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Title: MACROPHAGES AND REGULATORY T CELLS IN FOLLICULAR LYMPHOMA (FL): A TISSUE MICROARRAY (TMA) STUDY ON 181 PATIENTS

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Background: Gene array studies on FL have associated characteristic intratumoral macrophage and/or T cell signatures with both increased and decreased survival. Other studies have associated very high macrophage numbers with decreased survival in patients younger than 60 years and high regulatory T cells numbers with increased survival.

Design: A TMA was constructed with duplicate cores from 252 archival follicular lymphoma samples from the Dept. of Pathology, University Hospital Zurich. Immunohistochemistry was performed for CD68 (clone PGM-1) and FOXP3 (ab10563) on a Ventana Discovery module and quantified by conventional counting of stained cells and determination of stained area fraction after grey scale thresholding at three different levels. In addition, large epithelioid macrophages were counted. Survival information (median follow up 9.4 years) could be obtained from 181 patients. Kaplan-Meier survival analysis was performed after grouping patients into quartiles according to cell numbers and stained area fractions. Alternatively a cut-off was selected that separated the 10% patients with highest macrophage numbers from the rest. Separate curves were generated for patients up to and above 60 years of age at diagnosis.

Result: In patients up to 60 years of age at diagnosis both increased macrophage numbers and CD68 stained area fractions associated with longer survival ($p<0.013$ to 0.046). This difference did not reach statistical significance in patients above 60 years . In patients above 60 years highest numbers of large epithelioid macrophages associated with shorter survival. This difference was not observed in patients below 60 years. No association of FOXP3 cell numbers and survival was found.

Conclusion: Both overall tumor infiltrating macrophages as well as a subpopulation of large epithelioid macrophages show - albeit diametrically opposed - associations with survival in patients with follicular lymphoma. These findings corroborate the findings of previous gene array studies. Most importantly, they show that emulations of gene array studies on an immunohistochemical level need to address specific subpopulations of macrophages. The failure to find an association of regulatory cell numbers and survival should prompt for the analysis of other T cell populations by immunohistochemistry.