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ORIGINAL REPORT

International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: Altered Utility in the Modern Era

Alden A. Moccia, Jane Donaldson, Mukesh Chhanabhai, Paul J. Hoskins, Richard J. Klasa, Kerry J. Savage, Tamara N. Shenkier, Graham W. Slack, Brian Skinnider, Randy D. Gascoyne, Joseph M. Connors, and Laurie H. Sehn

All authors: British Columbia Cancer Agency and the University of British Columbia, Vancouver, British Columbia, Canada.

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Corresponding author: Laurie H. Sehn, MD, MPH, British Columbia Cancer Agency and the University of British Columbia, 600 West 10th Ave, Vancouver, British Columbia, Canada V5Z 4E6; e-mail: lsehn@bccancer.bc.ca.

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ABSTRACT

Purpose
The International Prognostic Score (IPS) is the most widely used risk stratification index for Hodgkin's lymphoma (HL). It is based on patients treated before 1992 and predicts 5-year freedom from progression (FFP) and overall survival (OS) ranging from 42% to 84% and 56% to 89%, respectively. The IPS has not been validated in a recently treated population in which outcomes have improved compared with historic results.

Patients and Methods
By using the British Columbia Cancer Agency Lymphoid Cancer Database, we identified all patients age ≥ 16 years newly diagnosed with advanced-stage HL (stage III to IV, or stage I to II with "B" symptoms or bulky disease ≥ 10 cm) from 1980 to 2010, treated with curative intent with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or an ABVD-equivalent regimen with complete clinical information.

Results
In all, 740 patients were identified. Five-year FFP and OS were 78% and 90%, respectively. The IPS was prognostic for both FFP ($P < .001$) and OS ($P < .001$), with 5-year FFP ranging from 62% to 88% and 5-year OS ranging from 67% to 98%. Analysis limited to patients age 16 to 65 years (n = 686) demonstrated a narrower range of outcomes, with 5-year FFP ranging from 70% to 88% and 5-year OS ranging from 73% to 98%.

Conclusion
The IPS remains prognostic for advanced-stage HL, but the range of outcomes has narrowed considerably. This improvement in outcome with ABVD should be acknowledged before consideration of alternate initial therapies and when comparing results from current trials with those of historic controls.

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INTRODUCTION

At the present time, Hodgkin's lymphoma (HL) can be cured in more than 80% of all patients. In advanced-stage disease, multiagent chemotherapy remains the mainstay of treatment, with involved field radiation therapy (IFRT) frequently administered to sites of initial bulk or residual disease. Historically, clinical trials have demonstrated the superiority of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and ABVD hybrid regimens over mechlorethamine, vincristine, procarbazine, and prednisone (MOPP).[1-3] Because ABVD has a more favorable toxicity profile, it has been the standard of care for more than two decades.[4] More recently, dose-intensive chemotherapy regimens have challenged the role of ABVD. The German Hodgkin Study Group (GHSG) HD9 trial demonstrated superiority of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escalated BEACOPP) over ABVD, but at a cost of considerably greater toxicity and with questionable long-term benefit.[5,6] Accurate prognostication of outcome is becoming increasingly important to help guide the choice of individualized risk-adapted therapy.

For patients with limited-stage disease, prognostic factor models have little relevance, since cure rates exceed 95%. However, in advanced-stage HL (defined as stages III or IV, or stages I or II with "B" symptoms or bulky disease ≥ 10 cm), prognostic indices may help to identify patients at a very low risk of treatment failure to be considered for treatment reduction or patients at a higher risk to be considered for more intensive therapy, and may also be useful for comparing clinical trial results. The

most widely accepted risk stratification tool for HL is the International Prognostic Score (IPS), a robust clinical model based on the outcome of approximately 5,000 patients with advanced-stage HL, most of whom were treated before 1990.[7] The IPS incorporates seven clinical parameters that were demonstrated to be independently associated with a poorer outcome (male sex, age $\geq$ 45 years, stage IV, hemoglobin $<$ 105 g/L, WBC count $\geq 15 \times 10^9$/L, lymphocyte count $< 0.6 \times 10^9$/L or $<$ 8% of differential, albumin $<$ 40 g/L). On the basis of the number of factors present at diagnosis, the IPS identified subgroups of patients with 5-year freedom from progression (FFP) ranging from 42% to 84%.

Although the IPS continues to be widely used, it may no longer accurately reflect the outcome of patients with advanced-stage HL. Since the original publication of this scoring system, outcome in patients treated with ABVD has significantly improved.[5,8-11] The reason for this improvement is likely multifactorial, due in part to increased diagnostic accuracy resulting in the exclusion of patients with non-Hodgkin's lymphoma, previously mistaken for HL[12-14]; greater preservation of dose intensity with or without the use of neutrophil growth factors[15,16]; better supportive care; stage migration as recent-generation imaging techniques (new computed tomography [CT] and positron emission tomography [PET]/CT scanners) upstage patients previously thought to have more limited disease[17,18]; and more frequent use of high-dose chemotherapy and autologous hematopoietic stem-cell transplantation, the latter of which would impact only overall survival (OS). There could also be additional factors that may be difficult to define. The aim of this study is to assess the prognostic relevance of the IPS in patients with advanced-stage HL treated in the modern era.

PATIENTS AND METHODS

Study Design

The British Columbia (BC) Cancer Agency Centre for Lymphoid Cancer database was used to identify all newly diagnosed patients age $\geq$ 16 years with advanced-stage HL between January 1, 1980, and December 31, 2010, treated in the province of BC with curative intent ABVD or an ABVD-equivalent regimen and with complete clinical information, including all IPS factors. The BC Cancer Agency Lymphoid Cancer Database captures information on more than 95% of all patients diagnosed with HL in the province and therefore is representative of the general population. All diagnostic biopsies were centrally reviewed by a BC Cancer Agency hematopathologist. Advanced-stage disease was defined as stages III or IV, or stages I or II with B symptoms or bulky disease $\geq$ 10 cm. Clinical staging procedures included a full history and physical examination, laboratory parameters, and CT scans of the neck, chest, abdomen, and pelvis. Bone marrow biopsy was performed in patients presenting with B symptoms or cytopenias. Fluorodeoxyglucose PET (FDG-PET) scanning was not performed for staging. All patients were HIV negative.

Planned treatment consisted of six to eight cycles of ABVD chemotherapy or an ABVD-equivalent regimen. Growth factors were not routinely used but were administered when necessary to maintain dose intensity. The decision regarding consolidative IFRT was left to the discretion of individual treating physicians but was generally recommended for patients with sites of initial bulky disease or residual masses. Since 2005, FDG-PET scans have been performed post-treatment for patients with residual masses (abnormality $\geq$ 2 cm on CT scan) and consolidative radiation administered selectively to sites of PET positivity when feasible. Patients were routinely monitored for recurrence every 3 months in the first 2 years post-therapy, followed by every 6 months for an additional 3 years and then annually. This study was approved by the University of British Columbia's BC Cancer Agency Research Ethics Board.

Statistical Analysis

This analysis is based on follow-up through September 1, 2011. FFP was measured from the date of diagnosis to the date of first progression or relapse, need for alternate therapy, or death as a result of treatment toxicity; deaths from unrelated causes were censored. OS was calculated from the date of diagnosis to the date of death as a result of any cause or date last known alive. The Kaplan-Meier method was used to estimate FFP and OS, and comparison between risk groups was performed by using the log-rank test.[19,20] Multivariate regression analysis assessing the significance of individual IPS factors on FFP was performed by using a Cox proportional hazards model with backward selection.[21] Data were analyzed by using SPSS, version 11.0 for Windows (SPSS, Chicago, IL).

RESULTS

Patient Characteristics

A total of 740 patients meeting the inclusion criteria were identified. During this same time period, an additional 566 patients were identified who met all study criteria but were excluded because of incomplete information on IPS variables. Excluded patients were similar to the study cohort with respect to age, sex, and stage distribution, and overall outcome was comparable (Appendix Fig A1, online only), suggesting that there was no systematic bias introduced by their exclusion. The primary reason for exclusion (n = 559) was a missing albumin level, which was not routinely performed in all patients.

Baseline clinical characteristics of the study population are presented in Table 1. The median age at diagnosis was 32 years (range, 16 to 85 years), and 54% of the patients were male. The most prevalent

Table 1. Patient Characteristics at Diagnosis

Characteristic	No. (n = 740)	%
Age, years		
Median	32	
Range	16-85	
Ann Arbor stage		
I	9	1
II	299	40
III	255	35
IV	177	24
Bulky disease $\geq$ 10 cm	288	39
B symptoms	477	64
IPS factors		
Age $\geq$ 45 years	196	26
Albumin $<$ 40 g/L	474	64
WBC $\geq 15 \times 10^9$/L	114	15
Hemoglobin $<$ 105 g/L	147	20
Lymphocyte count $< 0.6 \times 10^9$/L or $<$ 8% of differential	160	22
Male sex	403	54
Stage IV	177	24
Histology		
Nodular sclerosis	577	78
Mixed cellularity	53	7
Lymphocyte rich	9	1
Lymphocyte depleted	12	2
Nodular lymphocyte predominant	20	3
Classical HL, NOS	69	9

Abbreviations: HL, Hodgkin's lymphoma; IPS, International Prognostic Score; NOS, not otherwise specified.

adverse prognostic factor was low albumin, which was present in almost two thirds of the patients. With the exception of sex, other risk factors were present in 26% of patients or fewer. As expected, the most common histologic subtype was nodular sclerosis HL, which was present in 78% of the patients. Thirty-nine percent of patients had bulky disease, and IFRT was administered to 174 patients (24%) as part of primary therapy.

Outcome According to IPS

With a median follow-up in living patients of 77 months (range, 1 to 296 months), 640 patients (86%) remain alive, and 100 (14%) have died. Fifty-eight patients died as a result of HL, eight died from treatment-related toxicity, and 34 died from unrelated causes (13 secondary cancer, five cardiac disease, five respiratory illness, three neurologic disorder, three gastrointestinal disorder, three other, two unknown). The 5-year FFP and OS estimates for the entire cohort were 78% and 90%, respectively. The IPS was prognostic for both FFP ($P < .001$) and OS ($P < .001$; Fig 1) The 5-year FFP ranged from 62% for patients with more than four adverse prognostic factors to 88% for patients with no adverse factors, whereas 5-year OS ranged from 67% to 98%, respectively. Outcome according to the IPS for this cohort compared with outcome reported in the original publication by Hasenclever et al[7] is listed in Table 2. In an analysis restricted to patients age $\leq$ 65 years, as in the original index (n = 686), the IPS remained prognostic for FFP ($P = .003$) with 5-year FFP ranging from 70% for patients with more than four IPS factors to 88% for patients with no adverse factors and for OS ($P < .001$) with 5-year OS ranging from 73% to 98%, respectively (Table 2 and Fig 2). Although the IPS remains prognostic for patients with HL, outcome in all risk groups has substantially improved and, notably, the improvement appears most pronounced in the poorest-risk groups.

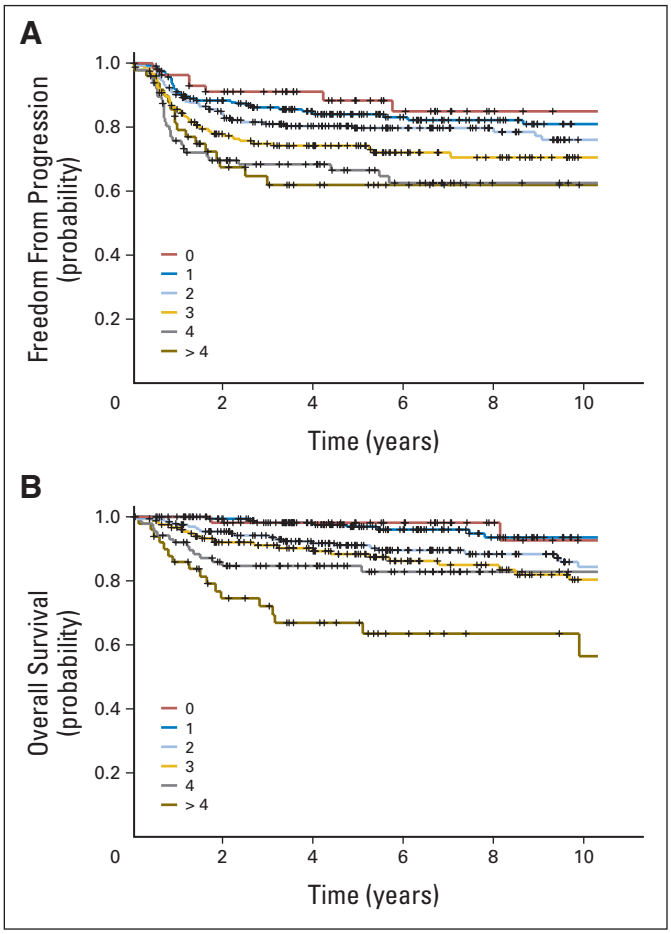

Fig 1. (A) Freedom from progression and (B) overall survival according to International Prognostic Score (IPS) factors (n = 740).

Univariate and Multivariate Analysis

Table 3 summarizes the results of univariate and multivariate analyses that examine the prognostic impact of individual IPS factors on 5-year FFP. On univariate analysis, all IPS factors remained prognostic for FFP with the exception of sex. On multivariate regression analysis, controlling for all IPS factors, only age and hemoglobin level retained independent significance.

DISCUSSION

More than a decade after the original publication of the IPS for advanced-stage HL, we have reassessed its utility to predict outcome for patients more recently treated with ABVD. Although the IPS retains its prognostic capacity, it predicts for a much narrower range of outcomes than previously noted. More specifically, outcome in patients with higher-risk scores has significantly improved, such that the 5-year FFP for patients with five or more factors has increased from 42% to 62%. Interestingly, the proportion of patients with low-risk scores (IPS 0 to 3; 81%) and high-risk scores (IPS $\geq$ 4; 19%) is identical to that previously reported[7]; however, the difference in 5-year FFP between these groups has diminished to 15%. The inability of the IPS index to identify a group of patients with sufficiently poor outcome to warrant an intensified treatment approach substantially limits its clinical relevance.

There are probably several reasons for this generalized improvement in outcome. First, improved diagnostic accuracy has largely eliminated patients with non-Hodgkin's lymphoma who may have previously been misdiagnosed as HL. The non-Hodgkin's lymphomas that may be mistaken for HL are generally associated with a poorer prognosis. Second, a greater appreciation for dose-intensity preservation, aided by the ready availability of neutrophil growth factors and improved supportive care have encouraged the administration of full-dose ABVD on the intended every-2-week schedule (without dose reduction or delay), which is crucial for optimizing efficacy.[16,22] Third, upstaging because of wide use of recent-generation imaging techniques, such as improved CT and PET/CT scanners, leads to stage migration of patients previously thought to have more limited disease. Fourth, more frequent use of high-dose chemotherapy and autologous hematopoietic stem-cell transplantation confers greater likelihood of cure in relapsed patients. This latter effect may largely account for the approximately 10% to 20% improvement in OS across all categories. Finally, although the majority of patients included in the original IPS cohort received ABVD or an equivalent regimen, more than 20% received regimens that did not contain doxorubicin, such as MOPP, which are associated with an inferior outcome.[1]

This study included patients with clinically advanced-stage disease according to the standard definition that is routinely applied for patient management (stages III or IV, or stages I or II with B symptoms or bulky disease $\geq$ 10 cm). Compared with the original IPS cohort,

Table 2. Rates of 5-Year FFP and OS According to International Prognostic Score

IPS	Patients No.	Patients %	FFP All Patients (N = 740)	FFP Age ≤ 65 Years (n = 686)	FFP Original Report	OS All Patients (N = 740)	OS Age ≤ 65 Years (n = 686)	OS Original Report
0	57	8	88 ± 5	88 ± 5	84 ± 4	98 ± 2	98 ± 2	89 ± 2
1	195	26	84 ± 3	85 ± 3	77 ± 3	97 ± 1	97 ± 1	90 ± 2
2	195	26	80 ± 3	80 ± 3	67 ± 2	91 ± 2	92 ± 2	81 ± 2
3	155	21	74 ± 3	74 ± 4	60 ± 3	88 ± 3	91 ± 3	78 ± 3
4	88	12	67 ± 5	68 ± 6	51 ± 4	85 ± 4	88 ± 4	61 ± 4
≥ 5	50	7	62 ± 7	70 ± 8	42 ± 5	67 ± 7	73 ± 7	56 ± 5
0-3	602	81	81 ± 2	81 ± 2	70 ± 2	93 ± 1	94 ± 1	83 ± 1
≥ 4	138	19	65 ± 4	69 ± 4	47 ± 2	78 ± 4	83 ± 4	59 ± 2

NOTE. Plus-minus values are rate estimates plus or minus standard error.
Abbreviations: FFP, freedom from progression; IPS, International Prognostic Score; OS, overall survival.

fewer patients in our study had stage III or IV disease (59% *v* 87%). Although this may, in part, contribute to the difference seen in outcome, it more likely reflects the degree of arbitrariness associated with the assignment of stage. In our institution, patients with locally extensive disease contiguously involving multiple extranodal sites are commonly designated as stage IIe, whereas in other centers, these patients may be designated as stage IV. The stage distribution within our cohort is similar to that reported within recent clinical trials of advanced-stage HL.[8-11]

Recently reported clinical trials have confirmed these favorable results following treatment with ABVD. In a multicenter randomized trial published by Hoskin et al,[10] patients with advanced-stage HL treated with six to eight cycles of ABVD exhibited 5-year progression-free survival and OS rates of 76% and 90%, respectively. Similarly, Gobbi et al[8] reported a 5-year failure-free survival rate of 78%, and Johnson et al[11] reported a 3-year event-free survival rate of 75% in

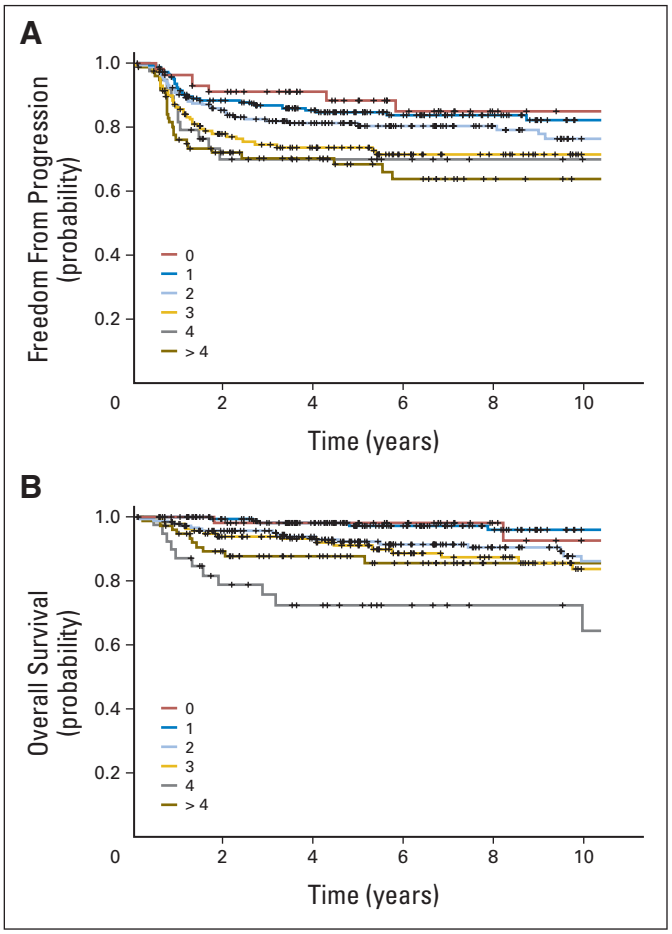

Fig 2. (A) Freedom from progression and (B) overall survival according to International Prognostic Score (IPS) factors for patients age ≤ 65 years (n = 686).

Table 3. Results of the Univariate and Multivariate Analysis of FFP at 5 Years

IPS Factor	Univariate Analysis No. of Patients	Univariate Analysis 5-Year FFP (%)	Univariate Analysis *P*	Multivariate Analysis HR	Multivariate Analysis 95% CI	Multivariate Analysis *P*
Age, years						
≥ 45	196	74 ± 3	.031	1.40	1.01 to 1.93	.042
< 45	544	79 ± 2				
Albumin, g/L						
< 40	474	75 ± 2	.036			N/S
≥ 40	266	82 ± 2				
WBC × 10^9/L						
≥ 15	114	70 ± 4	.047			N/S
< 15	626	79 ± 2				
Hemoglobin, g/L						
< 105	147	66 ± 4	< .001	1.90	1.36 to 2.64	< .001
≥ 105	593	81 ± 2				
Lymphocyte count × 10^9/L or < 8%						
< 0.6	160	71 ± 4	.038			N/S
≥ 0.6	580	80 ± 2				
Sex						
Male	403	76 ± 2	.190			N/S
Female	337	80 ± 2				
Stage						
IV	177	70 ± 4	.020			N/S
I to III	563	80 ± 2				

NOTE. Plus-minus values are rate estimates plus or minus standard error.
Abbreviations: FFP, freedom from progression; HR, hazard ratio; IPS, International Prognostic Score; N/S, not significant.

patients treated with ABVD. Finally, in the Eastern Cooperative Oncology Group trial of ABVD versus Stanford V,[9] 5-year failure-free survival of 73% and OS of 88% were seen in the ABVD arm.

It should be noted that the original IPS was developed in a cohort of patients age ≤ 65 years. We elected to include patients of all ages in our analysis to reflect outcomes of all patients encountered in routine clinical practice. In an analysis limited to younger patients (age ≤ 65 years; n = 686), outcome in the highest-risk group (IPS > 4) was even better with a 5-year FFP of 70% and a 5-year OS of 73%. Given the excellent prognosis following ABVD for all patients, including the poorest risk group, initial treatment with a more intensified therapy associated with additional toxicity becomes difficult to justify.

Evaluation of individual IPS factors demonstrated that all factors, with the exception of gender, were prognostic on univariate analysis, but only age and hemoglobin level retained significance on multivariate analysis. The intention of this study was not to create a new prognostic index but rather to evaluate outcomes according to the model as originally developed. It should be acknowledged that this study is likely underpowered to make definitive statements regarding the prognostic impact of individual factors.

Although the concept of a clinical index remains attractive because of ease of use and ready availability of data, there is a need to evolve beyond it to identify patients with the poorest risk. Greater insight into the biology of HL has demonstrated that there is an intimate relationship between the malignant cells and reactive cells of the microenvironment that enables the tumor to thrive and evade immune surveillance.[23] Novel biomarkers identified through gene expression profiling studies may eventually allow for a more accurate determination of the biologic correlates of treatment failure.[24-26] Similarly, the correlation of early FDG-PET response with long-term outcome may provide a valuable early predictor to enable individual tailoring of therapy.[27]

In the meantime, until such indices are developed and validated, the IPS will likely continue to be routinely used. This study confirms that the IPS remains prognostic in patients receiving ABVD, but the range of outcomes it delineates would seem insufficient to justify a change in initial clinical management. However, results from recently completed trials, such as European Organisation for Research and Treatment of Cancer (EORTC) 20012 [Comparison of Two Combination Chemotherapy Regimens in Treating Patients With Stage III or Stage IV Hodgkin's Lymphoma] evaluating BEACOPP versus ABVD in high-risk advanced-stage HL, will provide further guidance in this regard. The generalized improvement in outcome seen in recent years with ABVD must be acknowledged, particularly when comparing current trial results with historical outcomes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Alden A. Moccia, Joseph M. Connors, Laurie H. Sehn
Provision of study materials or patients: Paul J. Hoskins
Collection and assembly of data: Alden A. Moccia, Jane Donaldson, Paul J. Hoskins, Brian Skinnider, Joseph M. Connors, Laurie H. Sehn
Data analysis and interpretation: Alden A. Moccia, Mukesh Chhanabhai, Richard J. Klasa, Kerry J. Savage, Tamara N. Shenkier, Graham W. Slack, Brian Skinnider, Randy D. Gascoyne, Joseph M. Connors, Laurie H. Sehn
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Canellos GP, Anderson JR, Propert KJ, et al: Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 327:1478-1484, 1992
2. Canellos GP, Niedzwiecki D: Long-term follow-up of Hodgkin's disease trial. N Engl J Med 346:1417-1418, 2002
3. Duggan DB, Petroni GR, Johnson JL, et al: Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: Report of an intergroup trial. J Clin Oncol 21:607-614, 2003
4. Bonadonna G, Zucali R, Monfardini S, et al: Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 36:252-259, 1975
5. Diehl V, Franklin J, Pfreundschuh M, et al: Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 348:2386-2395, 2003
6. Viviani S, Zinzani PL, Rambaldi A, et al: ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. N Engl J Med 365:203-212, 2011
7. Hasenclever D, Diehl V: A prognostic score for advanced Hodgkin's disease: International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 339:1506-1514, 1998
8. Gobbi PG, Levis A, Chisesi T, et al: ABVD versus modified Stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: Final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol 23:9198-9207, 2005
9. Gordon LI, Hong F, Fisher RI, et al: A randomized Phase III trial of ABVD vs Stanford V +/− radiation therapy in locally extensive and advanced stage Hodgkin's lymphoma: An Intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). Blood 116, 2010 (abstr 415)
10. Hoskin PJ, Lowry L, Horwich A, et al: Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol 27:5390-5396, 2009
11. Johnson PW, Radford JA, Cullen MH, et al: Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: Results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519). J Clin Oncol 23:9208-9218, 2005
12. Braziel RM, Oyama K: Mistaken diagnoses of Hodgkin's disease. Hematol Oncol Clin North Am 11:863-892, 1997
13. Glaser SL, Swartz WG: Time trends in Hodgkin's disease incidence: The role of diagnostic accuracy. Cancer 66:2196-2204, 1990
14. Hartge P, Devesa SS: Quantification of the impact of known risk factors on time trends in non-Hodgkin's lymphoma incidence. Cancer Res 52:5566s-5569s, 1992
15. Brosteanu O, Hasenclever D, Loeffler M, et al: Low acute hematological toxicity during chemotherapy predicts reduced disease control in advanced Hodgkin's disease. Ann Hematol 83:176-182, 2004
16. Landgren O, Algernon C, Axdorph U, et al: Hodgkin's lymphoma in the elderly with special reference to type and intensity of chemotherapy in relation to prognosis. Haematologica 88:438-444, 2003
17. Feinstein AR, Sosin DM, Wells CK: The Will Rogers phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 312:1604-1608, 1985
18. Hutchings M, Gallamini A: Functional imaging, in Engert A, Horning S (eds): Hodgkin Lymphoma: Berlin, Germany, Springer-Verlag, 2011, pp 81-82
19. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
20. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

21. Cox DR: Regression models and life tables. J R Stat Soc B 34:187-220, 1972

22. van Rijswijk RE, Haanen C, Dekker AW, et al: Dose intensity of MOPP chemotherapy and survival in Hodgkin's disease. J Clin Oncol 7:1776-1782, 1989

23. Steidl C, Connors JM, Gascoyne RD: Molecular pathogenesis of Hodgkin's lymphoma: Increasing evidence of the importance of the microenvironment. J Clin Oncol 29:1812-1826, 2011

24. Chetaille B, Bertucci F, Finetti P, et al: Molecular profiling of classical Hodgkin lymphoma tissues uncovers variations in the tumor microenvironment and correlations with EBV infection and outcome. Blood 113:2765-3775, 2009

25. Sánchez-Aguilera A, Montalbán C, de la Cueva P, et al: Tumor microenvironment and mitotic checkpoint are key factors in the outcome of classic Hodgkin lymphoma. Blood 108:662-668, 2006

26. Steidl C, Lee T, Shah SP, et al: Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. N Engl J Med 362:875-885, 2010

27. Gallamini A, Hutchings M, Rigacci L, et al: Early interim 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: A report from a joint Italian-Danish study. J Clin Oncol 25:3746-3752, 2007

