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CHAPTER 19

Prognostic Factors of Hodgkin's Disease

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HISTORICAL PERSPECTIVE

Early descriptions of the natural history of untreated or palliatively treated patients with Hodgkin's disease showed a disease with a highly variable clinical course, although the disease eventually proved fatal in virtually all cases (1–5). The disease might remain localized in one lymph node region for many years without causing any deterioration in the patient's physical condition. Some uncured patients have been reported to have survived more than 20 years. At the other end of the spectrum, the disease might disseminate rapidly to other lymph node regions and internal organs and cause progressive asthenia, cachexia, and death. This highly variable course prompted and continues to prompt numerous clinical studies designed to identify new prognostic factors or improve already-established prognostic factors, so that clinicians can predict outcome more accurately in individual patients.

As early as the beginning of this century, the concept had developed that Hodgkin's disease passes through successive clinical stages with an increasing spread of the disease and progressive worsening of prognosis (1). The validity of this concept has been repeatedly confirmed, and different staging classifications have been proposed over the years based on the anatomic extent of disease (6–25). A consensus was reached at the Workshop on the Staging of Hodgkin's disease at Ann Arbor in 1971 (26), and the Ann Arbor staging classification has since been universally adopted. Its prognostic significance has been amply demonstrated (27–40). The Ann Arbor staging classification remains the basis for the evaluation of patients with Hodgkin's disease. Survival curves according to clinical Ann Arbor stage for more than 14,000 patients in the International Database on Hodgkin's Disease (33) are shown in Figure 1.

Through the years, however, it became increasingly clear that the Ann Arbor staging system could not be relied on as the only prognostic tool in Hodgkin's disease. New features of prognostic importance became recognized, many of them related to the extent and volume of disease. The extent of disease may vary considerably in stages other than stage I, and the volume of disease in individual regions is not taken into account at all in the Ann Arbor classification. At a meeting in the Cotswolds region of England in 1988, a modification of the Ann Arbor staging system was devised to incorporate a designation for number of sites and bulk (41). However, the recommendations of the Cotswolds meeting have still not been universally adopted. A multitude of other prognostic factors for different Ann Arbor stages, presentations, treatments, and outcomes have been examined, and varying combinations of some of these factors are presently being employed by different centers and groups worldwide. Thus, there is a need for a general consensus on the use of prognostic factors in Hodgkin's disease.

DIFFERENT PROGNOSTIC FACTORS AND END POINTS, AND THEIR INTERRELATION

Definition and Use of Prognostic Factors

Prognostic factors are variables measured in individual patients that offer a partial explanation of the heterogeneity observed in the outcome of a given disease—in this case, Hodgkin's disease (42). There are many reasons for studying prognostic factors in Hodgkin's disease. Prognostic factors may be used to predict the outcome of a disease. However, we cannot predict exactly for individual patients. We can offer only statements of probability, and even these will be more accurate for groups of patients than for individual patients (43).

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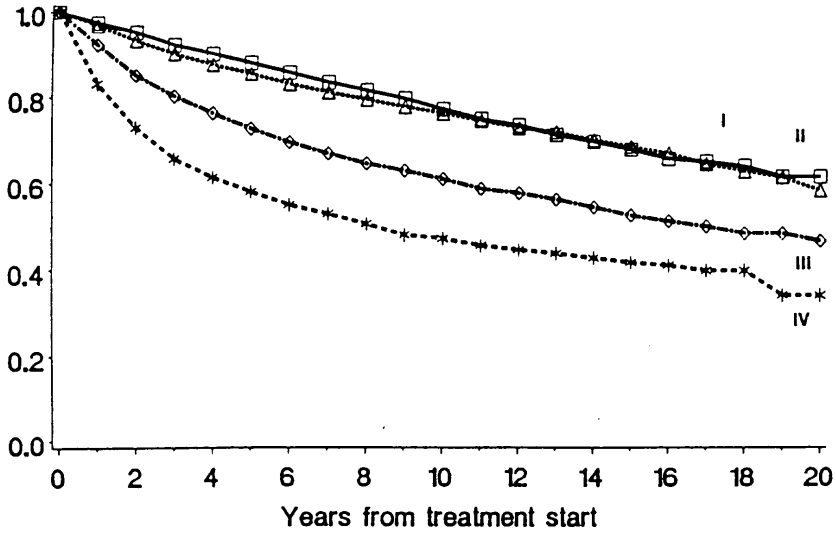

FIG. 1. Overall survival according to clinical stage for 14,037 patients in the International Database on Hodgkin's Disease treated over the past 25 years. (From ref. 33, with permission.)

On a practical level, prediction of outcome may be used to define risk groups and may thus be a determining factor in treatment selection. In the context of clinical trials, the prediction of outcome for groups of patients may be used beforehand to define eligibility and stratification criteria, and afterwards in the statistical analysis of the trial results to allow adjustments for more valid comparisons (42,43). However, it is important to realize that although known prognostic factors are important in the design and analysis of trials, they are rarely sufficiently explanatory to justify the comparison of treatments by use of nonrandomized data (44,45).

On a more theoretical level, if certain prognostic factors are found to be important, they may provide insight into a disease process and help us understand the natural history of a disease, including the effects of treatment on its course, thereby suggesting directions for future studies.

Types of Prognostic Factors

Prognostic factors can be divided into tumor-related factors and patient-related factors. Tumor-related factors reflect tumor type, extent of disease, and growth characteristics of the tumor, either directly or indirectly via surrogate measures, such as serum markers. Patient-related factors reflect the physiologic reserve of the patient (e.g., age and performance status). Both types of factors are important for outcome, but in many situations it is advisable to keep them separate, in particular if they are to form the basis for treatment selection.

Prognostic factors can also be divided according to the point in time at which they are recorded. It is generally assumed that the values of the prognostic factors are known at the point from which prognosis or time to response is measured (43). This type of prognostic factor, for which a single value is determined for each patient at the outset of the study, is called a fixed covariate. However, other prognostic variables (e.g., time to response, received dose intensity, toxicity of treatment) may be measured after the outset of a study and may even change over time. This type of prognostic factor is called a time-dependent covariate (42). Although the study of time-dependent covariates may be very interesting biologically, their use as prognostic factors is fraught with problems because the time-dependent covariates may well themselves be affected by treatment. Variables that are affected by treatment should never be used when adjusted treatment comparisons are performed (43).

Different End Points

Analyses of prognostic factors attempt to relate patient variables to an outcome variable (and to each other). In considering and comparing the results of prognostic factor analyses, it is important to define the outcome variable clearly. A simple outcome variable could be response to therapy (yes or no). However, the vast majority of patients with Hodgkin's disease respond to therapy, so a response to therapy is by no means an indication of cure or long-term survival. Disease-free survival or relapse-free survival would be a relevant outcome variable. However, strictly speaking, only patients achieving complete remission should be analyzed, and only from the time at which complete remission is achieved. It continues to be difficult to define complete remission accurately in Hodgkin's disease, particularly for disease in the mediastinum, and the exact time at which it is achieved is often uncertain. A more useful outcome variable is therefore freedom from progression or time to failure—that is, time from registration until recurrence after remission or progression or death without remission. The ultimate outcome variable remains survival. It is tempting to increase the sensitivity of analyses by analyzing cause-specific survival in Hodgkin's disease—that is, time from regis-

tration to death from Hodgkin's disease with censoring of deaths from other causes. However, it can be surprisingly difficult to be certain about the exact cause of death in particular patients, and the most certain outcome variable remains overall survival—that is, time from registration to death from any cause.

Interrelations among Different Factors

For a patient variable to qualify as a useful prognostic factor, it must be significant, independent, and clinically important (46). All patient variables are potentially of prognostic significance and many prove significant in univariate analysis. However, different variables are likely to be highly interrelated and may thus be partial substitutes for one another, and only a few in fact possess independent prognostic value. The independent prognostic information contained in a cluster of correlated variables can be equally well represented by several of the variables within the cluster. The choice of the representing variable(s) may not be entirely determined by the data but depends on medical insight, practicality considerations, and the strategy of model selection. Moreover, some factors may be prognostic for certain therapies only, some may be prognostic for certain stages only, and some may be prognostic only in the context of certain other factors. Therefore, multivariate statistical analyses, often complex, are needed to determine which factors are independently significant and which factors are merely related to well-known prognostic factors but are without independent prognostic significance. A large number of studies of prognostic factors in Hodgkin's disease in which multivariate regression techniques are used have been published. Comparisons of these studies may cause some bewilderment, as different studies seem to come up with widely differing results, both in regard to the factors found to be significant and in regard to the relative importance attributed to these factors. There are many reasons for these differences between studies, and some of the main reasons are the following (47):

- Studies vary with regard to selection criteria. Studies of highly selected patient populations may miss out important factors because patients with these factors are underrepresented in the patient population studied.
- Studies vary with regard to staging investigations. In general, if the evaluation of the anatomic extent and bulk of the disease is less accurate (e.g., no laparotomy), other factors correlated with the extent of disease (e.g., hematologic, biochemical, or immunologic factors) will acquire greater significance.
- Studies vary with regard to treatment approach. Prognostic factors found in a particular study will predict outcome for other patients only if they are treated in a roughly similar way. Treatment may also influence studies of prognostic factors in a more subtle but no less important way. Intensive treatment is a prerequisite for cure in Hodgkin's disease. If a subgroup of patients for some reason (e.g., old age or other medical problems) receives suboptimal treatment, this subgroup will have a poorer prognosis that is at least partly explained by insufficient treatment. Statistical analysis cannot fully compensate for this type of confounding (48).
- Studies vary with regard to the range of factors analyzed. Obviously, a study cannot identify prognostic factors that were not analyzed in the study.
- Studies vary with regard to the number of patients analyzed. The number of patients analyzed determines the size of the prognostic difference that can be detected or reproduced in a given set of data. Typical analyses of about 300 patients have an 80% chance of detecting a prognostic difference in the order of 15% if the smaller subgroups are not too small. For an 80% chance of reproducing a difference of 8% to 10%, 800 to 1,200 patients must be included in a study.
- Studies vary with regard to cut points chosen for different variables (e.g., age and laboratory values). Even if cut points are chosen systematically (e.g., by the optimal P method), different studies will come up with different cut points (49,50).
- Studies vary with regard to the methods used for analysis. This issue is perhaps the one that creates the most bewilderment for clinicians. First, investigators commonly perform multivariate prognostic factor analyses by using the Cox proportional hazards regression model (51). Regression models can make more accurate predictions than other methods, such as stratification and recursive partitioning, provided they are used wisely. However, regression models make assumptions that must hold, at least approximately, for valid prognostic estimates to be obtained. For a study to be valid, model assumptions must be thoroughly examined and appropriate steps taken if assumptions are violated (52–54). Second, multivariate analyses are commonly applied to data materials in an exploratory manner, without any prior hypothesis, except that some of the variables entered are likely to possess some prognostic significance. Different studies of this kind will invariably identify differing factors and prognostic indices. From a statistical point of view, this variation is unproblematic because if one is primarily interested in prediction, the actual factors used are not important (42). Moreover, it is important to realize that the majority of factors identified by this type of analysis probably reflect the same underlying biologic characteristics. The multiple regression model will select a factor for inclusion in the model if its χ^2 value is the highest among the factors examined. However, another factor may have a χ^2 value that is only a fraction smaller. This other factor may well, simply by chance, be the one selected in another, similar study. Therefore, prognostic indices from different studies may be quite diverse sim-

ply by chance. As long as the purpose of the studies is merely predicting outcome, this is perfectly acceptable, provided the different indices are roughly equally good at predicting outcome. However, if the primary purpose of a study is to understand the biologic reasons why certain factors seem to be related to outcome, clearly it is essential that the specific range of factors be included in the model.

PROGNOSTIC FACTORS FOR PATHOLOGIC STAGE I–II HODGKIN'S DISEASE

Patients with apparently early-stage Hodgkin's disease after clinical staging were previously usually staged further with laparotomy and splenectomy. The purpose of staging these patients more accurately was to differentiate those who could be treated with radiotherapy alone from those who required additional chemotherapy (55–63). However, it is important to realize that although additional chemotherapy can prevent recurrence, a meta-analysis of all randomized trials of radiotherapy versus radiotherapy plus additional chemotherapy gave no indication of an improvement in survival in any subgroup of early-stage patients (64). The value of laparotomy and splenectomy as part of the staging procedure has therefore been challenged in later years, and the procedure is performed less frequently than before. However, the information gathered in the past from large series of patients staged with laparotomy and splenectomy has provided us with invaluable data on the intra-abdominal distribution of Hodgkin's disease.

Our knowledge of the extent and anatomic distribution of disease is more accurate in patients with pathologic stage (PS) I and II than in any other patients with Hodgkin's disease. Consequently, we would expect to be able to predict outcome for these patients with a high degree of precision.

Patients Treated with Radiotherapy Alone

The precise prediction of the risk for relapse is particularly important for patients treated with radiotherapy alone because one important use of prognostic factors is to define groups with an acceptable risk for relapse, who can be treated with radiotherapy alone, and groups with an unacceptable risk, for whom combined-modality therapy is deemed advisable (63).

The anatomic extent of disease may vary considerably in stage II, and the number of involved regions has been shown to possess independent prognostic significance. An early study from the Royal Marsden Hospital found a high relapse rate in patients with multiple nodal areas involved (65). Follow-up studies from the same institution confirmed the importance of the number of sites of nodal involvement for disease-free survival and also showed an influence of borderline significance on overall survival (66,67). Figure 2 shows relapse-free survival curves according to the number of involved sites for 131 PS I and II patients treated with radiotherapy alone at the Royal Marsden. Another early study, from the University of Florida, in which about half the patients were staged with laparotomy, found that one of the most important factors in predicting relapse is the number of sites initially involved (68). Again, this was confirmed in a follow-up study, which also showed a highly significant influence on cause-specific survival (69). In the European Organization for the Research and Treatment of Cancer (EORTC) H_2 trial, the number of involved lymph node areas proved to be a highly significant independent factor for relapse-free survival and of borderline significance for overall survival (70,71). Studies from the University of Minnesota also showed that the number of involved sites is important for relapse-free survival and overall survival (72,73). A study from the Massachusetts General Hospital, in which most patients were staged with laparotomy, showed a significantly increased risk for relapse with increasing number of sites of involvement, but no difference for survival (74). The large Australasian study on patterns of care, in which most patients were staged with laparotomy, showed an increased risk for in-field relapse with an increasing number of involved lymph node sites, whereas there was no relation to out-of-field recurrences and to overall survival (75). However, in two other large series of patients, one from Stanford University and one from Harvard University, there was no significant independent prognostic influence of the number of involved regions (76,77). In the Danish National Hodgkin Study, the number of involved regions was sig-

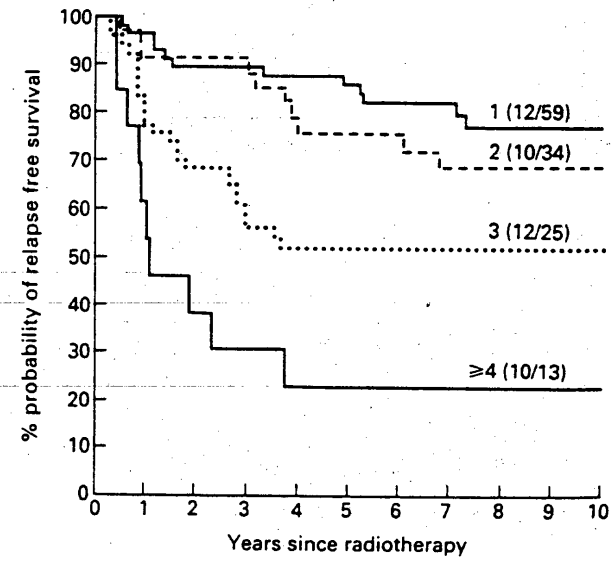

FIG. 2. Relapse-free survival according to number of involved sites for 131 patients in pathologic stage (PS) I–II treated with radiotherapy alone at the Royal Marsden Hospital. (From ref. 67, with permission.)

nificant both for relapse-free survival and overall survival (78,79). However, an estimate of the total tumor burden (*vide infra*) was an even more powerful prognostic factor, rendering the number of involved regions nonsignificant in multivariate analysis.

The volume of disease in individual regions is left out of consideration in the Ann Arbor classification. Realizing that the size of the tumor mass in single regions may be important, the Cotswolds modification of the Ann Arbor classification tried to remedy this by incorporating a designation of bulk. The extent of mediastinal involvement has attracted particular interest because mediastinal involvement, even bulky, is quite common. Measurement of mediastinal tumor mass has been carried out in different ways. Some studies have measured the maximal width of mediastinal disease in absolute terms (68,80–83). Others have used the ratios of maximum mediastinal width to maximum chest diameter (76,78,81,84–86), to chest diameter at T5-6 (87,88), to chest diameter at T6-7 (89), or to chest diameter at the carina (90). No one of these methods seems to be clearly superior to the others (91). The area of mediastinal disease on posteroanterior chest radiographs (92) and the volume of mediastinal disease on thoracic computed tomograms (93) have also been employed. Whatever method has been used, the general consensus is that disease-free survival is poorer for patients with large mediastinal masses than for patients with small or no mediastinal masses (76,77,80–83,85–90,92–100). However, the presence of a large mediastinal mass is correlated with other adverse prognostic factors, such as a large number of involved sites (84), stage II (vs. stage I) (80,87,94,97)), B symptoms (87,89), and hilar involvement (87). However, even in multivariate analyses that take other prognostic factors into account, a large mediastinal mass remains an important independent prognostic factor inversely related to disease-free survival (67,76,101). Figure 3 shows relapse-free survival curves according to mediastinal size for 315 patients in PS IA and IIA treated with radiotherapy alone at the Joint Center for Radiation Therapy. Most patients who relapse after initial radiotherapy for PS I and II are salvaged with chemotherapy. Consequently, the prognostic impact of large mediastinal adenopathy on overall survival is much smaller but still statistically significant in a number of studies (85,87,88,96). In regions other than the mediastinum, large tumor masses are uncommon in PS I and II. Most studies analyze mediastinal and peripheral bulk together, thus obscuring any independent significance of peripheral bulk (67,81,88). A study from the University of Florida did, however, show that the prognostic importance of maximum tumor dimension in any site is greater than the prognostic significance of the size of mediastinal mass alone, suggesting that bulky disease in sites other than the mediastinum is indeed prognostically significant (69).

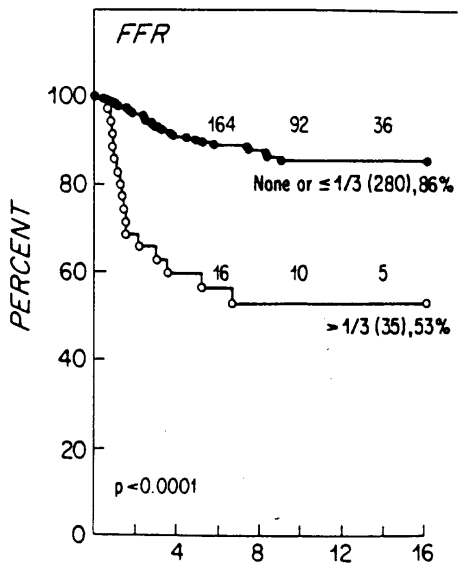

FIG. 3. Relapse-free survival according to mediastinal size for 315 patients in pathologic stages (PS) IA and IIA treated with radiotherapy alone at the Joint Center for Radiation Therapy. (From ref. 77, with permission.)

The number of involved regions and the tumor size in each region have thus been shown to be important for prognosis in PS I and II treated with radiotherapy alone. Multivariate analyses of data from the Danish National Hodgkin Study have shown that the estimated total tumor burden, combining the number of involved regions with the tumor size in each region, is by far the most important prognostic factor both for disease-free survival and overall survival (78,79,102). These findings were subsequently confirmed in a Swedish study (103). Figure 4 shows disease-free survival curves according to the estimated total tumor burden for 142 patients in PS I and II treated with radiotherapy alone in the Danish National Hodgkin Study.

The prognostic significance of different disease localizations has also been investigated. Mediastinal involvement has been associated with poorer disease-free survival (89) and overall survival (97,101). It would, however, seem to be tumor size rather than localization in the mediastinum that is important, because only bulky mediastinal involvement influences prognosis adversely, whereas nonbulky mediastinal involvement confers the same prognosis as no mediastinal involvement (67,82, 85–87,90,94,96,101,104,105). Hilar nodal involvement is rare in patients without mediastinal involvement (83,87, 89,98). A higher relapse rate was demonstrated in patients with small or no mediastinal involvement if hilar disease was present than if it was not (87), and poorer survival was demonstrated in patients with large mediastinal adenopathy if hilar disease was present (101). Other studies have not been able to demonstrate any prognostic effect of hilar adenopathy independent of mediastinal involvement (83,98). Infradiaphragmatic early-

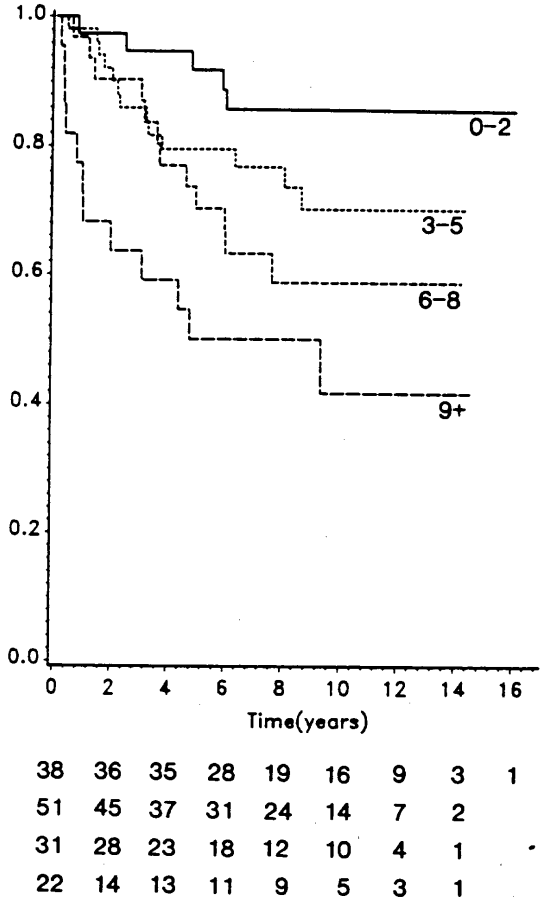

FIG. 4. Disease-free survival according to estimated total tumor burden for 142 patients in pathologic stage (PS) I–II treated with radiotherapy alone in the Danish National Hodgkin Study. (From ref. 154, with permission.)

stage disease is rare. In pathologically staged patients, infradiaphragmatic disease has not been shown to have a worse prognosis than supradiaphragmatic disease, except for patients presenting with intra-abdominal disease without peripheral adenopathy, who often have bulky disease at diagnosis and a high relapse rate (106–119). Localized extralymphatic (E) lesions were included in the Ann Arbor classification of stages I and II (26) because some studies had shown that the prognosis of patients with these lesions was no worse than that of other patients with the corresponding stages. For PS I and II patients treated with radiotherapy alone, some studies have found no prognostic influence of E lesions (76,96), whereas others have found a poorer prognosis in patients with E lesions (81,83,120). The question of whether E lesions are or are not of prognostic importance is still controversial, and it is further complicated by the fact that there is wide disagreement as to what is and what is not an E lesion (121,122). In conclusion, there seems to be no definitive evidence that particular localizations of PS I and II disease significantly affect prognosis. Prognosis seems to be determined by the bulk of disease rather than its precise anatomic localization, provided that appropriate therapy can be administered. With radiotherapy alone this may be a problem, and a number of studies suggest that patients with involvement of the pericardial nodes, extensive pericardial involvement, significant involvement of the lung or pleura, or bulky axillary disease may not be suitable for radiotherapy alone because of the toxicity associated with the large radiation volumes needed to treat these areas (63,100,123–130).

Systemic B symptoms (weight loss, unexplained fever, night sweats) have consistently been shown to influence prognosis adversely in PS I and II treated with radiotherapy alone (35,76,88,101). Repeated evaluations of the prognostic significance of B symptoms indicate that night sweats have no prognostic significance (95,131, 132) but that severe pruritus, although rarely encountered, confers a particularly ominous prognosis (131,133, 134). Fever seems to have a greater impact than weight loss, and the combination of fever and weight loss confers a significantly poorer prognosis than either symptom alone (95). Mild symptoms that do not qualify as B symptoms in the Ann Arbor definition had no prognostic influence at all (131), and symptoms that were more severe than is required to qualify as B symptoms did not further compromise prognosis (132). The presence of B symptoms is, however, correlated with the anatomic extent of disease. In studies in which the extent of disease was analyzed in greater detail, the systemic symptoms were correlated with the total tumor burden and lost their prognostic significance in multivariate analysis (78,79). This correlation of B symptoms with amount of tumor is consistent with the notion, supported by several lines of evidence, that B symptoms could be caused by aberrant production of endogenous cytokines, either by tumor cells or by reactive bystander cells (135–140).

A consensus on the histopathologic classification of Hodgkin's disease was reached in 1965 at the Rye conference (141). Slight modifications of the classification were proposed by the International Lymphoma Study Group in 1996 (142), the most important modification being the recognition of lymphocyte predominance as a distinct entity. Lymphocyte predominance is a rare subtype of Hodgkin's disease, affecting only 5% to 10% of patients with Hodgkin's disease. In cases of PS I–II treated with radiotherapy alone, patients who have lymphocyte predominance seem to have a favorable prognosis compared with patients who have other histologic subtypes, but this difference may partly be attributed to earlier stage at presentation (143–145). The precise prognostic significance of the lymphocyte predominance subtype, in particular whether the pattern of continuous late relapse found in some studies (146,147) is real, awaits further study. It is hoped that the final analyses of the multinational project on lymphocyte predominance Hodgkin's disease initiated by the European Task Force on Lymphoma will provide us with a clearer picture (148). Lymphocyte

depletion is rare, very rare in early-stage disease, and its incidence is decreasing, most likely as a result of changes in diagnostic criteria (149,150).

The overwhelming majority of PS I–II patients have either the nodular sclerosis or mixed cellularity subtype, and histologic subtype usually does not provide prognostic information (76,143,151–155). One of the problems with the histopathologic classification is that in many series nodular sclerosis constitutes up to 75% of all cases (35,151,156,157). Attempts have therefore been made to subdivide the nodular sclerosis type into prognostic subgroups (158–163). The British National Lymphoma Investigation has proposed a subdivision into grades 1 and 2 of the nodular sclerosis type according to the cellular composition of the nodules of tumor tissue (156,164). In their large series of PS I–II patients, they showed that cytologic subtypes with extensive and easily recognized areas of lymphocyte depletion or numerous pleomorphic Hodgkin's cells (nodular sclerosis grade 2) were associated with a decreased survival independent of stage (152,164). The prognostic significance of nodular sclerosis grades in PS I–II was confirmed in one study (165), but not in another, larger study (166). The issue is thus still unsettled. In the Danish National Hodgkin Study of PS I and II patients, the Rye classification and the British National Lymphoma Investigation subclassification of nodular sclerosis were compared with an alternative classification based on a simple count of tumor cells in sections (154). In this study, univariate analysis showed tumor cell count to be the more significant of these classifications for prognosis. None of these histologic classifications proved independently significant in multivariate analysis. Significantly, however, a combination of the estimate of the total macroscopic tumor burden and the tumor cell count, yielding an estimate of the total tumor cell burden, was shown to be the most powerful prognostic factor of all. In conclusion, histologic subtype is not at present an important prognostic factor in PS I and II and should not play a major part in treatment decisions. However, further research, particularly in lymphocyte predominance, is in progress.

Older age has frequently been associated with poor survival in studies of prognostic factors in Hodgkin's disease (11,19,21,24,28,29,31,32,35,36,39,66,67,73,103,167–174). In many of these studies, however, deaths from all causes have been included without any correction, thus inevitably leading to a poorer prognosis for older patients. Age remained an important prognostic factor even in studies in which survival was related to that of the general population (171,172,175), in which deaths from causes other than Hodgkin's disease were excluded (36), or in which other prognostic factors were taken into account in stratified (173) or multivariate analysis (33,152,176,177). Older patients commonly have underlying medical problems that may preclude adequate staging and treatment in some cases (155,168,173,178). Adequate staging and appropriate intensive therapy is a prerequisite for cure in Hodgkin's disease, and suboptimal staging and treatment of some older patients may well explain their poorer prognosis. Significantly, in a study of patients in PS IA and IIA treated with radiotherapy alone, an increased mortality was found in older patients, but this was caused by secondary tumors rather than by recurrent Hodgkin's disease (77). In another study, older patients with early-stage disease who were staged and treated aggressively had the same potential for cure as younger patients (168). In a series from St. Bartholomew's Hospital of stage II patients treated with radiotherapy alone, age had no influence on the duration of complete remission (179). The issue regarding the prognostic importance of age *per se* is still not settled, but evidence from more recent analyses would seem to indicate that the natural history of Hodgkin's disease in older patients does not differ from that in younger patients, but that the reduced tolerance to staging and treatment may largely explain the differences seen in outcome (155).

Sex is an established prognostic factor in Hodgkin's disease, with men having a poorer prognosis than women (8,11,16,19,21,24,31,32,132,167,175). Male patients are more likely to have adverse prognostic factors (35). Nevertheless, even in multivariate analyses of PS I and II, sex often comes out as an independent prognostic factor, although not a very important one (79,132,152). Data on the prognostic influence of race are very sparse. When other prognostic factors are taken into account, prognosis seems basically the same irrespective of race, but a low socioeconomic status is highly correlated with advanced disease at diagnosis and exerts a profound influence on prognosis, especially in third world countries (180–183).

Biologic parameters (e.g., hematologic, biochemical, or immunologic indicators) are not generally very important in PS I–II, in which our knowledge of the extent and volume of tumor is quite accurate. An elevated erythrocyte sedimentation rate (ESR) is a well-established adverse prognostic factor in Hodgkin's disease (32,152,184,185). However, the ESR is correlated with other prognostic factors, such as B symptoms, age, sex, mediastinal involvement, number of involved lymph node areas, histologic subtype, stage, and total tumor burden (32,33,78,79,170,184–186). In multivariate analyses of PS I–II patients treated with radiotherapy alone, an elevated ESR had no independent prognostic significance (67,78). In a study from Manchester, a low lymphocyte count and a low albumin level were independently significant for relapse-free survival (88). Many other biologic parameters have been shown to correlate with disease activity, but their independent prognostic significance in PS I–II has not been proved (187).

The prognostic factors known to be independently significant in PS I and II treated with radiotherapy alone are summarized in Table 1.

TABLE 1. *Prognostic factors shown to be independently significant in PS I–II treated with radiotherapy alone*

Number of involved regions
Large tumor mass, particularly mediastinal
Tumor burden (combination of number of involved regions and tumor size in each region)
B symptoms (fever, weight loss, possibly severe pruritus)
(Histologic subtype)
Age
Sex

PS, pathologic stage.

Patients Receiving Combined-modality Therapy

Today, patients subjected to laparotomy and splenectomy as part of the staging procedure are given combined-modality therapy only if they turn out to be in PS III or IV (63,188). Our knowledge of prognostic factors in this group of patients therefore stems from earlier results, mostly from trials in which PS I–II patients were randomized between radiotherapy alone and combined-modality therapy. As mentioned previously, a meta-analysis in which individual patient data were used showed that the addition of chemotherapy to radiotherapy prevents recurrence but does not improve survival (64). In the meta-analysis, comparisons were made of the reduction in risk for failure with combined-modality therapy between different prognostic subgroups. The size of reduction in risk for failure seen in patients with different stages of disease, with and without B symptoms, both male and female, and of different ages was remarkably similar. Thus, there is no indication that prognostic factors for patients who receive combined-modality therapy are different from the factors for patients treated with radiotherapy alone. However, as fewer recurrences are seen with combined-modality therapy, a larger number of patients need to be analyzed for a factor to show statistical significance for relapse-free survival.

Patients Treated with Chemotherapy Alone

Chemotherapy as the sole treatment of PS I–II patients is not standard, and few data are therefore available. Two randomized trials have tested radiotherapy versus chemotherapy in these patients. In one trial, 54 patients in PS I–II were treated with chemotherapy alone; seven of them relapsed, all in previously involved sites (189). B symptoms and sex seemed to influence relapse-free survival, but the number of patients was too small for meaningful analysis of prognostic factors. In another trial, 44 patients in PS I–IIA were treated with chemotherapy alone; 12 relapsed, eight of them in previously involved areas (190). Patients with bulky disease or three or more involved areas seemed to relapse more frequently, but numbers were small (191). The precise delineation of prognostic factors in PS I–II treated with chemotherapy alone thus awaits further studies.

PROGNOSTIC FACTORS FOR LAPAROTOMY FINDINGS IN CLINICAL STAGE I–II HODGKIN'S DISEASE

Staging laparotomy with splenectomy was previously performed in large numbers of patients in clinical stage (CS) I–II, yielding a PS that differed from CS in about 30% of patients (192–196). Staging laparotomy remains the most precise way to determine the presence and extent of abdominal involvement. However, because of the associated morbidity and the fact that no survival benefit has been found in patients staged with laparotomy (197–201), the procedure is used less often today and has been largely abandoned in Europe. Instead, prognostic factors predicting the likelihood of occult disease in the abdomen are potentially useful and may aid in treatment decisions.

A number of studies have examined clinical factors for prediction of abdominal involvement in patients with supradiaphragmatic CS I or II who were subsequently staged by laparotomy. A large multivariate study from the Joint Center for Radiation Therapy showed that the number of supradiaphragmatic sites, B symptoms, and male sex were independently predictive of positive laparotomy findings (196). Female patients with CS IA and male patients with CS IA and lymphocyte predominance histology or high cervical involvement had less than a 10% risk for occult abdominal involvement. Another large multivariate study, from Stanford, found the number of involved sites, sex, histology, and age to be significant (195). In CS I disease, female patients, patients with disease limited to the mediastinum, and male patients with lymphocyte predominance histology had less than a 5% chance of positive findings at laparotomy. In CS II, women less than 27 years of age with only two or three sites of disease had less than a 10% risk for subdiaphragmatic disease. The original Stanford data also demonstrated the predictive value of histology, sex, and age (high risk in both pediatric and older adult patients) (34). The International Database on Hodgkin's Disease analyzed laparotomy findings in a total of more than 4,000 CS I–II patients and showed that male sex, mixed cellularity and lymphocyte depletion histology, and age over 50 were associated with a higher probability of positive laparotomy findings in CS IA (33). In CS IIA, the absence of mediastinal involvement, four or more involved lymph node areas, mixed cellularity and lymphocyte depletion histology, male sex, and an elevated ESR were associated with a higher probability of positive laparotomy findings. In CS IB–IIB, male sex, absence of mediastinal involvement, and extranodal localization were associated with positive laparotomy. In the EORTC studies of favorable CS I–II patients, mediastinal involvement and male sex were correlated with positive laparotomy findings (170). The investigators also found that a combination of the number of involved regions above the diaphragm, B symptoms, and ESR was predictive of subdiaphragmatic disease. Early studies from the British National Lymphoma

TABLE 2. *Prognostic factors for laparotomy findings in supradiaphragmatic CS I–II*

Number of involved regions above the diaphragm
Disease confined to upper cervical nodes
Mediastinal involvement (variable influence)
B symptoms
Age (high risk in both pediatric and older adult patients)
Sex
Histology
Erythrocyte sedimentation rate

CS, clinical stage.

Investigation and from Australia found that the presence of B symptoms increases the risk for positive laparotomy, but no relation was found between particular sites of supradiaphragmatic disease or sex and risk for intraabdominal disease (59,202). A study from the Royal Marsden found young age and male sex to be predictive of positive laparotomy findings (203). Additionally, in CS I they found that nonbulky, high cervical nodes were associated with a low risk for abdominal disease. A study from Alabama found B symptoms, histology, and sex to be independently predictive of laparotomy findings (194). A Spanish study found B symptoms, histology, and number of involved regions to be predictive of laparotomy findings, and they found increasing size of the mediastinum to be inversely correlated with the risk for abdominal disease (204). Table 2 summarizes the prognostic factors found to be significant predictors of laparotomy findings in supradiaphragmatic CS I–II disease.

In CS I–II patients with infradiaphragmatic presentation, CS IA patients had a low risk for positive findings at laparotomy if the disease was confined to inguinofemoral nodes (108–112).

PROGNOSTIC FACTORS FOR CLINICAL STAGE I–II HODGKIN'S DISEASE

Prognostic factors in CS I and II disease are to some extent similar to the ones in PS I and II. However, because our knowledge of the extent and anatomic distribution of the disease is far less accurate in patients staged without laparotomy, there is greater variation in outcome in these patients. Factors predicting positive laparotomy findings will also be predictive for outcome in these patients, because they indicate patients with more extensive disease. Additional factors, usually providing an indirect or surrogate measure of the total tumor burden and possibly also the growth characteristics of the tumor, have also proved valuable in CS patients because the direct measures in these patients are less accurate than in PS patients.

Patients Treated with Radiotherapy Alone

For a number of years, many centers treated patients with radiotherapy alone only if a staging laparotomy had been carried out to ensure that no occult abdominal disease was present. However, a number of centers have treated CS I–II patients with radiotherapy alone, and it is now clear that although the relapse rate is higher than in PS I–II, there is no difference in survival results (197–201).

In the EORTC studies of CS I–II, the number of involved regions was found to be independently significant for both disease-free survival and overall survival (70,71,170,175). In multivariate analyses of the International Database on Hodgkin's Disease, stratified for treatment and laparotomy, the number of involved regions proved significant for both disease-free survival and cause-specific survival in CS IB and IIB (33). Analyses from the Princess Margaret Hospital in Toronto, which has a large experience with radiotherapy alone in CS I–II, did not show a significant influence of the number of sites (or tumor burden), but few patients with multiple sites (or large tumor burden) were included in their material (40,205).

Patients in CS I–II with large mediastinal masses have rarely been treated with radiotherapy alone because of the high risk for relapse known from studies of PS I–II patients. Data from Toronto did, however, show a significantly higher intrathoracic relapse rate in patients with mediastinal bulk (40). The prognostic importance of a large tumor in peripheral regions has not been documented.

In regard to disease localization, CS I and II patients with disease confined to the upper cervical region have a particularly good prognosis with radiotherapy alone (35,40,170), probably because these patients are unlikely to have occult abdominal disease (*vide supra*). Subdiaphragmatic presentation in CS I–II seemed to have a decreased disease-free survival with radiotherapy alone in a couple of studies, but this was probably because it seemed to be slightly more advanced at the time of diagnosis than supradiaphragmatic disease (40,113,206). Overall, as for PS I–II, there is no clear evidence that any particular disease localization affects prognosis, except in cases in which particular localizations are associated with a particularly small or large extent of disease.

The presence of B symptoms is correlated with the extent of disease and predicts for positive laparotomy findings (33,35,176,186). Hence, B symptoms are also prognostically significant in CS I–II treated with radiotherapy alone (33,40,170,175). Figure 5 shows overall survival curves according to B symptoms for 9,087 CS I–II patients in the International Database on Hodgkin's Disease, most of whom were treated with radiotherapy alone. Histologic subtype is also prognostic for laparotomy findings and is therefore prognostically significant in some studies of CS I–II (33,40,167,170,175,205).

Older age is associated with a higher risk for occult abdominal disease. Also, as mentioned above, underlying medical problems may preclude adequate staging and

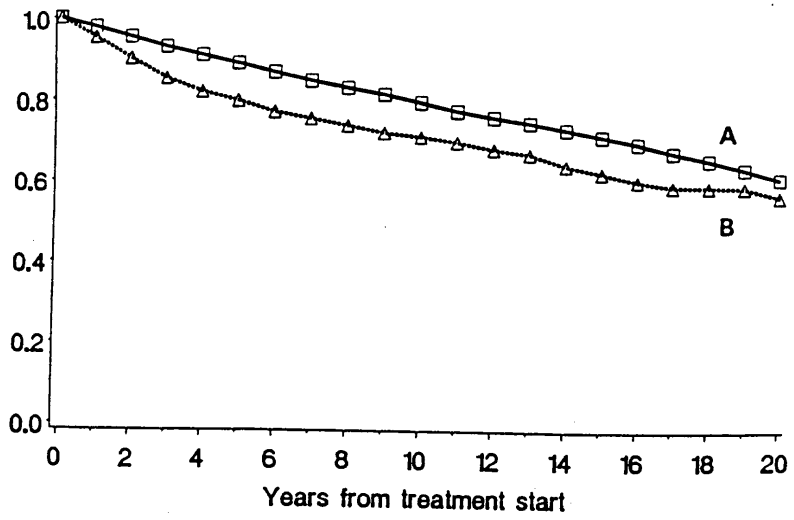

FIG. 5. Overall survival according to B symptoms for 9,087 patients in clinical stage (CS) I–II in the International Database on Hodgkin's Disease. (From ref. 33, with permission.)

treatment in some older patients. Older age was associated with poorer disease-free survival and overall survival in CS I–II patients treated with radiotherapy alone in a number of multivariate analyses (40,175,205). In the analyses of the International Database on Hodgkin's Disease, the influence of older age on disease-free survival was relatively small (33,176). Figure 6 shows disease-free survival curves according to age for 8,461 CS I–II patients achieving remission (most of them after radiotherapy alone) in the International Database on Hodgkin's Disease. The influence of age on overall survival is much greater, partly because relapse treatment seems to be less effective in older patients (*vide infra*). Sex often comes out as an independent prognostic factor in multivariate analysis, although not a very important one (33,167,170, 175,176).

Some biologic parameters (hematologic, biochemical, or immunologic) have been shown to be prognostically significant in CS I–II because they provide an indirect indication of disease extent in these patients, in whom staging was less accurate than in PS I–II (186). In the multivariate studies by the EORTC, an elevated ESR was an independent prognostic factor for both disease-free survival and overall survival in patients treated with radiotherapy alone. The EORTC has combined the ESR and B symptoms into one factor with a high prognostic significance (70,71,170,175). In the British National Lymphoma Investigation studies of CS IA and IIA and in the study from the Princess Margaret Hospital of CS I–II, an elevated ESR was also independently significant for both disease-free survival and overall survival (152,205). In the multivariate analyses of the International Database on Hodgkin's Disease, an elevated ESR had independent prognostic significance for disease-free survival in CS IA and IIA and for cause-specific survival in CS IB and IIB; most of these patients were treated initially with radiotherapy alone (33). Figure 7 shows disease-free survival curves according to ESR for 4,358 patients in CS I–II in

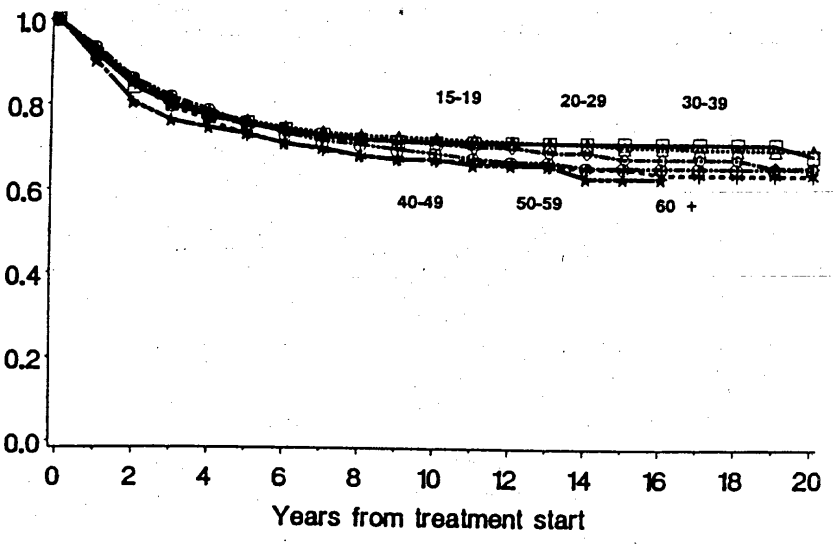

FIG. 6. Disease-free survival according to age for 8,461 patients in clinical stage (CS) I–II in the International Database on Hodgkin's Disease. (From ref. 33, with permission.)

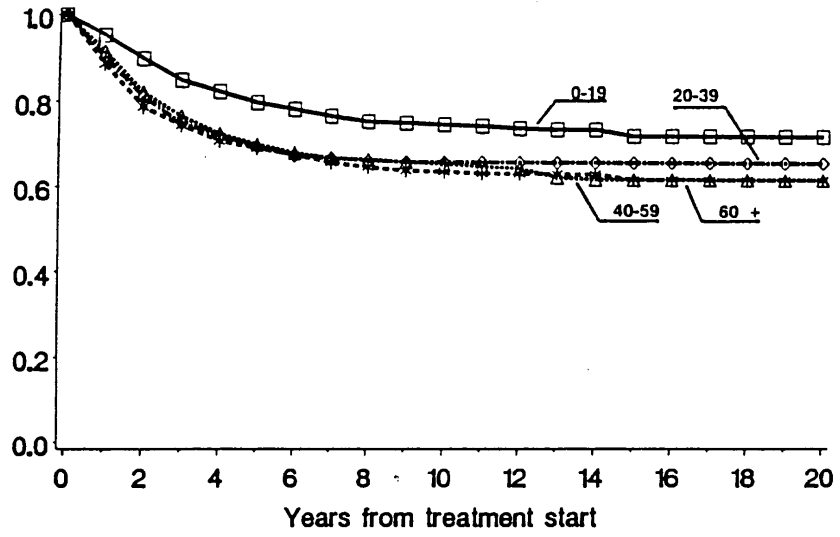

FIG. 7. Disease-free survival according to erythrocyte sedimentation rate (ESR) for 4,358 patients in clinical stage (CS) I–II in the International Database on Hodgkin's Disease. (From ref. 33, with permission.)

the International Database on Hodgkin's Disease. Anemia has been shown to be prognostically significant in several univariate analyses (24,184,185). In the multivariate analyses of the International Database on Hodgkin's Disease, anemia was independently significant for disease-free survival and cause-specific survival in CS IA, IB, and IIB (33). A decreased serum albumin level was prognostically significant in univariate analysis (184,207). In the multivariate analyses of the International Database on Hodgkin's Disease, a decreased serum albumin level was predictive of disease-free survival in CS IB and IIB (33). As mentioned previously, a host of other biologic indicators have been shown to be correlated with disease activity. However, their independent prognostic significance in CS I–II has not been proved (187).

The prognostic factors known to be independently significant in CS I–II treated with radiotherapy alone are summarized in Table 3.

TABLE 3. *Prognostic factors shown to be independently significant in CS I–II treated with radiotherapy alone*

Number of involved regions
Large mediastinal mass
Disease confined to upper cervical nodes
B symptoms
Histology
Age
Sex
Erythrocyte sedimentation rate
Anemia
Serum albumin

CS, clinical stage.

Patients Treated with Combined-modality Therapy

As was the case for pathologically staged patients, a meta-analysis of individual patient data showed that combined-modality therapy reduces the risk for relapse compared with radiotherapy alone, but does not improve survival (64). The size of reduction in risk for failure in patients with different stages of disease, with and without B symptoms, both male and female, of different ages, and staged with and without laparotomy was remarkably similar. Therefore, there is also no indication in CS I–II that prognostic factors for patients treated with combined-modality therapy are different from the factors for patients treated with radiotherapy alone. Today, patients in CS I–II with adverse prognostic factors are generally given combined-modality therapy. Hence, many of the published series are selected, consisting mainly of poor-risk patients, which makes the detection of prognostic factors difficult.

The number of involved regions was also independently significant for disease-free survival and overall survival in the EORTC studies for patients who received combined-modality therapy (175). Two other studies found the number of involved areas to be predictive for disease-free survival in patients who received combined-modality therapy (208,209). A large mediastinal mass is a highly important factor in CS I–II patients who receive combined-modality therapy (208,210–212). B symptoms, ESR, histology, age, and sex have also been shown to be prognostically significant in CS I–II patients who receive combined-modality therapy (175,209).

Patients Treated with Chemotherapy Alone

Like PS I–II patients, CS I–II patients have rarely been treated with chemotherapy alone in larger studies, and few data on prognostic factors are therefore available. In an Argentinian study in which 142 patients in CS I–II were treated with chemotherapy alone, 21 failed to achieve complete remission and 25 relapsed, 18 in previously involved areas (208). In multivariate analyses, age,

number of involved areas, and tumor bulk were significant for disease-free survival, and age and tumor bulk were significant for overall survival. In another, smaller study in which 23 patients in CS I–II were treated with chemotherapy alone, three patients with bulky mediastinal disease achieved only partial remission and three relapsed, all in previously involved areas (213). However, the numbers involved were too small for any meaningful analysis of prognostic factors.

PROGNOSTIC FACTORS IN ADVANCED DISEASE

The term advanced disease is not unequivocally defined. Stages IIIB and IV certainly qualify as advanced disease, and many groups also generally include stage IIIA. Nevertheless, certain PS IIIA patients may be successfully treated with radiotherapy alone, although this has become rare in recent times. On the other hand, certain stage I or II patients with multiple adverse prognostic factors may require full systemic treatment and are included in some trials of advanced disease.

Some groups also include patients with initially localized disease who relapse after radiotherapy alone in trials of advanced disease. These patients form a biologically selected group and are reported to have a better prognosis than patients presenting in advanced stages (214–218). Prognostic factors cannot be expected to be similarly distributed in this group. Consequently, the prognosis of these patients is considered separately below.

Patients with advanced disease require systemic treatment and are typically treated with conventional chemotherapy with or without additional radiotherapy. An overview based on individual patient data of all randomized trials comparing chemotherapy alone with combined-modality therapy in Hodgkin's disease shows no general advantage of the use of radiotherapy in advanced disease (219). Thus, data with these treatment variants may be pooled for analysis of prognostic factors, although radiotherapy might play a role to control large, bulky sites.

In the vast literature on prognostic factors in advanced Hodgkin's disease, two very large sets of data have evolved from international cooperation. The International Database on Hodgkin's Disease was set up in 1989, combining individual patient data from 20 study groups in all stages (33). Besides early-stage patients, it includes 5,217 patients in stages CS III–IV, mostly treated with MOPP-type (mechlorethamine, vincristine, procarbazine, prednisone) chemotherapy. In 1995, the International Prognostic Factors Project on advanced Hodgkin's disease combined data of 5,141 advanced-stage patients mainly treated with a doxorubicin-containing regimen (220). These international efforts are particularly useful to determine the relative prognostic importance of routinely documented variables. This task requires large patient numbers for statistical analysis because the independent contributions of single prognostic factors are quantitatively small to moderate (5% to 10% in tumor control) (220).

Patients Treated with Conventional Chemotherapy with or without Additional Radiotherapy

Age is well recognized as an important patient-related prognostic factor for overall survival in advanced Hodgkin's disease (31,168,221–233). Its prognostic influence on freedom from progression is less pronounced. Besides natural mortality and a greater tendency to toxicity or reduced disease control because of a reduced, age-adapted treatment in older patients, the greater impact of age on overall survival is mainly a consequence of poor results of salvage treatment in elderly relapsed patients: 5-year survival rates after progression/relapse decrease in an ordered fashion with advancing age from about 40% in the patients up to 35 years old to less than 5% in patients between 55 and 65 years of age at diagnosis (220). Nevertheless age (e.g., above 45 years) is also an independent prognostic factor for freedom from progression in patients up to 65 years old who may be assumed to be treated homogeneously. This may be related to tumor biology, as unfavorable histologic subtypes are more frequent in these patients (33).

Sex is correlated with disease stage at presentation, as about two-thirds of advanced-stage patients are men (33,220). Male sex is an independent, although quantitatively moderate, adverse prognostic factor within advanced stages (31,33,220,224,230,234–236).

Among the tumor-related prognostic factors, histologic subtype plays a minor role as a prognostic factor in advanced Hodgkin's disease. Some studies report mixed cellularity or lymphocyte depletion subtypes as unfavorable prognostic factors (31,33,224,228,237), but several other studies do not confirm these findings (214,217,220, 221,223,229,230,234,238,239). The lymphocyte depletion subtype has rarely been diagnosed in recent times (33). As mentioned previously, the prognostic relevance of grading the nodular sclerosis subtype remains controversial (164–166,240–244). Unfavorable subtypes are moderately correlated with male sex, age, lack of mediastinal involvement, stage, systemic symptoms, and related abnormal blood parameters (33,184). Given the relatively high reclassification rate under expert pathologic review, histology subtyping does not lend itself to prognostication, at least in multicenter settings (240).

The principle that a high tumor burden correlates with an unfavorable prognosis also holds for advanced disease (229,230). However, tumor burden is much more difficult to quantify in advanced stages because pathologic staging and splenectomy have become rare. Thus, information on the number of involved areas (223,229,245), the amount of tumor in the spleen (246–251), and the subdivision of

stage III (123,246–248,252–256), established as prognostic in the context of pathologic staging and radiotherapy alone, are not generally available.

Inguinal involvement may be a surrogate marker for maximal nodal spread and has been reported as independently prognostic (231). As described previously, there are various methods of measuring mediastinal bulk (257). Although very large mediastinal bulk (e.g., >0.45 of the thoracic aperture) is relatively rare, seen in fewer than 10% of cases of advanced disease (220), it has been reported as an adverse prognostic factor in some studies (231,258), but not in others (259). Large but not very large (e.g., 0.33–0.45 of the thoracic aperture) mediastinal mass is not related to prognosis in advanced Hodgkin's disease treated with modern chemotherapy (220).

Stage IV marks dissemination to extranodal sites and is independently prognostic within advanced disease (33,220,228). Bone marrow, lung or pleura, and liver involvement are each present in about 30% of cases of stage IV disease. It remains controversial whether any of these sites carries a particularly bad prognosis within stage IV. Bone marrow involvement was an adverse factor in some studies (214,230,231,260–264), but not in others (234,265,266). Pleura, lung, or liver involvement has been reported as prognostically unfavorable (238, 260,265,267), but other studies did not show a prognostic impact of any of these (214,230,231,234,245,262,268). The number of involved extranodal sites has also been reported to be independently prognostic (226,233,268), but this could not be confirmed in the International Prognostic Factors Project (220).

Several hematologic and biochemical laboratory parameters carry prognostic information in advanced Hodgkin's disease. Decreased serum levels of albumin (220,269,270) and hemoglobin (33,220,227,233,259,271) [or hematocrit (231)] as well as an elevated ESR (184, 272) or alkaline phosphatase level (232,272,273) are correlated (33,184,220,271) with one another as well as with the presence of B symptoms (33,264) and the anatomic extent of disease. These variables form a cluster of interrelated prognostic indicators that mirror both tumor burden and inflammatory processes (207). They have been variously reported as prognostic, individually or in combination. Serum albumin (220,269) and hemoglobin (220) levels show a remarkably consistent relation to prognosis over their full range of variation. Figure 8 shows freedom from progression according to serum albumin for 2,239 patients, and Figure 9 shows freedom from progression according to hemoglobin for 4,314 patients in the International Prognostic Factors Project. Moreover, hemoglobin and serum albumin levels change on a scale of weeks and are thus biometrically reliable measurements. This singles them out both as the most informative prognostic factors in advanced Hodgkin's disease and as representatives for this prognostic cluster of systemic symptoms. Given hemoglobin and serum albumin, the other members of this cluster, in particular B symptoms, lose their independent prognostic impact (220).

Leukocyte and lymphocyte counts form a second cluster of laboratory parameters. These parameters are interrelated but only weakly correlated with the first cluster mentioned above. Analysis of the joint distribution of leukocyte and lymphocyte counts in advanced Hodgkin's disease reveals a simultaneous shift away from the normal pattern toward both leukocytosis (220) and lymphocytopenia (227,230,232,233,274) that carries independent prognostic impact (220). These relatively unspecific measurements may indirectly capture dysregulation of hematopoiesis caused by cytokine release by Hodgkin's disease cells.

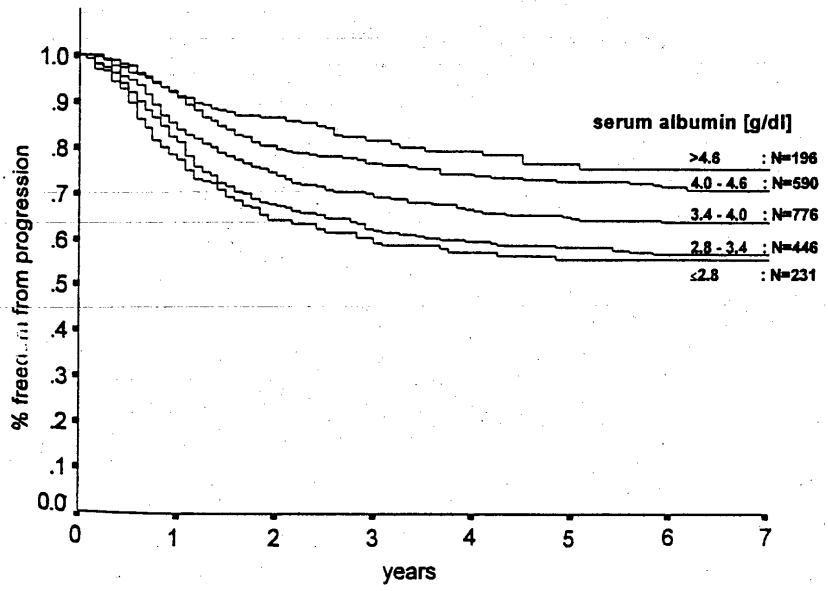

FIG. 8. Freedom from progression according to albumin levels for 2,239 patients with advanced disease in the International Prognostic Factors Project.

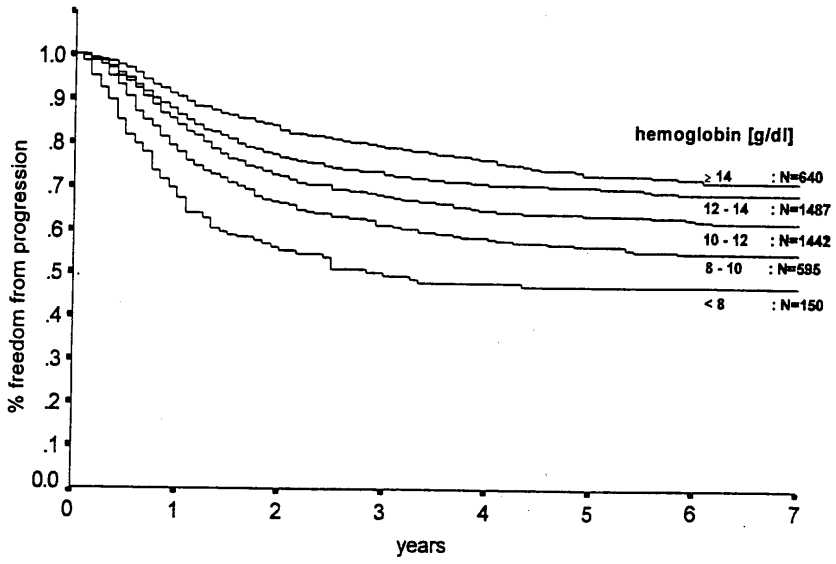

FIG. 9. Freedom from progression according to hemoglobin levels for 4,314 patients with advanced disease in the International Prognostic Factors Project.

Elevated serum lactic dehydrogenase was found to be independently prognostic by some groups (231,233), but not in the large databases of the International Database on Hodgkin's Disease and the International Prognostic Factors Project. Serum lactic dehydrogenase probably plays a lesser role in Hodgkin's disease than in high-grade non-Hodgkin's lymphoma (275). Elevated β_2-microglobulin is not generally documented but has been reported as prognostic (276). Table 4 summarizes the prognostic factors in advanced disease.

It is important to stress that the clinical features and laboratory parameters discussed so far are in biologic terms relatively nonspecific. The neoplastic cells in Hodgkin's disease are known to produce and express a number of cytokines and antigens. Increased levels of some cytokines and soluble forms of membrane-derived antigens have been detected in the serum of a majority of patients with untreated Hodgkin's disease. They are thought to correlate both with the number of tumor cells and with the activity of the Hodgkin's disease cells. Of particular interest is the CD30 surface molecule, which is consistently expressed by Hodgkin and Reed-Sternberg cells. The soluble form of the CD30 molecule is released by the cells, and with sensitive techniques it is detectable in the serum of virtually all untreated patients (135,277–279). The level of soluble CD30 is correlated with disease spread and burden. It maintains independent prognostic significance in multivariate analysis (279) and is currently one of the most promising tumor markers in Hodgkin's disease (135). It will be a task for future investigators to accumulate more extensive scientific and clinically relevant data on soluble CD30 and other specific biologic indicators, such as soluble interleukin-2 receptor (CD25) (135,138,278,280–282) and other cytokines (135–138,283,284), some of which may eventually provide the objective scientific factors needed to predict outcome more accurately for patients with advanced-stage Hodgkin's disease.

TABLE 4. *Prognostic factors in advanced disease*

Age
Sex
Histology
Stage IV disease
Tumor burden
Inguinal involvement
Very large mediastinal mass
B symptoms
Anemia
Serum albumin
Erythrocyte sedimentation rate
Serum alkaline phosphatase
Leukocytosis
Lymphocytopenia
Serum lactic dehydrogenase
Serum β_2-microglobulin

Prognostic Indices or Scores in Advanced Hodgkin's Disease

Prognostic indices or scores for advanced Hodgkin's disease may be clinically important, both for selecting patients who may be overtreated and, in particular, for identifying patients in whom standard treatment is likely to fail to eliminate disease and who may be appropriate candidates for experimental approaches.

Several groups developed prognostic indices or scores based on a few hundred cases and defined high-risk groups. Wagstaff et al. (232,285) defined risk groups based on age above 45 years, male sex, absolute lymphocyte count below 0.75×10^9/L, and stage IV disease. Straus et al. (231) proposed a five-factor score: age above 45 years, elevated serum lactic dehydrogenase, low

TABLE 5. *Adverse prognostic factors incorporated in the International Prognostic Factors Project score for freedom progression in advanced Hodgkin's disease*

Age ≥45 years
Male sex
Stage IV disease
Hemoglobin <10.5 g/dL
Serum albumin <4.0 g/dL
Leukocytosis ≥15 × 10^9/L
Lymphocytopenia <0.6 × 10^9/L or <8% of white blood cell count

hematocrit, inguinal involvement, and a mediastinal mass larger than 0.45 of the thoracic aperture. Proctor et al. (227,258) developed a numeric index to predict overall survival based on age, stage, hemoglobin level, absolute lymphocyte count, and tumor bulk (>10 cm). Gobbi et al. (31,286) set up a predictive equation based on age, sex, stage, histology, B symptoms, mediastinal mass, ESR, hemoglobin, and serum albumin.

However, none of these indices has received general acceptance. The first three of these models and the inclusion criteria used in an ongoing European Bone Marrow Transplant Group study in high-risk advanced Hodgkin's disease (287) have been compared by Fermé et al. (233). All prognostic models were reproduced, but none of the models was successful in identifying a high-risk group with a 3-year survival rate of less than 50%.

Gobbi et al. in 1994 (236) developed a parametric model to derive numeric estimates of expected survival in all stages. Seven factors were incorporated: stage, age, histology, B symptoms, serum albumin, sex, and distribution of involved areas (infradiaphragmatic disease or more than three supradiaphragmatic areas). This work was based on 5,023 patients in both early and advanced stages from the International Database on Hodgkin's Disease (33). They were treated rather heterogeneously with radiotherapy alone or mainly MOPP-type chemotherapy with or without radiotherapy. All these models used overall survival as the main end point.

The International Prognostic Factors Project on advanced Hodgkin's disease (220) was organized to develop a prognostic score to predict treatment outcome in patients with advanced-stage Hodgkin's disease treated with modern combination chemotherapy with or without radiotherapy. To focus on the effects of the first-line treatment only, the major end point was freedom from progression; deaths in remission not preceded by progression of Hodgkin's disease were censored. Data were collected from 23 centers or study groups on 5,141 patients in whom advanced-stage Hodgkin's disease had been diagnosed and who had been treated with chemotherapy with and without radiotherapy according to a defined protocol. Individual patient data on course of disease and 19 generally documented clinical features at diagnosis were collected. A prognostic score was developed from this set of data in patients up to 65 years of age. The score incorporates seven binary adverse prognostic factors (summarized in Table 5) of approximately similar prognostic impact: age of 45 years of more, male sex, stage IV disease, albumin level below 4.0 g/dL, hemoglobin level below 10.5 g/dL, leukocytosis (leukocyte count >15 x 10^9/L), and lymphocytopenia (lymphocyte count <0.6 x 10^9/L, or <8% of leukocytes, or both). The prognostic score predicts expected 5-year rates of tumor control in the range of 45% to 80%. Each additional factor reduces the prognosis by about 8%. Figure 10 shows freedom from progression according to the

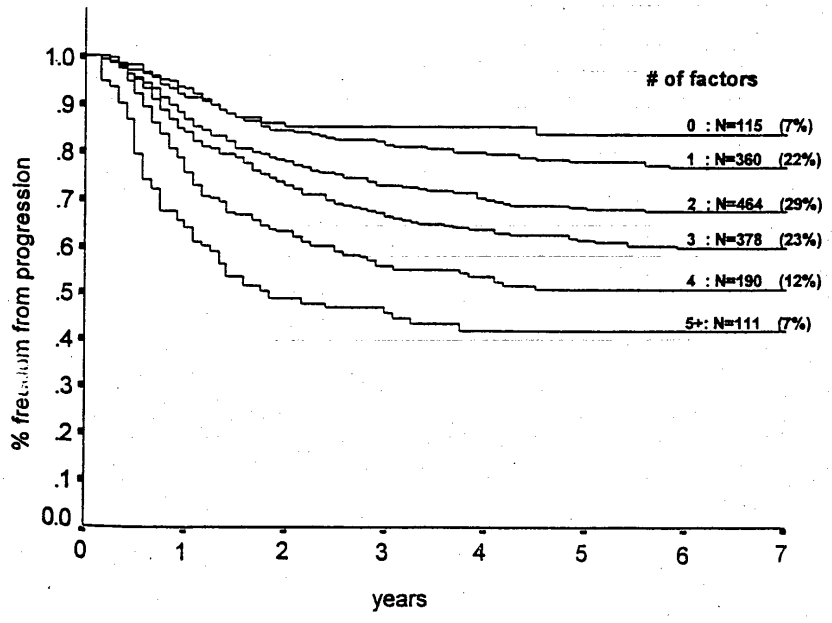

FIG. 10. Freedom from progression according to the number of adverse prognostic factors (see Table 5) for 1,618 patients with advanced disease in the International Prognostic Factors Project.

number of adverse prognostic factors for 1,618 patients with advanced disease in the International Prognostic Factors Project.

This international prognostic score was developed from the combined experience of most major study groups from the 1980s in treating advanced Hodgkin's disease mainly with doxorubicin-containing regimens. Until markers that are biologically more specific become available, the score may be useful in the design of future therapeutic trials in patients with advanced Hodgkin's disease, in the description of patient populations, and in tailoring treatment to individual patients. However, no distinct very high-risk group in advanced Hodgkin's disease can be defined in advance by routinely documented clinical features. This is particularly important to note in the context of early high-dose chemotherapy with autologous stem cell support, typically considered for consolidation in responding patients (259,270,287–290) who nevertheless remain at high risk for relapse. It should be highlighted (291,292) that the rates of tumor control at 5 years in the selected group of patients achieving a complete remission are even higher than those in all patients: 73 ± 2%, 70 ± 2%, and 65 ± 4% in the groups with at least two, at least three, and at least four adverse factors, respectively. Thus, nearly two-thirds of these patients are already cured with conventional treatment.

PROGNOSTIC FACTORS FOR OUTCOME AFTER RELAPSE

Relapses of Hodgkin's disease after radiotherapy alone are qualitatively different from relapses after chemotherapy alone or combined-modality therapy. Both freedom from second relapse and overall survival are considerably better for patients relapsing after radiotherapy alone than for the others (63,293).

Patients Relapsing after Initial Treatment with Radiotherapy Alone

About 30% of early-stage patients treated with radiotherapy alone relapse. However, most of these patients can be successfully salvaged with chemotherapy, and durable remissions are achieved in about 60% of cases (293–304).

The extent of disease at relapse has consistently been shown to be important for prognosis. In studies in which systematic restaging at relapse was carried out, relapse stage was independently significant for achievement of second complete remission (293,301), freedom from second relapse (302), and overall survival after relapse (301). Relapse site (nodal only vs. extranodal with or without nodal relapse) is highly correlated with relapse stage (293). Hence, in studies in which systematic restaging at relapse was not carried out, the importance of extent of disease at relapse was reflected in the adverse prognostic influence of extranodal relapse for achievement of second complete remission (300), freedom from second progression (305), cause-specific survival after relapse (303,304), and overall survival after relapse (295,303,304). Figure 11 shows cause-specific survival after first relapse according to type of relapse for 448 patients in the International Database on Hodgkin's Disease staged initially with laparotomy and relapsing after

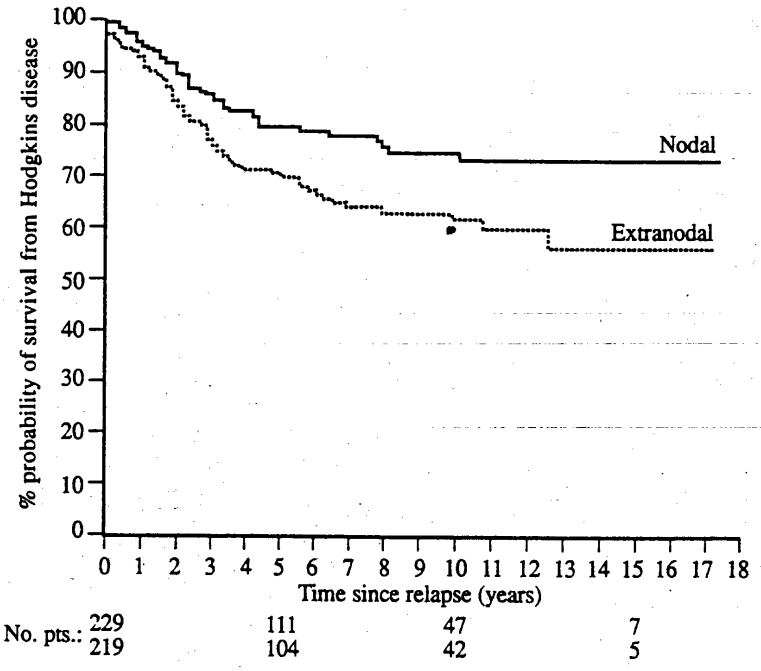

FIG. 11. Cause-specific survival from Hodgkin's disease after first relapse according to type of relapse for 448 patients in the International Database on Hodgkin's Disease who were initially staged with laparotomy and treated with irradiation alone. (From ref. 303, with permission from Elsevier Science.)

initial treatment with irradiation alone. In early studies, initial stage was important for prognosis (297,305) and a more advanced initial stage was shown to be correlated with increased risk for extranodal relapse (305). However, the prognostic significance of initial stage was not found in later studies, probably because they included fewer patients with advanced disease at presentation.

In contrast to the findings at initial treatment (*vide supra*), the histologic subtype has in many studies been found to be independently significant for achievement of second complete remission (293,299,301), freedom from second relapse (293), cause-specific survival after relapse (303,304), and overall survival after relapse (293,295,303).

Age, which had only a small effect on results of initial treatment (*vide supra*), has consistently been shown to be independently significant for prognosis after relapse, the efficacy of salvage chemotherapy being much lower in older patients (175). Older age is an independent adverse prognostic factor for achievement of second complete remission (298), freedom from second relapse (298,299,302), cause-specific survival after relapse (177,303,304), and overall survival after relapse (177,293,298,299,303,304). Whether this finding reflects a true biologic difference in the behavior of Hodgkin's disease between age groups is uncertain. It is quite possible that a significant part of the difference should be ascribed to suboptimal staging and treatment at relapse for some older patients (177). Figure 12 shows cause-specific survival after first relapse according to age (at initial treatment) for 681 patients in the International Database on Hodgkin's Disease staged initially with laparotomy and relapsing after initial treatment with irradiation alone.

The length of the initial disease-free interval has been shown in many studies not to influence prognosis after relapse, the prognosis being equally good whether relapse occurs within a year of initial radiotherapy or after many years (293,296,298,300,302–306). This is in stark contrast to the findings in patients relapsing after chemotherapy or combined-modality therapy (*vide infra*).

The prognostic factors known to be independently significant for outcome after relapse after primary treatment with radiotherapy alone are summarized in the first part of Table 6.

Patients Relapsing after Initial Treatment with Chemotherapy Alone or Combined-modality Therapy

Patients relapsing after treatment with chemotherapy or combined-modality therapy, whether for early-stage or advanced disease, have a much poorer prognosis than patients relapsing after radiotherapy alone. With second-line chemotherapy, durable remissions are obtained in only 10% to 30% of cases (190,221,293,307–329).

By far the most important prognostic factor for outcome after relapse in these patients has consistently been shown to be the extent and durability of the initial remission, irrespective of the specific initial or second-line treatment used. Patients relapsing from complete remission after more than 12 months have a much better

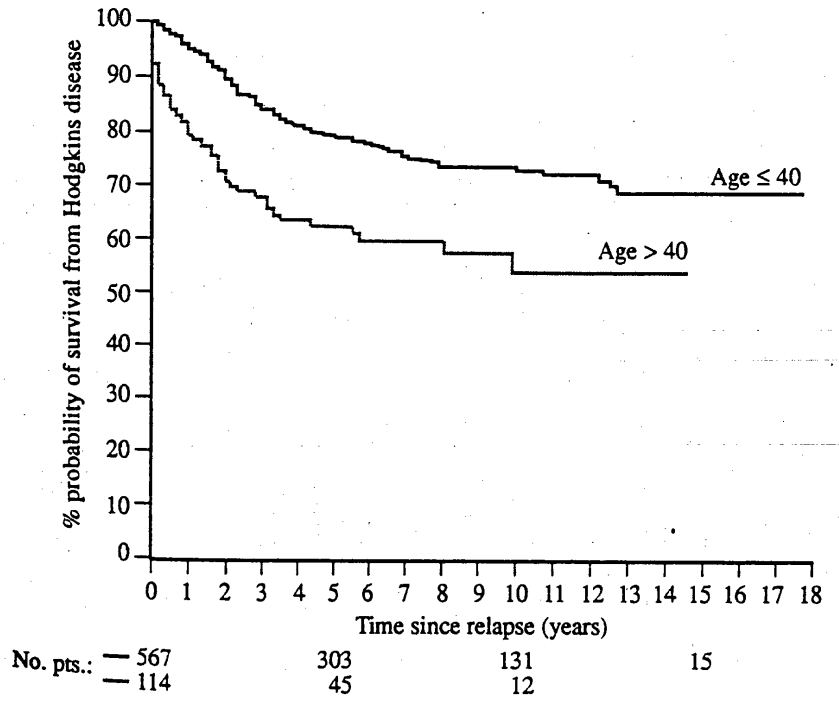

FIG. 12. Cause-specific survival from Hodgkin's disease after first relapse according to age (at initial treatment) for 681 patients in the International Database on Hodgkin's Disease who were initially staged with laparotomy and treated with irradiation alone. (From ref. 303, with permission from Elsevier Science.)

TABLE 6. *Prognostic factors shown to be independently significant for outcome after relapse*

Relapse after radiotherapy alone
Relapse stage
Extranodal relapse
Histology
Age
Relapse after chemotherapy or combined-modality therapy
Extent and duration of first remission
Relapse stage
Extranodal relapse
Number of involved sites at relapse
B symptoms at relapse
Histology
Stage IV disease at original presentation
Age
Performance status

chance of achieving a durable complete remission with second-line treatment than patients whose first remission period is less than 12 months (308,312,317–320,322, 324,328). Figure 13 shows overall survival curves from the date of relapse according to duration of initial remission for 107 patients from the National Cancer Institute relapsing after initial treatment with chemotherapy or combined-modality therapy. Patients who do not achieve complete remission even during primary treatment have the worst prognosis of all, rarely achieving durable complete remission with second-line treatment (311,312, 318,321,322,327). As would be expected, patients relapsing more than once have a dismal prognosis (323–326).

The extent of disease at relapse has also been shown to influence prognosis after relapse from chemotherapy or combined-modality therapy. Patients with advanced stage (III or IV) at relapse (320), with extranodal disease at relapse (310,322,324,326,328,329), or with more than three involved sites (328) have a significantly poorer prognosis than patients without these adverse factors. The presence of B symptoms at relapse has likewise proved significant (310,312,317,319,322,328). Histologic subtype other than nodular sclerosis (328,329), stage IV disease at original presentation (317), older age (318), and poor performance status (321) have also been shown to be associated with a poorer prognosis.

The prognostic factors known to be independently significant for outcome after relapse following primary treatment with chemotherapy or combined-modality therapy are summarized in the second part of Table 6.

A subgroup of patients relapsing after chemotherapy have anatomically limited relapse in nodal sites alone. A number of small series have shown that for selected patients in this subgroup, wide-field radiotherapy with or without additional chemotherapy offers a reasonable chance of durable disease control (317,330–340). Prognostic factor analyses in some of the larger series indicate that patients suitable for this kind of relapse treatment are those relapsing exclusively in supradiaphragmatic nodal sites, with no B symptoms at relapse, with favorable histology (lymphocyte predominance or nodular sclerosis), and after a disease-free interval of more than 12 months (334,339,340). Patients with these favorable characteristics may expect to achieve durable remission with radiotherapy in about 50% of cases.

Patients Undergoing High-dose Chemotherapy and Stem Cell Transplantation for Relapsed or Refractory Disease

High-dose chemotherapy with stem cell transplantion with or without additional radiotherapy seems to im-

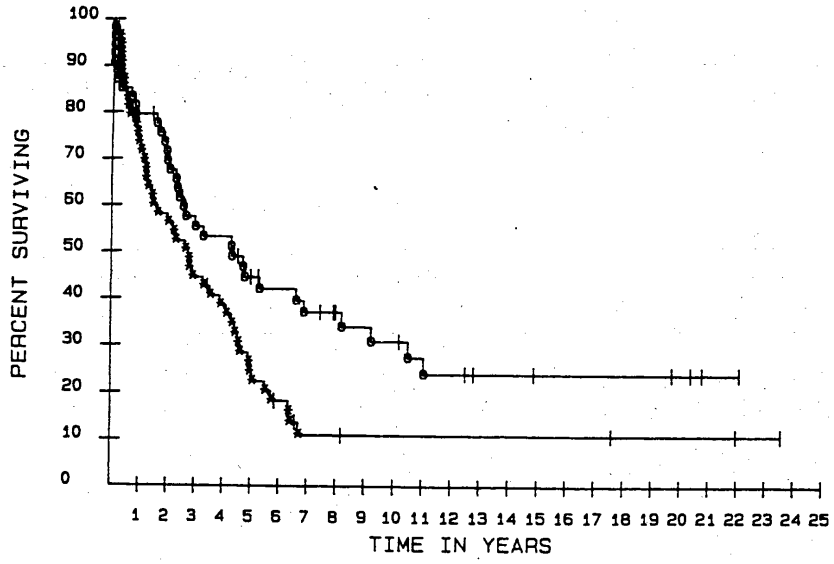

FIG. 13. Overall survival from the date of relapse for 107 patients from the National Cancer Institute relapsing after initial treatment with chemotherapy or combined-modality therapy. Patients are divided according to length of the initial remission (*upper curve*, >1 year; *lower curve*, <1 year). (From ref. 318, with permission.)

prove the prognosis for patients failing after chemotherapy or combined-modality therapy. However, randomized evidence supporting this notion is at present sparse (341), and results of phase II studies are difficult to interpret because of differences in patient selection in the various studies. Analyses of prognostic factors in several published series have demonstrated a number of independent factors affecting outcome of high-dose chemotherapy.

The chemosensitivity of the disease is a critical determinant of outcome. The response to initial therapy (342, 343), duration of initial remission (344,345), number of prior failed regimens (346–352), and response to conventional salvage therapy before transplant (347,348, 52–354) have all been shown to influence prognosis.

Disease burden before transplantation has also been shown to be important for prognosis. Stage of disease at transplantation (348), bulky disease at transplantation (348,350,355,356), extranodal relapse (344,348,351), pleural involvement or multiple pulmonary nodules at relapse (354), B symptoms at relapse (344), and an elevated serum lactic dehydrogenase level before transplantation (357) have all been shown to be prognostically important, reflecting directly or indirectly the tumor burden at the time of transplantation. As would be expected with intensive treatment, a poor performance status has proved to be an important adverse prognostic factor (346,348,349,357,358). A single study found that female patients had a significantly poorer prognosis (350). Older patients have only rarely been treated with high-dose chemotherapy and stem cell transplantation, so that the prognostic significance of older age has not been examined. Pediatric patients, however, have the same outcome as their adult counterparts (359).

The prognostic factors known to be independently significant for outcome after high-dose chemotherapy and stem cell transplantation are summarized in Table 7.

TABLE 7. *Prognostic factors shown to be independently significant for outcome after high-dose chemotherapy and stem cell transplantation*

Chemosensitivity of the disease
Response to initial therapy
Duration of initial remission
Number of prior failed regimens
Response to conventional salvage therapy
Disease burden before transplantation
Stage of disease at transplantation
Bulky disease at transplantation
Extranodal relapse
Pleural involvement or multiple pulmonary nodules at relapse
B symptoms at relapse
Elevated serum lactic dehydrogenase level at transplantation
Performance status

USE OF PROGNOSTIC FACTORS IN CLINICAL TRIALS

Rationale for Use of Prognostic Factors as Entry and Stratification Criteria

In the context of clinical trials, prognostic factors are used for three purposes: in the definition of the study population (entry and exclusion criteria), in *a priori* stratification of the study population to balance randomization within prognostic subgroups, and to describe the actual study population and adjust the analysis according to prognostic factors.

Entry and exclusion criteria are tailored specifically to a given trial. They select a study population in which the main question under study is open and in which the therapeutic difference may be expected to be clearly demonstrable if it exists and is clinically relevant.

Knowledge of prognostic factors plays a key, but not exclusive, role in the formulation of entry criteria. Ethically, only those patients may be included for whom the risks and benefits of the treatment arms are sufficiently uncertain to justify randomization. Biometrically, except in equivalence trials, patients should be excluded in whom the difference is probably negligible. On the other hand, enough cases must be retained for a meaningful trial with sufficient statistical power, and consequently entry criteria should not be overly selective so as not to preclude a result that can be generalized.

There is some debate on the adequate degree of formalization and selectivity of entry criteria (360). Some propose strictly formalized criteria designed to select a prognostically homogeneous study population because variance in the study population decreases the statistical power of the trial. Others advocate relaxation of eligibility criteria to maximize accrual and not preclude extrapolation from trial results.

In Hodgkin's disease, as in most other tumors, patient heterogeneity is pronounced and the known prognostic factors account for only a relatively small part of it. The results of a reasonably focused and powered trial may be expected not to depend markedly on a precise definition of the inclusion criteria. The treatment effect may quantitatively vary by subgroup and may be reduced or increased at the extremes of the prognostic distribution in the study population. However, the main effect will typically have the same direction in all subgroups except in rare situations (with competing risks, such as toxicity vs. treatment effectiveness). Thus, the trial outcome will typically not depend on minor variations of the eligibility criteria (361).

The decision to enter a patient in a trial eventually lies with the responsible local physician. The physician will and should decide the borderline cases that inevitably emerge. Uncontrolled selection processes at the extremes of the prognostic distribution are difficult to prevent unless a strictly consecutive entry of all qualifying

patients is enforced. This is practically impossible in multicenter settings and conflicts with the imperative of informed consent.

Therefore, a certain arbitrariness in the selection of the study population is unavoidable; however, in reasonably powered trials this will not materially alter results. Nevertheless, at least in large multicenter trials with possibly less experienced participants, the decision to enter a patient in a trial should be guided by clear eligibility criteria summarizing the expert opinion of those responsible for the trial with regard to the study population in which the study question is relevant.

Randomization is the method of choice to achieve comparability in the prognostic composition of the treatment groups to be compared in a clinical trial (362,363). Proper randomization avoids not only imbalances in known prognostic factors (for which one can adjust the analysis to a certain degree by using statistical modeling) but also imbalances that are not detectable concerning unknown factors.

Randomization techniques generally work well with large numbers of patients. In small randomized trials, some imbalances by chance may occur. Stratified randomization is randomization particularly designed to balance treatment allocation within predefined subgroups. Stratification may be indicated if the study population consists of clearly different prognostic groups that are definable *a priori* by well-established prognostic factors. As it is possible to adjust the analysis statistically for moderate imbalances in known prognostic factors, stratification should be restricted to markedly different subgroups. The number of strata should remain small, as overstratification may compromise the main task of randomization, which is to balance unknown or undocumented factors.

Prognostic factors serve to describe the composition of a study population. In addition, they play a role in the final analysis. The estimate of the treatment effect in a trial may be biased and the statistical power reduced if important known or unknown prognostic factors are not accounted for (364). Thus, a trial analysis should comprise both a simple univariate test for treatment effect and one based on multivariate modeling. The trial results will be most convincing if both analyses approximately agree.

Combinations of Prognostic Factors Currently Used by Major Trial Groups

Inclusion criteria that are currently used differ by trial and study group. This is not surprising; prognosis varies on a continuum from low-risk, minimal disease to high-risk, maximally advanced disease. The population of patients with Hodgkin's disease thus does not fall into naturally defined groups that differ in prognosis and clearly require different treatment approaches. The delineation of study populations depends on prognosis, the respective therapeutic challenge, and study history. Any sharp borderline is artificial to a certain degree. Nevertheless, certain clusters of comparable selection criteria have emerged.

The classic Ann Arbor (26) or Cotswolds (41) staging systems are based on the anatomic distribution of disease. Stage correlates reasonably with prognosis, although combinations of prognostic factors in which additional information is used show better correlation. The Ann Arbor staging system is well established and universally accepted and still forms the reference system for most definitions of study entry criteria. However, most study groups currently use hybrid systems to define their study entry criteria, basically using stage and also the presence or absence of unfavorable prognostic factors (also called risk factors in this context). Prognosis of stage groups overlaps considerably; for example, a stage IIB patient with additional risk factors may have a worse prognosis than a limited IIIA patient.

Entry criteria are tailored to study questions. Combinations of prognostic factors to define entry criteria may therefore be grouped by study aims and the composition of the menu of therapeutic options. Most study groups have at least one trial in early stages and one in advanced stages. Tables 8 and 9 describe inclusion criteria currently or recently used by study groups for early-stage and advanced disease, respectively. Table 10 attempts to describe and systematize the current practice. Entry criteria may change in the future with more widespread use of prognostic scores or indices to select study populations, in particular in studies of advanced disease, as discussed below.

In early stages, patients are included from the favorable end of the prognostic distribution, in which full systemic treatment is considered overtreatment. As the prognosis in this group is excellent, study questions focus on how to cure with minimal toxicity or cost. Treatment options comprise radiotherapy alone, or reduced or less toxic chemotherapy with or without radiotherapy. Table 8 illustrates that early stages are typically defined as stage I or II without risk factors, with lists of unfavorable prognostic factors that vary by study group and have been derived mainly from radiotherapy-alone relapse data.

In addition, some groups single out for minimal treatment a small group within early stages who have minimal disease. The EORTC (365) entered a small, "very favorable" group of patients without risk factors and with a very low probability of infradiaphragmatic disease (CS IA, female sex, age under 40 years, with lymphocyte predominance or nodular sclerosis histologic subtype) in a trial of mantle-field radiotherapy alone ("minimal disease"). The British National Lymphoma Investigation (366) treated CSIA–IIA patients with lymphocyte predominance subtype, nodular sclerosis grade 1 subtype, and ESR below 10 mm/h or CS IA high cervical involvement with involved-field radiotherapy only.

TABLE 8. *Eligibility criteria of recent or current studies of early-stage disease (typically defined as stage I or II and absence of certain unfavorable prognostic factors)*

Study group	Criteria for early-stage versus intermediate-stage/advanced disease Early stage = stage I or II without any of the listed risk factors
EORTC [H_7 study (365), H_8 study]	Age >50 y 4+ involved nodal sites ESR >50 mm/h, or B symptoms and ESR >30 mm/h Bulky mediastinum (mediastinal-thoracic ratio ≥0.35) (Infradiaphragmatic disease)
BNLI (366)	Lymphocyte depletion, mixed cellularity, nodular sclerosis II, and ESR ≥60 mm/h
Manchester Lymphoma Group 1989	B symptoms Mediastinal bulk
GHSG (HD_7 study)	Large mediastinal mass (>1/3 of the thoracic aperture) Massive spleen involvement E lesions ESR >50 mm/h, or B symptoms and ESR >30 mm/h 3+ involved lymph nodal areas
Milano 1990	Stage II B symptoms Bulk
SWOG (9133 study) and CALGB (9391 study)	B symptoms Mediastinal mass ≥1/3 maximum thoracic diameter Infradiaphragmatic presentation
NCI-C (HD-6)/ECOG (IHD06)	B symptoms Mixed cellularity or lymphocyte depletion Age >40 y ESR >50 mm/h 4+ disease sites
Stanford [G_1 study (369)]	B symptoms (except night sweats only) Mediastinal mass >1/3 of maximum intrathoracic diameter 2+ E lesions

ESR, erythrocyte sedimentation rate; EORTC: European Organization for Research and Treatment of Cancer; BNLI, British National Lymphoma Group; GHSG, German Hodgkin Study Group; SWOG, Southwest Oncology Group; CALGB, Cancer and Leukemia Group B; NCI-C, National Cancer Institute of Canada; ECOG, Eastern Cooperative Oncology Group.

TABLE 9. *Eligibility criteria of recent or current studies of advanced disease*

Study group	Eligibility criteria for trials in advanced disease
EORTC [H_{34} study (370)]	III–IV
BNLI [PA(BI)OE study]	All with chemotherapy indication (i.e., IA–IIA "poor prognosis," IB–IIB, III, IV)
Manchester Lymphoma Group (VAPEC-B study)	I–II with B symptoms or bulk, III, IV
GHSG (HD_9 study)	IIB with bulk, massive spleen, or E lesion PS IIIA S PS IIIA N with bulk, E lesion, or elevated ESR CS IIIA with bulk, massive spleen, E lesions, elevated ESR or ≥3 lymph node areas IIIB–IV
Milano [MAMA study (371)]	IB, IIA bulk, IIB, III, IV
GELA [H_{89} study (233)]	IIIB, IV
NCI-US (372)	III, IV
SWOG (373)	III, IV
CALGB (221)	IIIA2, IIIB, IV
CALGB (8952 study) and SWOG (8952 study) and ECOG (5489 study) and NCI-C (HD_5 study)	III–IV + recurrent Hodgkin's disease after radiotherapy
Stanford (374)	IIB with mediastinal bulk, III, IV

PS, pathologic stage; CS, clinical stage; ESR, erythrocyte sedimentation rate; EORTC, European Organization for Research and Treatment of Cancer; BNLI, British National Lymphoma Group; GHSG, German Hodgkin Study Group; GELA, Groupe d'Etudes des Lymphomes de l'Adulte; NCI-US, National Cancer Institute of the United States; SWOG, Southwest Oncology Group; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; NCI-C, National Cancer Institute of Canada.

TABLE 10. *An attempt to describe and systematize current eligibility criteria (see text)*

	Typical form of entry criteria, prognostic composition	Typical study aims	Main therapeutic options
Early stage	Stages I and II without RF	Cure with minimal toxicity	Radiotherapy alone Reduced or "less toxic" chemotherapy with or without localized radiotherapy
Intermediate stage: separate study or (partially) included in early or advanced disease	± Stages I and II with RF ± Stage IIIA without RF ± Stage II with multiple RF ± Stage IIIA with RF	Overlap of aims	Overlap of treatment options
Advanced disease	IIIB–IV lower risk IIIB–IV higher risk	Improve unsatisfactory results	Full systemic treatment with or without radiotherapy required

RF, risk factors.

Studies of advanced stage include patients from the unfavorable end of the prognostic scale for whom full systemic treatment appears to be required. As the prognosis in this group is less than satisfactory, trials focus on improving results. Most study groups have patients with stage IIIB–IV as the core group for advanced disease (Table 9). Studies differ in whether they include all stage IIIA patients, none, or only selected stage IIIA patients with unfavorable prognostic factors. Some groups also include stages I and II patients with systemic risk factors.

An ongoing European Bone Marrow Transplant Group Trial (287) of the role of early high-dose therapy with autologous stem cell transplant attempts to select a higher-risk advanced-stage study population. It includes advanced-stage patients with two or more of the following factors: large mediastinal mass (>0.45 of the maximum chest diameter), bone marrow involvement, stage IV disease with more than one extranodal site, inguinal involvement, high serum levels of lactic dehydrogenase, and low hematocrit.

Stages I and II with risk factors and stage IIIA form what may be called "intermediate" stages. In these patients, the prognosis is neither excellent nor unsatisfactory. Study aims and treatment modalities therefore overlap. Study groups either have a separate trial for intermediate-stage patients or split this group, including part of it in early-stage or advanced-stage trials depending on available accrual and the particular question under study. Intermediate stage thus essentially denotes a gray zone between early and advanced disease.

Two groups [The Scotland and Newcastle Lymphoma Group (258) and Grupo Argentino de Tratamiento de la Leucemia Aguda (367)] have abandoned what was referred to above as the stage hybrid system and currently use prognostic indices or scores that cover the whole range of Hodgkin's disease to define trial entry criteria. In these approaches, stage has become one factor among others and has ceased to be the backbone of the system. Indeed, if predicting outcome is the only task, stage information is not privileged, and the best available predictor, possibly numeric, should be used. On the other hand, entry criteria do not depend on prognosis only. Stage codes the anatomic distribution of disease and may thus be particularly important to define the applicability of radiotherapy. If group-specific prognostic indices are used, intergroup comparability may be compromised. As stage is well established, at least a population description in terms of stage with and without risk factors should be provided.

The Scotland and Newcastle Lymphoma Group has challenged the classic staging system, pointing out that with their prognostic index, 10% of stage I–IIIA, 20% of stage IIB, 37% of stage IIIB, and 46% of stage IV patients belong to the high-risk category (368). Thus, the majority of stage IIIB–IV patients are predicted to do well with standard chemotherapy. The International Prognostic Factor Project (220) confirmed that prognosis within stage IIIB–IV is not homogeneous: 34%, 50%, and 81% of patients in stages IIIB, IVA, and IVB, respectively, have three or more adverse prognostic factors and may therefore be expected to demonstrate about 55% tumor control at 5 years, as opposed to 74% tumor control in patients with up to two factors. Thus, prognostic factors now make it possible to split advanced-stage patients in a lower- and a higher-risk group. Trials with aggressive experimental treatment might be restricted to the higher-risk advanced disease group. This decision depends on practical considerations, on complex toxicity-benefit trade-offs, and, in particular, on whether 74% tumor control at 5 years is considered satisfactory.

CONCLUSION AND FUTURE ASPECTS

As demonstrated in this chapter, a large number of variables have been shown to possess prognostic significance in Hodgkin's disease. Many of these factors appear to be more or less directly correlated with the total tumor mass. In current clinical practice, the move is toward tai-

loring treatment according to prognostic factors, decreasing treatment intensity for patients with favorable prognostic factors to reduce toxicity, and increasing treatment intensity for patients with unfavorable prognostic factors to increase the chance of cure.

In the absence of a general consensus on which factors or combinations of factors should be employed, different centers and groups worldwide currently use varying combinations of factors when allocating patients to different treatments and clinical trials. This makes it increasingly difficult to undertake large-scale analyses and comparisons between different patient series. A general consensus on which prognostic factors should be employed in clinical research and in the treatment of Hodgkin's disease in the future would be highly valuable.

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