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LETTER TO THE EDITOR

Is there an optimal method for measuring baseline metabolic tumor volume in diffuse large B cell lymphoma?

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Dear Editor,

We thank the authors of this letter [1] written in response to our publication [2] for their interest and for engaging in the discussion about this important topic. Dr. Cottereau et al. [1] reiterate the key message from our publication that metabolic tumour volume (MTV) is a strong predictor of prognosis irrespective of the method; however, cut-offs used to divide patients into high and low risk groups by MTV are highly dependent on the patient population and the method used.

The authors indicate that their objective was to discuss the strengths and weaknesses of each segmentation method, which was the purpose of our study. However, they do not conclude that there is an optimal method yet, and indeed the letter's title seems to suggest that there is not one. We concur that all methods have strengths and limitations and estimate prognosis well, but it is important to reiterate that the widespread adoption of MTV into routine practice will rely on two main factors; the ease of use and reproducibility of the methods between observers. We attempted to evaluate the first point in our study, and Dr. Cottereau et al. raised the second issue in their letter, i.e., the high dependency of the 41% method on VOI selection process, which can result in differences in results between observers.

We would like to answer some of the specific points raised in the letter. The cut-offs we reported using SUV ≥ 2.5 are in line with those reported by other groups [2]. The median value using the liver threshold (PERCIST) to measure MTV was 443cm^3 in our study. The median using the liver threshold for MTV stated in the letter by Dr. Cottereau et al. [1], from a presentation by Dr. Kostakoglu et al. at a recent meeting [3] measuring MTV in the GOYA study in patients with DLBCL, was 336cm^3. We note there were more patients with higher IPI and worse performance status in our study than in the report from the main GOYA study [4]. The median MTV we reported using the 41% cut-off is lower than the other studies quoted, as is the optimal cut-off [1]. We acknowledge the experience of the group of Dr. Cottereau et al., who have undertaken these analyses using different software [5], but as stated in our manuscript 'the variability in the cut-offs reported for the 41% method raises concerns that the optimal cut-off may be more dependent on how regions are selected by different groups, when there is considerable tumour heterogeneity'.

The software used clearly has an impact on the computation of MTV [5]. The software we used depended on a region growing approach using 'point-picking' by the observer of tumour for the SUV2.5 and the 41% methods (Hermes Hybrid Viewer 3D, Hermes Medical Solutions AB, Stockholm, Sweden). This has an advantage compared to a fully automated method because only pixels around the tumour above the specified cut-off are selected, meaning areas with high physiological uptake can often be avoided. However, if the tumour lies in close proximity to brain, heart, or urinary system, areas of physiological uptake need to be manually edited. The number of tumour regions selected and the degree of editing depends on the extent and distribution of disease. Figure 6 in our publication showed a patient scan where outlining was quick for the SUV 2.5 method, as a click in the middle of the large and very intense mediastinal mass selected all visible tumour; a second click selected the mass adjacent

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to the psoas muscle. There was limited editing required of physiological uptake. Outlining in this illustrative example was more complex using the 41% method, as the observer had to divide the mediastinal mass into several regions then constrain the subregions to avoid missing areas of tumour. This is recommended by the group of Prof Meignan, Dr. Cottereau et al. where counts within a mass vary by more than 10% [6]. On the other hand, the Hermes software used a fully automated approach for the liver [PERCIST] method, which had the advantage of selecting all pixels (tumour and non- tumour) above a particular cut-off, with no interaction by the observer to select tumour regions. However, this typically includes some physiological uptake, and editing is always required to delete physiological structures compared with a 'point picking' approach. Nonetheless, we tried to give the reader an appreciation of what was involved by timing how long outlining took using the different methods for 50 patients selected across the range of MTV values. A structured approach to determine what method works best for the majority of patients across multiple software platforms is needed. We have attempted to evaluate various methods using our routine reporting software in this report.

We recognise that partial volume may influence tumour outlining; nonetheless, the SUV2.5 method and other methods worked well to measure MTV in a representative population of consecutive patients at a single institution receiving standard treatment. A higher threshold than SUV2.5 may work better with newer reconstruction methods. The influence of uptake time, different cut-offs, and newer reconstruction methods requires further work.

With regard to the comment on statistical analysis, none of the MTV calculations revealed a normal distribution, so a non-parametric approach was used for the Bland–Altman plots. In this manner, the limits of agreement are not necessarily symmetrical, and though we did not have the sample size to explore it, it is very possible these vary with MTV. In addition, our interpretation of the good agreement between the software also took into account the high intraclass correlation coefficient and Kendall's tau (Table 2 in [2]).

We strongly support the need for better automated methods, improved delineation, and cooperative studies. We are pleased that our work has stimulated the debate and opened up the field with regard to the need to explore different methods for tumour segmentation in lymphoma patients.

Yours faithfully,

Hajira Ilyas, N George Mikhaeel, Joel T Dunn, Fareen Rahman, Henrik Møller, Daniel Smith, and Sally F Barrington.

Compliance with ethical standards

Ethical approval Patient data were extracted from case records and reviewed only by members of the responsible clinical team, in compliance with the UK Data Protection Act; consequently, specific Research Ethics Approval and individual patient consent were not required.

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