Risk factors and staging systems in early stage Hodgkin lymphoma patients have significant impact on treatment outcome after modern combined modality treatment

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Purpose
In early-stage Hodgkin Lymphoma (HL), treatment according to the early favorable or unfavorable subgroup is guided by risk factors (RF), which differ between various study groups worldwide (Figure 1). However, the relevance of the staging systems is not well determined. We thus analyzed risk factors used in different international staging systems and their impact on the outcome of early-stage HL patients.

Patients and methods
In 1173 early-stage HL patients treated homogeneously with 4 cycles of ABVD followed by involved-field radiotherapy within the German Hodgkin Study Group (GHSG) trials HD10 and HD11 (Figure 2), the impact of three staging systems developed and used by the GHSG, the European Organization for Research and Treatment of Cancer (EORTC), and the National Comprehensive Cancer Network (NCCN) in discriminating risk groups for progression-free survival (PFS) and overall survival (OS) was assessed. Risk factors were tested for sensitivity and specificity for HL-related failure (HFL) within 2.5 years. Univariate and multivariate analyses of risk factors were used to assess the relevance of single factors.

Fig. 1: RF definitions in early-stage HL

<table>
<thead>
<tr>
<th>GHSG</th>
<th>EORTC</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large mediastinal mass (ratio ≥1/3)</td>
<td>Large mediastinal mass (ratio ≥3)</td>
<td>Large mediastinal mass (ratio ≥1/3)</td>
</tr>
<tr>
<td>ESR ≥ 50 mm (A) or ≥ 30 (B)</td>
<td>EHRT ≥ 10 cm</td>
<td>ESR ≥ 50</td>
</tr>
<tr>
<td>≥ 3 nodal areas (out of 11 GHSG areas)</td>
<td>≥ 4 nodal areas (out of 5 EORTC areas)</td>
<td>≥ 4 nodal regions (out of 11 Ann Arbor regions)</td>
</tr>
<tr>
<td>≥ 1 extranodal lesion</td>
<td>Age ≥ 50 years</td>
<td>B-Symptoms</td>
</tr>
</tbody>
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* Early-stage unfavorable, if CS-II and at least one RF present

Results
Median observation time was 80 months. All three staging systems define an unfavorable risk group having a significantly poorer PFS and OS as compared to the early favorable group; five-year differences between early favorable and early unfavorable in terms of PFS were 9.4%, 6.7% and 8.6% with the GHSG, EORTC, and NCCN definition, respectively (Figure 3).

Sensitivity for HFL was high for all systems (84%, 79%, and 83%); however, there were high rates of false-positive results (1-sensitivity 54%, 53%, and 55%). Models of high sensitivity included risk factors associated with large tumor burden and high tumor activity, such as large mediastinal mass, the involvement of numerous lymph node areas, and an elevated ESR.

In multivariate analyses, the GHSG staging definition had 4/4, the EORTC definition 2/4, and the NCCN definition 3/5 risk factors with significant impact (P<.05) on the event rate (Figure 4). Most risk factors for tumor-specific endpoints were also predictive for OS (data not shown).

Conclusion
The relevance of differentiating between a favorable and an unfavorable risk group in early-stage HL patients was proven in this large cohort of homogeneously treated patients, with significant impact on PFS and OS. Discriminating early-stage patients and using risk adapted treatment strategies is thus recommended in the modern combined modality treatment era.

Literature

Disclosures: There are no relevant conflicts of interest to disclose. This work was previously presented as oral at ASH 2012 and invited for re-presentation.