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EDITORIAL COMMENTARY

# Baseline metabolic tumour volume in Hodgkin lymphoma: the prognostic value of accessory cells

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At the present time Hodgkin lymphoma (HL) can be cured in more than 80 % of all patients [1]. Over 90 % of patients with early-stage HL are cured with contemporary combined-modality therapy, but there are still 25 – 30 % of patients with advanced-stage disease who are not cured with the ABVD regimen alone [1, 2]. The International Prognostic Score (IPS) fails to recognize these patients with a high risk of treatment failure since the range of outcomes it delineates has narrowed with treatment improvement [1]. Although clinical prognostic scores continue to be routinely used, the need to identify patients with poorer risk has focused research on the tumoral microenvironment to find valuable prognostic information. Indeed, the tumour tissue in HL is composed of a few scattered neoplastic cells called Hodgkin and Reed-Sternberg (HRS) cells, which account for less than 1 % of all the cells found in biopsy specimens, that are surrounded by an overwhelming population of nonneoplastic mononuclear bystander cells. These cells (CCR4-expressing cell subsets, including eosinophils, histiocytes, macrophages, plasma cells, and Th2 and Treg lymphocytes) are recruited by chemokines produced by the HRS cells and induce the expression of antiapoptotic proteins in HRS cells and their immortalization via a paracrine loop [3, 4]. There is an intimate relationship between the HRS cells and reactive cells of the microenvironment that enables the tumour to thrive and evade immune surveillance. Some recent studies have suggested a prognostic role for the nonneoplastic surrounding cells.

In classic HL (CHL) tumour-associated macrophages (TAMs) have been shown to be associated with inferior outcomes [5]. Steidl et al. showed that a macrophage gene expression signature is associated with primary treatment failure in CHL and subsequently showed, using an independent validation cohort, that an increase in CD68-positive macrophages in the microenvironment is associated with inferior outcomes [5]. In the E2496 Intergroup trial, a multicentre phase 3 randomized controlled trial comparing ABVD and Stanford V chemotherapy in 287 patients with locally extensive and advanced stage CHL, increased CD68 or CD163 expression was significantly associated with inferior 5-year failure-free survival (FFS; 64 % vs. 78 % and 63 % vs. 82 %) and 5-year overall survival (OS; 81 % vs. 94 % and 81 % vs. 96 %). Multivariate analysis with clinical and biological factors linked to FFS (lymphocyte count, stage 4 disease) and OS (age ≥45 years) showed that increased CD68 or CD163 expression are significant independent predictors of inferior FFS and OS [6]. However, prognostic indices using these results in routine have not yet been built.

HL is a lymphoma showing FDG avidity with 100 % of patients positive at baseline, and FDG PET is currently the most accurate staging modality [7]. It has been shown that different mechanisms of glucose uptake, e.g. via GLUT1 in HRS cells and via GLUT3 in the microenvironment, contribute to PET positivity of the tumour [8]. In a recent study no correlation was found between GLUT1 expression in HRS cells and PET standard uptake values, and significant differences in progression-free survival (PFS) or OS between patients exhibiting different GLUT1 expression patterns could not be demonstrated. Indeed the surrounding mononuclear cells account for 99 % of the Hodgkin tumour and it has been shown that HL cell lines cultured in vitro were characterized by a very high metabolic activity [8]. This suggests that these environmental cells are responsible in vivo for the FDG uptake in baseline FDG PET scans. Therefore FDG PET when performed at baseline is chiefly a biomarker of the accessory cells in HL [4] as the signal coming from the HRS cells is overwhelmed and consequently the metabolic tumour volume

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computed from the FDG PET scan represents a volumetric estimate of the accessory cells.

In early-stage HL the presence of a bulky tumour is one of the risk factors recognized by the European Organization for Research and Treatment of Cancer/Lymphoma Study Association and the German Hodgkin Study Group. By contrast, in advanced stage disease bulk is not a risk factor in the IPS. This is not unexpected since bulk measurement is limited to the single largest mass and can underestimate a diffuse tumour burden. The tumour volume assessed at baseline on CT has been shown to have a prognostic impact and has been demonstrated to be the best predictor of early failure in patients with early-stage and advanced-stage disease being superior to the multiparameter IPS [9]. The measurement of the total metabolic tumour volume (TMTV) on baseline FDG PET gives more insight into the metabolic tumour burden by encompassing all invaded sites.

The paper by Kanoun et al. published in the current issue of EJNMMI is the first study exploring at baseline the prognostic value of the most active part of the TMTV in HL [10]. In 59 consecutive patients with HL of all stages (60 % stages III/IV) with a median follow-up of 50 months Kanoun and colleagues showed that the baseline TMTV with a cut-off of 225 $cm^3$ is highly predictive of PFS and disease-specific survival (DSS). Patients with a TMTV <225 $cm^3$ had significantly better 4-year PFS and DSS than did those with TMTV >225 $cm^3$ (85 % vs. 42 %, $p$=0.001, and 88 % vs. 45 %, $p$=0.0015, respectively). As expected TMTV >225 $cm^3$ was related to advanced disease with more frequent Ann Arbor stage IV. The methodology used in this paper for TMTV computation is highly reproducible (interobserver $\kappa$=0.9) and relies on EANM guidelines in using a fixed SUVmax threshold of 41 % for each individual tumour volume measurement [11, 12]. The volume computed corresponds to the part of the tumour with the highest SUV. Consequently it gives an index of TMTV linked to the portion of the tumour with maximal metabolic activity that in HL most probably reflects the accessory cells [11]. By contrast, in the few previously published studies analysing the impact of TMTV on outcome in HL the nonmetabolic part of the tumours was included in the delineation of the mean tumour volume. As correctly noted by Kanoun et al., in one study in which no prognostic impact of metabolic volume was found, for methodological reasons the necrotic part of the lesions were systematically included and the true SUVmax of the tumour was underestimated [13]. In the other study an absolute SUV >2.5 was used for volume delineation. This led to overestimation of the metabolic volume by including voxels from the background which in patients with stage I/II HL resulted in finding a median TMTV higher than the median reported by Kanoun et al. in patients with more advanced disease [14].

The second important and stimulating result of the study by Kanoun and colleagues is the impact on outcome of the combination of the baseline TMTV and the results of interim PET. All patients in the study also had a PET scan after two cycles of an anthracycline-based regimen. In the same series, Rossi has shown previously that the ΔSUVmax between baseline and after two cycles of chemotherapy with a 71 % cut-off is highly predictive of PFS [15]. Patients with a ΔSUVmaxPET0-2 >71 % had significantly better 4-year PFS than did those with ΔSUVmaxPET0-2 ≤71 % (82 % vs. 30 %, $P$<0.0001). Combining the TMTV and the ΔSUVmaxPET0-2 allowed the identification of three prognostic categories by splitting the high and low TMTV groups according to the quality of the response. The patients who had low TMTV with a fast response to treatment (ΔSUVmaxPET0-2 >71 %) had an excellent outcome with a 92 % 4-year PFS and 94 % DSS. By contrast patients with a high TMTV and a ΔSUVmaxPET0-2 ≤71 % had a poor outcome with a 20 % 4-year PFS and 20 % DSS. A third category included patients with other combinations of TMTV and early response who had an intermediate outcome (48 % 4-year PFS, 54 % DSS).

This integrated approach combining prognostic indices obtained from two examinations performed at two time points before and early in the course of therapy makes the most of the quantitative parameters that we can get from FDG PET [16]. TMTV measured on a baseline PET scan in HL is a biomarker of the activity of the microenvironment cells. The early response to treatment expresses the switch-off of activity of these cells under the first two cycles of chemotherapy and is an indirect surrogate of tumour chemosensitivity [17]. In this study both TMTV and ΔSUVmaxPET0-2 were independent predictors of outcome, and each had a strong prognostic value. Their combination improves the prognostic value of interim PET as has already been shown in other types of lymphoma [18] and allows the identification of 60 % of patients with a very low risk (6 %) of treatment failure and a very small group of patients with a particularly high risk (80 % of progression at 1 year). Interestingly, these parameters are obtained from relative and not absolute measurements: a SUVmax fixed thresholding method for TMTV and the percentage variation in SUVmax from ΔSUVmaxPET0-2. They are less sensitive to technical parameters such as PET physics corrections, data reconstruction and processing quantitation algorithms than methods using the absolute value of SUVmax and can easily be used in multicentre trials provided the same protocol is used for both PET acquisitions. In this regard, methods such as total lesion glycolysis or ΔTMTV between the baseline and posttreatment PET scans with similar SUVmax thresholds are strongly affected by technical errors.

In the study by Kanoun et al. TMTV is more relevant than tumour size in predicting outcome in HL even in patients with early stage disease, which was not unexpected. The presence of a bulky tumour of ≥10 cm has a lower predictive value for PFS and does not reach significance in predicting DSS, and

finally does not retain significance in predicting PFS in multivariate analysis in contrast to TMTV and ΔSUVmaxPET0-2. Whether TMTV could be included in the clinical scoring system to define risk categories better is a question which needs to be addressed in large prospective series of patients to determine the best cut-off. One of the main advantages of TMTV as measured in the study by Kanoun et al. over biological markers is that its prognostic value represents a global estimate of the activity of accessory cells when the level of CD68 or CD163 expression on immunohistochemistry (IHC) is limited to the biopsied material with a lower prognostic value for FFS [6]. Moreover, for biological markers the lack of reproducibility and inconsistency of manual or visual IHC scoring has been identified as a potential pitfall in their routine clinical use, and optimal and reproducible thresholds of expression need to be defined.

The stimulating study by Kanoun et al. pushes us to investigate the correlation between TMTV and the expression of TAMs to understand better the meaning of the metabolic volume in HL and to confirm that the baseline FDG PET signal is mainly related to accessory cells. The study has opened an exciting field by showing the possibility of defining a risk-adapted treatment strategy by integrating the data from a quantitative baseline PET scan and an interim PET scan.

## References


1. Moccia AA, Donaldson J, Chhanabhai M, Hoskins PJ, Klasa RJ, Savage KJ, et al. International Prognostic Score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era. J Clin Oncol. 2012;30:3383–8.
2. Canellos GP, Rosenberg SA, Friedberg JW, Lister TA, Devita VT. Treatment of Hodgkin lymphoma: a 50-year perspective. J Clin Oncol. 2014;32:163–8.
3. Steidl C, Connors JM, Gascoyne RD. Molecular pathogenesis of Hodgkin's lymphoma: increasing evidence of the importance of the microenvironment. J Clin Oncol. 2011;29:1812–26.
4. Gallamini A. Positron emission tomography scanning: a new paradigm for the management of Hodgkin's lymphoma. Haematologica. 2010;95:1046–8.
5. Steidl C, Lee T, Shah SP, Farinha P, Han G, Nayar T, et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. N Engl J Med. 2010;362:875–85.
6. Tan KL, Scott DW, Hong F, Kahl BS, Fisher RI, Bartlett NL, et al. Tumor-associated macrophages predict inferior outcomes in classic Hodgkin lymphoma: a correlative study from the E2496 Intergroup trial. Blood. 2012;120:3280–7.
7. Weiler-Sagie M, Bushelev O, Epelbaum R, Dann EJ, Haim N, Avivi I, et al. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. J Nucl Med. 2010;51:25–30.
8. Hartmann S, Agostinelli C, Diener J, Döring C, Fanti S, Zinzani PL, et al. GLUT1 expression patterns in different Hodgkin lymphoma subtypes and progressively transformed germinal centers. BMC Cancer. 2012;12:586–92.
9. Gobbi PG, Bassi E, Bergonzi M, Merli F, Coriani C, Iannitto E, et al. Tumour burden predicts treatment resistance in patients with early unfavourable or advanced stage Hodgkin lymphoma treated with ABVD and radiotherapy. Hematol Oncol. 2012;30:194–9.
10. Kanoun S, Rossi C, Berriolo-Riedinger A, Dygai-Cochet I, Cochet A, Humbert O, et al. Baseline metabolic tumour volume is an independent prognostic factor in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging. 2014. doi:10.1007/s00259-014-2783-x.
11. Meignan M, Sasanelli M, Casasnovas RO, Luminari S, Fioroni F, Coriani C, et al. Metabolic tumour volumes measured at staging in lymphoma: methodological evaluation on phantom experiments and patients. Eur J Nucl Med Mol Imaging. 2014;41:1113–22.
12. Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2010;37:181–200.
13. Tseng D, Rachakonda LP, Su Z, Advani R, Horning S, Hoppe RT, et al. Interim-treatment quantitative PET parameters predict progression and death among patients with Hodgkin's disease. Radiat Oncol. 2012;7:5.
14. Song MK, Chung JS, Lee JJ, Jeong SY, Lee SM, Hong JS, et al. Metabolic tumor volume by positron emission tomography/computed tomography as a clinical parameter to determine therapeutic modality for early stage Hodgkin's lymphoma. Cancer Sci. 2013;104:1656–61.
15. Rossi C, Kanoun S, Berriolo-Riedinger A, Dygai-Cochet I, Humbert O, Legouge C, et al. Interim 18F-FDG PET SUVmax reduction is superior to visual analysis in predicting outcome early in Hodgkin lymphoma patients. J Nucl Med. 2014;55:569–73.
16. Meignan M. Reporting interim positron emission tomography in diffuse large B-cell lymphoma: the Zeno's paradox. Leuk Lymphoma. 2014;55:730–2.
17. Gallamini A, Kostakoglu L. Interim FDG-PET in Hodgkin lymphoma: a compass for a safe navigation in clinical trials? Blood. 2012;120:4913–20.
18. Casasnovas RO, Sasanelli M, Berriolo-Riedlinger A, Morschhauser F, Itti E, Huglo D, et al. Baseline metabolic tumor volume is predictive of patient outcome in diffuse large B cell lymphoma. Blood. 2012;120(21):abstract 1598.