigh approximately 60–80 min after ^{18}FDG administration employing 3-D acquisition technique. Subsequent diagnostic CT images were used for attenuation correlation and production of fusion images. The images were reconstructed by ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm with and without attenuation correction.

^{18}F-FDG-PET/CT analysis

All ^{18}F-FDG-PET/CT studies were reviewed by two nuclear medicine physicians using qualitative (visual) analysis and quantitative analysis using the maximum standardized uptakes (SUVmax) values. The SUV was calculated using the equation: SUV = mean activity [region of interest (ROI)] (MBq/ml) / injected dose (MBq) / total body weight (g). Among these SUVs from the targeted ROI, the SUVmax were considered as the highest SUVs of pixels in the ROI. Residual lesions in the 2nd ^{18}F-FDG-PET/CT performed for assessment of response to therapy; are analyzed according to the 5 point scale as recommended by the Lugano criteria [11]staging, and response assessment of patients with Hodgkin lymphoma (HL.

The 5 point scale (5-p-s) is scored as follows: 1 = no uptake; 2 = uptake < mediastinum; 3 = uptake > mediastinum and < liver; 4 = uptake moderately higher than liver at any site; 5 = markedly increased uptake at any involved site. Scores of 4 and 5 are considered positive, while scores of 1–3 are considered negative [12].

Statistical methods

Categorical data were described as counts and percentages while numerical data as SUVmax were reported as mean and standard deviation. Pearson's Correlation was performed to examine the relationship between SUVmax and both tumor size and LDH level. Survival analysis was conducted by Kaplan-Meier method. The Overall Survival is defined as the duration from date of diagnosis to date of last contact or death date, while Event Free Survival is the duration from date of diagnosis to date of last contact or date of first event. Events are: developing 2ry malignancy, death, progression, or relapse. P values less than 0.05 in any test were considered to be statistically significant.

Results

Eighteen patients were included (14 males and 4 females; median age, 13 years), 11 had T-cell (61.1%) while 7 had B-cell lymphoblastic lymphoma (38.9%). Most common presentation site was mediastinal mass (55.5%) followed by head and neck (27.8%), bone marrow infiltration by < 25% blasts (11.1%) and enlarged inguinal LNs (5.6%).

Evaluation of ^{18}F-FDG-PET/CT in initial staging

All lymphoma involvement lesions (n = 43) were FDG-avid and the intensity of nodal FDG uptake was variable. Patients'

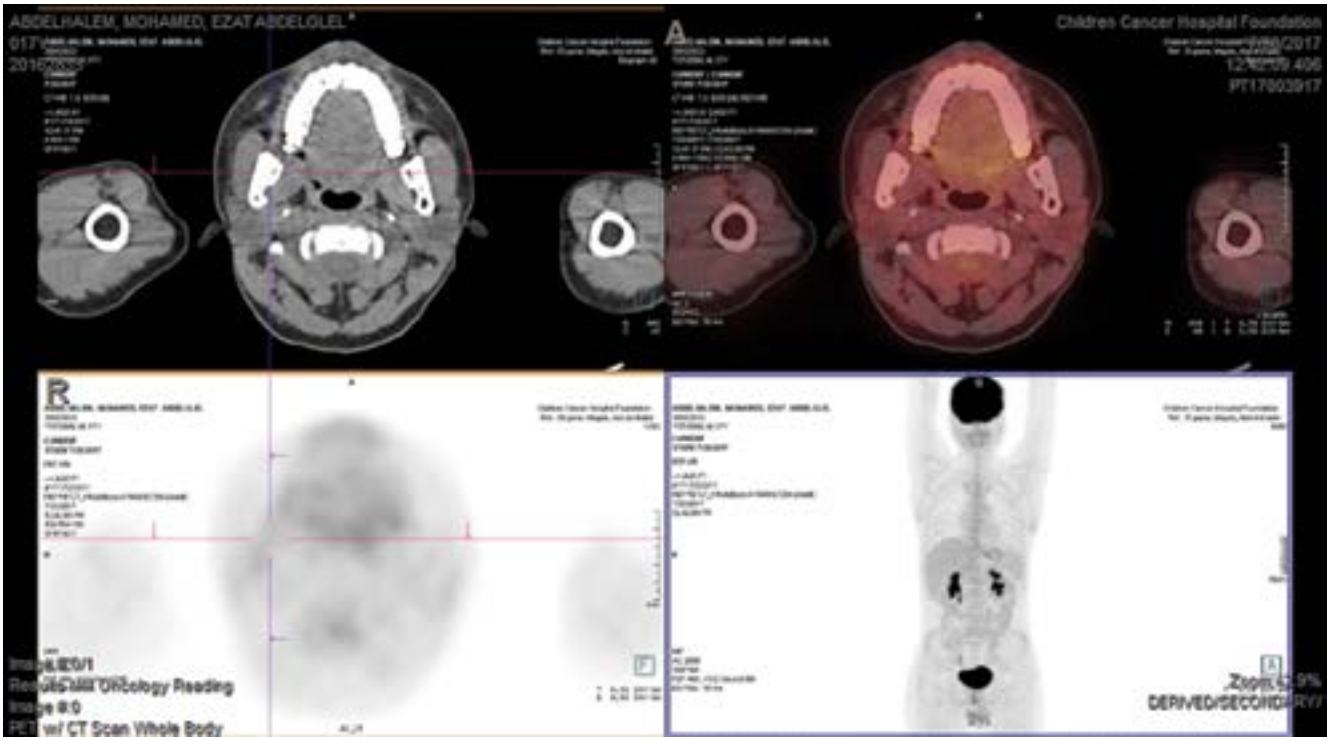

Figure 4. Axial and MIP images of PET/CT and fused ^{18}F-FDG-PET/CT images of the mentioned patient at W18 showing complete metabolic remission of the involved mandibular lesion

characteristics with involved areas and the highest SUVmax are shown in Table 1.

The mean SUVmax of the involved lesions was 5.5. The higher SUVmax at diagnosis was most commonly observed in involved mediastinal lymph nodes, with a mean SUVmax of 5.7.

Two patients (11%) had BM involvement by < 25% blast cells with corresponding positive BM focal uptake in FDG-PET/CT (SUVmax = 4 and 4.5).

There was non-significant correlation between SUVmax of involved lesions and both tumor size (r = 0.356, p = 0.161) and LDH level (r = 0.347, p = 0.172).

Evaluation of ^{18}F-FDG-PET/CT during assessment of response after induction of chemotherapy

Comparison of ^{18}F-FDG-PET/CT results and both CT and BMB was done post induction phase. CT detected 8 residual lesions in 8 patients (44.5%), while FDG-PET/CT detected that only 3 of them (16.7%) considered Deauville-positive.

Ten patients were in CR by CT and BMB (55.5%, n = 10) and all had negative ^{18}F-FDG-PET/CT. On the other hand, 8 patients (44.5%) were in PR; 5 of them (27.8%) had negative ^{18}F-FDG-PET/CT, while 3 were positive (16.7%). No intensification of therapy was done in all post-induction positive patients.

Repeated ^{18}F-FDG-PET/CT at week 18 for post-induction patients revealed cleared all Deauville-positive residual lesions. On the other hand, CT at week 18 detected regression but still residual in 4/8 (50%) post-induction CT lesions with clearance of the rest (50%).

At the time of last follow-up (mean 23.5 months), 15/18 patients (83.3%) were alive. No patient experienced relapse or progression. Two patients died out of progressive infection and sepsis during maintenance course of chemotherapy ALL Total Therapy XV protocol after week 22 and 55. One patient developed acute myeloid leukemia (AML) after 10 weeks of maintenance course of chemotherapy with poor response to therapy and died after 4 courses of AML chemotherapy protocol; none of these patients had positive Deauville score post induction.

We also calculated the sensitivity, specificity, positive and negative predictive values of ^{18}F-FDG-PET/CT in prediction of outcome using last clinical and radiological follow-up as control criteria. We found the specificity of post-induction ^{18}F-FDG-PET/CT was 81% while the negative predictive value was 87% compared to 50% and 80% for post-induction CT respectively (Fig. 1).

Survival Analysis

The 2 years OS was 80.2% (95% confidence interval 59.8% – 100.0%), similar to the 2 years EFS which was 80.2% (95% confidence interval 59.8% – 100.0%) (Fig. 2).

Discussion

In the present study, all disease sites detected by ^{18}F-FDG-PET were concordant with CT and BMB. This was similar to adult studies on lymphoblastic lymphoma where all involved lymph nodes, bone marrow and extra-nodal lesions were FDG-avid [13].

In the current study ^{18}F-FDG-PET/CT did not contribute in up- or down-staging of any of included patients. Similar results had been detected in Nakatani et al study which included 3 patients with LL [14]. Our results also were concordant to Park et al. study on nine

Table 1. Patients' characteristics and ^{18}F-FDG-PET/CT findings at initial staging

Pt.	Gender	Age	Histology	LDH	Area with the highest SUV	SUVmax	Other areas involved	Stage
1	Male	13	T-LL	2942	Mediastinal adenopathy	6.9	Pleura	III
2	Male	16	B-LL	349	Mandibular lesion	4.5	Cervical adenopathy	II
3	Female	13	B-LL	556	Skull bone	8.6	Intracranial lesion	IV
4	Male	6	B-LL	1232	Both femur bones	6.2	Nasopharyngeal mass and BM	IV
5	Male	11	T-LL	442	Mediastinal adenopathy	8.7	Cervical, axillary, abdominal and inguinal adenopathy	III
6	Male	15	T-LL	6064	Mediastinal adenopathy	9.2	Cervical, axillary, abdominal, inguinal adenopathy and pleura	III
7	Male	15	T-LL	1269	Mediastinal adenopathy	5.2	Cervical and inguinal adenopathy, renal focal lesions and pleura	III
8	Male	11	T-LL	581	Mediastinal adenopathy	2.5	Cervical and axillary adenopathy	III
9	Male	15	T-LL	1162	Mediastinal adenopathy	7.3	Cervical adenopathy and pleura	III
10	Female	6	T-LL	663	Mediastinal adenopathy	2.7	Pleura	III
11	Male	12	B-LL	605	Cervical adenopathy	2.3	Cervical adenopathy	I
12	Male	18	T-LL	500	Cervical adenopathy	N/A	--	I
13	Male	3	B-LL	1512	Cervical adenopathy	7.8	Abdominal adenopathy	III
14	Female	13	T-LL	861	Mediastinal adenopathy	7.3	Cervical adenopathy	III
15	Male	11	T-LL	467	Inguinal adenopathy	3.7	Cervical, mediastinal and abdominal adenopathy	III
16	Male	16	T-LL	621	Mediastinal adenopathy	2.5	--	III
17	Female	8	B-LL	539	Abdominal adenopathy	3.8	--	III
18	Male	3	B-LL	1769	Cervical adenopathy	5.3	Mediastinal adenopathy and BM	IV

T-LL: T-cell Lymphoblastic Lymphomas B-LL: B-cell Lymphoblastic Lymphomas, BM: Bone Marrow, LDH: Lactate Dehydrogenase

Table 2. Response criteria using CT, 18F-FDG-PET/CT and IRC

Pt.	Response to Induction				Evaluation at Week 18		Relapse/Progression	Follow up duration (months)	Fate
	CT and BMB	FDG-PET	IRC	Deauville Score	FDG-PET	CT			
1	CR	Negative	CR	0	--	--	No	37	A
2	PR	Positive	PR	4	Negative	Positive	No	15	A
3	CR	Negative	CR	0	--	--	No	30	A
4	CR	Negative	CR	0	--	--	No	21	D
5	PR	Positive	PR	4	Negative	Negative	No	29	A
6	CR	Negative	CR	0	--	--	No	18	D
7	PR	Negative	CRu	0	--	Positive	No	25	D
8	CR	Negative	CR	0	--	--	No	24	A
9	PR	Negative	CRu	0	--	Negative	No	17	A
10	CR	Negative	CR	0	--	--	No	18	A
11	CR	Negative	CR	0	--	--	No	18	A
12	CR	Negative	CR	0	--	--	No	18	A
13	PR	Negative	CRu	2	--	Positive	No	24	A
14	PR	Negative	CRu	2	--	Negative	No	26	A
15	CR	Negative	CR	0	--	--	No	31	A
16	PR	Positive	PR	4	Negative	Positive	No	31	A
17	PR	Negative	CRu	0	--	Negative	No	17	A
18	CR	Negative	CR	0	--	--	No	24	A

CT: Computed Tomography FDG-PET: Fluorodeoxyglucose Positron Emission Tomography, BMB: Bone Marrow Biopsy, IRC: International Response Criteria, CR: Complete Remission, PR: Partial Response, CRu: Complete Remission Uncertain, A: Alive, D: Dead

adult Korean patients with T-LL, where no difference in staging occurred between FDG-PET and CT [13].

In the current study, 2 patients had bone marrow infiltration in both ^{18}F-FDG-PET/CT and BMB while the other 16 patients had negative bone marrow in both modalities. In Park et al. study, eight of the studied patients were found to have bone marrow involvement and all had abnormal bone FDG uptake, indicating that ^{18}F-FDG-PET may be useful for assessing the disease extent in T-LL [13].

In our study, all LL patients who did or didn't have residual after induction therapy, in both ^{18}F-FDG-PET and CT, didn't show signs of progression or relapse. This was different than results by Jain et al. who found that all T-cell LL adult patients who had residual masses on PET-CT (3/22) relapsed during later phase of therapy (all within 6 months) and the authors concluded that such patients should be considered for treatment intensification [15].

Another study that was done by the Swedish Lymphoma Registry included 39 adults with T-LL, of whom none had a PET scan at baseline but 13 had a PET scan at various times before consolidation. All 13 patients were negative, but seven relapsed (54%). Based on this, the authors concluded that PET was not predictive of survival, although there was limitations in their study as FDG-PET/CT was not performed in a uniform manner [16].

A recent retrospective study by Becker et al. on adult patients with T-cell LL concluded that the five-point Deauville score of residual lesions after induction chemotherapy was not predictive of the outcome — 7/20 of patients (35%) who had Deauville score ≤ 3 relapsed and in the same time 3/7 of patients (42.8%) had score 4–5 also relapsed [17].

In conclusion, in initial staging; ^{18}F-FDG-PET/CT is a useful tool for disease extent evaluation of pediatric LL. Moreover, it could provide a diagnostic hint for BM involvement. ^{18}F-FDG-PET/CT done after induction therapy has a good negative predictive value with higher specificity than CT alone, but is not an indication for treatment intensification due to false positive results. However, larger sample size is required for better conclusion.

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