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**Objectives:** FDG PET/CT is now the gold standard for staging and assessing response in Diffuse Large B Cell Lymphoma (DLBCL) patients. The total metabolic tumor volume (MTV) calculated from baseline PET/CT images is prognostic of outcome and able, when combined with the ECOG performance status, to identify an ultra-high risk group in DLBCL patients (Vercellino et al, Blood 2020). Recently, the largest Euclidian distance between lymphoma lesions normalized by the body surface area (BSA), called SDmax, has been introduced as a dissemination biomarker and reported to be an independent prognosticator of DLBCL outcome (Cottureau et al, Ann Oncol 2020) Here, we investigate alternative dissemination metrics and compare their prognostic values in a large prospective cohort of DLBCL patients.

**Methods:** A total of 290 patients from an ancillary study of the REMARC trial ([NCT01122472](#)) and for whom a baseline PET/CT scan was available were retrospectively analyzed. All patients fasted for at least 6 hours before the injection of  $4.2 \pm 1$  MBq per kilogram of 18F-FDG (mean  $\pm$  std) and whole-body PET/CT were acquired using different scanner models from different vendors (Capobianco et al, J Nucl Med 2021). Metabolic tumor volumes were defined using 41% SUVmax threshold by two nuclear medicine physicians blinded to patient outcome, including bone marrow involvement only when there was focal bone marrow uptake. The centroid of each lesion was used as the lesion location. For each patient, seven dissemination metrics normalized by the patient BSA were calculated. The maximum Euclidean distance (SDmax\_Euc), the maximum Manhattan distance (SDmax\_Man) and the maximum Tchebychev distance (SDmax\_Tch) between the centroids of the two lesions were computed. The same distances were also measured directly from the voxels included in the delineated lesions, regardless of the lesion each voxel belongs to (SDmax\_Euc\_vox, SDmax\_Man\_vox and SDmax\_Tch\_vox respectively). Last, the solution to the Travelling Salesman Problem (SD\_TSP) was obtained, corresponding to the shortest possible path that connects every lesion centroid. Progression Free Survival (PFS) and Overall Survival (OS) analyses were performed for each metric using Kaplan-Meier estimates, Log-rank tests and Cox proportional hazard models. The ability of these metrics to discriminate patients with PFS events and patients with OS events was compared using ROC curves.

**Results:** For PFS, the areas under the curve (AUC) were between 0.63 and 0.64 for the 7 metrics while they were between 0.62 and 0.65 for OS, without any significant difference between metrics. Patients with high

SDmax or SD\_TSP had a significantly poorer outcome than patients with low SDmax or SD\_TSP whatever the method of calculation (log-rank tests,  $p < 0.003$ ) with similar separation between high and low risk groups for all methods. In multivariate analysis with MTV and ECOG (see Table below), SDmax\_Man and SD\_TSP had independent prognostic value for both PFS and OS, whereas SDmax\_Euc and SDmax\_Tch did not reach significance for OS ( $p = 0.09$  and  $p = 0.08$  respectively). In a sub-analysis of Ann Arbor advanced III-IV stage patients ( $n = 264$ ), each SDmax remained a significant prognosticator for both PFS ( $p < 0.0001$  for SDmax\_Euc,  $p < 0.001$  for SDmax\_Man,  $p < 0.0001$  for SDmax\_Tch,  $p < 0.005$  for SD\_TSP) and OS ( $p < 0.01$ ,  $0.05$ ,  $0.01$  and  $0.001$  respectively).

**Conclusions:** The spread of the lymphoma lesions measured on baseline PET is a strong independent prognostic factor whatever the method used for distance measurement. These dissemination metrics can predict PFS and OS when calculated directly from the voxels identified as belonging to a tumor region without assigning these voxels to a specific lesion, making them applicable even when lesion voxels are identified without assigning them to a specific lesion focus.