

Added Value of Semi-quantitative Analysis in Interim FDG-PET/CT in Pediatric Lymphoma

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Pediatric lymphoma (PL) is one of the few pediatric malignancies that shares aspects of its biology and natural history with adult lymphoma. However, it differs from the adult counterparts, mainly in terms of histopathology and therapeutic strategies (1). It comprises 6% of all childhood cancers worldwide (2). In Egypt, childhood lymphoma represents 1.3% of all incident cancers and 28.7% of all childhood cancer occupying the second rank among all childhood malignancies (3).

PL is highly sensitive to standard chemotherapy, radiation therapy, or combined-modality therapy (4). Approximately 90- 95% of PL can be cured with 5-year survival rate of around 96%; prompting increased attention to the long-term morbidity for these patients (5).

The conventional anatomic imaging for early treatment response monitoring is based on the change in tumor size, which is not an accurate predictor of outcome (6), however, functional assessment of response using FDG-PET

performed early after two cycles of therapy (interim PET) represents a useful non-invasive imaging method to monitor the treatment benefits in adulthood and pediatric lymphomas (7). Moreover, it has been demonstrated to predict therapy outcome at an earlier stage of treatment allowing a risk-adapted treatment strategy (8).

The Imaging Subcommittee of the “International Harmonization Project in Lymphoma” has defined criteria for PET interpretation after completion of chemotherapy (9); that cannot be applied in interim PET that needs special criteria to assess response (10). These criteria have not been sufficiently validated, especially in pediatric patients.

Practically speaking; the methods of data analysis used have been broadly categorized into two groups: (1) qualitative analysis, i.e. visual assessment; (2) semi-quantitative analysis, i.e., standardized uptake value (SUV) and recently, volume-based metabolic parameters.

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1- Qualitative (visual) assessment:

In 2009, the 1st international workshop on interim PET in lymphoma was held in Menton, France and it resulted in so-called “Deauville criteria” recommendation (10). Deauville criteria propose simple, reproducible rules for visual interpretation of interim PET in malignant lymphomas, these criteria were contained in three major statements: (i) Visual assessment is preferred, but SUV determination can be used in some cases; (ii) Interim-PET interpretation should always be made by comparing the foci of FDG uptake to those recorded in the baseline study; (iii) The intensity of FDG uptake should be graded according to a five-point scale in which a reference organs should be the mediastinum and the liver, are used to define different grades of FDG uptake (10).

“Minimal residual uptake” (MRU) is a term which has been used to describe low-grade uptake that may be seen after treatment for lymphoma (11). The significance of MRU in interim PET scans may differ according to the lymphoma type (e.g. HL vs. NHL), stage (early vs. advanced) and possibly the treatment (12). In patients with early HL receiving ABVD chemotherapy and involved field radiotherapy with a low pretest likelihood of disease, MRU is associated with a very good prognosis. Conversely MRU appears to be associated with a poor prognosis in patients with advanced NHL receiving systemic chemotherapy and a higher pretest likelihood of disease (11, 12).

2- Semi-quantitative assessment:

A-The Standardized uptake value (SUV):

It is calculated from the counts-per-pixel and normalized to body weight (BW) (13), using the following formulas:

$$\text{SUV}_{\text{BW}} = \text{Tissue activity (KBq/ml)} / \text{Injected activity* (MBq)/weight (Kg)}$$

Where *activity was decay-corrected from the delay between injection and image acquisition.

SUV_{max} is the count in the most active pixel in the VOI.

SUV_{mean} is the average of the counts in all pixels in the Volume of Interest (VOI).

Δ **SUV_{max}** is the percent of change between SUV_{max} on the PET2 scan (interim PET) versus the PET1 scan (initial PET). This method of assessing metabolic response has been recommended by the 1999 European Organization for Research and Treatment of Cancer (EORTC) position paper on measurement of metabolic tumor response with FDG (14). It is calculated using the following formula; $\Delta \text{ SUV}_{\text{max}} = (\text{SUV}_{\text{max}1} - \text{SUV}_{\text{max}2}) / \text{SUV}_{\text{max}1} \times 100$

SUV_{max} is proved to improve the prognostic value of early ¹⁸F-FDG PET/CT when it is added to a visual analysis (15); however, in some studies SUV_{mean} may be potentially more valuable. This may be attributed to that a single voxel value may not be representative of the overall tumor uptake in a non homogeneous tumor (16).

SUV normalized to body surface area (SUV_{bsa}) or lean body mass (SUL) could be more precise

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in pediatric population than SUV normalized to body weight (SUV_{BW}), as they are almost independent of body parameters in the pediatric population and would serve as better metabolic activity markers (17).

B- Volume-based metabolic parameters:

Such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have become potentially important semi-quantitative PET indices (18).

MTV was measured by generating 3D iso-count contours to define tumor boundaries (VOI) using semi-automatic contouring software after applying a pre-defined threshold of the SUV_{max} value within this VOI, this may fail in case of low tumor-to-background ratios or in the vicinity of organs showing high uptake (bladder, heart, brain, kidneys), in these cases the automatically generated VOI should be visually checked and manually drawn so it will be large enough to include all the tumor volume and careful enough to exclude areas of physiological uptake (19). Δ MTV is calculated as the percent of change between MTV on the PET2 scan versus the PET1 scan using the following formula;

$$(MTV1 - MTV2) / MTV1 \times 100$$

TLG was calculated by multiplying the selected PET volume (MTV) on the investigated lesions as mentioned above by the SUV_{mean} within that volume: $TLG = MTV \times SUV_{mean}$

Δ TLG: is calculated according to Larson-Ginsberg Index (LGI), and known as Δ TLG (LGI) (18):

$$[(SUV_{mean})_1 \times (Vol)_1 - (SUV_{mean})_2 \times (Vol)_2] / (SUV_{mean})_1 \times (Vol)_1 \times 100$$

These volume based parameters are theoretically more relevant parameters than are single pixel values (17) They were thought to provide valuable information regarding tumor aggressiveness and consequently, they may be considered as potential prognostic indices for tumors (20, 21, 22, 23).

The main obstacle to the wide implementation of TLG as a parameter for assessing response is the method used to measure the MTV which is considered as a combined metabolic radiological marker. The choice of the thresholding method for MTV may affect the absolute value of the MTV (24). Multiple studies demonstrate that the best thresholding methods are either an SUV within the range (2-3) or a fixed threshold of 40 % of the SUV_{max} as this approximates tumor volume best and are optimal for differentiating benign from malignant lesions, and minimizes inclusion of unwanted physiological FDG uptake in normal tissues (25). However, other studies have demonstrated that one specific adaptive threshold for determination of MTV, either fixed SUV cut-off or percentage threshold, will not yield volumes exactly corresponding to those produced by manual contouring of CT scans nor to those obtained from pathology, while individualizing MTV calculation to tumor size and SUV_{max} may be worthwhile to optimize its prognostic stratifying value (26).

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