Dmax: a simple and reliable PET/CT-derived new biomarker of lymphoma outcome?

Running Title: New PET biomarker in HL ?

Key words: 18FDG-PET/CT; HL; Dmax; PET metrics; prognostic models

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Number of words

Body text	1149 words
Tables	0
Figures	0
References	19

No abstract.

Prognostic stratification of lymphoma patients is an important factor for treatment selection in a modern personalized medicine approach. E.g., early identification of the patient at high risk of treatment failure may drive the choice of more aggressive therapeutic strategies that can guarantee a more effective treatment of the disease. This therapeutic approach defined as "risk-adapted strategy" can only benefit from the increasingly precise biological characterization of lymphomas. For this reason, the selection of new biomarkers is a field of active research.

In the last years, positron-emission tomography/computed tomography with 2-deoxy-2-fluorine-18-fluoro-D-glucose (18FDG-PET/CT) has emerged as a powerful prognostic tool, which contributed to an effective and reliable improvement in the staging of FDG-avid lymphomas as well as in the assessment of their response to treatment. Indeed, a complete metabolic remission in PET/CT scans after the end of treatment is nowadays the best outcome predictor in lymphoma patients [1,2]. Moreover, the interim 18FDG-PET/CT scans during treatment also have a prognostic impact and PET/CT response-adapted treatment algorithms drive the current management of Hodgkin lymphoma (HL)[3,4].

Increasing evidence has then suggested that baseline PET quantitative parameters, mainly the metabolic tumor volume (MTV) and the total lesion glycolysis (TLG), can be reliable early predictors of patient outcome. Several studies demonstrated the value of TLG and MTV in the prognostic stratification of HL and aggressive non-HL [5-7], although the lack of technical standardization in their measurement has prevented till now their integration in the clinical setting[8].

More recently the application of the radiomic analysis has increased the number of achievable PET quantitative parameters and consequently the possibility to explore new predictive biomarkers [9]. The metabolic heterogeneity and the maximal distance between the two farthest lesions (Dmax) have emerged as new promising predictors of Progression Free (PFS) and Overall Survival (OS) in patients with lymphomas [10,11].

These two parameters have been proposed substantially as complementary biomarkers to MTV. Their combination with MTV in predictive models showed a significant improvement of the prognostic value of the only tumor burden estimation (by MTV) [12-14].

The study published by Durmo et al. [15] tested the capacity of Dmax to predict treatment outcome in a retrospective cohort of patients with classical HL treated with ABVD regimen confirming the prognostic role of this biomarker in this type of lymphoma. In a multivariate analysis including the most common clinical parameters and baseline PET metrics (MTV, TLG and SUVmax), Dmax resulted the only independent predictor of PFS.

The higher predictive value of Dmax with respect to MTV has not usually emerged from the prior studies investigating Dmax. Hence, this finding needs further validations in other large cohorts of HL patients. However, regardless of its prognostic superiority as an individual parameter over volume-based PET metrics, some recent studies demonstrated -in both Hodgkin and non-Hodgkin lymphoma cohorts- that combining Dmax with texture features or clinical characteristics may lead to better predictive models compared to the only MTV [13,16-18].

Moreover, Durmo et al.[15] reported a maintained high predictive value of Dmax when combined with interim PET (iPET) results. In particular a high Dmax value identified a subgroup of patients with negative iPET (i.e.,Deauville score 1 to 3 after 2 cycles of therapy), who despite the early metabolic remission have an increased risk of relapse.

In a similar model, thus far presented only as a meeting report [18], the combination of elevated Dmax and a poor international prognostic score (IPS) identified (among 331 patients with negative iPET after 2 cycles of ABVD, treated in the GITIL/FIL HD0607 clinical trial) a subset of 103 (31%) patients with a reduced 3-year PFS of 72% (95% CI, 65-82%). The 3-year PFS in the entire cohort was 84% (95% CI 81% to 87%)[18]. Notably, the estimation of Dmax was done with a different methodology compared to Durmo et al.[15]. Interestingly, in the same GITIL/FIL HD0607 cohort, a model based on the combination of MTV and IPS was previously reported to discriminate a smaller poor-risk subset of 23 patients (7%), with a 3-year PFS of 56% (95% CI, 39-81%)[19]. A direct comparison of the two models has not yet been published but these findings may further indicate that Dmax and other volume-derived PET metrics may have a complementary value for outcome prediction.

Dmax seems to propose again the dissemination of the disease as a pivotal factor in the prognostic stratification of lymphomas. Overall, PET metrics seems outperforming the standard Ann Arbor classification. However, although a promising biomarker, Dmax (as well as most quantitative PET parameters) needs further methodology refinement before any routine use.

There are critical not resolved issues. First, Dmax can be applied only in cases with more than one lesion, excluding from the analysis a significant proportion of patients (14% of the initial population selected in the study of Durmo et al.). This, besides limiting its usefulness, does not allow a complete and real comparison between Dmax and the other parameters that can be estimated in all patients. Comparative analyses should be performed including also patients with a single lesion, setting their Dmax value to 0.

Moreover, the reproducibility of Dmax values is not as straightforward as it might appear. The proposed method for calculating Dmax based on the distance between the centroids of the two most distant lesions seems to make its calculation easy and independent of the different segmentation methods applied to estimate lesion volumes[11]. This may represent an undeniable advantage over other PET metrics. However, different segmentation algorithms may respectively exclude or include small lesions that could change the distribution of disease, the maximum distance between lesions and, thus, the Dmax value itself. Therefore, the calculation of Dmax is also affected by the methodology used for PET volume segmentation and could benefit from effective standardization of this procedure[8].

Finally, Dmax was initially proposed as the absolute distance between the two farthest lesions[11]. Subsequently, some works have shown a better performance of the same parameter normalized to body size using the body surface area (BSA) as standardization factor[13,16]. The harmonization of the parameter definition would hopefully allow a better comparison and reproducibility of the results of different studies and the generation and validation of prognostic models with high positive and negative predictive value that may help treatment tailoring also in the routine clinical setting.

In conclusion, this interesting study proposed the early definition of a risk-adapted therapeutic strategy in classical HL based on Dmax, a measure of the distance between the two farthest lesions in the individual patient.

As noted by the authors, these preliminary results should be considered as a proof of concept of the prognostic utility of this PET biomarker of tumor dissemination, which otherwise warrants further studies for its methodological refinement and clinical validation.

Nevertheless, Durmo's findings are in line with several other studies that make increasingly credible the hypothesis that once the unresolved problems of standardization and reproducibility are eventually settled, a PET-based distinction between localized and extensive disease could replace the current staging system.

Authorship Contributions

L. Ceriani E. Zucca analyzed the data, wrote the manuscript, and shared final responsibility for the decision to submit.

Conflict of interest

All authors declare no competing interests that are related, directly or indirectly, to the present commentary.

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