Clinical risk models in primary mediastinal large B-cell lymphoma (PMBCL) have limited application and have yielded inconsistent results. [1,2] Hence, there is a need for novel biomarkers that can robustly predict disease failure, guide treatment approaches, and facilitate study comparisons.

Tumor heterogeneity, and in particular metabolic heterogeneity (MH) assessed from pre-treatment FDG PET scans, has emerged as a significant predictor of early relapse [3].

In this study, we hypothesized that MH quantification may also be helpful in the post-treatment evaluation, and investigated the prognostic utility of MH computed from PET scans after the initial course of chemotherapy.

**STUDY OBJECTIVE:** to evaluate the significance of metabolic heterogeneity computed from post-chemotherapy PET scans for predicting early PMBCL relapse.

**METHODS**

**Data source and description**
- The study included 52 subjects, 11 of whom had early progression of disease (PD).
- All subjects were treated with curative intent with R (rituximab) chemotherapy.
- The study included 52 subjects, 11 of whom had early progression of disease (PD).
- All subjects were treated with curative intent with R(rituximab)-CHOP.
- PET/CT images with $^{18}$F-FDG were acquired after 3-6 chemotherapy cycles.
- FDG-avid lesions were manually segmented by a nuclear medicine physician.

**Image features**
In keeping with previous work on pre-treatment PET [ref], the following metrics were computed:
- SUVmax
- Total lesion glycolysis (TLG)
- Cumulative SUV histogram (CSH)

CSH was used as a measure of metabolic heterogeneity. Feature values for post-chemotherapy PET were found to be substantially different from those computed at baseline by Ceriani et al. [3].

**RESULTS (1)**

**Univariate discrimination analysis**
In univariate group discrimination analysis, CSH for the PD group was significantly lower compared to CCR group (p<0.0001). Other metrics, lesions in subjects with progressive disease were significantly more heterogeneous.

- CSH had the highest area under the ROC (AUC) of 0.90 among all imaging metrics (second best SUVmax, AUC = 0.88).

**Univariate Kaplan-Meier survival analysis**
In univariate survival analysis with dichotomized variables, CSH was highly significant, with a hazard ratio (HR) of 17.45 between the low-CSH and high-CSH groups. In comparison, the HR for the Deauville score of 5 vs. <5 was 14.89. The table below shows data for 6 different univariate models.

<table>
<thead>
<tr>
<th>CSH had the highest area under the ROC (AUC(R)) of 0.90 among all imaging metrics (second best SUVmax, AUC = 0.88).</th>
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<tbody>
<tr>
<td>$p$</td>
</tr>
<tr>
<td>SUVmax</td>
</tr>
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<td>1.7 x 10$^{-3}$</td>
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</table>

**RESULTS (2)**

**Multivariate Cox proportional hazards regression**
In multivariate stepwise Cox regression analysis with continuous variables, only the CSH term remained to be statistically significant.

- With added stepwise variable selection, only lower CSH and elevated TLG remained independently associated with shorter progression-free survival.

**Dichotomized variables**
In multivariate Cox regression with dichotomized variables, likewise only the CSH was found to be statistically significant.

<table>
<thead>
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<th>Dichotomized variables</th>
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<tr>
<td>$p$</td>
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**CONCLUSIONS**
- Tumor metabolic heterogeneity, assessed on post-chemotherapy FDG PET images, is an independent and highly significant prognosticator of early disease progression and length of progression-free survival in PMBCL.
- Our findings are in agreement with similar results reported with pre-treatment PET scans.
- The dichotomized CSH metric to quantify metabolic heterogeneity has a comparable strength to dichotomized SUVmax, while being independent.
- Clinical management of lymphoma can benefit from routine CSH quantification, to identify subjects at high risk of relapse and for whom a more aggressive or alternative therapy is advised.

**REFERENCES**

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