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In search of a platinum metre bar to measure metabolic tumor volume in lymphoma.

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In the present manuscript Barrington and Meignan report the outline of an international project aimed to reach a consensus among experts on a possible standardization of Metabolic Tumor Volume (MTV) computing, with the scope of providing clinicians with a strong and reproducible biomarker to predict the lymphoma treatment outcome [*1*]. As a matter of fact MTV turned out as a very strong predictive tool whatever the tumor segmentation method is used and in the different lymphoma subtype (till now) considered. Nonetheless, though all the studies so far published in different lymphoma subtypes invariably conclude that MTV has a strong predictive role on treatment outcome, several methodological flaws such as retrospective designs, small sample sizes, heterogeneity of populations, different software for Standardized Uptake Value (SUV) thresholding and tumor segmentation and different methods for physiological uptake subtraction substantially limit the reproducibility of the results. Therefore MTV is still very far from being used in daily clinical practice for a risk-adapted therapeutic strategy in precision medicine. . This unusually high predictive value of this quantitative PET-derived biomarker across all the above studies is interpreted as a typical result of a continuous variable, such as Lactate Dehydrogenase (LDH) or beta2-microglobulin. As a matter of fact, Ceriani et al reporting the value of MTV and TLG in predicting treatment outcome in primary mediastinal B-cell lymphoma found that "The analysis of Q-PET parameters as a continuous variable showed that a significantly higher risk of progression was associated with an increase of MTV"[*2*]. However, beside all the above methodological limitations, all the caveats of quantitative readout of PET/CT images exploiting SUV as an absolute variable remain a hurdle toward MTV reproducibility. This has been efficaciously commented by Shoder in this way: "it is unknowable whether the same TMTV would have been calculated if the same patient, under the same biologic conditions, would have undergone PET imaging on two different scanners" [*3*].

The clinicians will favorably accept standardization and prospective validation of a "gold standard" for MTV computing in lymphoma, as the latter could potentially affect or change the standard of care of several lymphoma subsets. In early stage Hodgkin Lymphoma (HL), for example, Cottereau et al showed that MTV was able to identify a smaller subset of patients compared to the unfavorable group of the H10 trial with an even worse prognosis among patients enrolled in the standard arm of the H10 trial treated with ABVD treatment plus involved field radiotherapy [*4*]. These results are so important that they could potentially impact the standard of care of early stage HL, where constant efforts are ongoing to assess the feasibility and safety of omitting radiotherapy to reduce its long-

term effects of treatment-related morbidity and mortality. A similar scenario but with opposite aim could be sketched for a risk-adapted frontline therapeutic strategy of follicular lymphoma, as patients with a high MTV at baseline and a high Follicular Lymphoma Prognostic Index-2 (FLIPI-2) do show a 5-Y PFS of 20% with an HR of 5.0 compared to patients with low MTV and low FILIPI-2 [*5*]. On the contrary, the predictive value of MTV is less evident in Diffuse Large B-Cell Lymphoma (DLBCL) for several reasons [*6*], but mainly because of the mounting evidence that under the broad category of DLBCL, a number of diseases harbor with different genotype, heterogeneous clinical behavior and different response to immunochemotherapy [*7*]. Nonetheless, a very good correlation was preliminarily shown in DLBCL between MTV and cell-free circulating DNA (Alizadeh AA, data not published). Different by tumor burden assessment with traditional radiological tools, MTV assessment with functional imaging with FDG-PET/CT allows for correlation with lymphoma physiopathology and clinical behavior. MTV, in fact, does not merely represent tumor burden, but it recapitulates also the reactivity of the host immunity against the tumor, as shown in HL, where the host immunoreactive cells present in the microenvironment account for the majority of the cellularity present in the tumor sample [*8*], or in non-small cell lung cancer, where PD-1+ positive Tumor Infiltrating Lymphocytes (TIL) showed a very high glycolytic activity and a great affinity for FDG [*9*]. MTV combined with other biomarkers such as tumor dissemination assessed by a radiomics technique superseded MTV alone in predicting treatment outcome in DLBCL [*10*].

All the above obstacles have been debated during the Paris meeting cited by the authors in their paper, and people participating to this meeting agreed on the following roadmap:

1) Collecting a fixed number of PET/CT scan images of baseline staging in HL, FL and DLBCL treated with standard therapy and fulfilling the prerequisite for PET scanning, according to the European Association of Nuclear Medicine (EANM) guidelines. The images will be then uploaded in the web site of the study and sent to the study Core Lab.
2) In the core lab, images will be first checked for compliance to standard quality and will be then distributed to a panel of nuclear medicine experts, representing different cooperative groups, who will perform MTV delineation according to their experience and using their preferred software. A consensus workshop will be held afterwards to discuss case per case the criteria for MTV computing in nodal and extranodal areas including rules for region pre-selection based on SUV threshold and threshold-volumes of clusters, removal of physiological uptake, removal/addition of

regions using easy-to-define criteria, and special criteria for assessing MTV in bone marrow and spleen.

3) The final results of the segmentation consensus, the "platinum standard MTV" (PSM) obtained by consensus agreement both in training and validation sets will be kept in the core lab and not disclosed to anyone. Both images and PSM of training set will be distributed publicly. The images of the validation set will be distributed on demand to guest institution that will agree to participate to the project, while the PSM values calculated in the validation set will not be disclosed.
4) The medical imaging experts of the guest institutions will compute MTV of the training set, with an open access to the PSM, thus having the chance of verifying and tuning their segmentation approach.
5) They will hence compute MTV in the validation set and will post their segmentation results to the core lab. The latter will assess the obtained MTV results and will provide the guest institutions with a final report.

The present roadmap for reaching an international agreement on a procedure for tumor segmentation and MTV computing in lymphoma could look somehow cumbersome at a first glance, but the search for a standard reference (the so called platinum bar) for measuring MTV is compelling and cannot longer be delayed.

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REFERENCES

1) Barrington SF, Meignan MA Time to prepare for risk adaptation in lymphoma by standardising measurement of metabolic tumour burden. *J Nucl Med.* 2019 Apr 6. pii: jnumed.119.227249. doi: 10.2967/jnumed.119.227249. [Epub ahead of print]
2) Ceriani L.,Martelli M, Zinzani PL et al. Utility of baseline 18FFDG-PET/CT functional parameters in defining prognosis in primary mediastinal (thymic) large B-cell lymphoma. *Blood* 2015; 126 (8), 950-56.
3) Schoder M: Metabolic tumor volume in lymphoma: hype or hope? *J Clin Oncol* 2016; 34(30), 3591-4.
4) 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: 1456-63.
5) Meignan M, Cottereau SA, Versari A. et al Baseline metabolic tumor volume predicts outcome in high-tumor burden follicular lymphoma : a pooled analysis of three multicenter studies. *J Clin Oncol* 2016; 34:3618-26.
6) Cottereau AS, Buvat I, Kanoun S Is there an optimal method for measuring baseline metabolic tumor volume in diffuse large B cell lymphoma? *Eur J Nucl Med Mol Imaging.* 2018 Jul; 45:1463-1464.
7) Schmitz R, Wright GW, Huang DW, Johnson CA, Phelan JD, Wang JQ et al.: Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2018 Apr 12; 378: 1396-1407.
8) Küppers R, Engert A, Hansmann ML: Hodgkin lymphoma. *J Clin Invest.* 2012 Oct 1; 122: 3439–3447.
9) Lopci E1, Toschi L2, Grizzi F3et al. Correlation of metabolic information on FDG-PET with tissue expression of immune markers in patients with non-small cell lung cancer (NSCLC) who are candidates for upfront surgery. *Eur J Nucl Med Mol Imaging.* 2016 Oct;43: 1954-61.
10) Cottereau AS, Nioche C, Dirand AS et al.: 18F-FDG PET dissemination features in diffuse large B-cell lymphoma are prognostic of outcome. *JNUMED/2019/229450,* submitted.