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CHAPTER 42

Contributions of the International Database on Hodgkin's Disease

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Throughout this textbook several authors repeatedly refer to the International Database on Hodgkin's Disease (IDHD) and analyses performed in this context. The IDHD initiative has been a milestone in the history of international collaboration in the field. This chapter serves as a description of what has been done by the IDHD, what results have been obtained, and the impact it has had on further research.

The idea for the IDHD originated at the First International Symposium on Hodgkin's Disease held 1987 in Cologne, Germany. Several prognostic-factor analyses had been performed by various groups by that time. However, there was no consensus about which prognostic factors should be taken into account, what their relative importance was, and how this depends on the endpoints considered. Available analyses differed remarkably in the spectrum of patients included, parameters considered, and statistical methodology. A second controversy at the Cologne Symposium centered around the long-term sequelae experienced by Hodgkin's disease patients, particularly those who had achieved a complete remission. Reports were available indicating increased risks of secondary neoplasms and other health hazards. However, the data sets reported by various groups were small and potentially biased. Several investigators therefore agreed at the Cologne meeting to plan a systematic metaanalysis on these issues.

The initiative was then taken over by the colleagues of the European Organization for Research and Treatment of Cancer (EORTC), who coordinated the project, aiming to present a first analysis on the occasion of an international symposium planned to be held in Paris in 1989 to commemorate the retirement of Professor Maurice Tubiana. Drs. Michel Henry-Amar and Reiner Somers deserve the credit for having pursued this tremendous effort.

Most of the larger institutions and cooperative groups in the Western World with extensive experience in the management of Hodgkin's disease were approached in 1988 for potential interest in contributing to the development of such a large database. A steering committee was formed to promote the IDHD, to regulate access to the data, and to stimulate new studies using the data collected. Twenty institutions/cooperative groups (see Appendix) agreed to participate by sending data in a standardized coding format to be analyzed by a common statistical design specified in a written protocol. In a sequence of meetings held in London, Paris, and Toronto, study protocols and regulations for data submission, publication, and data access were agreed on. During these meetings, adjustments of the study protocol and of the biostatistical evaluation strategies were discussed.

Data were obtained from patients randomized on prospective trials and from patients treated by standardized observational protocols. Requested data were restricted to factors previously reported to be of prognostic importance. Initial clinical presentation, extent of staging, type of treatment, treatment outcome, site and time to relapse, length of survival, cause of death, and development of second cancers were requested. Data were often simplified to facilitate statistical analysis. For example, radiation therapy was categorized into three groups: localized or involved-field, regional, or extended-field radiation therapy. Data were analyzed by one of us

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(M. H.-A.) with the use of a specific database management program developed at the Institut Gustave Roussy Department of Biostatistics and Epidemiology in Paris. The data were first presented at the Paris International Workshop and Symposium held on June 28–30, 1989. The proceedings were published in 1990 (1,2). The collaborative group subsequently had several plenary meetings on the occasion of international meetings related to lymphomas in Lugano 1990, Cologne 1991, Lugano 1993, and Cologne 1995 and 1998. A summary of the important results is presented subsequently.

After 1990, several additional studies were initiated, which are also discussed below: (a) salvage of relapse of early Hodgkin's disease initially treated with radiotherapy; (b) direct estimate at diagnosis of the prognosis of Hodgkin's disease patients; (c) risk of intercurrent death after Hodgkin's disease; and (d) treatment-related acute leukemia risk after Hodgkin's disease.

General meetings of all contributors were organized at the Second and Third International Symposia on Hodgkin's Lymphoma held in Cologne, Germany, in 1991 and 1994, during which updated information was presented (3–5).

THE INTERNATIONAL DATABASE ON HODGKIN'S DISEASE DATA SET

Overall data on 14,308 adult patients diagnosed from the early 1960s to 1984 were collected. Table 1 describes the contributions of the cancer centers and study groups. Table 2 provides a description of the study cohort. Most of the patients were treated in the 1970s, and only a few in the 1960s. Radiotherapy alone was the most frequent therapy, but combined-modality treatment has become more popular in the last decade. It should be noted that most of the patients registered were treated with MOPP or MOPP-like regimens if chemotherapy was applied. Adriamycin-containing modalities are rare in this data set. Although complete data were submitted for most parameters, there were some with a great deal of missing data, such as hemoglobin, ESR, albumin, and the extent of massive mediastinal tumor. Futhermore, several data items were not collected, such as date of primary treatment evaluation, treatment duration, dose of chemotherapy or radiotherapy, relapse treatment, and outcome.

In several respects the data submitted had varying degrees of accuracy. Some but not all trial groups coded histopathologic diagnosis reviewed by an expert panel. Coding of causes of death also varied with regard to completeness and accuracy. Biological parameters often could not be provided in relation to the normal values used in the respective laboratories. It therefore became obvious that the dataset and any analyses based on it would have limitations related to data completeness, accuracy, and consistency. On the other hand, the data set comprised the vast majority of all data collected in prospective trials available at that time. It can therefore be considered as representative of the status achieved in diagnosis and treatment in Western Europe, North America, and other countries meeting these standards.

TABLE 1. *Distribution of patients included by center and clinical stage*

Center	Clinical Stage				Total
	I	II	III	IV	
B.N.L.I. (UK)	623	837	615	463	2,538
EORTC Lymphoma Group	593	987	110	111	1,801
Stanford Univ Med Center (USA)	186	886	481	110	1,663
Princess Margaret Hospital (Canada)	228	430	229	160	1,047
Southwest Oncology Group (USA)	72	274	334	255	935
M. D. Anderson Cancer Center (USA)	190	422	157	101	870
Royal Marsden Hosp., London (UK)	214	357	159	0	730
St. Bartholomew's Hosp., London (UK)	129	231	146	104	610
G.A.T.L.A. (Argentina)	64	163	250	114	591
Universita di Pavia (Italy)	41	180	222	86	529
Joint Center for Radiation Therapy (USA)	133	303	83	3	522
Finsen Institute (Denmark)	122	182	88	86	478
Fondation Bergonié Bordeaux (France)	117	179	116	29	441
German Hodgkin Study Group (FRG)	29	140	144	87	400
Groupe Pierre et Marie Curie (France)	105	204	26	0	335
Christie Hospital, Manchester (UK)	38	76	58	127	299
The Institute of Oncology, Lubljana (Yugoslavia)	47	64	71	18	200
University of Minnesota Health Sciences Center (USA)	39	135	7	0	181
University of Nebraska (USA)	10	32	28	8	78
Yale University (USA)	6	23	23	8	60
Total	2,986	6,105	3,347	1,870	14,308

BNLI, British National Lymphoma Investigation; EORTC, European Organization for the Research and Development of Cancer; GATLA, Grupo Argentina de Tratamiento de la Leucemia Agoda.

TABLE 2. *Description of the IDHD cohort*

Initial Patient characteristics	
Sex	
Male	59.8%
Age (mean, in years)	33.5
15–19	12.4%
20–29	36.3%
30–39	23.6%
40–49	12.8%
50–59	8.2%
60–69	4.9%
70–79	1.4%
80+	0.4%
Clinical stage	
I	23.5%
II	45.1%
III	22.1%
IV	9.3%
Histologic type	
Lymphocytic predominance (LP)	7.7%
Nodulor sclerosing (NS)	62.0%
Mixed cellularity (MC)	25.9%
Lymphocytic depletion (LD)	2.1%
Unclassified	2.3%
Date of diagnosis	
1960–1969	8.2%
1970–1979	57.4%
1980–1984	34.4%
Treatment characteristics	
Splenectomy	45.0%
Irradiation alone	46.9%
Localized	6.5%
Regional	17.8%
Extended	22.6%
Chemotherapy alone	18.4%
MOPP-like	16.0%
Other types	2.4%
Combined modalities	34.7%
Localized RT and MOPP-like	9.2%
Localized RT and CT other types	2.1%
Regional RT and MOPP-like	8.4%
Regional RT and CT other types	2.7%
Extended RT and MOPP-like	11.9%
Extended RT and CT other types	0.4%

RT, radiotherapy; CT, chemotherapy; localized RT, involved-field RT; regional RT, mantle-field or inverted-Y RT; extended RT, (sub)total nodal RT; MOPP-like chemotherapy, combination of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) or alternatives with minor variations; CT other types, mostly Adriamycin-containing regimens.

TRENDS

The IDHD dataset shows several systematic trends in diagnostic and treatment policies over the years. It is remarkable that the relative frequency of nodular sclerosis subtype was steadily increasing while those of the mixed-cellular and lymphocyte predominant subtypes were diminishing from the 1960s to the 1980s. The reasons are unclear but are likely related to a shift in diagnostic techniques than to epidemiologic changes.

Laparotomy frequency changed. For example, it was performed in fewer than 20% of the CS III patients in the 1960s and 1980s, but over half of the patients underwent this procedure in the 1970s. This was accompanied by a gradual shift from radiotherapy alone to combined modality and chemotherapy alone over the years.

An important result of the IDHD was the insight that a remarkable gain in disease control and a reduction of mortality were obtained in the 1970s compared with the 1960s. However, surprisingly little further improvement was evident in the cohort diagnosed in the 1980s. Figure 1 illustrates this finding for overall survival and relapse-free survival. It is noteworthy that the trials conducted in the 1960s frequently were unicenter trials with a standardized strategy whereas data of the later periods stem from cooperative multicenter trials. Hence, one can speculate about a certain regression-to-the-mean effect in Figure 1. However this effect is unlikely to change the general judgment of only very limited improvement of treatment outcomes between the 1970s and the 1980s.

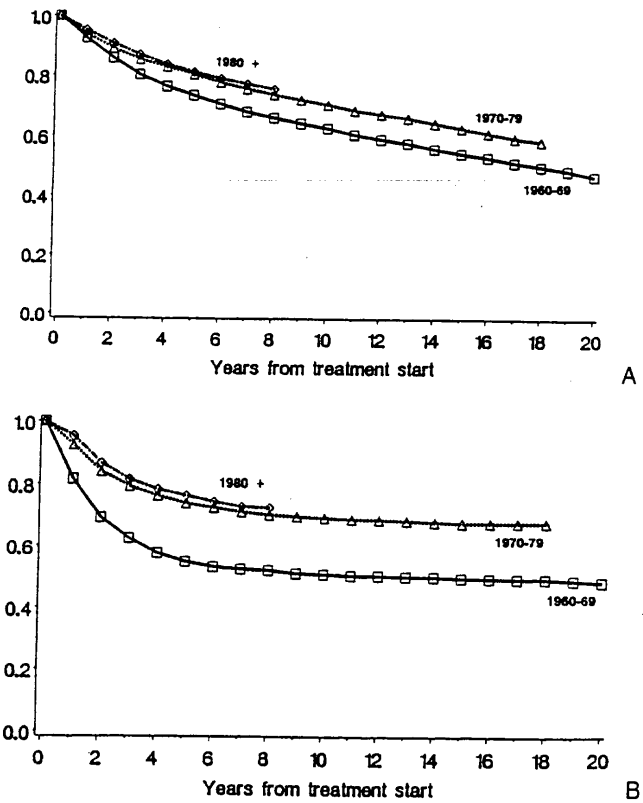


FIG. 1. Trends in treatment efficacy over the decades. **A:** Overall survival of all stages by treatment period (1960–1969, 1,115 patients; 1970–1979, 8,104 patients; 1980–, 5,096 patients). **B:** Relapse-free survival for all stages by treatment period (1960–1969, 1,008 patients; 1970–1979, 6,970 patients; 1980–, 4,338 patients). (Modified from ref. 1.)

TABLE 3. *Prognostic factors for positive laparotomy findings in patients staged clinically*

	CS IA	CS IIA	CS IB, CS IIB
Adverse factors			
Male gender	+	+	+
MC, LD histology	+	+	
Age over 50	+		
No mediastinal involvement		+	+
Many lymph node areas involved		+	+
Extranodal disease			+
High ESR		(+)	
Observed proportion of positive laparotomy			
No risk factor	0.11	0.19	0.11
All risk factors	0.38	0.69	0.51

CS, clinical stage; MC, mixed cellularity; LD, lymphocyte depletion, ESR, erythrocyte sedimentation rate.

PROGNOSTIC FACTORS FOR LAPAROTOMY FINDINGS

An important question addressed by the IDHD was whether the outcome of a staging laparotomy could be reliably predicted on the basis of the clinical stage and additional noninvasive measurements, that is, serum parameters.

Data on 4,049 laparotomized patients in CS I and II were analyzed using logistic regression methodology. Table 3 summarizes the results. In stage CS IA, only male gender, mixed cellularity and lymphocyte depletion histology, and age over 50 were associated with a higher probability of a positive laparotomy. In CS IIA, male gender, mixed cellularity and lymphocyte depletion histology, absence of mediastinal involvement, involvement of many lymph node areas, and high ESR were associated with positive laparotomy. In CS IB and IIB, male gender, absence of mediastinal involvement, and extranodal disease were predictive for infradiaphragmatic involvement.

It is, however, remarkable that in over 10% of the patients having none of these adverse factors, abdominal disease was detected by laparotomy. On the other hand, patients with many or all factors present frequently had no infradiaphragmatic disease. Depending on the clinical stage, this proportion varied between 30% and 60%. A more detailed description of these issues is presented in this volume in Chapter 18.

Thus, although a variety of noninvasive factors could be shown to be of prognostic value for laparotomy findings, the overall sensitivity and specificity obtained by the best prediction models were generally not sufficient to base rigorous treatment decisions (e.g., radiation alone to involved fields based on clinical staging) on them.

PROGNOSTIC FACTORS FOR ACHIEVING COMPLETE REMISSION

Table 4 summarizes the prognostic factors for achieving complete remission after primary treatment. They were analyzed separately for each clinical stage, and two different multivariate logistic regression models were used. In the first model (A) serum parameters were ignored. In this case, age, histology (lymphocyte depletion or mixed cellularity) and B symptoms were prognostic, with relative risks between 1.2 and 1.5. In the alternative model (B) systemic symptoms were deliberately ignored to assess the role of serum parameters. In this case, ESR and serum albumin took over the role of B symptoms. This is understandable because a strong correlation between serum parameters and B symptoms was revealed. However, taken together, only a few factors appeared to be prognostic for achievement of a complete response. Ann Arbor stage and B symptoms were confirmed to be the most reliable predictors, and other parameters were of minor importance.

TABLE 4. *Prognostic factors for CR (nonlaparotomized patients)*[a]

Models	CS I (n = 1,509)	CS II (n = 2,880)	CS III (n = 1,856)	CS IV (n = 1,512)
Model A	Age	Age	Age	Age
B symptoms included	Histology	B symptoms	B symptoms	Infradiaphragmatic
Serum parameters excluded				
Model B	ESR	Age	Age	Age
B symptoms excluded		ESR/albumin	ESR/albumin	Albumin
Serum parameters included				Infradiaphragmatic

[a]Relative risks between 1.2 and 1.5.

CR, complete remission; CS, clinical stage; ESR, erythrocyte sedimentation rate.

TABLE 5. *Prognostic factors for relapse*[a]

CS I (n = 2,783)	CS II (n = 5,414)	CS III (n = 2,568)	CS IV (n = 819)
Age	Age	Age	Age
Gender	Gender	Gender	
Histology[b]	Histology[b]	Histology	Histology
Laparotomy	Laparotomy	Laparotomy	
B symptoms[b]	B symptoms	B symptoms	
Infradiaphragmatic[b]	No. LN areas	No. LN areas	
ESR, Hb[b]	ESR, Hb, Alb[b]	MT	

CS, clinical stage; LN, lymph node; MT, mediastinal disease; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; ALB, albumin.
[a]Relative risks between 1.2 and 1.8.
[b]RR > 1.5.

PROGNOSTIC FACTORS FOR RELAPSE-FREE SURVIVAL

In contrast to complete response, more factors were found to contribute to the prediction of the quality of a complete response once it was achieved. Table 5 summarizes the result of a multivariate analysis based on the proportional hazard model, which was stratified for treatment period and type of treatment. These models were constructed under the simplifying assumptions that prognostic factors are effective over the entire time of the observation and that there are no interactions with treatment modalities. Because data were pooled from various risk-adapted treatment protocols, it was evident that expectations of detecting many new prognostic factors had to be moderate. It was therefore remarkable to find evidence that several factors beyond the Ann Arbor factors had independent contributions to the prediction of relapse-free survival. Old age and male gender were already well known to be unfavorable; lymphocyte depletion and mixed cellularity histology had an adverse role in all stages but most prominently in CS I and CS II, where the relative risks exceeded 1.5. B symptoms and infradiaphragmatic disease appeared to be associated with unfavorable prognosis in stage I. It was particularly noteworthy that clinical stages II and III proved to be heterogeneous. The extent of the disease, as measured by the number of lymph node areas involved, plays a role in stages II and III. This finding suggests a considerable heterogeneity of these stages, which could be taken into account in the treatment allocation. Furthermore, serum parameters such as ESR, hemoglobin, and serum albumin appeared to play a role in stages I and II if added as single factors to the above models. However, because of the missing-value problem, their role had to be interpreted with some caution. No relevant prognostic factors could be identified for stage IV. As a conclusion of the IDHD analysis, it was not considered justified to identify a very high-risk group that might be submitted to very aggressive forms of primary treatments such as high-dose chemotherapy.

A few years later an improved prognostic metaanalysis for advanced-stage disease was undertaken by Hasenclever et al. (6). In their analysis a more complete and better standardized data set was submitted, and the endpoints considered were time to treatment failure and disease-specific survival. The analysis showed seven independent factors to be relevant, the first five of which were similar to findings in the IDHD: stage, old age, male gender, low hemoglobin, low serum albumin, leukocytosis, and lymphocytopenia (for details see Chapter 19).

PROGNOSTIC FACTORS FOR DISEASE-SPECIFIC SURVIVAL

Disease-specific survival was also analyzed using proportional hazard models as mentioned above. In contrast to relapse-free survival, the prognostic factors for survival remained few (Table 6). The role of age and gender is not surprising. The lymphocyte-depleted subtype, and to a smaller degree the mixed-cellularity subtype were unfavorable indicators. This was not new. A new factor was the number of lymph node areas involved in stages I, IIB, and

TABLE 6. *Prognostic factors for death from Hodgkin's disease*

CS I and IIA	CS I and IIB	CS IIIA	CS IIIB	CS IV
Age[a]	Age[a]	Age[a]	Age[a]	Age[a]
Histology[a]	Gender	Histology[a]	Histology	Gender
	Histology[a]	No. LN areas		Histology
	No. LN areas			

CS, clinical stage; LN, lymph node; MT, mediastinal disease; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; ALB, albumin.
[a]RR > 2.0.

IIIA. This parameter quantifying the extent of the disease added to the information of the stage. No contribution could be detected for serum parameters or for bulky disease, but this may have been because of the missing-value problem.

The three preceding analyses about prognostic factors for complete remission, relapse free survival, and disease-specific survival were all conducted in the first round of analyses published in 1990 (1). The key lessons were that the Ann Arbor staging system and the histopathologic classification were confirmed to be major prognostic factors for the disease with respect to all endpoints. However, there was evidence that this list could and should be amended by additional parameters related to more details on the spread of disease and tumor burden (e.g., infradiaphragmatic disease, number of lymph node areas), to biological activity (e.g., hemoglobin, ESR, serum albumin), and to constitutive parameters such as age and gender.

SURVIVAL AFTER RELAPSE

The data gathered in the IDHD permitted some insight into survival after relapse. When occurrence of a relapse was included as a time-dependent covariate into proporional hazard models, it was by far the most prominent adverse prognostic factor with respect to overall survival. Relative risks increased by more than fivefold. Figure 2 illustrates that relapses after initial stage I and II disease had a somewhat better prognosis than after an initial advanced stage. Only 30% of advanced-stage patients experiencing a relapse survived more than 10 years.

Recently a more detailed reanalysis of the IDHD data was undertaken to investigate survival in patients with limited disease who were initially treated with radiotherapy alone. In patients who relapsed after a laparotomy staged PS I or PS II disease treated with radiation alone, over 30% died within 10 years of Hodgkin's disease (7). It was irrelevant in this context whether the relapse occurred within the first year after the initial treatment or many years later. Disease-specific survival after relapse was shown to be worse if the patient was over 40 years of age or had MC histology or extranodal involvement. Almost identical results were found when the analysis was repeated for patients in clinical stages I and II who underwent radiotherapy alone (8).

PROGNOSTICATING OVERALL SURVIVAL

An analysis of prognostic factors for long-term outcomes usually has the objective of investigating heterogeneity in a population with respect to specific endpoints. For this purpose, proportional hazard models are widely used. They belong to a family of semiparametric models that specify relative risks under restrictive assumptions about the proportionality of hazard functions. However, these models do not require quantitative specifications of the shape of these hazard functions or the related survival functions.

If the objective of modeling is not to analyze population heterogeneity but to predict the survival of individual patients, it is advantageous to have a quantitative specification of the survival function. In a reanalysis of IDHD data, Gobbi and co-workers (9) investigated a variety of different parametric survival functions. They found that a log-normal model would fit the observed overall survival data best. This model was then fitted to the data on 12,647 patients treated from 1970 to 1984, adjusting for several prognostic factors.

As a result, the authors derived an equation for the median expected survival time. In this equation the following seven factors were taken into account: stage, B symptoms, age, gender, histopathology, serum albumin, and number of lymph node areas involved. Thus, this model also illustrated the role of several prognostic factors besides Ann Arbor stage with respect to survival.

CAUSES OF DEATH

The IDHD data set permitted an analysis of the causes of death. Figure 3 illustrates that the mortality after diagnosis of Hodgkin's disease is increased over the mortality

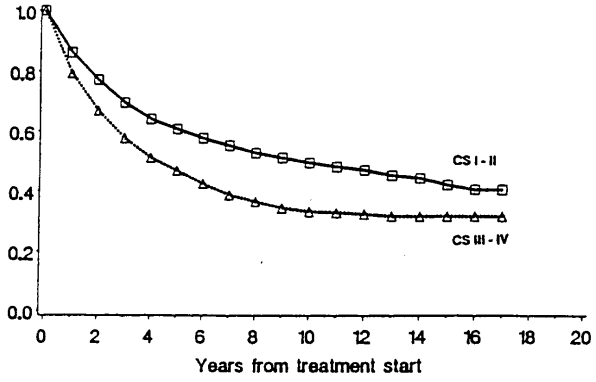


FIG. 2. Survival after relapse in patients treated between 1970 and 1984 by clinical stage at first presentation (CS I–II, 1,878 patients; CS III–IV, 1,257 patients). (Modified from ref. 1.)

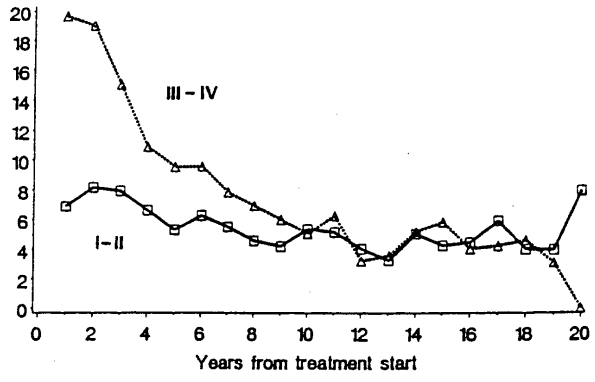


FIG. 3. Standardized mortality ratio (SMR) for all stages as a function of time by clinical stage including all causes of death (CS I–II, 9,041 patients; CS III–IV, 5,184 patients). (Modified from ref. 1.)

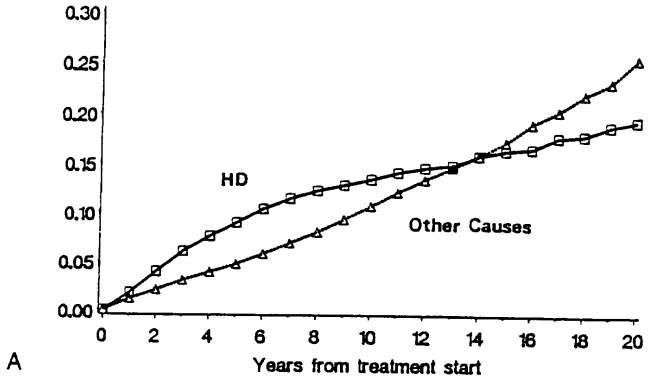
in the normal reference population not only in the first years after diagnosis but for at least 20 years thereafter. The high mortality in CS III and IV is certainly expected, and the elevation for several years reflects to some degree the high risk for relapse. However, there remains a four- to sixfold increase in risk of death compared with a comparable general population. With regard to clinical stages I and II, it is even more remarkable that the initial risk of death is only slightly higher than the risk in subsequent years.

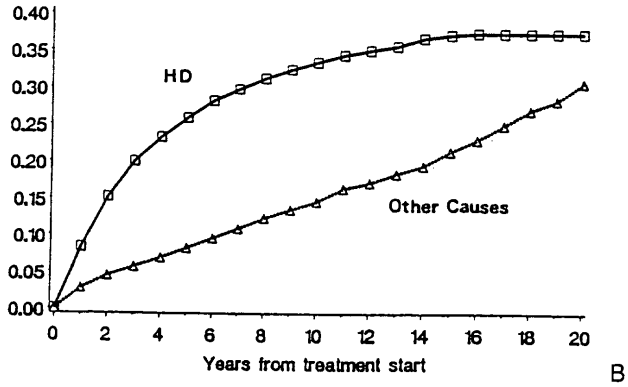
Figure 4 provides some more detailed insight. It describes the cumulative incidence in the IDHD cohort, separating death from Hodgkin's disease from that of other causes. It is evident that death from disease was the overwhelming process in advanced stages. After a steep increase in the first 6 to 8 years, the disease continued to cause death virtually over 20 years at a low rate. In limited stages, the cumulative incidence of death from disease had a strikingly different pattern. Death from disease and other causes of death were of the same order of magnitude over the entire time course and finally the disease contributed less than other causes.

A more detailed analysis was undertaken to discriminate causes of death not related to the disease (1,2). Figure 4C shows that treatment-related mortality had a prominent contribution with a cumulative incidence of almost 3% after 20 years. Another important cause of death was the occurrence of secondary neoplasms. A total of 413 deaths were reported to be caused by either acute leukemias, non-Hodgkin's lymphomas, or solid tumors. The cumulative incidence of this cause of death rose continuously over the observation period and reached about 10% after 20 years. Taken together, treatment-related deaths and secondary neoplasms accounted for about half of the deaths not caused by the disease. Because, however, the standard mortality ratio was increased about four- to sixfold (see Fig. 3), a large proportion of the deaths coded as "intercurrent death" or "cause unspecified" must be assumed to be associated with the disease and/or treatment as well. This issue is discussed in greater depth in Chapters 32, 34, and 35 of this volume.

SECONDARY NEOPLASMS

An important contribution of the IDHD was an insight into the epidemiology of secondary neoplasms following Hodgkin's disease. When the analysis was restricted to those 12,411 patients who had survived at least 1 year after diagnosis, overall, 631 secondary neoplasms were observed. Of these, 158 were acute leukemias or myelodysplastic syndromes (AL), 106 were non-Hodgkin's lymphomas (NHL), and 367 solid tumors (ST, male 229, female 138). The most frequent solid tumors in men were long carcinomas (68), basal cell carcinoma of the skin (31), and carcinomas of the digestive tract (53). In women, long carcinomas (27), breast cancer (39), basal cell carcinoma of the skin (14), and *in situ* cervical carcinomas (9) were most frequent.





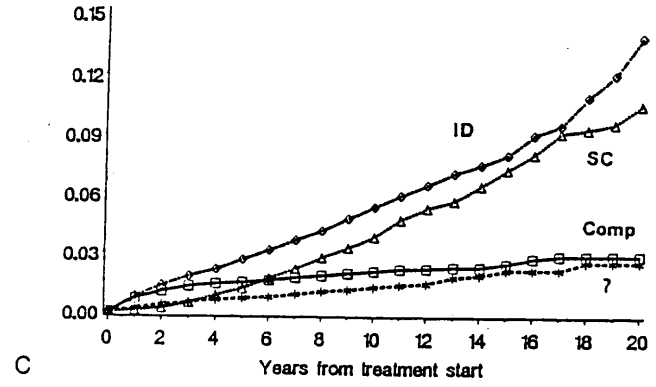


FIG. 4. Cumulative incidence of death by stage and cause of death. **A:** Early stages (9,041 patients; deaths from disease, 1,242; other causes, 715). **B:** Advanced stages (5,184 patients; death from disease, 1,768; other causes, 414). **C:** Causes of death other than disease (ID, intercurrent death, 577 patients; SC, secondary cancers, 413 patients; TRD, treatment-related death, 233 patients; ?, cause unspecified, 139 patients). (Modified from ref. 1.)

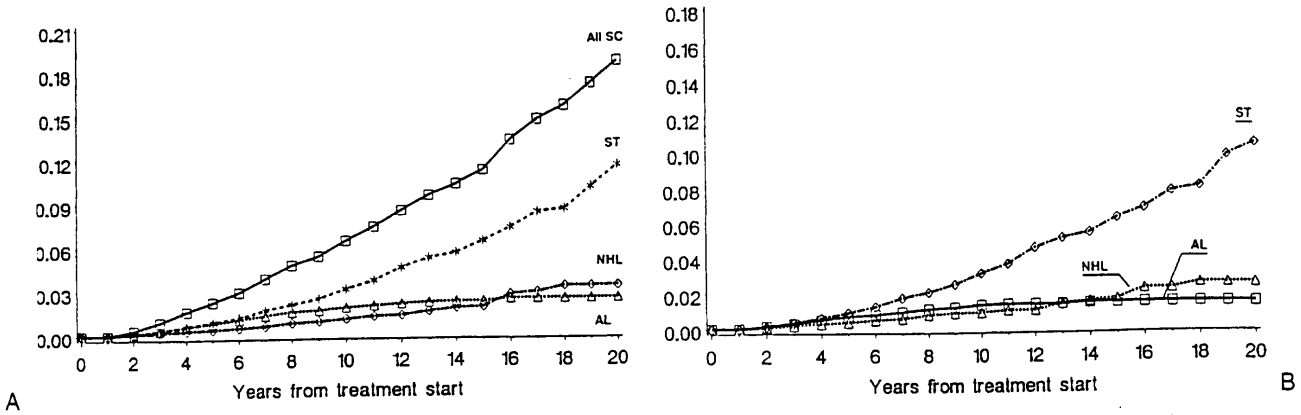


FIG. 5. Cumulative incidence of secondary neoplasms. **A:** All patients who survived primary treatment at least 1 year (12,411 patients; acute leukemia, 158; NHL, 106; solid tumors, 367). **B:** All patients in continuous complete remission who survived primary treatment at least 1 year (11,241 patients; acute leukemia, 87; NHL, 68; solid tumors, 231). (Modified from ref. 1.)

TABLE 7. *Time-dependent proportional hazards model on selected second cancer risk (relative risk) for 12,411 patients who survived at least 1 year after Hodgkin's disease diagnosis*

	AL (204–208)	NHL (200)	ST (140–194)
Sex ratio (male/female)	1.1	1.9	1.2
Age			
15–19 years	1.0	1.0	1.0
20–29 years	1.3	1.4	0.8
30–39 years	1.4	3.7[d]	1.3
40–49 years	2.5[d]	6.0[e]	3.1[e]
50–59 years	4.0[e]	10.5[e]	8.4[e]
≥60 years	4.5[e]	21.6[e]	12.0[e]
Histology			
LP	1.5	1.8[e]	0.9
NS	1.0	1.0	1.0
MC	0.9	1.0	0.9
LD	0.6	0.4	1.2
Unclassified	0.9	2.1	1.6
Response to initial treatment			
No complete remission/CR	2.1[d]	0.9	1.0
Initial treatment			
Splenectomy (yes/no)	1.3[b]	1.4[b]	1.0
Localized RT	1.0	1.0	1.0
Regional RT	1.2	0.9	1.2
Extended RT	1.3	1.2	1.7[e]
MOPP-like CT	3.5[d]	2.0[b]	1.2
Other CT	4.3[c]	2.4	1.0
RT (any type) and MOPP-like CT	5.3[e]	1.8	—
Localized/regional RT and MOPP-like CT	—	—	0.8
Extended RT and MOPP-like CT	—	—	1.8[b]
RT (any type) and CT other types	3.0	4.5[d]	0.7
Clinical outcome (time-dependent covariate)			
No relapse	1.0	1.0	1.0
First relapse treated with RT	1.7	3.7[d]	1.1
First relapse treated with CT	5.3[e]	2.3[d]	1.2
First relapse treated with RT + CT	2.8[e]	2.2[d]	1.3[b]
Global chi-square	168	159	411
p value (df)	<.001 (22)	<.001 (22)	<.001 (23)

[a]AL, acute leukemia; NHL, non-Hodgkin's lymphoma; ST, solid tumor. IC D0-9 codes shown in parentheses. ICD0-9 173 and 180 excluded from ST. Relative risk for a model allowing all the variables to be considered together.

[b]$p < .10$; [c]$p < .05$; [d]$p < .01$; [e]$p < .001$; two-sided test.

LP, lymphocyte predominance; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion; RT, radiation therapy.

When compared to the general population, the ratio of observed (O) to expected (E) cases was 1.7 in both male and female patients for solid tumors. This risk increase appears moderate but accounted for about 170 excess tumors. In contrast the O/E-risk was found to be elevated for about 10 years by a factor of 30, accounting for about 150 excess cases.

Figure 5A illustrates the cumulative incidence measures for all secondary neoplasms and the various subtypes for the entire cohort. The cumulative incidence for ST increased from 6% after 10 years to 11% after 15 years and to 19% after 20 years. For acute leukemia the respective rates were 1.8%, 2.2%, and 2.4%. For non-Hodgkin's lymphoma they were 1.0%, 1.8% and 3.2%, respectively. Figure 5B describes the same analysis restricted to patients who were in continuous complete remission. The difference between the two figures illustrates the contribution treatment for relapse makes with repect to the occurrence of secondary neoplasms.

A more thorough analysis of prognostic factors for incidence of secondary tumors was performed (1,5). Variables included in the model were gender, age, histology, response to initial treatment, initial treatment type (involved-field or extended-field irradiation, total nodal irradiation, MOPP-like chemotherapy, combined-modality therapy), relapse, and type of treatment at relapse. Results are summarized in Table 7. Factors significantly correlated with an increased risk of acute leukemia were age above 40 and MOPP-like chemotherapy given alone or in combination with radiation therapy. In addition, chemotherapy-treated relapses were associated with a higher risk for acute leukemia. This was considered an indication that chemotherapy played a role in leukemia induction. However, it was not clear whether Hodgkin's disease itself is associated with an intrinsic risk for leukemia.

Factors associated with increased risk of secondary non-Hodgkin's lymphoma were age above 30, male gender, combination chemotherapy other than MOPP and radiation therapy, as treatment for relapse.

Only age above 40 and extended-field radiation given alone or in combination with chemotherapy were associated with an increased incidence of solid tumor.

To further highlight the remarkable contribution of relapse treatment to this phenomenon, Figure 3B illustrates the cumulative incidence of these malignancies if restricted to those patients who are in continuous complete remission. For acute leukemia the incidence was 1.3% and 1.5% after 10 and 15 years, respectively. A separate prognostic analysis was performed for these patients. Combined-modality treatments including MOPP-like chemotherapies were associated with the higher risk of secondary acute leukemia. In contrast, MOPP-like chemotherapy alone had only slightly increased risks. Furthermore, there was a small but significant relationship between acute leukemia and splenectomy.

SPECIFIC ASPECTS OF LEUKEMIA INDUCTION

Some further insight into the induction of AL was recently obtained by a sophisticated reanalysis of IDHD data using a novel biometric technique (10,11). The approach was based on a parametric model of latent carcinogenesis, which had been shown to be an effective method in analyzing time to tumor occurence. The basic model assumptions can be summarized as follows. It is assumed that there is an induction step that causes preleukemic lesions (e.g., microscopic clones). The number of such lesions indicates the strength of the induction process and may be related to dose and timing of the hazardous process. Such lesions are assumed to follow a Poisson distribution. The development of such lesions to a manifest leukemia usually depends on a complex sequence of events. For simplicity, it is assumed that this time, called progression time, has a distribution that, in particular, considers that some lesions never develop into a leukemia. If several lesions are induced, the time for the first to develop a manifest leukemia is called latency time. Clearly, such latency times are also distributed over a population.

When this model was fit to the IDHD data, it was considered that leukemia induction could occur during initial treatment and during relapse treatment. Relapse treatment implied that lesions could be induced at later times in addition to the lesions left from initial treatment. Two groups of patients in the IDHD were considered. One group received radiotherapy alone as primary treatment (5,403 cases) and MOPP-like treatment in case of relapse (1,777 such relapses). A second group received MOPP-like chemotherapy as primary treatment (6,113 cases) and some other kind of chemotherapy in case of relapse (1,223 such relapses).

The major findings are summarized in Figure 6. Of the treatment regimens considered, radiotherapy alone had the lowest leukemia induction potency. MOPP-like chemotherapy, in contrast, had a much higher potency (about sevenfold) to lead to leukemia than radiation alone. An even higher leukemia induction was revealed by relapse treatments with chemotherapy other than the primary MOPP-like schemes. Unfortunately, the IDHD did not provide more detailed data on the type of these relapse treatments, but it can be assumed to have incorporated a wide variety of schemes including high-dose chemotherapy and subsequent bone marrow transplantation. The most remarkable finding, however, is that the hazard curves in fact had very similar shapes, with peaks at about 4 years, medians at about 8 years, and steep declines after 10 years. This was true following primary and relapse treatment. This finding can hence be interpreted as strong evidence for treatment-related effects.

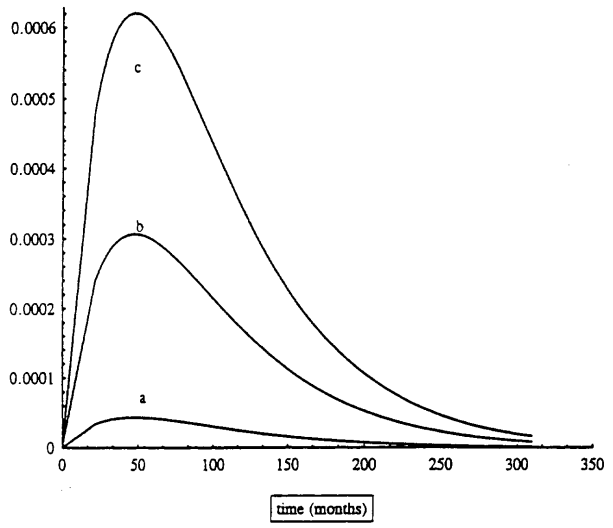


FIG. 6. Hazard functions and latency times for acute leukemia. Estimates based on parametric modeling: *lower curve,* radiotherapy alone; *middle curve,* MOPP-like chemotherapy; *upper curve,* relapse chemotherapy other than MOPP-like.

DISCUSSION

The IDHD is a historic milestone in the research on Hodgkin's disease, as it represented for the first time a collaborative effort among many of the leading cancer centers and cooperative trial groups to answer burning questions in the management of the disease. This type of metaanalysis, pooling individual patient data into one comprehensive database and analyzing them according to a jointly designed study protocol, turned out to be feasible and subsequently encouraged a couple of successor metaanalyses in this field. In particular, it encouraged the project that led to the international index for high-grade non-Hodgkin lymphomas (11), the international prognostic factor project for Hodgkin's disease (6), and a meta-analysis on chemotherapy versus combined-modality treatment in advanced-stage Hodgkin's disease (12).

The IDHD analyses have certainly influenced the scientific community remarkably. They made clear that the Ann Arbor staging system needed amendments if one were to use them to decide on treatment strategies. The analyses provided a sound platform to establish a series of such factors. They showed that prediction of laparotomy outcomes on the basis of noninvasive parameters is limited. They showed a variety of prognostic factors other than stage and their dependency on the choice of the endpoint. They revealed important insights into the mortality patterns in relation to the corresponding population but also with repect to the causes of death. In particular, they focused attention on the issue of secondary neoplasms and their relation to treatment. The data also highlighted the necessity to investigate in greater detail the so-called intercurrent deaths and treatment-related mortality.

Despite these remarkable aspects, the IDHD suffered from several limitations. One limitation was the quality of the data submitted. There were many missing values for biological parameters (e.g., size of mediastinal tumors, reviewed histology, serum parameters). There were defects in the data abstraction process (e.g., no date of primary treatment outcome, no coding of outcomes other than CR, no distinction between treatment intended and treatment given, limited attempts to quantify treatment intensity). The major limitation, however, was that any treatment comparisons were strictly excluded. It was decided that all data would be blinded with respect to the centers and treatment protocols from which they stemmed. Hence, it was impossible to compare arms of randomized trials. Therefore, it was also impossible to investigate whether prognostic factors depend on treatment strategies. Another limitation is that data on children were hardly included.

Now, 10 years after the IDHD was inaugurated, perhaps the most important limitation is that it only contains data on patients diagnosed before 1984. In particular, the contribution of Adriamycin-containing regimens was small in the database, but these regimens are now widely used. We, however, do not know to what extent the results discussed above for prognostic factors are different under these regimens. There is some evidence that leukemia induction from primary treatment might have decreased, but we do not know whether more aggressive relapse treatments outweigh this effect.

In summary, the International Database on Hodgkin's Disease collected data on over 14,000 individual patients treated in different cancer centers and trial groups according to standardized observational or randomized trial protocols. The data were collected to be submitted to a joint statistical analysis on prognostic factors for various endpoints and investigations on mortality patterns and on late sequelae. The IDHD was a milestone in the international cooperation of many trial groups, and many successor projects have directly or indirectly originated from this highly successful effort.

APPENDIX

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