

# 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 homogenously 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 (HLF) 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

GHSG	EORTC	NCCN
Large mediastinal mass (ratio $\geq 1/3$ )	Large mediastinal mass (ratio $\geq 0.35$ )	Large mediastinal mass (ratio $> 1/3$ ) or Bulk $> 10\text{cm}$
ESR $\geq 50$ (A) or $\geq 30$ (B)	ESR $\geq 50$ (A) or $\geq 30$ (B)	ESR $\geq 50$
$\geq 3$ nodal areas (out of 11 GHSG areas)	$\geq 4$ nodal areas (out of 5 supradiaphragm. EORTC areas)	$\geq 4$ nodal regions (out of 17 Ann Arbor regions)
$\geq 1$ extranodal lesion	Age $\geq 50$ years	B-Symptoms

\* Early-stage unfavorable, if CS I-II and at least one RF present

Fig. 2: Treatment of HL patients included in RF analysis

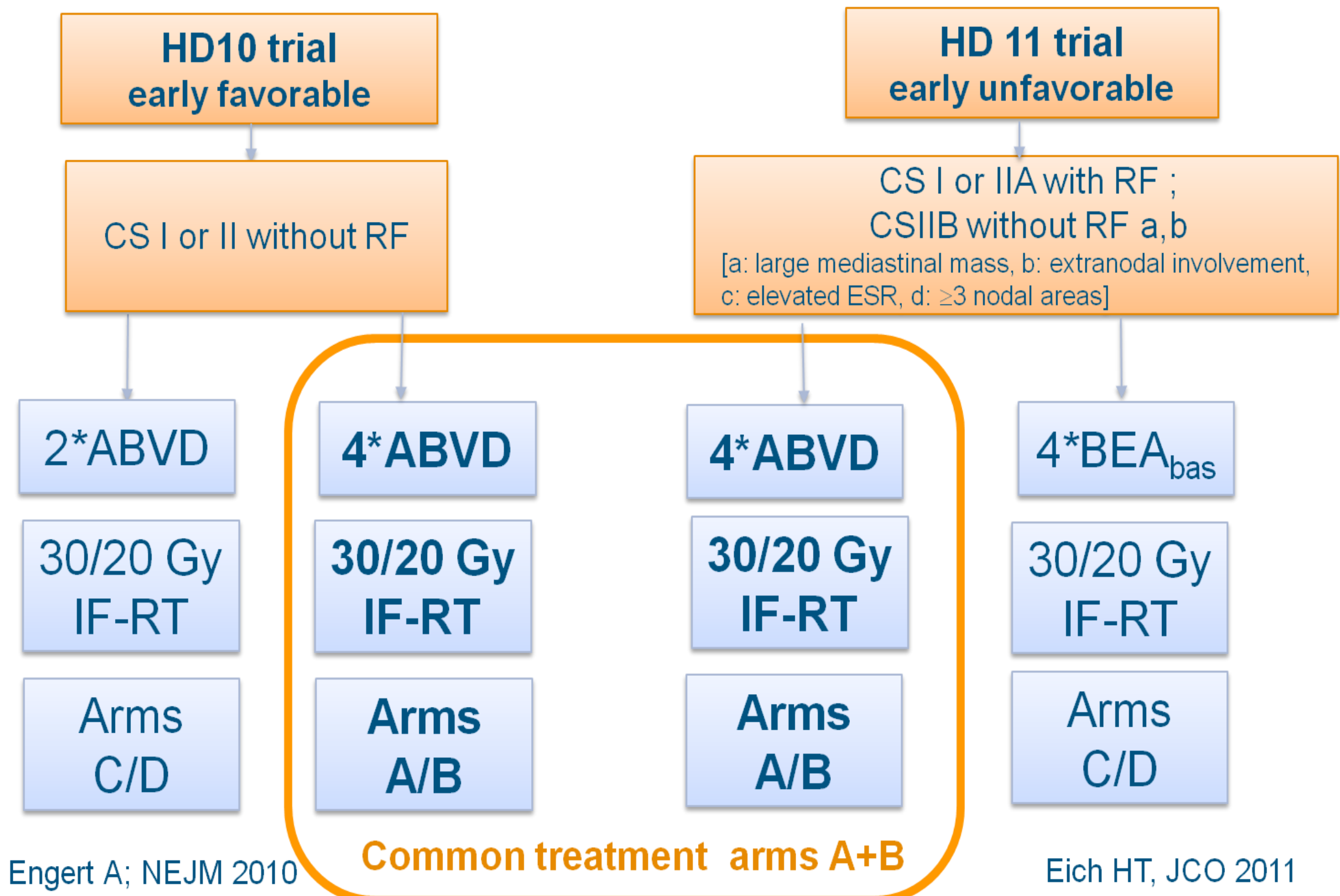


Fig. 3: KM-analysis on PFS

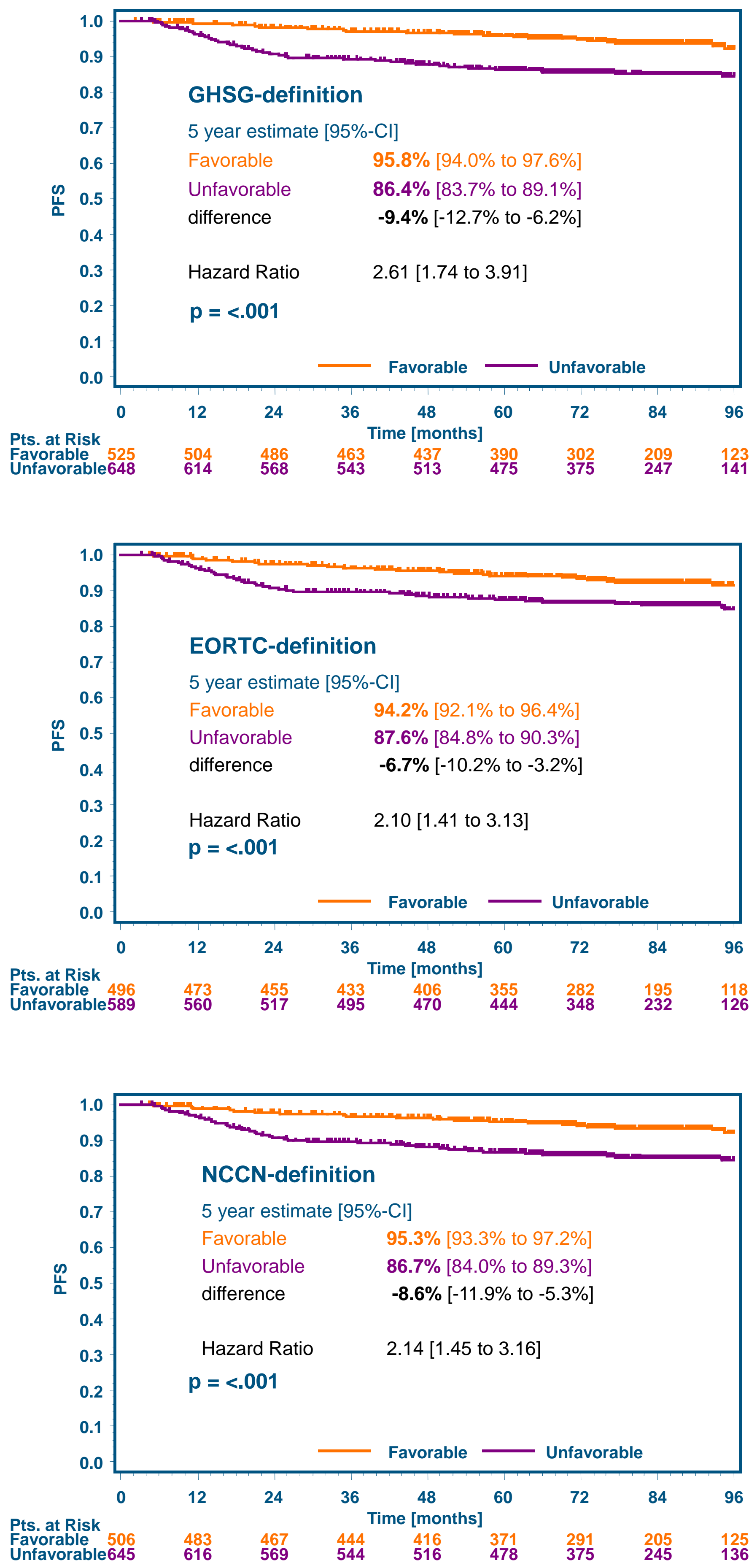


Fig. 4: Multivariate analysis of staging systems

2.5-year analysis set, N=1107			
	Odds ratio for HL-failure within 2.5 years	[95% Confidence Limits]	P-Value
<b>GHSG system, N=1107</b>			
Large mediastinal mass (ratio $\geq 1/3$ )	3.3	[2.0-5.5]	<b>&lt;0.001</b>
Extranodal disease	2.3	[1.1-4.8]	<b>0.03</b>
ESR $\geq 50$ mm/h (A) or $\geq 30$ mm/h (B)	1.6	[1.0-2.5]	<b>0.04</b>
$\geq 3$ nodal areas (out of 11 GHSG areas)	2.6	[1.6-4.1]	<b>&lt;0.001</b>
<b>EORTC system, N=1018</b>			
Large mediastinal mass (ratio $\geq 0.35$ )	3.9	[2.4-6.4]	<b>&lt;0.001</b>
Age $\geq 50$ years	0.8	[0.3-2.0]	0.6
ESR $\geq 50$ mm/h (A) or $\geq 30$ mm/h (B)	1.5	[0.9-2.4]	0.1
$\geq 4$ nodal areas (out of 5 supradiaphragmatic EORTC areas)	2.1	[1.3-3.4]	<b>0.003</b>
<b>NCCN system, N=1077</b>			
Large mediastinal mass (ratio $> 1/3$ )	2.2	[1.1-4.3]	<b>0.03</b>
Bulky disease $> 10$ cm	2.0	[1.0-4.0]	<b>0.046</b>
ESR $\geq 50$ mm/h	1.6	[1.0-2.5]	0.07
B-Symptoms	1.0	[0.5-1.9]	0.9
$\geq 4$ nodal regions (out of 17 Ann Arbor regions)	2.4	[1.5-3.8]	<b>&lt;0.001</b>

## 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 HLF was high for all systems (84%, 79%, and 83%); however, there were high rates of false-positive results (1-specificity 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 homogenously 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

- Engert A, Plutschow A, Eich HT et al. Reduced Treatment Intensity in Patients with Early-Stage Hodgkin's Lymphoma. N Engl J Med 2010; 363(7):640-652.
- Eich HT, Diehl V, Goergen H et al. Intensified Chemotherapy and Dose-Reduced Involved-Field Radiotherapy in Patients With Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD11 Trial. Journal of Clinical Oncology 2010; 28(27):4199-4206.