Editorial, PET/CT.

Prognostic Value of Volume Based Parameters of PET/CT in Malignant Lymphoma.

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ABSTRACT:

[18]F FDG PET/CT has long been the corner stone for staging. It resulted in upstaging of up to 20 % of patients. Its main advantage is that it can detect metabolic changes in involved areas long before structural changes become visible. Furthermore, it's the main stay for evaluating therapeutic response especially in situations where CT has very limited role as differentiating viable residual from necrotic/fibrotic lesions and detecting nature of small lesions.

Of all semi quantitative parameters of ^{18}F FDG PET/CT, SUV max has always been the leading parameter for Nuclear Medicine. However it doesn't represent the whole tumour metabolic burden because it's only measured from single voxel and therefore it's sensitive to image noise which is impacted by patients characteristics and imaging parameters.

Recently, researchers have been minded by Metabolic Tumour Volume (MTV), which is measurement of tumour volume with a high metabolism, and Total Lesion Glycolysis (TLG), which is the product of mean SUV and MTV. Recent studies suggest that MTV and TLG are more inclusive parameters that better present the whole Metabolic Tumour Burden than SUV max, but with a limitation point that these parameters require accurate segmentation of the tumour and standardization of tumour segmentation. These studies suggest usefulness of MTV and TLG for expectation of treatment response, prognosis of clinical outcome, tumour delineation for radiotherapy planning, however there's no consensus on optimal way to measure MTV using ^{18}F FDG PET/CT.

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INTRODUCTION:

^{18}F-FDG PET/CT scan has been extensively utilized in the managing of malignant lymphoma patients and there is an increasing evidence of the prognostic significance of PET/CT parameters.

SUV max is the most frequently used relatively because of the suitability and great reproducibility of measurement. It reveals the metabolic activity of the most aggressive tumor cell [1].

Although, MTV and TLG can reveal more information than SUV max and rising evidences have specified their possible significance. Lately, many researches have verified the prognostic value of volume-based parameters in multiple tumors, such as pleural mesothelioma, small lung cell cancer [2].

Cottereau et al., reported in a prospective study that included 258 patients initially diagnosed with early stage Hodgkin's Lymphoma the predictive value of baseline ^{18}F-FDG PET/CT TMTV and interim ^{18}F-FDG PET/CT response after two cycles of chemotherapy assessed with Deauville score. Patients having a high TMTV (>147 cm3) had significantly shorter progression free survival (PFS) and overall survival (OS).

Patients with baseline ^{18}F-FDG PET/CT high TMTV had significantly worse outcome of a 5-year PFS and OS of 71% and 83% vs 92% and 98% for patients with a lower baseline ^{18}F-FDG PET/CT TMTV [3].

Prognostic Value of Volume Based Parameters:

Akhtari et al., assumed that 3-dimensional measurements of tumor burden measured on baseline ^{18}F-FDG PET/CT scans, such as MTV and TLG, might more precisely risk stratify patients. They evaluated 267 patients with a median follow up of 4.96 years, of which 27 patients had relapsed or were diagnosed with a refractory disease and 12 died. They stated that baseline ^{18}F-FDG PET/CT TMTV and TLG interrelated significantly with freedom from progression (FFP); patients having TMTV >268 and TLG >1703 in their study group had worse FFP rates, shorter FFP times, and were more expected to harbor bulky disease and staged as IIB advanced disease [4].

Moskowitz et al., demonstrated the essentiality of prognostic factors for patients with relapsed/refractory Hodgkin's disease used to optimize therapy with risk-adapted approaches.

They assessed quantitative ^{18}F-FDG PET/CT parameters in PET/CT adapted salvage therapy with brentuximab vedotin (BV) and augmented ifosfamide, carboplatin, and etoposide (augICE).

Transplant-eligible patients diagnosed with relapsed/refractory HL were treated with 2 or 3 cycles of weekly BV; patients with negative ^{18}F-FDG PET/CT results (Deauville score ≤2) continued to autologous stem cell transplantation (ASCT) while patients with positive ^{18}F-FDG PET/CT results were further treated with augICE prior to ASCT. They obtained MTV and TLG from baseline, after BV, and after augICE ^{18}F-FDG PET/CT scans. They stated that baseline ^{18}F-FDG PET/CT TMTV and refractory disease were independent prognostic factors for event free survival (EFS). Moreover, they improved the prognostic power of pre-ASCT ^{18}F-FDG PET/CT scan [5].

On the contrary, *Mettler et al*., in a retrospective study including 310 patients with baseline ^{18}F-FDG PET/CT scans available stated that baseline ^{18}F-FDG PET/CT scan TMTV unsuccessfully predicted PFS and OS in patients diagnosed with advanced-stage Hodgkin lymphoma patients.

Hence interim ^{18}F-FDG PET/CT scan therapy response assessment cannot be omitted for further adaption of therapy [6].

Rossi et al., conducted a retrospective study of 59 patients initially diagnosed with Hodgkin's disease, in which they demonstrated that semi quantitative analysis of baseline and interim ^{18}F-FDG PET/CT scans response using SUV max reduction (ΔSUV max) is superior to visual analysis centered on the 5-point Deauville score criteria. The visual analysis resulted in an excess of observer positive findings leading to an unreliable positive predictive value for therapy failure. SUV max calculation seems to be less subjective and aids in differentiating positive results that might be associated with significant residual lymphoma, leading to an improved prognostic significance.

However, SUV max calculation might also result in false positive results. This happened in 3 patients, whom baseline SUV max was low, resulting in a SUV max lower than a predefined cutoff value. They concluded that semi quantitative analysis appears to be a worthy method for early stratification of patients who might benefit from other treatment regimens [7].

Vercellino et al., analyzed 301 baseline ^{18}F-FDG PET/CT scans for patients initially diagnosed with DLCBCL and concluded that, by using multivariate analysis, baseline TMTV and Eastern Cooperative Oncology Group Performance Status (ECOG PS) were independently correlated with PFS and OS. They stated that, even in patients responding after 2 cycles of chemotherapy, high baseline ^{18}F-FDG PET/CT scan TMTV was a strong prognosticator of lower PFS and OS. Additionally, TMTV along with ECOG performance status may possibly classify an ultra-risk in diffuse large B cell lymph's (DLBCL) patient [8].

Cottereau et al., evaluated prognostic value of MTV in baseline ^{18}F-FDG PET/CT in a retrospective study including 108 patients initially diagnosed with Peripheral T-Cell Lymphoma (PTCL). They stated that high baseline TMTV was remarkably related with an inferior prognosis with two years PFS 26 % versus 71 % in patients having low baseline TMTV, while OS was 50% versus 80%, respectively. In multivariate analysis, they concluded that TMTV obtained from baseline ^{18}F-FDG PET/CT scan was the solitary significant independent parameter for both PFS and OS. Baseline TMTV associated with prognostic index for T-cell lymphoma (PIT) stratified high risk patients even well than baseline TMTV only. They settled that baseline TMTV seems to be an independent prognosticator of PTCL outcome, accompanied with PIT, they might discriminate different risk groups at initial diagnosis [9].

Liang et al., analyzed ^{18}F-FDG PET/CT scans of 48 patients initially diagnosed with Follicular Lymphoma (FL). Upon performing a multivariable analysis, they found that TMTV and TLG were both independent prognosticators of progression free survival and overall survival. ROC curve analysis showed the optimal cut-off values for ΔTMTV and ΔTLG were 66.3% and 64.5 % respectively. Their publication stated that baseline ^{18}F-FDG PET/CT scans TMTV and TLG are significant predictors of PFS and OS in FL. Moreover, interim ^{18}F-FDG PET/CT scan TMTV (ΔTMTV more than 66.3%) and TLG (ΔTLG more than 64.5%) reduction are appreciated parameter that may predict early therapy response evaluation in FL patients [10].

Itti et al., retrospectively analyzed 114 patients initially diagnosed with DLBCL. Their baseline and interim ^{18}F-FDG PET/CT scans were interpreted using the Deauville five points scoring system and SUV max between baseline and interim PET/CT was calculated.

They inferred the inferiority of interim ^{18}F-FDG PET/CT scan when evaluated using only the Deauville five point scoring system. Even though the Deauville five point scoring system is a valid tool for evaluating prognostic significance of interim ^{18}F-FDG PET/CT scan in DLBCL, calculation of the ΔSUV max leads to an improved performance, inter-observer reproducibility, and ought to be preferred to if a baseline ^{18}F-FDG PET/CT scan is available [11].

Shagera et al., conducted a retrospective study encompassing 103 patients initially diagnosed with DLBCL. Every patient's baseline ^{18}F-FDG PET/CT scan was evaluated using several metabolic parameters including TMTV and SUV max. They established that patients having low baseline TMTV (less than 249 cm3) had a three years progression free survival rate of 83% and overall survival rate of 92%, contrary to 41% and 57%, respectively, in patients having high baseline TMTV (higher than 249 cm3). On performing a univariante analysis, they found that high TMTV associated with National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) ≥4 were accompanied by worse PFS and OS as well as a high TLG value. In the multivariate analysis, they found that baseline TMTV associated with NCCN-IPI were independent prognostic factors of PFS and OS. They mentioned that baseline TMTV has the ability to segregate patients a high risk NCCN-IPI of ≥ 4 into two different clusters with remarkably diverse outcomes; patients having low baseline TMTV had a three years PFS rate of 75% and an OS rate of 88%, whereas patients having a high baseline TMTV had a three years PFS rate of 32% and an OS rate of 47%.

Accordingly, the association of baseline TMTV along with National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) might improve the predictive value and might be a supportive guide for an intensive treatment regimen [12].

Ceriani et al., conducted a cohort study including 103 patients initially diagnosed with Primary Mediastinal B cell Lymphoma (PMBCL). They observed the prognostic impact of functional parameters, including SUV max, MTV, and TLG, attained from baseline ^{18}F-FDG PET/CT scans at initial diagnosis. They claimed that, using univariante analysis, elevated MTV and TLG were significantly related to inferior PFS and OS. Only TLG maintained its statistical significance for both OS and PFS in the multivariate analysis.

The five years OS rate was 100% in patients having low baseline TLG vs 80% for those having high baseline TLG, while PFS was 99% vs 64%, respectively. They concluded that TLG obtained on baseline ^{18}F-FDG PET/CT scan seemed to be an influential predictor of PMBCL outcomes [13].

CONCLUSION:

Prognostic value of volume based parameters of PET/CT in Malignant Lymphoma using TMTV and TLG are independent predictor of survival in malignant lymphoma especially in high-risk patients and may be an influential predictor of lymphoma outcome.

REFERNCES:

1. *Freudenberg LS, Antoch G, Schütt P, et al.* FDG-PET/CT in re-staging of patients with lymphoma, Eur J Nucl Med Mol Imaging. 31: 325 – 329; 2004.

2. *Zhou M, Chen Y, Huang H, et al.* Prognostic value of total lesion glycolysis of baseline 18F-fluorodeoxyglucose positron emission tomography/computed tomography in diffuse large B-cell lymphoma, Oncotarget. 7(50): 83544 – 83553; 2016.

3. *Cottereau A, 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. 131 (13): 1456 – 1463; 2018.

4. *Akhtari M, Milgrom SA, Pinnix CC, et al.* Reclassifying patients with early-stage Hodgkin lymphoma based on functional radiographic markers at presentation, Blood. 131 (1): 84 – 94; 2.018.

5.   *Moskowitz A, Schöder H, Gavane S, et al.* Prognostic significance of baseline metabolic tumor volume in relapsed and refractory Hodgkin lymphoma, Blood. 130 (20): 2196 – 2203; 2017.

6.   *Mettler J, Müller H, Voltin CA, et al.* Metabolic Tumour Volume for Response Prediction in Advanced-Stage Hodgkin Lymphoma, J. Nucl. Med. 60: 207 – 211; 2019.

7.   *Rossi C, Kanoun S, Berriolo-Riedinger A, et al.* Interim ^{18}F-FDG PET SUVmax reduction is superior to visual analysis in predicting outcome early in Hodgkin lymphoma patients, J. Nucl. Med. 55(4): 569 – 573; 2014.

8.   *Vercellino L, Cottereau AS, Casasnovas O, et al.* High total metabolic tumor volume at baseline predicts survival independent of response to therapy, Blood. 135(16): 1396 – 1405; 2020.

9.   *Cottereau AS, Becker S, Broussais F, et al.* Prognostic value of baseline total metabolic tumor volume (TMTV0) measured on FDG-PET/CT in patients with peripheral T-cell lymphoma (PTCL), Ann. Oncol. 27(4): 719 – 724; 2016.

10.   *Liang JH, Zhang YP, Xia J, et al.* Prognostic Value of Baseline and Interim Total Metabolic Tumor Volume and Total Lesion Glycolysis Measured on ^{18}F-FDG PET-CT in Patients with Follicular Lymphoma, Cancer Res. Treat. 51(4): 1479 – 1487; 2019.

11.   *Itti E, Meignan M, Berriolo-Riedinger A, et al.* An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and ΔSUV max, Eur. J. Nucl. Med. Mol. Imaging. 40(9): 1312 – 1320; 2013.

12.   *Shagera QA, Cheon GJ, Koh Y, et al.* Prognostic value of metabolic tumor volume on baseline ^{18}F-FDG PET/CT in addition to NCCN-IPI in patients with diffuse large B-cell lymphoma: further stratification of the group with a high-risk NCCN-IPI, Eur. J. Nucl. Med. Mol. Imaging. 46 (7): 1417 – 1427; 2019.

13.   *Ceriani L, Martelli M, Zinzani PL, et al.* Utility of baseline 18FDG-PET/CT functional parameters in defining prognosis of primary mediastinal (thymic) large B-cell lymphoma, Blood. 126(8): 950 – 956; 2015.