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# Prognostic factors in Hodgkin lymphoma

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ABSTRACT

During the last decades, the prognosis of Hodgkin lymphoma (HL) has been improved significantly with the introduction of effective chemotherapy and the implementation of risk-adapted treatment approaches. Identification of reliable risk factors is crucial to guide treatment over the course of disease. Both clinical and biological factors have been implicated in the prognosis of HL and are often used in prognostic scores to discriminate risk groups. To prevent under- or overtreatment, patients are usually assigned to one of the three widely established risk groups for first-line treatment, based solely on clinical risk factors. To further individualize therapeutic approaches, functional imaging with positron emission tomography (PET) is becoming more widely implemented and precisely investigated within clinical trials. Biological prognostic factors have been widely evaluated but are still not a part of standard prognostication. This review will discuss the currently established factors and risk models at first diagnosis and in the setting of relapsed/refractory disease and also focus on biological factors and PET, summarizing current standards and future perspectives.



## 1. Introduction

Identification of reliable prognostic factors and corresponding risk groups is crucial to guide treatment of patients with Hodgkin lymphoma (HL) and prevent under- or overtreatment. Beyond currently used prognostic systems [1,2], both clinical and biological factors have been implicated in the prognosis of HL at diagnosis or in the relapsed/refractory setting. To further individualize therapeutic approaches, functional imaging with positron emission tomography (PET) is becoming more widely implemented. This review will provide an overview on current standards and future perspectives in the prognostication of HL.

## 2. Current prognostic stratification at initial diagnosis

In the context of the Ann Arbor staging (AAS) classification, HL can be grouped into non-advanced (localized) and advanced (mostly disseminated) stages. Non-advanced stages can be classified into early favorable and unfavorable (or intermediate) stages, according to the absence or presence of $\geq 1$ risk factors: a combination of elevated erythrocyte sedimentation rate (ESR) and B-symptoms, mediastinal bulk, and the number of nodal areas are common factors of the German Hodgkin Study Group (GHSG) and European Organization for Research and Treatment of Cancer (EORTC) classification schemes; the fourth stratification factor is extranodal extension (E-disease) for the GHSG [1–3] and age $\geq 50$ for the EORTC classification [4] (Fig. 1).

Other risk factors, such as leukocytosis, may also be significant, but have not been incorporated into current prognostic systems to define treatment groups [5]. More importantly, it appears that the number of risk factors or the presence of specific individual factors of higher significance (large mediastinal mass, elevated ESR or B-symptoms) may further stratify these patients [3,5]. Recently, the adverse significance of such risk factors was overcome by more intensive treatment, consisting of two cycles of $BEACOPP_{escalated}$ ($BEACOPP_{esc}$; BEACOPP = bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) plus two cycles of ABVD (ABVD = adriamycin, bleomycin, vinblastine, dacarbazine) followed by radiotherapy (RT) [3].

In advanced HL, the International Prognostic Score (IPS) was developed in 1998 based on 1,618 patients and identified seven independent factors that additively predicted failure-free survival (FFS): age $\geq 45$ years, male sex, stage IV, anemia (hemoglobin $< 10.5$ g/dL), leukocytosis ($\geq 15 \times 10^9$/L), lymphocytopenia ($< 0.6 \times 10^9$/L or $< 8\%$), and hypoalbuminaemia. Each risk factor reduced FFS rates by 7%–8% and the IPS reliably identified a group of patients (IPS $\geq 4$; 19%) with long-term FFS of approximately 50% or less [6]. Subsequently, several studies have evaluated the IPS in more recent cohorts treated in the era of anthracyclines: while the IPS remains predictive, the differences among risk groups have diminished.[7–13] Interestingly, even in patients with IPS $\geq 4$, long-term FFS remains relatively high, usually exceeding

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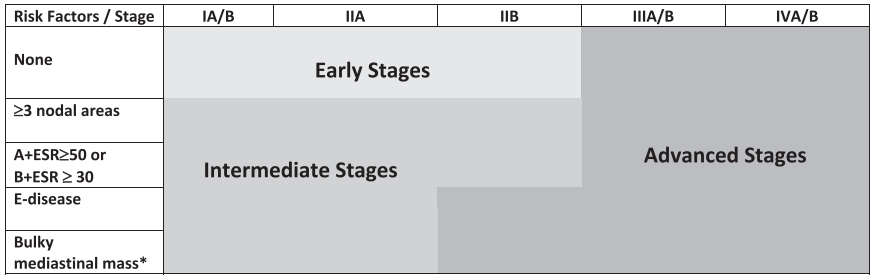
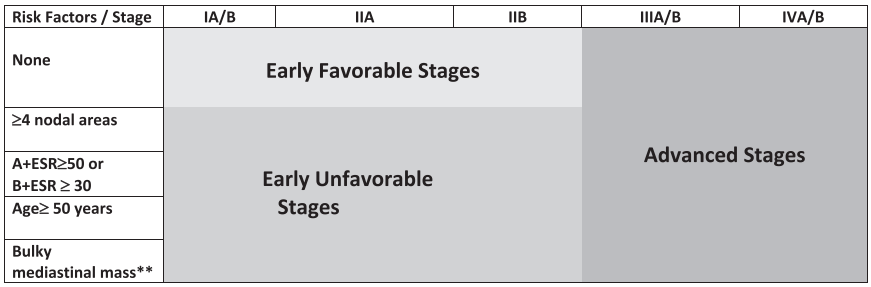



A: German Hodgkin Study Group (GHSG) Classification Scheme




B: European Organization for the research and treatment of Cancer (EORTC)) Classification Scheme

**Fig. 1.** Selected current models for risk classification in patients with initial diagnosis of Hodgkin lymphoma. (A) German Hodgkin Study Group (GHSG) classification scheme and (B) European Organization for Research and Treatment of Cancer (EORTC) classification scheme. *GHSG: tumor ≥⅓ of the maximal transverse internal diameter of the thoracic cage, usually close to the diaphragm. **EORTC: ≥0.35 of the transverse internal diameter of the thoracic cage at the T5-6 level. RF = risk factors; E-disease = extranodal extension of the disease.

60%, as summarized in another chapter of this issue [14]. Recently, a modified IPS has been proposed based on three parameters (age, stage, and hemoglobin; IPS-3), which can discriminate groups of patients with different prognosis in a simpler and potentially more accurate way than classical IPS [13].

For the time being, the GHSG and EORTC classifications and the IPS remain the standard tools for risk stratification at initial diagnosis of HL. However, there clearly is a need for improvement based on conventional and biological prognostic factors or data derived from functional imaging.

## 3. Other conventional prognostic factors at initial diagnosis

### 3.1. Demographics and patient characteristics

Older age, incorporated in the IPS and the EORTC classification [4,6], should be used as a risk factor with caution, because it is an "obligatory" prognostic factor for both FFS and overall survival (OS), if deaths of any cause are considered as events. Serving as surrogate parameter for tolerance to intensified regimens, its role as a marker for aggressive disease and unfavorable prognosis may be questionable [15,16]. Performance status is used to determine prognosis in HL mainly in primary refractory disease [17], while male sex is a part of the IPS but its role in non-advanced disease is not well established.

### 3.2. Markers of disease extent

AAS and B-symptoms have been effectively incorporated in the IPS and the GHSG and EORTC classifications. However, AAS, a historic anatomic classification reflecting the contiguous spread of HL and the potential cure by RT only, may not accurately reflect tumor burden. Disease bulk, especially mediastinal, affects the outcome of localized disease but has no impact in advanced stages [6]. The number of involved anatomic sites is also a part of GHSG/EORTC classifications of localized stages [1–4], but was not examined in the development of IPS. Subsequent studies suggest that the number of involved sites [18] or a semi-quantitatively estimated tumor burden [19] may be risk factors independent of the IPS. These factors should be reconsidered in the PET era. Thus, PET parameters, such as the estimated metabolic tumor volume (MTV) [20] and total lesion glycolysis (TLG), which integrates MTV and the intensity of FDG uptake, are under intensive investigation and constitute promising novel prognostic factors.

Specific disease localizations have also been studied. Pure infradiaphragmatic disease is rare, accounting for 4%–13% of all stage I–II cases. Inferior outcomes are probably related to its association with other adverse features [21], but recent data suggest that infradiaphragmatic localization itself may be an independent prognostic factor in intermediate stages [22]. Specific extranodal localizations or the number of extranodal sites have not reproducibly provided prognostic information independent of the assignment to stage IV.

### 3.3. Histologic findings

Mixed cellularity (MC) and lymphocyte depletion (LD) had been associated with worse prognosis in the RT-only era [23]. With modified diagnostic criteria during the last 20 years, most HL cases are now classified as nodular sclerosis (NS), while LD has almost disappeared with most cases re-classified as anaplastic large cell lymphomas or NSHL of the syncytial variant, now being extremely rare (<1% of cases). Despite association with other adverse features, an independent adverse impact on outcome may still be present for LD, although it appears to be overcome by intensive chemotherapy with $BEACOPP_{esc}$ [24]. In the era of modern treatment, the favorable outcome of nodular lymphocyte predominant HL (NLPHL) appears to vanish after adjustment for risk level [25]. Lymphocyte-rich subtype (LR) is also strongly associated with other favorable prognostic factors; its further independent favorable effect on outcome remains questionable [26,27]. Additional studies have attributed prognostic importance