

Hodgkin's lymphoma: treatment and prognosis

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INTRODUCTION

In the era of anthracycline-based combination chemotherapy Hodgkin's lymphoma (HL) is considered a highly curable malignancy, since approximately 90% of early stage and 60-70% of advanced stage patients achieve long-term disease free survival. The high cure rate in early stages has accentuated the importance of late -frequently fatal- side effects. Indeed, after 14 years from diagnosis, mortality due to other causes, which are frequently treatment-related, exceeds that of HL in young, early stage patients¹. On the other hand, patients who fail primary therapy or relapse after complete remission (CR) have a poor outcome and should be identified early in the course of the disease in order to be treated more aggressively²⁻⁵.

CURRENT RISK CLASSIFICATION⁶⁻¹³

Ann Arbor clinical stage (AAS), which was designed primarily for radiotherapy (RT)-treated patients, still remains the major determinant of the out-

come. AAS I/IIA are definitely non-advanced for most study groups. Non-advanced stages are further classified as "early" or "early favourable" and "intermediate" or "early unfavourable" according to the presence of adverse features. Table 1 summarizes the variability of early, intermediate and advanced stage definitions as used various investigational groups⁶⁻¹³.

The classification of AAS IIB is controversial, being non-advanced according to the EORTC definition or advanced according to British and Italian definitions. According to the German Hodgkin study Group (GHSg) AAS IIB is classified in the advanced stages only in the presence of extranodal extension or mediastinal bulky disease. The remaining patients belong to the intermediate stages, except of few patients without adverse features, who belong to the early stages.

AAS III/IV are generally classified as advanced. Only the GHSg includes a small minority (~5%) of AAS IIIA patients without risk factors as non-advanced disease.

TREATMENT OF NON-ADVANCED STAGES

Combined modality (CMT) approaches have definitively replaced staging laparotomy followed by RT alone, as suggested by many individual randomized

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Table 1. Risk classification of patients with Hodgkin's Lymphoma, according to various investigational groups⁶⁻¹³.

	Investigational Groups			
	GHSG	EORTC	Italian*	British
Risk Factors	a. ≥ 3 nodal sites b. A + ESR >50 or B + ESR >30 c. Mediastinal bulk d. E-disease	a. ≥ 4 nodal sites b. A + ESR >50 or B + ESR >30 c. Mediastinal bulk d. Age >50 years e. MC/LD histology	a. AAS IB b. Bulky disease c. E-disease d. Hilar involvement	a. B-symptoms b. Mediastinal bulk
Definition of Stages				
Early	I, II & no r.f.	I, II & no r.f.	I, IIA & no r.f.	IA, IIA without mediastinal bulk
Intermediate	I, IIA & any r.f. a-d IIB & r.f. a and/or b IIIA & no r.f.	I, II & any r.f. a-e	IA, IIA & any r.f. b-d IB	
Advanced	IIB & r.f. c and/or d IIIA & any r.f. a-d IIIB, IV	III, IV	IIB, III, IV	IA, IIA & mediastinal bulk IB, IIB, III, IV

* Patients with clinical stage IA and IIA, who were classified in either early or intermediate stages, were not treated differently⁹
r.f. denotes risk factors, E-disease denotes extranodal extension, MC/LD: Mixed cellularity or lymphocyte depletion

trials and a meta-analysis¹⁴. CMT has resulted to a marked reduction in relapse rates, in the absence however of overall survival benefit¹⁴. The chemotherapy regimens used in the studies of the meta-analysis did not contain anthracyclines¹⁴. So far only the H8F trial of the EORTC has demonstrated an overall survival difference for MOPP/ABV plus RT versus RT alone¹⁵. Other trials of anthracycline-based CMT have failed to show improvements in overall survival over RT alone, presumably because RT failures are effectively salvaged with combination chemotherapy and the follow-up of such trials is still relatively short^{8,16,17}. Further follow-up and probably a new meta-analysis focusing to anthracycline-based CMT might clarify this point in the future.

Based on these considerations the combination of ABVD and RT is the treatment of choice in non-advanced HL, although questions regarding the optimal number of chemotherapy cycles, field and dose of RT remain unanswered.

Radiotherapy Fields

After effective chemotherapy, involved field (IF) RT is equally effective to extended field (EF) in early

and intermediate stage HL^{9,18,19}. IF-RT is now included as standard treatment in all arms of recent and ongoing randomized trials of the GHSG and the EORTC (Tables 2 and 3)^{20-22,24,25}. Thus IF is the RT field of choice. The definition of IF is under discussion with the aim to limit the extent of RT from the "involved field" to the "involved nodes".

Radiotherapy Dose

Although curative RT monotherapy required doses of 36-45 Gy, the introduction of chemotherapy allowed meaningful reductions of RT dose.

Recently completed and ongoing trials compare IF RT at doses of 30 or 36 Gy versus 20 Gy or even no RT, in early and intermediate stages (Tables 2 and 3). Preliminary data from HD10 and HD11 trials of the GHSG have not revealed significant differences in the outcome of patients, who received 30 Gy or 20 Gy of IF-RT after ABVD or equivalent chemotherapy^{20,22}. However the GHSG included 30 Gy IF-RT in all arms of the subsequent trial generation (HD13 and HD14, Table 3)²¹.

From 1988 we have used 4-6 cycles of ABVD or EBVD (E=epirubicine) followed by low-dose IF-RT,

Table 2. Recently completed GHSG and EORTC randomized trials for Hodgkin's lymphoma.

Arms	Patients	Failure Free Survival	
		Timepoint	Comparisons
HD10, GHSG, Early Stages²⁰			
ABVDx2 + IF-RT 30 Gy	Evaluable: 847	2 years	4 vs 2 cycles: 96% vs 97% 30 vs 20 Gy: 97% vs 98%
ABVDx2 + IF-RT 20 Gy	Total: 1131		
ABVDx4 + IF-RT 30 Gy			
ABVDx4 + IF-RT 20 Gy			
H8F, EORTC/GELA, Early Stages^{15,21}			
MOPP/ABVx3 + IF-RT 36-40 Gy	Evaluable: 543	4 years	99%*, [‡]
Subtotal Nodal RT + Spleen			77%*, [‡]
HD11, GHSG, Intermediate Stages²²			
ABVDx4 + IF-RT 30 Gy	Evaluable: 1051 Total: 1363	2 years	ABVD vs BEACOPP: 89% vs 91% 30 vs 20 Gy: 93% vs 91%
ABVDx4 + IF-RT 20 Gy			
BEACOPP-basex4 + IF-RT 30 Gy			
BEACOPP-basex4 + IF-RT 20 Gy			
H8U, EORTC/GELA, Intermediate Stages¹⁹			
MOPP/ABVx6 + IF-RT 36-40 Gy	Evaluable: 995	4 years	89%
MOPP/ABVx4 + IF-RT 36-40 Gy			92%
MOPP/ABVx4 + STLI			92%
HD12, GHSG, Advanced Stages²³			
BEACOPP-escx8 + 30 Gy bulk/res**	Evaluable: 1396 Total: 1661	2 years	BEACOPP esc vs 4+4: 90% vs 88% RT vs no RT: 93% vs 91%
BEACOPP-escx8 without RT			
BEACOPP(escx4+basex4) + 30 Gy bulk/res			
BEACOPP(escx4+basex4) without RT			

Differences are not statistically significant unless otherwise reported

* p < 0.0001, [‡] Overall survival was 99% vs 95% (p=0.02) in favour of CMT, ** RT to sites of bulky and/or residual disease
STLI denotes subtotal lymphoid irradiation**Table 3.** Ongoing GHSG and EORTC randomized trials for Hodgkin's lymphoma.

German Hodgkin Study Group (Arms)	EORTC (Arms)
HD13, GHSG, Early Stages²¹ (initiated 1/2003)	H9F, EORTC, Early Stages²⁴ (initiated 1999)
ABVD × 2 + IF-RT 30 Gy	EBVP × 6 + IF-RT 36 Gy
ABV × 2 + IF-RT 30 Gy	EBVP × 6 + IF-RT 20 Gy
AVD × 2 + IF-RT 30 Gy	EBVP × 6 without RT*
AV × 2 + IF-RT 30 Gy	
HD14, GHSG, Intermediate Stages²¹ (initiated 1/2003)	H9U, EORTC, Intermediate stages²⁵ (initiated 1999)
ABVD × 4 + IF-RT 30 Gy	ABVD × 6 + IF-RT 30 Gy
BEACOPP-escalated × 2+ ABVD × 2 + IF-RT 30 Gy	ABVD × 4 + IF-RT 30 Gy
	BEACOPP × 4 + IF-RT 30 Gy
HD15, GHSG, Advanced Stages²¹ (initiated 2/2003)	International, headed by EORTC, Advanced stages, IPS ≥ 3 or stratified for IPS
BEACOPP-esc × 8 + 30-Gy RT to PET ⁺ residuals, >2.5 cm	BEACOPP (esc × 4 + base × 4) without RT
BEACOPP-esc × 6 + 30-Gy RT to PET ⁺ residuals, >2.5 cm	ABVD × 8 without RT
BEACOPP-14 × 8 + 30-Gy RT to PET ⁺ residuals, >2.5 cm	

* The EBVP alone arm was discontinued because of excess relapse rate

defined as ≤ 32 Gy, if CR, CR_u or very good partial remission had been achieved with chemotherapy. Retrospectively we observed a superior relapse-free survival rate in patients treated with 28-32 Gy versus those treated with < 28 Gy (mostly 20-28 Gy), mainly due to better infield control of the disease²⁶.

Based on the above data, 30 Gy remains the preferred RT dose after adequate response to chemotherapy until the final report of recent randomized trials.

Can Radiotherapy be Omitted?

The third arm (no RT) of the H9F EORTC trial (EBVPx6 plus IF-RT 36 Gy vs 20 Gy vs no RT) was terminated early because of excess relapse rate²⁴. The use of chemotherapy alone is also discouraged by the initial results of the NCIC-HD6 trial of the National Cancer Institute of Canada²⁷. On the other hand a recently published randomized trial from Memorial Sloan Kettering failed to show a difference between the combination of ABVDx6 and RT, mostly extended field, versus ABVDx6 alone for non-bulky stage I, II, and IIIA HL²⁸. However this trial was designed to detect a 20% difference between the arms and does not definitely exclude a smaller benefit from the addition of RT to a full course (6 cycles) of ABVD.

In conclusion, for the time being RT is considered necessary for non-advanced stage HL, particularly if less than 6 cycles of ABVD are to be administered.

Number of Chemotherapy Cycles for Early (Early Favourable) Stages

The GHSG favours the use of 2 cycles of ABVD in this low risk subgroup of non-advanced HL. The second interim analysis of the HD10 GHSG trial did not demonstrate any superiority of 4 cycles over 2 cycles (Table 2)²⁰. Overall the 2-year failure free survival (FFS) rate was 97%. The final results of this trial are pending, since 70% of patients were evaluable and – at a median follow-up of 28 months- only 20% of the expected failures had been observed. The results of the second interim analysis of HD10 can only be interpreted as trend that treatment intensity in CMT of early stages might be further reduced both in terms of chemotherapy cycles and RT dose. The NCI-Canada and British groups follow strategies of brief chemotherapy (ABVDx2 or 4 weeks of VAPEC-B) followed by RT in

non-bulky AAS IA or IIA patients with 5-year FFS rates of 85-90%^{12,27}. In contrast ABVDx4 is the approach used by the Milan group⁹, while the EORTC continues to treat early (early favourable) HL with 6 cycles of EBVP²⁴, which is probably inferior to ABVD.

At present 4 cycles of ABVD appear to be a reasonable option, followed by 30 Gy IF-RT. Only 2 cycles of ABVD may prove sufficient in the future.

Number of Chemotherapy Cycles for Intermediate (Early Unfavourable) Stages

According to the major investigational groups 4 cycles of COPP/ABVD or MOPP/ABV plus IF-RT constitute the evidence-based treatment of choice for intermediate stages^{18,19}. However the long-term FFS remains unsatisfactory in the order of 80-85%. Based on the equivalence between ABVD and alternating or hybrid regimens in advanced HL^{29,30}, and the considerable toxicity of the latter in terms of secondary leukaemias and gonadal toxicity, 4 cycles of ABVD appear also adequate^{22,25}. This is supported by the 4th interim analysis of the GHSG HD11 trial, in which 4 cycles of ABVD were equally effective to 4 cycles of BEACOPP-baseline, followed by the same RT²². However, at 2-years, FFS was already approximately 90%, a figure which is considered not acceptable for non-advanced disease. This prompted the GHSG to incorporate 2 cycles of BEACOPP-escalated in the treatment of intermediate stage HL (HD 14 trial, table 3)²¹. The question whether 6 cycles of ABVD are superior to 4 cycles is currently being addressed by the H9U EORTC trial²⁵.

In contrast to these strategies, patients with AAS IIB are treated with protocols of advanced disease in Italian and British trials and receive at least 6 cycles of ABVD-like chemotherapy^{10,11,13}.

Based on these considerations, CMT with 6 cycles of ABVD followed by 30 Gy IF-RT is the current standard therapy for the intermediate stages of HL. Four cycles are probably sufficient for selected patients, for example those without B-symptoms who have a rapid response to chemotherapy, but this is not an evidence-based strategy. Given the relatively poor results of the described approaches, powerful prognostic factors are needed to discriminate patients with the most unfavourable outcome and classify them in the advanced stages.

Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL)

This rare subtype frequently presents with non-bulky stage IA or IIA without risk factors. These patients are usually treated with brief chemotherapy (1-3 cycles of ABVD) followed by IF-RT^{31,32}. Due to the indolent nature of NLPHL³², IF-RT alone at doses of 20-30 Gy is a reasonable option according to some experts²¹. A conservative strategy of complete surgical excision followed by a "watch and wait" policy and further intervention only in case of disease progression may also not compromise survival at least in paediatric patients with localized disease³³. Patients with more extensive disease should be treated similarly to classical HL²¹. As a general rule, aggressive therapy should be given with caution in NLPHL in order to avoid toxicity. Given the invariable expression of CD20 in NLPHL, rituximab has been tested in relapsed and refractory disease with very promising results³⁴. The first-line use of rituximab is currently investigational.

TREATMENT OF ADVANCED STAGES

Chemotherapy

MOPP was the first regimen which led to the cure of approximately 35% of the patients with AAS III/IV (updated 15-year results of the CALGB trial, 2002)²⁹. ABVD was introduced by the Milan Group and proved to be superior than MOPP, at least in terms of FFS. However the cure rate after ABVD±RT is in the order of 65%, and did not exceed 50% at 15 years after ABVD alone in the above mentioned CALGB trial²⁹. Efforts to improve these results with alternating cycles of MOPP (or COPP) and ABVD or hybrid regimens of 7 (MOPP/ABV) or 10 drugs (MOPP/EBV/CAD and COPP/ABV/IMEP) were not successful^{10,11,29,30,35,36}. Consequently ABVD remains the gold standard for randomized trials of advanced HL according to most groups.

In 1993 the GHSG introduced BEACOPP-escalated, a new dose-and time- intensified regimen. The final results of the HD9 trial published in 2003 demonstrated that BEACOPP-escalated was superior in terms of both FFS and overall survival as compared with COPP/ABVD -an equivalent of ABVD-as well as BEACOPP-baseline, which included lower drug doses than the escalated version⁷. Updated results,

presented in the 6th International Symposium on Hodgkin's Lymphoma (Cologne, September 2004), showed 7-year FFS rate of 85%, 75%, and 67% for BEACOPP-escalated, BEACOPP-baseline and COPP/ABVD respectively. Overall survival rates were 90%, 84%, and 79% respectively. The 5-year results of this trial in terms of efficacy and toxicity are presented in **Table 4**. Based on HD9 trial, BEACOPP-escalated emerged as the new standard regimen for patients with advanced HL younger than 65 years old, according to the GHSG. The use of BEACOPP-baseline is not recommended, because it did not improve overall survival over COPP/ABVD.

An indirect comparison of toxicity between BEACOPP-escalated and ABVD is presented in table 4, based on the results of published trials^{7,23,28,30,37,38}. According to the data presented in table 4, BEACOPP-escalated provided a clear overall survival benefit, which was large for patients with IPS ≥4 but rather non-significant for those with IPS 0-1 or even those with IPS 2-3. Furthermore the acute haematologic toxicity of BEACOPP-escalated is significant and long-term toxicity is not negligible^{7,37,38}.

In an attempt to reduce toxicity while maintaining high cure rates, the GHSG initiated the 4-arm HD12 trial comparing 8×BEACOPP-escalated (8B) with or without 30Gy RT to bulky or residual disease sites versus 4×BEACOPP-escalated plus 4×BEACOPP-baseline (4+4) with or without the same RT²³. In the fourth interim analysis with median follow-up 2.5 years, there is not yet any difference in terms of 2-year FFS (90.4% vs. 88.1%) and 2-year overall survival (95.5% vs 94.1%) for the comparison of 8B vs 4+4. There was also no difference in the RT vs no RT comparison (2-year FFS 93.0% vs. 91.4%). However treatment toxicity, treatment-related deaths and occurrence of secondary MDS/ANLL were also similar between the two chemotherapy arms. Based on the preliminary results of HD12, the GHSG selected 8×BEACOPP-escalated as the standard arm of the subsequent HD15 trial, which was initiated in February 2003²¹. In conclusion, the GHSG -in contrast with other groups- considers BEACOPP-escalated as the gold standard for the treatment of advanced HL, against which new approaches should be compared.

Another intensified multidrug regimen -Stanford V- was developed in Stanford and produced impressive results in advanced and/or bulky HL when combined with RT³⁹. In a recent Italian randomized trial Stanford V was compared with ABVD and MOPP/

Table 4. Comparison of BEACOPP-escalated and ABVD in terms of efficacy and toxicity, in patients with advanced stage Hodgkin's lymphoma^{7,23,28,30,37,38}.

Indexes of efficacy and toxicity	BEACOPP-escalated (%)	ABVD (%)	References
Early progression	2	10	7*
5-year FFS	87	69	7*
IPS 0-1	92	79	7*
IPS 2-3	87	67	7*
IPS 4-7	82	59	7*
5-year OS	91	83	7*
IPS 0-1	95	92	7*
IPS 2-3	90	84	7*
IPS 4-7	82	67	7*
Toxic deaths	2-3	1-2	7*, 23, 28, 30
Leukopenia, grade 3/4	98	71	7*
Thrombocytopenia, grade 3/4	70	6	7*
Anaemia, grade 3/4	66	5	7*
Infection, grade 3/4	22	3	7*
Acute Myeloid Leukaemia (5 years)	2.3	0.4**	7*, 30
Definitive Amenorrhea	52	1	37
Permanent Azoospermia	?	0	38

* BEACOPP-escalated versus COPP/ABVD (considered as ABVD-equivalent)

** Only after salvage therapy; practically absent after ABVD alone with or without RT (ref #30 and our unpublished data)

EBV/CAD. RT to bulky and/or residual sites was scheduled in all three arms. At 5 years FFS was 76%, 86% and 93% for Stanford V, ABVD and MOPP/EBV/CAD respectively ($p < 0.01$), but no overall survival difference was detectable at that point (83% vs 90% vs 89%, $p = 0.16$)¹¹. The results of a Mexican randomized trial comparing EBVD with a slightly modified version of Stanford V were also in favour of EBVD⁴⁰.

In another randomized trial patients with high-risk advanced HL, who responded to 4 cycles of ABVD or equivalent chemotherapy, were randomized to receive either high-dose-therapy and autologous stem cell transplantation as consolidation or 4 further cycles of the same chemotherapy for a total of 8 cycles. No difference was detected between the arms and consequently high-dose therapy is not considered as appropriate option for high-risk advanced HL in first CR⁴¹.

Ongoing trials in Europe and North America further compare BEACOPP-escalated-based strategies with ABVD (Table 3) or Stanford V with ABVD²¹. Until the completion of such trials both ABVD (usually 8 cycles) and BEACOPP-escalated are reasonable chemotherapy options for advanced HL, given their different efficacy but also different toxicity profiles. Higher-risk patients probably gain the greatest benefit from BEACOPP-escalated⁷.

Is Radiotherapy Needed in Advanced HL?

Several trials have attempted to address this question with variable results. The recently completed EORTC #20884 trial demonstrated that 24Gy IF-RT does not improve the outcome of patients achieving CR after MOPP/ABV hybrid⁴². Instead there was a trend towards higher incidence of second malignancies in the RT arm. However patients in PR were frequently converted to CR with RT (30 Gy IF plus boost to residual) and had similar outcome with patients who attained CR with chemotherapy. A potential limitation of this study was the definition of response. CR was defined as the disappearance of all measurable disease by conventional imaging procedures, resulting to a CR rate of 421/739 or 57% and a PR rate of 250/739 or 34% after chemotherapy. One might argue that some PR patients may have not had active disease, since gallium or PET scan results were not reported. However almost 90% of PR patients actually converted to CR at evaluations made 3-38 months after RT. This observation indirectly indicates that a proportion of patients actually had active disease prior to RT⁴².

The H89 GELA trial did not reveal differences between 2 additional cycles of chemotherapy or 30 Gy subtotal or total nodal RT (with 35 Gy given to the IF

and 40 Gy to residual sites) for patients with AAS IIIB/IV HL, who had achieved CR or >75% remission after 6 cycles of MOPP/ABV or ABVPP⁴⁴.

The fourth interim analysis of the GHSG HD12 trial has not yet revealed any benefit for RT to bulky or residual disease sites after 8 cycles of effective, BEACOPP-escalated-based chemotherapy²³. Thus, in the next HD15 trial, 30 Gy RT is administered only to patients with residual lesions >2.5 cm, who have positive PET scans²¹.

In conclusion, RT is not necessary for patients with advanced stage HL, who achieve CR with 6-8 cycles of chemotherapy. For the time being 30 Gy IF-RT plus boost to residual sites could be recommended for patients with PR after chemotherapy. There is no formal evidence to support the delivery of RT only to the sites of residual disease. The use of PET-scan will probably reduce the need of RT in the future.

PROGNOSTIC FACTORS

Prognostic factors are meaningful when derived from homogeneously and effectively treated patient populations. For this reason we will present information on prognostic factors in patients treated with current standard treatment approaches, e.g. chemotherapy with ABVD or equivalent regimens with or without RT. Established prognostic factors may not however be valid under more effective treatment approaches, as for example BEACOPP-escalated.

Non-Advanced Stages

The distinction of non-advanced HL into early and intermediate stages has mainly been derived from RT-treated patient populations. The presence of B-symptoms is considered as a prognostic indicator in optimally treated patients as well. Information regarding prognostic factors for AAS IA/IIA patients treated with ABVD+RT is sparse. One study delineated the impact of very bulky mediastinal disease (>0.45) as the only pretreatment adverse prognostic indicator⁴⁵. In our series of 367 patients treated with ABVD or EBVD plus RT, age ≥45 years, male gender, leukocytes ≥10×10⁹/l, extranodal extension and bulky disease emerged as independent prognostic factors for FFS and overall survival. Among 289 patients with complete data, 52% had 0-1, 34% had 2, and 14% had 3-5 adverse factors, with 10-year FFS rates of approxi-

mately 95%, 82%, and 66% respectively (Figures 1A, B). The outcome of the latter subgroup resembles that of advanced HL. The analysis of H8F, H8U, H9F, H9U, HD10 and HD11 trials (Tables 2 and 3) may provide more reliable information for the prognostic classification of non-advanced HL under anthracycline-based CMT.

Advanced Stages

Although several models have been described, the International Prognostic Score (IPS), based on 1618

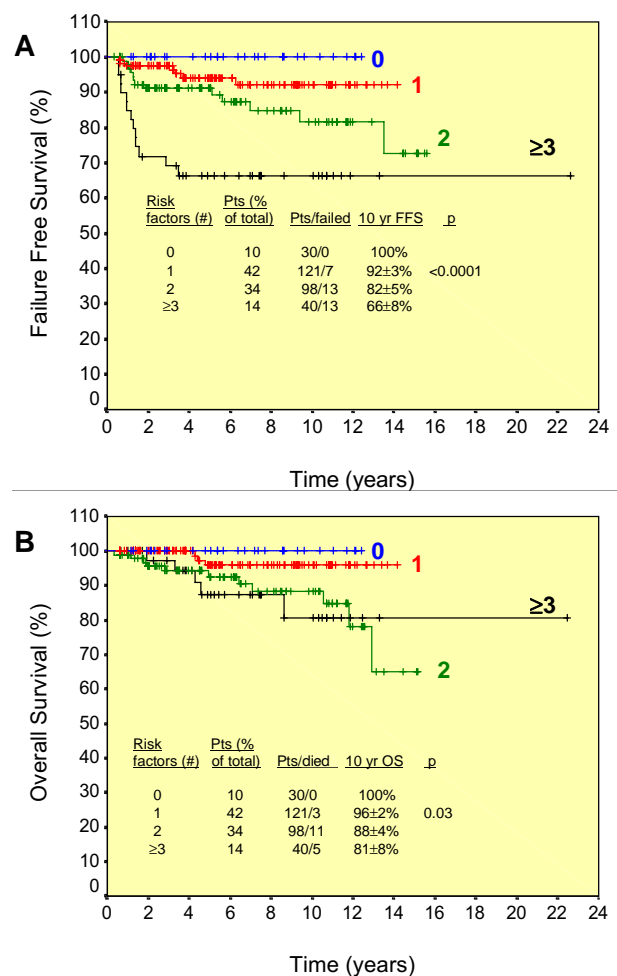


Figure 1. Outcome of patients with clinical stage IA/IIA Hodgkin's lymphoma treated with ABVD and radiotherapy according to the number of adverse prognostic factors. Adverse prognostic factors included age ≥45 years, male gender, leukocytes ≥10×10⁹/l, extranodal extension and bulky disease (mediastinal and/or peripheral). (A) Failure Free Survival and (B) Overall Survival.

patients predominantly treated with anthracycline-based chemotherapy, has prevailed⁴⁶. The IPS includes 7 factors: Age ≥ 45 years, male gender, stage IV, haemoglobin < 10.5 g/dl, leukocytes $\geq 15 \times 10^9/l$, lymphopenia $< 0.6 \times 10^9/l$ or $< 8\%$ and serum albumin < 4 g/dl. According to the number of adverse features, the value of the IPS ranges from 0 to 7. The presence of each additional factor diminished the 5-year FFS rate by approximately 7%-10% in the original sample (Table 5)⁴⁶. Among conventional prognostic factors, the number of involved sites may improve the discriminative potential of IPS⁴⁸. The quantitative estimation of tumour burden with spiral CT provides independent prognostic information but needs further evaluation⁴⁹.

Biological Prognostic Factors

At present, conventional prognostic factors cannot reproducibly identify sizeable subgroups of patients with HL with FFS $< 50\%$, who might be candidates for first-line intensified experimental therapy. Recent progress in the understanding of the biology of HL resulted to the identification of potent prognostic factors, including elevated serum interleukin-10 levels (IL-10)^{50,51}, elevated serum soluble CD30 levels (sCD30)⁵², expression of the antiapoptotic protein bcl-2⁵³, and low expression of activated caspase-3 by Hodgkin-Reed-Stenberg cells^{54,55}. All these factors add independent prognostic information to conventional parameters. Furthermore the information derived from bcl-2 and activated caspase-3 expression is independent each other⁵⁵. The same is probably the case for serum IL-10 and sCD30 as well (unpublished data). Global efforts to incorporate biological markers into prognostic systems and combine them reliably

with conventional prognostic factors are still in progress (for review of the topic of biological prognostic factors see ref. #56).

COMMENT

HL is now curable in approximately 75% of the patients. Further improvement is depended on the minimization of long-term side effects in low-risk patients and the aggressive treatment of high risk ones. However the definitions of risk groups –especially the intermediate stages- should become more accurate, hopefully with the integration of biological data. Functional imaging may identify patients who are in need of additional RT or early treatment modification.

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Table 5. Application of the International Prognostic Score (IPS) for advanced Hodgkin's lymphoma. Adverse factors include age ≥ 45 years, male gender, stage IV, haemoglobin < 10.5 g/dl, leukocytes $\geq 15 \times 10^9/l$, lymphopenia $< 0.6 \times 10^9/l$ or $< 8\%$ and serum albumin < 4 g/dl.

IPS	Original Sample ⁴⁶	Duggan et al, 2003 ³⁰	Our data ^{47*}	HD9 GHSG Study ⁷	
				COPP/ABVD	BEACOPP Escalated
0 (7% of total) ⁴⁶	84	76	89		
1 (22% of total) ⁴⁶	77	72	85	79 ⁺	92 ⁺
2 (29% of total) ⁴⁶	67	81	72		
3 (23% of total) ⁴⁶	60	69	56	67 [§]	87 [§]
4 (12% of total) ⁴⁶	51	64	59		
≥ 5 (7% of total) ⁴⁶	42	67	77	59 ^{**}	82 ^{**}

All figures represent 5-year failure free survival rates, *Updated as of 2004, ⁺IPS 0-1, [§]IPS 2-3, ^{**}IPS 4-7

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