Review Article, PET/CT.

Does Volumetric Metabolic PET/CT Parameters have impact in Prognosis in Pediatric Lymphoma patients?

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ABSTRACT:

Aim of work: we aimed to evaluate the role of metabolic parameters extracted from volumetric PET images in predicting early metabolic therapy response, and to investigate the prognostic and predictive value of initial volumetric based PET/CT in pediatric Hodgkin lymphoma on therapy outcome and disease-free survival rate. HD has shown improvement in survival, which shifted the current interest towards early identification and stratifications of the patients who are at risk of treatment failure (poor response to first-line therapy or initial response with subsequent relapse). This will reduce treatment-related Sequelae, which include secondary malignancies and cardiovascular events. Unfortunately, current risk-stratification criteria fail to identify these children. ^{18}F-FDG PET/CT is established as a powerful tool for both initial staging and early response assessment in HL. However, there is a paucity of studies that identify the role of baseline ^{18}F- FDG PET/CT for risk stratification and prediction of OS and PFS. Some studies have assessed the value of various baseline metabolic parameters (namely whole-body metabolic tumor volume, [WB MTV] and total lesion glycolysis [TLG]) for risk stratification and prediction of OS and PFS. However, data are limited (especially in pediatric patients) and somewhat conflicting; therefore, we aimed to further investigate these promising parameters. **Conclusions:** Interim PET/CT in pediatric Hodgkin lymphoma using Deauville score remains the best indicator for prediction of therapy response, different patients' characteristics could have correlation with clinical outcome and response to therapy using SUVmax.

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INTRODUCTION:

Hodgkin lymphoma (HL) is a malignant neoplasm usually derived from B-lymphocytes, accounting for approximately 10% of all lymphomas. In paediatric population, 40 % of lymphomas are considered Hodgkin's lymphoma (HL). In the last few years, many attempts are present to identify the most important prognostic factor that may be capable of early identification and stratification of high-risk patients who need to be subjected to more intensified treatment protocols [(1)]. Therapeutic options for HL are various combinations of systemic chemotherapy and radiotherapy, which depend on the stage of the disease at the time of initial diagnosis, separating early/localized stages and advanced/disseminated stages [(2)]. This emphasizes the requirement of adequate initial staging before choosing therapy lines, taking into consideration the balance between efficacy and risks of toxicity and long-term side effects [(3)]. ^{18}F-FDG PET/CT is now a very important functional imaging modality used in initial staging, detection of early response to therapy and identification of relapse/recurrence. Supporting evidence has led to the integration of ^{18}F-FDG-PET/CT imaging into the routine staging and restaging algorithm of different types of lymphomas [(4)]. PET/CT has greater sensitivity for sites of extra-nodal involvement and therefore has been found to improve baseline staging, an interim PET scan after two cycles of chemotherapy can detect early response-adapted therapy in Hodgkin lymphoma [(4)]. Assessment of response-to-therapy in paediatric Hodgkin lymphoma patients by PET/CT has considered an even more powerful tool for the differentiation between responders and non-responders. Thus, the incorporation of information provided by PET into the "Revised Response Criteria in Lymphoma" was inevitable. In addition to the visual PET reading the authors stated that semi-quantitative assessment, for example using the standardized uptake value (SUV), may provide a more uniform and potentially more accurate assessment of mid therapy PET assessment (synonym to interim PET) studies [(5)]. Improvements and advances in PET/CT technology and image reconstruction have led to increasing interest from researchers and clinicians in the quantitation of metabolic parameters.

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Maximum standardized uptake value (SUVmax), total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG) are the most frequently used parameters in the clinical and research settings nowadays. In this context of individualized background correction, the liver is reported to be especially well suited as it demonstrates little variance in FDG-accumulation total lesion glycolysis (TLG), appears to be a promising tool for response prediction in HL as well [(6)].

A risk-adapted treatment approach based on interim response assessment with PET/CT is recommended in patients with HL for this purpose. Studies in patients with HL have shown that a positive interim PET/CT scan can predicts higher chance of relapse and poorer outcome [(7)].

HD has shown improvement in survival, which shifted the current interest towards early identification and stratifications of the patients who are at risk of treatment failure (poor response to first-line therapy or initial response with subsequent relapse). This will reduce treatment-related Sequelae, which include secondary malignancies and cardiovascular events. Unfortunately, current risk-stratification criteria fail to identify these children. ^{18}F-FDG PET/CT is established as a powerful tool for both initial staging and early response assessment in HL. However, there is a paucity of studies that identify the role of baseline ^{18}F-FDG PET/CT for risk stratification and prediction of OS and PFS. Some studies have assessed the value of various baseline metabolic parameters (namely whole-body metabolic tumor volume, [WB MTV] and total lesion glycolysis [TLG]) for risk stratification and prediction of OS and PFS. However, data are limited (especially in paediatric patients) and somewhat conflicting; therefore, we aimed to further investigate these promising parameters.

Rogasch et al. reported in retrospective study that included 50 children with HL aimed to identify quantitative parameters from pre-therapeutic FDG-PET to assist prediction of response to induction chemotherapy. Inadequate response was seen in 28/50 patients, they concluded that patients of high total MTV best predicted inadequate response to induction therapy in paediatric HL of all pre-therapeutic FDG-PET parameters – in both low and advanced stages [(8)].

Hutchings et al. reported in prospective study that included 77 patients newly diagnosed adult patients with HL aimed to identify the value of PETCT parameters done at staging and after 2 cycles of CTH for prediction of progression free survival and overall survival, survival analyses showed strong associations between early FDG-PET after 2 cycles and PFS (P < .001) and OS (P < .01), it showed that for prediction of PFS, interim FDG-PET was as accurate after 2 cycles as later during treatment and superior to computerized tomography, early interim FDG-PET is a strong and independent predictor of PFS in HL.

Also, positive early interim FDG-PET is highly predictive of progression in patients with advanced-stage or extra-nodal disease **(9)**.

Cottereau et al. reported in a prospective study that included 258 patients initially diagnosed with early-stage Hodgkin's Lymphoma aimed to investigate the predictive value of baseline ^{18}F-FDG PET/CT TMTV and interim ^{18}F-FDG PET/CT response assessed with Deauville score. TMTV was a prognosticator of PFS (P<.0001) and OS (P5.0001), with 86% and 84%specificity, respectively.

Five-year PFS and OS were 71% and 83% in the high-TMTV (>147 cm3) group (n =46), respectively, versus 92% and 98% in the low-TMTV group (>147 cm3).

In multi-variable analysis including iPET2, TMTV was the only baseline prognosticator and improves baseline risk stratification of patients with early-stage HL compared with current staging systems and the predictive value of early PET/CT response as well **(10)**.

Herraz et al. reported in a retrospective study that included 101 patients diagnosed with Hodgkin lymphoma (HL) that aimed at studying new ways to assess tumor burden through volume based PET parameters, found that higher metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were significantly associated with a higher incidence of III-IV Ann Arbor stages, B-symptoms, hypo-albuminemia, lymphopenia, and higher IPS n the univariate survival analysis. PFS was significantly influenced by MTV (p= 0.007) and TLG (p= 0.003) but not the Ann Arbor stage , Sensitivity was 100%, 100%, 81%, 57%, and 26% for MTV,TLG, SUVmax, Ann Arbour staging, and interim PET/CT, respectively. Specificity was 29%, 32%, 42%, 47%, and 93%, respectively.

Positive predictive value was 27%, 28%, 27%, 22%, and 50%, they concluded that TLG or the combination of all three parameters (SUVmax, TLG, and MTV) significantly improved the HL risk assessment when compared to Ann Arbour staging [(11)].

Heek et al. reported in prospective study that included 107 patients diagnosed with HL aimed to investigate the predictive value of MTV and TLG PET/CT based parameters, measured at different threshold methods (SUV4.0, SUV41% and $SUV140\%_{L)}$ and then performed ROC curve analysis to assess the predictive impact of these parameters in predicting an adequate interim therapy response with PET negativity after 2 cycles of chemotherapy, they concluded that MTV and TLG do have a predictive value after two cycles ABVD in early stage Hodgkin lymphoma, particularly when using the fixed threshold of SUV4.0 for MTV and TLG calculation [(12)].

Song et al. reported in a retrospective study that included 127 patients with initial diagnosis with HL aimed to investigate the prognostic value of MTV PET/CT based parameters in assessment of response to 2 different types of therapy, 61 patients received 6 cycles of ABVD only and the other group of 61 patients received CMT (involved-field radiotherapy after 4–6 cycles of ABVD). The MTV was delineated on PET ⁄ CT by the threshold ≥SUVmax, 2.5. The calculated MTV cut-off value was 198 cm3. Clinical outcomes were compared with several prognostic factors. Older age, B-symptoms and MTV were significant independent prognostic factors. Survival of high MTV groups treated with ABVD only and CMT were lower than the group with low MTV values (PFS, P< 0.012; OS, P< 0.045). They concluded that MTV would be helpful for deciding different therapeutic modalities in patients with early-stage Hodgkin's lymphoma [(13)].

CONCLUSION:

Prognostic PET/CT parameters including SUV Max, MTV and TLG have influence in both early assessment of response and survival in paediatric lymphoma.

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