Article published online: 2025-03-10

Can ^{18}F-FDG PET/CT Metabolic Tumor Volume Contribute to Better Prognostication in Pediatric Hodgkin's Lymphoma?

Sangeetha Ramdas[1] Saumya Sara Sunny[2] Hema Nalapalu Srinivasan[1] Rikki Rorima John[1] Rajeev Zachariah Kompithra[3] Mahasampath Gowri[4] Leenu Lizbeth Joseph[1] Julie Hepzibah[2] Leni Grace Mathew[1]

[1] Pediatric Hematology-Oncology, Department of Pediatrics, Christian Medical College, Vellore, Tamil Nadu, India
[2] Department of Nuclear Medicine, Christian Medical College, Vellore, Tamil Nadu, India
[3] Department of Pediatrics, Christian Medical College, Vellore, Tamil Nadu, India
[4] Department of Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India

Address for correspondence Leenu Lizbeth Joseph, MD, DM, Associate Professor, Pediatric Hematology/Oncology Unit, Department of Pediatrics, Christian Medical College and Hospital, Vellore, Tamil Nadu, India (e-mail: leenujoseph@gmail.com).

Ind J Med Paediatr Oncol

Abstract

Introduction Studies in adults have shown that metabolic tumor volume (MTV) in fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) is a strong predictor of event-free survival (EFS) and overall survival (OS) in Hodgkin's lymphoma, often outperforming clinical scores and molecular predictors. However, there very few studies on pediatric Hodgkin's lymphoma (PHL), with conflicting results.

Objectives This retrospective study was conducted to evaluate the feasibility of MTV assessment in PHL and to assess its prognostic role, given the paucity of data from the developing world and the technical expertise required.

Materials and Methods Children with PHL, treated per EuroNet-PHL-C1 interim guidelines/C2 protocol at our center from 2017 to 2020 who had baseline and interim PET (iPET) scan done at our institution were included. MTV was measured in tumor areas with standardized uptake value (SUVmax) $\geq$2.5. MTV and SUVmax were compared at diagnosis and after two chemotherapy courses.

Results Sixty-one children (male:female = 1.5:1; mean age: 10.10 years) were recruited and categorized into four stages (SI: 11; SII: 15; SIII: 21; and SIV: 14) and three treatment groups (TG1: 16; TG2: 11; and TG3: 34). Based on iPET, 47 and 14 children were adequate and inadequate responders, respectively. At a median follow-up period of 54 months, the OS was 96.7% and the EFS was 85.2%. The median SUVmax and MTV were both found to increase with advancing disease stage with a positive correlation ($r = 0.41$; $p = 0.002$). The difference in the median MTV was statistically significant for SII versus SIII ($p = 0.004$) but not for the median SUVmax ($p = 0.13$). Similarly, the difference in the median MTV was statistically significant for TG2 versus

Keywords
- ^{18}F-FDG PET/CT
- event-free survival
- metabolic tumor volume
- overall survival
- pediatric Hodgkin's lymphoma
- prognostication
- standardized uptake value

DOI https://doi.org/10.1055/s-0045-1805091.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

TG3 ($p = 0.001$) but not for the median SUVmax ($p = 0.06$). The median MTV in baseline PET/CT with Deauville score–based treatment response groups for adequate and inadequate responders was 98.35 (37.93–298.2) mL and 145 (84.43–463.5) mL, respectively ($p = 0.31$), and for those with events versus no events, the median MTV was 304 (30.45–452.7) mL and 105.35 (37.9–309.2) mL, respectively ($p = 0.82$).

Conclusion Baseline PET/CT MTV showed better correlation than SUVmax in delineating stage and treatment groups. However, MTV in isolation was not sensitive or specific enough in prognosticating treatment response or EFS (relapse or death) in this study setting. The addition of significant clinico-biochemical parameters with MTV for future studies could enhance prognostication.

Introduction

Pediatric Hodgkin's lymphoma (PHL), accounting for 5 to 6% of all childhood cancers, has a peak incidence at younger ages in developing countries, unlike in developed countries.[1,2] With major advancements in PHL treatment protocols, the 5-year event-free survival (EFS) rates have improved dramatically over the last several decades, approaching 90 to 95% overall for all stages in the West.[3,4] Developing countries have progressively bridged the gap, with recent studies in India pegging the 5-year EFS for early-stage PHL at 94%, which is comparable to Western data.[5] There was also marked improvement in the outcomes of advanced-stage PHL to 81.1% 5-year EFS.[6] Despite these excellent 5-year EFS rates, the late morbidities such as second malignancies and cardiovascular risks occur even in those with early-stage disease. Thus, newer PHL treatment protocols call attention to optimal strategies that reduce cumulative therapy, thereby mitigating potential long-term toxicity, while maintaining treatment efficacy.[7] Toward this objective, "risk-based" and "response-adaptive" strategies for PHL are based upon pretreatment prognostic factors and interim evaluation of disease response, respectively.

The "risk-based" strategy involving multiagent chemotherapy, with pretreatment prognostic risk factors defining treatment intensity, is the standard of care for all patients. Radiation therapy is "response-adapted," being reserved for patients with residual disease based on interim positron emission tomography (PET)/computed tomography (CT).[8,9] Although PHL stage, presence of B symptoms (fever, weight loss, night sweats), tumor bulk, erythrocyte sedimentation rate (ESR), and extranodal involvement have significant prognostic values, these are interrelated. Hence, factors with independent prognostic implications have become more difficult to pin down, as the treatment outcomes continue to improve.[10]

Since almost all lymphomas are fluorine-18 fluorodeoxyglucose (^{18}F-FDG) avid, ^{18}F-FDG PET/CT, which integrates morphological and metabolic function information, has now become the primary investigation for lymphoma staging, which translates to risk stratification. The interim PET assessment is also useful in prognostication, with reduction in avidity correlating with treatment response.[11,12] Metabolic tumor volume (MTV), total lesion glycolysis (TLG), and standardized uptake value (SUV) have been reported as diagnostic and prognostic parameters in PET/CT since the late 1990s for several adult cancers.[13] Of these, the most commonly used parameter for the quantification of tumor metabolic activity is the SUV.[14]

In lymphomas, MTV, a parameter extracted from baseline FDG PET/CT has been proposed as a prognosticator at diagnosis, with strong correlation with EFS and overall survival (OS), often outperforming clinical scores, molecular predictors, and interim PET/CT results.[12] MTV and consequently TLG are considered to better reflect metabolic tumor burden and more accurately portend prognosis than maximum standardized uptake value (SUVmax).[14] Several studies have shown that MTV predicts survival in various non-Hodgkin's lymphoma (NHL) subtypes in children[15–17] including a study from India on anaplastic large cell lymphoma (ALCL) by Mathew et al.[15] However, only a few retrospective studies have confirmed this promising role in early HL in adults.[18]

In PHL, a few studies evaluating the prognostic value of SUVmax and MTV in predicting EFS have been published, with rather conflicting results.[19,20] The usefulness of volumetric PET/CT indices is limited by lack of consensus in determining tumor boundary and the need for advanced software.[12,21,22] As there is a paucity of studies from the developing world, this retrospective study was conducted to evaluate the prognostic role and feasibility of MTV assessment in PHL, and compare its performance with SUVmax.

Materials and Methods

Children aged younger than 18 years with classic Hodgkin's lymphoma (HL) diagnosed and treated in the Pediatric Hematology Oncology unit of our tertiary care hospital between the years 2017 and 2020 and who had a diagnostic and interim assessment with PET/CT scan done at the study center were included. Demographic data and basic clinical details were obtained from the electronic medical records.

^{18}F-FDG PET/CT Image Acquisition and Analysis

For baseline and interim PET/CT image acquisition, a minimum of 6 hours of fasting prior to imaging and blood glucose

levels of ≤11 mmol/L was ensured in all included cases. The dose of ^{18}F-FDG was 3 MBq/kg body weight (minimum dose of 14 MBq) as per the European Association of Nuclear Medicine (EANM) guidelines. Image acquisition was commenced at 60 ± 5 minutes after ^{18}F-FDG injection using Biograph 40 Truepoint PET/CT scanner (Siemens Medical Solutions, Illinois, United States). Oral (iohexol) and intravenous contrast (iopamidol) were administered, adjusted for the patient's weight, the former 1 hour before imaging and the latter with a scan delay time of 60 to 80 seconds. The CT parameters for children younger than 13 years and ≥13 years were 120 keV, 60 mA, section width of 3 mm, and pitch of 0.8 and 120 keV, 150 mA, section width of 5 mm, and pitch of 0.8, respectively.

PET/CT scans of the included patients were uploaded on the syngoMMWP VE61A software and were evaluated by a nuclear medicine expert who was blinded to clinical outcome. Following qualitative analysis for visual identification of nodal/extranodal disease and abnormal metabolic activity on PET/CT, quantitative parameters—SUVmax and MTV—were evaluated considering the spherical volumes of interest as necessary, drawn manually, so as to include all areas of lymphomatous involvement. The same method was used in the entire study cohort for calculation of the study parameters as discussed in the following sections.

Study Parameters

Visual Deauville Score

The Deauville score is a 5-point internationally recommended scale, based on visual interpretation of FDG uptake, in the initial diagnostic staging as well as assessment of treatment response of lymphomas. Diagnostic and interim ^{18}F-FDG PET/CT assessment is based on visual Deauville score (VDS) aided by semi-quantitative measures like SUV.[23] VDS for response evaluation in HL in adults has been validated in developed countries as well as India, including this study center.[24]

Standardized Uptake Value

The most commonly used parameter for the quantification of tumor metabolic activity is the SUV. SUVmax is the maximum voxel value of SUV in the tumor. Although observer independent, it is limited by its value being from only one voxel and inherent image noise sensitivity. However, it is the most widely used metabolic parameter in the assessment of PET/CT scans.[12,21,22]

Metabolic Tumor Volume

MTV is a quantitative measure of the total volume of tumor FDG uptake that exceeds a certain threshold defined as SUVmax ≥2.5 or SUVmax ≥40%. MTV is the measurement of the total FDG activity contained by every voxel of the image of the lymphoma lesions, summing up all nodal and extranodal lesions, the voxel activity expressed as SUV.[12,21,22] From both baseline and interim FDG PET/CT scans, SUVmax of the involved area was calculated. MTV was calculated by semiautomated algorithm using an SUV of 2.5.[25,26]

PHL Risk Stratification: Stage and Treatment Groups

All children diagnosed with PHL were risk stratified and treated as per the EuroNet-PHL-C1 interim guidelines/C2 protocol standard arm. Baseline PET/CT was performed. The children were divided into three treatment groups (TGs) based on the stage of the disease, presence of B symptoms, extranodal involvement, and presence of additional risk factors (ESR > 30 mm/h or tumor bulk ≥200 mL). Patients with Ann Arbor stage IA, IB, or IIA without risk factors or extranodal involvement were assigned to TG1, those with stages IA, IB, and IIA with extranodal involvement or additional risk factors as well as Ann Arbor IIB and IIIA were taken as TG2 with stages IIBE, IIIAE, IIIBE, IIIB, IVA, or IVB treated as TG3.[27,28]

Treatment Protocols

All children received two courses of OEPA (Vincristine [oncovin], etoposide, prednisolone, Adriamycin) and then underwent an interim response assessment by PET/CT. If interim PET/CT showed good response, TG1 patients received one cycle COPDAC (cyclophosphamide, vincristine, prednisolone, dacarbazine), TG2 patients received two cycles of COPDAC, and TG3 patients received four cycles of COPDAC.[27,29]

Treatment Response Assessment and Indications for Radiotherapy

Indications for radiotherapy were based on response assessment on the interim PET/CT. The patients were classified as "adequate responders" and "inadequate responders." Children with Deauville score ≤3 were classified as adequate responders and they received only chemotherapy as mentioned earlier. Those with a Deauville score ≥4 were classified as inadequate responders and were given radiotherapy to the involved fields (in the interim PET) at the end of COPDAC cycles as per TG.[27,29]

Outcome

The children were followed up till July 2024 for OS and EFS. OS was calculated from diagnosis till last follow-up or death, and event was defined as disease progression, recurrence, second malignancy, or death due to any cause.

Statistical Analysis

For continuous variables, mean value with standard deviation was calculated. The mean SUVmax and MTV in the baseline PET/CT were compared for correlation. The study parameters (SUVmax and MTV) were compared and analyzed based on the PHL stage, TGs, response groups, and outcome. A comparison of the median baseline PET/CT MTV was done among the four stages at diagnosis and three TGs using paired *t*-tests. Based on the interim PET/CT response, the patients were divided into "adequate" and "inadequate" responders. The Median SUVmax and MTV in the baseline

PET were compared between the two groups using paired *t*-test. Percentage reduction of MTV from baseline to interim PET was assessed and compared with stage, TGs, and response groups using the rank-sum nonparametric test. The study patients were further classified into two outcome groups with or without an event. The median SUVmax and MTV in the baseline PET/CT were compared between the two outcome groups using paired *t*-test. Receiver operating characteristic (ROC) analysis was used to identify sensitivity and specificity of PET/CT for predicting EFS. Using the ROC curve, the 85th percentile MTV value cutoff was determined to identify the subjects with high MTV. A *p*-valve of less than 0.05 was considered statistically significant.

Ethical Approval

All procedures performed in the study subjects were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments/comparable ethical standards. This retrospective study was approved by the Institutional Review Board (IRB) of the institution (IRB Min No. 14743/6.7.22).

Results

Sixty-one children with PHL were included in the study; their baseline characteristics with subjects classified by age, gender, stages, TGs, and response assessment are shown in ►**Table 1**. The mean age at diagnosis was 10.10 years, with a male-to-female ratio of 1:0.6. The majority were in stage III (21/61) at diagnosis, and designated to TG3 (34/61).

MTV and SUVmax were assessed for all patients in the baseline as well as interim PET/CT scan. The mean SUVmax in the baseline PET/CT was 11.1 (±3.5) and that in the interim PET/CT was 1.9 (±3.4). Similarly, the mean MTV in diagnostic and interim PET/CT was 232.73 (±206) and 72.7 (±192.4) mL, respectively. Percentage change in MTV and SUVmax between the two PET/CT scans were compared, and both showed significant reduction in the values ($p = 0.001$). The positive correlation between SUVmax and MTV ($r = 0.41$, $p = 0.002$) is shown in ►**Fig. 1**.

►**Table 2** shows the median SUVmax and MTV of various stages of disease and TGs. The median SUVmax and MTV were found to increase with advanced stages of the disease. The difference in the median MTV was statistically significant for stage II versus stage III ($p = 0.004$), but not for the median SUVmax ($p = 0.13$). The difference in the median MTV was statistically significant for TG2 versus TG3 ($p = 0.001$) but not for the median SUVmax ($p = 0.06$)

PET/CT Parameters and Treatment Response

Further analysis was done to compare the SUVmax and MTV on the diagnostic PET/CT scan between "adequate" and "inadequate" responders as well as those who had or did not have an event. Among the 61 patients, 47 patients were classified as "adequate responders" according to the interim PET/CT and 14 as "inadequate responders" (►**Table 1**). Twelve

Table 1 Baseline characteristics of subjects

Baseline characteristics	Number
Age (y)	Mean: 10.10 (4–17)
0–5	5
6–10	30
11–15	22
16–18	4
Gender	Male:female = 1:0.6
Male	37
Female	24
Stage	
IA	11
IIA	10
IIB	5
IIIA	7
IIIB	14
IVA	7
IVB	7
Treatment levels	
Level 1	16
Level 2	11
Level 3	34
SUVmax	
Baseline PET	11.1 (±3.5)
Interim PET	1.9 (±3.4)
Metabolic tumor volume	
Baseline PET	232.73 (±206)
Interim PET	72.7 (±192.4)
Response assessment	
Adequate response	47
Inadequate response	14

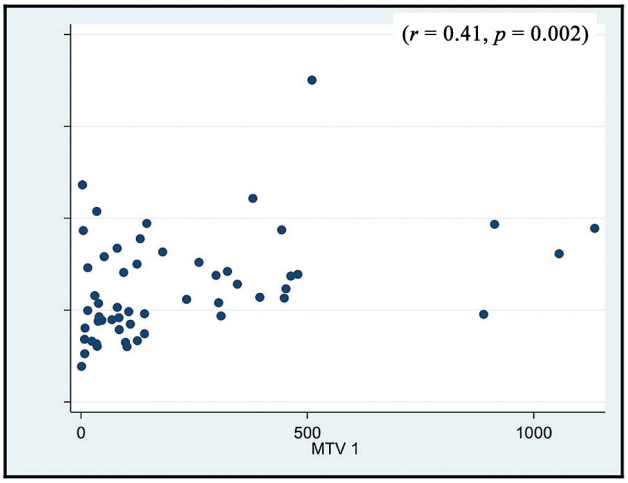

Fig. 1 Correlation between maximum standardized uptake value (SUVmax) and metabolic tumor volume (MTV) in the baseline PET scan.

Table 2 Median maximum standardized uptake value (SUVmax) and metabolic tumor volume (MTV) versus stage of disease and treatment groups

Median SUVmax and MTV vs. stage of disease				
Stage	**Median SUVmax (interquartile range [IQR])**	***p*-value between**	**Median MTV (IQR), mL**	***p*-value between**
I	8.04 (6.06–10.7)	I and IV: 0.009	36.8 (7.9–46.1)	I and IV: 0.0001
II	9.95 (7.4–16.7)	I and II: 0.2	39.9 (14.8–105.3)	I and II: 0.8
III	10.3 (9.12–15.01)	II and III: 0.13	140 (83.6–309.2)	II and III: 0.004
IV	14 (11.4–16.3)	III and IV: 0.5	362.4 (180–478.8)	III and IV: 0.1
Median SUVmax and MTV vs. treatment groups				
Treatment groups (TG)	**Median SUVmax (IQR)**	***p*-value between**	**Median MTV (IQR), mL**	***p*-value between**
1	8.2 (6.5–12.7)	1 and 3: 0.005	36.8 (8.8–51.1)	1 and 3: 0.001
2	9.6 (8.54–11.57)	1 and 2: 0.9	39.9 (14.8–105.3)	1 and 2: 0.6
3	13.7 (9.5–16.3)	2 and 3: 0.06	304 (123.7–452.7)	2 and 3: 0.001

out of these 14 inadequate responders attained complete remission (CR) with chemotherapy and radiotherapy. The remaining two had disease progression and were treated with salvage chemotherapy followed by radiotherapy; one attained remission; however, the second child succumbed to the disease.

For each patient, MTV and SUVmax were calculated in the baseline and interim PET/CT. ►**Table 3** presents median MTV and SUVmax in "adequate" and "inadequate" responders. Both the median MTV and the SUVmax from diagnostic PET/CT were higher in the "inadequate" responders compared to "adequate" responders, but were not significantly different. The median change in MTV between the response groups were analyzed. The group of children with "inadequate" response showed significantly wider variation in reduction of MTV ($p = 0.001$) compared to those with "adequate" response. The MTV range among "inadequate responders" varied from good response of greater than 90% volume reduction to a paradoxical increase in volume.

As further subgroup analysis, the median MTV reduction was compared between initial stage and treatment levels against response groups. However, there was no significant association between stage at presentation, TGs, and median percentage reduction in MTV.

Further analysis was done, based on the Milgrom et al study on the prognostic value of baseline MTV in pediatric and adolescent HL anticipating relapse/refractory disease in about 15% of patients. They opined that a subgroup analysis using the 85th percentile PET/CT MTV value may aid in identifying those who are likely to have refractory disease/disease relapse.[19] In our cohort, the 85th percentile was determined using the ROC curve area under the curve (AUC), and the cutoff was found to be 449. Based on the cutoff value, the study subjects were divided into two groups, high MTV ($n = 9$) and low MTV ($n = 52$) at presentation. The nine patients who had baseline MTV more than the 85th centile included five (55.6%) with stage IV disease, three (33.3%) with stage III disease, and one patient (11.1%) with stage IIBE disease; hence, all belonged to TG3. Three of nine (33%) children had "inadequate response" during interim assessment. Of the nine children with high baseline MTV, one had disease progression and another had disease relapse (both

Table 3 Comparison of median metabolic tumor volume (MTV) and median maximum standardized uptake value (SUVmax) in diagnostic PET/CT with Deauville score–based treatment response groups

Comparison of median MTV and median SUVmax in diagnostic PET/CT with Deauville score–based treatment response groups		
Outcome	**Median MTV (interquartile range [IQR]), mL**	**Median SUVmax (IQR)**
Responders	98.35 (37.93–298.2)	10.73 (8.47–14.61)
Inadequate responders	145 (84.43–463.5)	12.25 (8.54–18.66)
p-value	0.31	0.37
Comparison between occurrence of event with median MTV and median SUVmax in the diagnostic PET/CT		
Outcome	**Median MTV (IQR), mL**	**Median SUVmax (IQR)**
Event	214.3 (32.45–420.7)	11.1 (7.6–13.49)
No event	101.6 (37.9–298.2)	10.3 (8.5–15.3)
p-value	0.63	0.68

were stage 4 at presentation); however, both attained CR postsalvage therapy.

The 52 patients with low MTV belonged to the following stages: stage I = 11, stage II = 14, stage III = 18, and stage IV = 9. Sixteen of 52 children were in TG1, 11 of 52 were in TG2, and 25 of 52 were part of TG3. In all, 43 of 52 children had adequate response in the interim PET. Nine of 52 children, however, had inadequate response in the interim PET. One had progressive disease requiring salvage chemotherapy; however, the remaining eight attained CR at the end of chemotherapy with radiotherapy.

PET/CT Parameters and Follow-Up Outcome

At a median follow-up period of 54 months (5–97 months), the OS was 96.7% (59/61) and the EFS was 85.2% (52/61). Among the study subjects who had an event ($n = 9$), eight of nine children had stage IV disease at initial diagnosis (TG3). All but one child who had a relapse had adequate response in the iPET. Two of nine children had primary progressive disease: one attained remission with salvage chemotherapy and radiotherapy, whereas the other child did not respond to therapy and expired. Seven of nine children had disease relapse: one had an early relapse (3 months after completion of initial treatment) and six had late relapse (after 1 year of initial treatment). Six of seven children who relapsed are in complete remission now, following salvage treatment for first relapse, and one succumbed to the illness.

Children who had an event were studied according to their initial SUVmax, initial MTV, percentage reduction in MTV, and response to treatment. As depicted in ►**Table 3**, the median MTV and SUVmax values in the children with an event were found to be higher, but the difference when compared to those who remained event free was not statistically significant. In addition, the median reduction of MTV between the above two groups also showed no significant difference.

The ROC curve was constructed to assess sensitivity and specificity of diagnostic PET/CT MTV as a prognostic parameter in assessing EFS; the AUC was 0.52 (95% confidence interval [CI]: 0.243–0.815); hence, further analysis was not feasible.

Discussion

In our PHL cohort of 61 subjects, the ^{18}F-FDG PET/CT parameters (MTV and SUVmax) were measured in baseline and interim PET/CT. The median values of both parameters in the baseline PET/CT scan were found to increase as the stage advanced and there was a significant positive correlation. The percentage reduction in MTV and SUVmax between baseline and interim PET/CT was statistically significant. MTV in baseline PET/CT distinguished stages II and III and TG2 and TG3 significantly better than SUVmax, similar to the German study on 50 subjects with PHL by Rogasch et al who were treated according to the EuroNet-PHL-C1 or EuroNet-PHL-C2 treatment protocol.[25] In their study, the mean MTV values were 386.2 mL (137.9–537.8 mL) in stage III and 350.6 mL (207.4–555.9 mL) in stage IV, in comparison to our study values of 140 (83.6–309.2) and 362.4 (180–478.8) mL for the corresponding stages, alluding to a more significant positive correlation with advancing stage.[25] Our study had almost equal distribution of patients across all stages, unlike the Rogasch et al study, which had only one subject in stage I; thus, we were able to demonstrate more convincingly that there was a positive correlation of MTV with advancing stage.[25]

The MTV and SUVmax values in the baseline PET/CT were evaluated as treatment response prognosticators in this study. Although these were noted to be higher among "inadequate" responders as compared to "adequate" responders, the difference was not statistically significant. Nevertheless, the median change in MTV values between the response groups showed wider variation in reduction for the group with "inadequate" response compared to the group with "adequate" response, which was statistically significant. Our study results contrast the Rogasch et al observation, where log-linear analysis showed a significant correlation between a high MTV and response to induction therapy ($p < 0.001$).[25] Similarly, the Reed et al study on 69 subjects in South Africa showed that only MTV on baseline PET/CT, not SUVmax or TLG, was predictive of treatment response.[20] The subjects across stages in our study were more uniformly represented compared to the studies by Rogasch et al and Reed et al, in which stage 1 had only one subject each.

At a median follow-up of 54 months, the OS and EFS in this study were 96.7 and 85.2%, respectively. Baseline PET/CT parameters (MTV and SUVmax median values), although higher in the group with an event, were not significantly different from the group without an event, even on univariate analysis. This is similar to that observed by Reed et al, where none of the metabolic parameters (SUVmax, MTV, or TLG) in the baseline PET/CT were independent predictors of neither EFS nor OS in PHL.[20] The above two contrasts the findings of Milgrom et al, who assessed the prognostic value of baseline MTV in intermediate-risk PHL patients treated with chemoradiation therapy as per the children's oncology group (COG) AHOD0031 trial. This group was able to demonstrate that total-body MTV based on four thresholds (MTV20% SUVmax, MTV1.5Lv, MTV1.5Lv + 2SD, and MTV2BP) and TLG based on two thresholds (TLG60% SUVmax and TLG2BP) were significantly associated with EFS on univariate Cox regression analysis. MTV2BP could distinguish high from low tumor burden and showed the highest sensitivity (91%) and specificity (60%) in identifying the 5-year EFS. This significance was retained on multivariate analysis ($p = 0.012$) after controlling for other prognostically influential covariates, such as disease bulk and response to chemotherapy.[19] A study from China by Zhou et al on 47 PHL subjects, with a median follow-up of 36 months, showed that unlike SUVmax, MTV and TLG in the baseline PET/CT of patients with disease progression were significantly higher than those without disease progression ($p = 0.036$ for MTV and $p = 0.015$ for TLG). However, on multivariate analysis, only TLG was found to be an independent prognostic factor for PFS ($p = 0.021$).[30] Lopci and Mascarin analyzed the usefulness of MTV and TLG in the prediction of outcomes in 150

children with high-risk PHL (stage III/IV disease) who were treated on the EuroNet-PHL-C2 protocol.[31] They were able to show that a high baseline tumor burden (defined as TLG >1,841) correlated with EFS. There was a statistically significant difference for all baseline parameters and treatment evaluation at early response assessment PET/CT (interim PET) between adequate and inadequate responders ($p < 0.05$), with logistic regression confirming significant association for MTV ($p = 0.008$) and TLG ($p = 0.009$).[31]

The difference between varying study groups may be related to sample size and subject characteristics. MTV in children, unlike in adults, could be significantly influenced by the proportion of the tumor burden in relation to the body weight. This has not been factored in by most pediatric studies, despite being an obvious confounder.[20] Studies have also shown that liver SUVmean and liver SUVmax may show variation with age, which may result in variation in MTV calculation in different age groups as well.[32] The other confounders that have been studied are blood glucose levels during the PET/CT scan, differential uptake time, contrast decay, and lack of standardization/consensus in tumor boundary assessment.[12,16,17] The differences in ethnicity, coexisting comorbidities in the recruited subjects, differences in definitions of treatment responders, and median follow-up times postinterim PET/CT[12,19,20,25,33] could also contribute to interstudy variations. However, as most studies, like ours, were single-center retrospective studies on small sample cohorts, we expect them to have lower intra and intercenter variability in technique as well as interpretation of PET/CT as compared to large multicenter trials.[31]

In our study, diagnostic ^{18}F-FDG PET/CT MTV and SUVmax increased with advanced stages of the disease. Diagnostic PET/CT MTV was a better correlate than SUVmax in delineating stage and TGs. However, we found that diagnostic PET/CT MTV or SUVmax alone was not sensitive or specific enough in prognosticating treatment response or EFS (relapse or death).

We note as a limitation that in our study diagnostic and interim PET/CT TLG was not performed. Interim PET/CT MTV and SUVmax were also not analyzed against outcomes. However, given that treatment is modified ("response adapted") based on the interim PET/CT results, the true predictive/prognostic value derived from the interim PET/CT MTV and SUVmax values in HL is difficult to predict.[34]

Conclusion and Future Directions

In our PHL cohort of 61 subjects, we used diagnostic PET/CT MTV and SUVmax values to assess their discriminating ability among staging and TG allocation, as well as their ability in predicting treatment response, EFS, and OS. Baseline PET/CT MTV was a better correlate than SUVmax in delineating stage and TGs as the difference in the value of baseline MTV showed a significant difference between each group. However, MTV in isolation, in our setting, was not sensitive or specific enough in prognosticating treatment response, EFS, or OS. Future studies should involve larger sample sizes with validated clinico-biochemical parameters such as Childhood Hodgkin International Prognostic Score[35] in addition to PET/CT parameters to more accurately prognosticate outcomes in PHL.

Authors' Contributions

S.R. and S.S.S. contributed to the design of the study, literature search, clinical studies, data acquisition and analysis, and manuscript preparation. H.N.S. contributed to the concepts, literature search, clinical studies, data analysis, and manuscript editing. R.R.J. contributed to the concepts, design, literature search, clinical studies, data analysis, manuscript editing, and manuscript review. R.Z.K. contributed to the design, literature search, clinical studies, data analysis, and manuscript editing. M.G. contributed to the design, data analysis, statistical analysis, and manuscript editing. L.L.J. contributed to the concepts, design, literature search, clinical studies, data analysis, statistical analysis, and manuscript review. J.H. contributed to the concepts, design, literature search, clinical studies, statistical analysis, and manuscript review. L.G.M. contributed to the concepts, design, definition of intellectual content, literature search, clinical studies, statistical analysis, and manuscript review, and served as a guarantor.

The authors wish to state that the manuscript has been read and approved by all the authors, that the requirements for authorship have been met, and that each author believes that the manuscript represents honest work.

Patient Consent

Individual patient consent was not required for this retrospective study, as approved by the Institutional Review Board (IRB) of the institution (IRB Min No. 14743/6.7.22).

Funding

This study was funded by the Christian Medical College, Fluid Research Grant.

Conflict of Interest

None declared.

Acknowledgments

The authors wish to thank Mr. Balamurugan Durai for help with data acquisition and collation.

References

1 Thomas RK, Re D, Zander T, Wolf J, Diehl V. Epidemiology and etiology of Hodgkin's lymphoma. Ann Oncol 2002;13(Suppl 4): 147–152

2 Macfarlane GJ, Evstifeeva T, Boyle P, Grufferman S. International patterns in the occurrence of Hodgkin's disease in children and young adult males. Int J Cancer 1995;61(02):165–169

3 PDQ Pediatric Treatment Editorial Board. Childhood Hodgkin Lymphoma Treatment (PDQ®): Health Professional Version. In: PDQ Cancer Information Summaries. National Cancer Institute (US); 2002. Accessed July 11, 2024 at: http://www.ncbi.nlm.nih.gov/books/NBK65726/

4 Arya LS. Current strategies in the treatment of childhood Hodgkin's disease. Accessed July 11, 2024 at: https://www.indianpediatrics.net/nov2005/nov-1115-1128.HTM
5 Mahajan A, Singh M, Bakhshi S, et al. Treating early-stage Hodgkin lymphoma in resource-limited settings: InPOG-HL-15-01 experience. Pediatr Blood Cancer 2021;68(10):e29219
6 Jain S, Bakhshi S, Seth R, et al. Risk based and response adapted radiation therapy for children and adolescents with newly diagnosed advanced stage Hodgkin lymphoma treated with ABVD chemotherapy: a report from the Indian pediatric oncology group study InPOG-HL-15-01. Leuk Lymphoma 2022;63(05):1111–1118
7 Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. Blood 2009;114(10):2051–2059
8 Daw S, Hasenclever D, Mascarin M, et al. Risk and response adapted treatment guidelines for managing first relapsed and refractory classical Hodgkin lymphoma in children and young people. Recommendations from the EuroNet Pediatric Hodgkin Lymphoma Group. HemaSphere 2020;4(01):e329
9 Kahn JM, Mauz-Korholz C, Hernandez T, Milgrom SA, Castellino SM. Pediatric and adolescent Hodgkin lymphoma: paving the way for standards of care and shared decision making. Am Soc Clin Oncol Educ Book 2024;44(03):e432420
10 National Cancer Institute. Childhood Hodgkin Lymphoma Treatment. PDQ. NCI. 2024. Accessed July 11, 2024 at: https://www.cancer.gov/types/lymphoma/hp/child-hodgkin-treatment-pdq
11 Ansell SM. Hodgkin lymphoma: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol 2022;97(11):1478–1488
12 Meignan M, Cottereau AS, Specht L, Mikhaeel NG. Total tumor burden in lymphoma: an evolving strong prognostic parameter. Br J Radiol 2021;94(1127):20210448
13 Kido H, Kato S, Funahashi K, et al. The metabolic parameters based on volume in PET/CT are associated with clinicopathological N stage of colorectal cancer and can predict prognosis. EJNMMI Res 2021;11(01):87
14 Im HJ, Bradshaw T, Solaiyappan M, Cho SY. Current methods to define metabolic tumor volume in positron emission tomography: which one is better? Nucl Med Mol Imaging 2018;52(01):5–15
15 Mathew B, Vijayasekharan K, Shah S, et al. Prognostic value of ^{18}F-FDG PET/CT-metabolic parameters at baseline and interim assessment in pediatric anaplastic large cell lymphoma. Clin Nucl Med 2020;45(03):182–186
16 Chen S, He K, Feng F, et al. Metabolic tumor burden on baseline ^{18}F-FDG PET/CT improves risk stratification in pediatric patients with mature B-cell lymphoma. Eur J Nucl Med Mol Imaging 2019;46(09):1830–1839
17 Yang J, Yan J, Li J, Zhang H, Zhao Q, Xu W. Prognostic value of metabolic parameters in baseline 18F-FDG PET/CT for pediatric lymphoblastic lymphoma. Eur J Nucl Med Mol Imaging 2024;51(07):1955–1964
18 Cottereau AS, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. Blood 2018;131(13):1456–1463
19 Milgrom SA, Kim J, Chirindel A, et al. Prognostic value of baseline metabolic tumor volume in children and adolescents with intermediate-risk Hodgkin lymphoma treated with chemo-radiation therapy: FDG-PET parameter analysis in a subgroup from COG AHOD0031. Pediatr Blood Cancer 2021;68(09):e29212
20 Reed JD, Masenge A, Buchner A, et al. The utility of metabolic parameters on baseline F-18 FDG PET/CT in predicting treatment response and survival in paediatric and adolescent Hodgkin lymphoma. J Clin Med 2021;10(24):5979
21 Hirata K, Tamaki N. Quantitative FDG PET assessment for oncology therapy. Cancers (Basel) 2021;13(04):869
22 Weiss GJ, Korn RL. Interpretation of PET scans: do not take SUVs at face value. J Thorac Oncol 2012;7(12):1744–1746
23 PDQ Pediatric Treatment Editorial Board. Childhood Hodgkin Lymphoma Treatment (PDQ®): Health Professional Version. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002 [cited 2025 Feb 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK65726/
24 John JR, Oommen R, Hephzibah J, et al. Validation of Deauville score for response evaluation in Hodgkin's lymphoma. Indian J Nucl Med 2023;38(01):16–22
25 Rogasch JMM, Hundsdoerfer P, Hofheinz F, et al. Pretherapeutic FDG-PET total metabolic tumor volume predicts response to induction therapy in pediatric Hodgkin's lymphoma. BMC Cancer 2018;18(01):521
26 Weisman AJ, Kim J, Lee I, et al. Automated quantification of baseline imaging PET metrics on FDG PET/CT images of pediatric Hodgkin lymphoma patients. EJNMMI Phys 2020;7(01):76
27 Mauz-Körholz C, Landman-Parker J, Balwierz W, et al. Response-adapted omission of radiotherapy and comparison of consolidation chemotherapy in children and adolescents with intermediate-stage and advanced-stage classical Hodgkin lymphoma (EuroNet-PHL-C1): a titration study with an open-label, embedded, multinational, non-inferiority, randomised controlled trial. Lancet Oncol 2022;23(01):125–137
28 Mauz-Körholz C, Hasenclever D, Dörffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. J Clin Oncol 2010;28(23):3680–3686
29 Radhakrishnan V, Kapoor G, Arora B, Bansal D, Vora T, Prasad M, et al. Management of Hodgkins Lymphoma: ICMR Consensus Document. Indian J Pediatr 2017;84(05):371–381
30 Zhou Y, Hong Z, Zhou M, et al. Prognostic value of baseline ^{18}F-FDG PET/CT metabolic parameters in paediatric lymphoma. J Med Imaging Radiat Oncol 2020;64(01):87–95
31 Lopci E, Mascarin M. Role of volumetric analyses on [^{18}F]FDG PET/CT in pediatric Hodgkin lymphoma. Expert Rev Hematol 2023;16(09):629–631
32 Cao Y, Zhou K, Diao W, et al. Age-related changes of standardized uptake values in the blood pool and liver: a decade-long retrospective study of the outcomes of 2,526 subjects. Quant Imaging Med Surg 2021;11(01):95–106
33 Parekh A, Keller FG, McCarten KM, et al. Targeted radiotherapy for early-stage, low-risk pediatric Hodgkin lymphoma slow early responders: a COG AHOD0431 analysis. Blood 2022;140(10):1086–1093
34 Al-Ibraheem A, Anwer F, Juweid ME, et al. Interim FDG-PET/CT for therapy monitoring and prognostication in Hodgkin's lymphoma. Sci Rep 2022;12(01):17702
35 Schwartz CL, Chen L, McCarten K, et al. Childhood Hodgkin International Prognostic Score (CHIPS) Predicts event-free survival in Hodgkin Lymphoma: a report from the Children's Oncology Group. Pediatr Blood Cancer 2017;64(04):e26278

