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Definition of Cure for Hodgkin's Disease

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Summary

"We can speak of cure for Hodgkin's disease when in time–probably a decade or so after treatment–there remains a group of disease-free survivors whose progressive death rate from all causes is similar to that of a normal population of the same age and sex constitution." Analysis of survival curves for patients with Hodgkin's disease indicates that even for patients with Stage I and II disease there is excessive mortality per unit time as compared to the control population for at least 10 years after treatment. Thus, while the above definition is acceptable, the lag period required for the evaluation of potentially curative treatment is very long. In an attempt to determine the presence and degree of curative treatment in a shorter time, the relapse-free interval following treatment has been studied. For patients with Stage I and II disease, at least 80% of those destined to relapse do so within 4 years and in excess of 90% do so within 10 years. These are average data from a number of studies including those where case accrual started in 1932 to those where case accrual started as late as 1957. For those studies where the major case accrual occurred prior to lymphangiography staging, late relapses (between 4 and 10 years) are somewhat more common than in later series. This is probably because the retroperitoneal area is relatively "silent" and it may take several years for such relapses to become clinically evident. In contrast for studies wherein case accrual occurred after the introduction of lymphangiography, there is evidence that relapse after the 4th year is rare and may occur in less than 5% of patients. While the data are preliminary, there is evidence that the relapse-free interval of patients with Stage III and IV disease treated with total nodal radiotherapy or intensive combination chemotherapy follows a qualitatively similar curve. Finally, there is evidence that the relapse-free curve may be influenced by the histopathological type of Hodgkin's disease. Lympocyte-predominant Hodgkin's disease is cytokinetically slow moving, and late relapses would appear to be more common than for mixed cellularity and nodular sclerosis. These data plus the distribution of relapses during the first 4 years can be used to make relatively precise estimates of cure rates within 5 years following treatment. The use of such data in clinical trails is discussed.

Introduction

Easson and Russel (4) have suggested a definition for the cure of Hodgkin's disease. This is a modification of an earlier definition by Greenwood (7) and reads as follows. "We can speak of cure when in time–probably a decade or so after treatment–there remains a group of disease-free survivors whose progressive death rate from all causes is similar to that of a normal population of the same sex and age constitution." I would add that it should also be unassociated with continuing morbidity from the disease or its treatment. While this excellent definition is quite acceptable for Hodgkin's disease (or for most cancers, for that matter), it has the major limitation that it takes years to determine the cure rate of a given form of treatment. The rapid progress in therapeutic research has brought focus on the need for determining the probability of cure as early as possible.

Survival Data for Selected Other Cancers

For several cancers, it can be stated with confidence (probably greater than 95%) that patients who remain relapse free for a given time after treatment are cured. Thus in patients with localized Wilm's tumor treated with surgery and radiotherapy and, in some instances, actinomycin D, tumor-free survival beyond 2 years is associated with cure in over 95% of the instances (11). The same holds for the chemotherapy of disseminated choriocarcinoma and localized Burkitt's lymphoma where patients who survive in complete remission for 1 year have a minimal (less than 5%) chance of relapsing after that time (8). In Chart 1, the *relative* survival rates of patients with several forms of cancer are plotted semilogarithmically (2). The relative survival rate is the ratio of the observed percentage of survival to the percentage expected on the basis of general population experience adjusted for age, sex, race, and calendar year. By our definition, a population of patients that is cured after a given period of time time would be represented by a horizontal straight line in a plot such as that in Chart 1. The continuing risk of recurrence and death for patients with breast cancer is well known and is illustrated both for all patients and for patients with localized forms of breast cancer (Chart 1). This phenomenon is less evident but nonetheless obtains for patients with localized forms of colon cancer wherein a 5% excess mortality for the 5-year periods ranging from the 5th to the 20th year occurs. For localized forms of endometrial cancer, survival beyond 5 years is associated with cure in 95% of the patients, as evidenced by the facts that there is only a 5% excess mortality from the 5th to the 20th year and that between the 15th and 20th year the curve is flat. Three of the 4 curves in Chart 1 represent the survival curve of localized forms of cancer wherein all clinically evident disease was removed by the surgeon. It is evident that there is a substantial variation among cancers with respect to relative survival following treatment. For some diseases, patients who survive and remain relapse free at a given point in time have a very high probability of cure,

whereas for others, such as breast cancer patients, who survive 5 years beyond treatment, a 15 to 25% excess mortality rate continued over a period of 15 years.

Survival of Patients with Hodgkin's disease

Most of the statistics relating to Hodgkin's disease are reported from major referral centers. Since such centers rarely see a true cross-section of patients, our initial focus for Hodgkin's disease will be the data from the End Results Section, National Cancer Institute, which collects material from registries in many parts of the country and is thus a representative experience for Hodgkin's disease (all stages) (2). In Chart 2, the relative survival for patients with Hodgkin's disease (all stages) are presented separately for patients accrued during different time periods ranging from 1940 to 1964. Of interest, but not germane to this discussion, is the fact that the 5-year relative survival rate has improved from 24 to 41% over that time period. The major point to be made from this figure is that excess mortality obtains for these patients after the 5th year and up to at least the 15th year. Thus between 5 and 10 years, there is a 10% excess mortality; between 10 and 15 years, there is a 5 to 7% excess mortality; and beyond 15 years, there is a suggestion for a lessening but continuing excess mortality.

Excess mortality does not necessarily result from recurrence and death from the original disease if the tumor is associated with other factors which increase the mortality. A hypothetical example is lung cancer. Let's assume that treatment cured 50% of patients with lung cancer. "Cured" patients would nevertheless have an excess morbidity and mortality over the general population because of other diseases related to smoking, such as emphysema and cardiac disease. The careful follow-up and study of different cancer categories

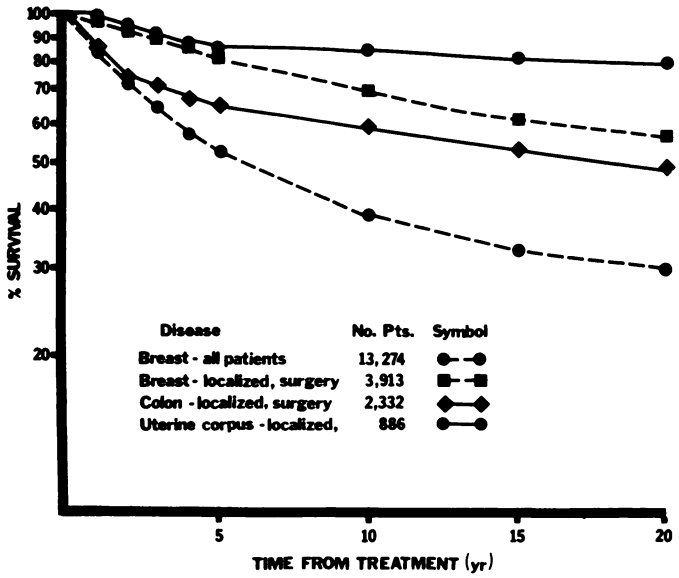

Chart 1. Relative survival rates for cancer. Ratio of observed percentage of survival to percentage expected on the basis of general population experience (from the End Results Section, National Cancer Institute, NIH).

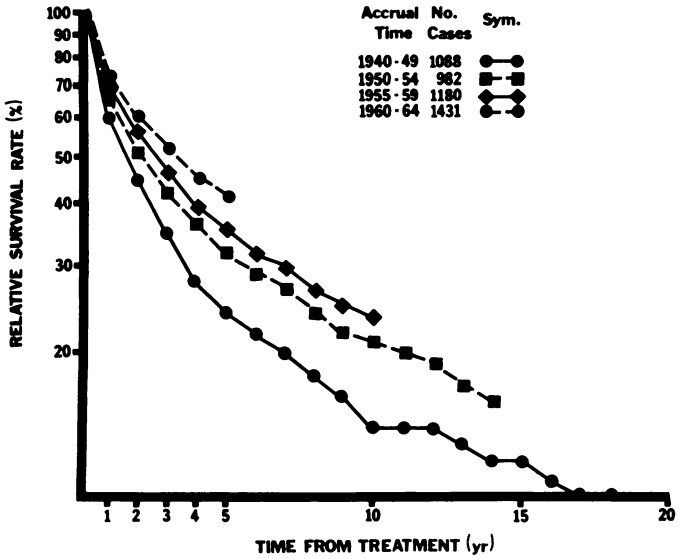

Chart 2. Relative survival rates for Hodgkin's disease. Ratio of observed percentage of survival to percentage expected on the basis of general population experience (from the End Results Section, National Cancer Institute, NIH).

following treatment could provide important leads with respect to the etiology and pathogenesis of cancer.

In order to determine this for the Hodgkin's disease patients included in Chart 2, the death certificates for all patients dying after the 5th year were examined. Death certificates generally provide limited information. The distinction between death due to recurrent Hodgkin's disease and death due to other causes can be made with confidence. In Table 1, the interval of 6 to 10 years beyond treatment of Hodgkin's disease was associated with 20% mortality, and the majority of this was due to Hodgkin's disease. The risk of death from Hodgkin's disease decreased from 15 to 10 to 5% in the 5-year intervals after the 6th year, and after the 20th year no deaths occurred from Hodgkin's disease in the 87 patients who were at risk at the start of that interval. The deaths from other causes did not change with time and were not significantly greater than those expected in the general population. Thus we could not find evidence that etiological, pathogenetic, or other factors in Hodgkin's resulted in associated, potentially fatal, disease. These data indicate a decreasing risk of death from Hodgkin's disease with time but cure, by our definition, does not occur until after the 20th year. These data are consistent with the generally known fact that Hodgkin's disease patients may frequently live for long periods with or without recurrent disease. Thus there are many patients with relatively indolent disease who are repetitively treated with radiotherapy and/or chemotherapy and who survive for long periods.

Relapse-free Interval

The relapse-free interval, or the duration of unmaintained remission, has been used as a measure of the reduction in neoplastic cells by treatment. In experimental *in vivo* tumor systems, the duration from cessation of treatment to death has been shown to be a precise measure of

the number of persisting neoplastic cells at the end of treatment (12). In those homogenous transplanted tumor systems, survival beyond a given point after treatment is associated almost invariably with cure. It seems reasonable to postulate that, for human cancers subjected to treatment designed to kill or remove neoplastic cells, the relapse curve should have 2 components. The 1st component would consist of a progressive increase in the number of relapses but a decrease in the relapse rate as patients with decreasing numbers of neoplastic cells at the end of treatment relapse. The 2nd component would consist of a leveling off of the relapse curve and would be composed of those patients in whom there were no persisting neoplastic cells after treatment. In animal models, there are 2 components to the survival curve, and the duration of the 1st component correlates inversely with the proliferative activity (generation time, growth fraction, cell loss) of the neoplastic cells. This, in general, would appear to be true also for man in that rapidly proliferating tumors have a short 1st component (*e.g.* Burkitt's tumor and choriocarcinoma, 1 year), whereas the more slowly growing tumors have a long 1st component (colon cancer, 4 years; breast cancer, greater than 5 years). However, in man the components of the relapse curve will be damped because of the cytokinetic heterogeneity of the neoplastic cells, variable host defenses (which are likely to be more effective against small numbers of neoplastic cells), the possibility of tumor reinduction, and other factors.

With all these qualifications, it remains probable that in man the transition from the 1st to the 2nd component of the relapse-free curve marks the transition from palliative to curative therapy. In view of this and particularly in view of the very great need for techniques for defining cure rates with reasonable probabilities within a few years of treatment (rather than after a 20-year follow-up), the relapse-free interval has been carefully studied in patients with Hodgkin's disease. The very major changes and improvements which have occurred in the staging and radiotherapy of Hodgkin's disease and most particularly the limited number of relapse-free patients at risk beyond 4 years makes this analysis difficult. In Table 2, the risk of relapse for various time intervals following treatment is presented. Data were obtained from a number of major centers. The reported series with the longest follow-up and thus the largest number of patients at risk after the 5th year is that of Peters (V. Peters, personal communication). These were cases of Stage I and II Hodgkin's disease accrued between 1932 and 1960. All were treated with large-dose radiotherapy. The minimum follow-up time for all of these patients was 10 years, and 20-year follow-up was available for 75% of the patients. The majority of the patients who relapsed did so within the 1st 4 years, and there were 180 patients relapse free at 4 years. The relapse rate by yearly increments from the 4th to the 7th year was 7 to 8%; from the 7th to the 10th year, it was 1 to 4%; from the 11th to the 15th year, it was 1.5% per year; and from the 16th to the 20th year, only 2 of 94 patients at risk relapsed. The relatively high risk of relapse after 4 years in this study as compared to others (Table 1) results from factors (definable and undefinable) relating to the fact that the case accrual time preceded by 15 to 20 years the accrual time of the other studies.

Undoubtedly, a number of patients considered to be Stage II prior to 1960 had Stage III disease, and the involved paraaortic nodes were not treated with radiation. This is a relatively "silent" area and could account for the late relapses in the Peters series. Peters has observed that relapses after 4 years commonly develop in "silent" areas such as the abdomen and that relapses from Stage I disease almost never occur after the 4th year.

In Fuller's series (5), 13 (22%) of 62 patients relapse free at 4 years subsequently relapsed. Many of these patients were treated prior to lymphangiography staging. This represents a minimum figure because, in contrast to Peters' series, the proportion of patients at risk after the 4th year drops off very sharply. In patients with Stage I and II disease reported by Kaplan (9) and Kligerman (M. Kligerman, personal communication) the risk of relapse after the 4th year and particularly after the 5th year is minimal although the number of patients at risk is small.

The risk of relapse of patients with Stage I and II disease is

Table 1

Hodgkin's disease, all stages; death rate and cause of death

	Alive at start of interval		Died during interval		Died of Hodgkin's		Died of other causes	
Interval (yr)	No.	%	No.	%	No.	%	No.	%
			1940–1949;[a] Total cases, 1088					
6–10	240	22	53	22	41	17	12	5
11–15	152	14	20	15	15	10	5	3
16–20	120	11	15	12	8	7	7	6
>20	87	8	3	3	0	0	3	3
			1950–1954;[a] total cases, 982					
6–10	285	29	53	19	44	15	9	3
11–15	196	20	22	11	12	6	10	5
			1955–1959;[a] total cases, 1180					
6–10	378	32	76	20	56	15	20	5

[a]Case accrual interval; from End Results Section, National Cancer Institute.

Table 2
Risk of relapse by time interval following treatment

Author	Stages	Accrual time	Type of statistic	Risk of relapse at following Time interval from treatment												
				0 yr	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr	10 yr	11–15 yr	16–20 yr
Peters[a]	I and II	1932–1960	% relapse			51		8.8	7.3	7.2	3.5	3.6	1.4		7 (1.5%/yr)	2 (0.4%/yr)
			No. at risk			365		180	164	152	141	136	131		129	94
Kaplan (9)	I and II	1956–1968	% relapse	22	18	15	3	5	0	0	0	0				
			No. at risk	145	98	63	34	25	16	13	9	7				
Fuller (5)	I and II	1956–1968	% relapse	26	18	7.5	10	10	9.4	3.1	4	6.5	0	8		
			No. at risk	133	98	80	74	12	44	37	27	17	13	12		
Kligerman[b]	I and II	1957	% relapse	13	16	11	4	2	0	0	6	0				
			No. at risk	78	60	45	32	23	18	16	16	7				
Kaplan (9)	III and IV	1956–1968	% relapse	39	28	14	0	0								
			No. at risk	76	42	18	8	4								
Musshoff and Boutis (10)	All	1948–1966	% relapse	34	15		7				3.5				0	
			No. at risk	332	298		264				136				40	
DeVita *et al.* (3)	IIIB and IV	1965	% relapse	15	24	3	7									
			No. at risk	35	30	21	14									
Chawla *et al.* (1)															$\frac{13\%}{23}$	

[a] Patients at risk estimated from 5-year case accrual data. V. Peters, personal communication.
[b] Extrapolated from figure. M. Kligerman, personal communication.

approximately 20% the 1st year, 15% the the 2nd year and 5 to 10% the 3rd year. Thus the break in the 2 components of the relapse curve for Hodgkin's disease occurs at approximately the 4th year. For patients with Stage III and IV disease (Kaplan's series), there is a similar sharp decrease in the risk of relapse from the 1st to the 3rd year and, although the numbers are small, it would appear that such patients who remain relapse free for 3 to 4 years following treatment also have a substantial reduction in the risk of relapse. Musshoff's series (10) comprises approximately 40% of patients with Stage I and II disease and 60% of patients with Stage III and IV disease. The risk of relapse falls off sharply in the 1st 4 years and the patients at risk after this time are presumably largely Stage I and II patients. From the 5th through the 10th year, only 3.5% of 136 patients at risk relapsed. With the assumption of an average of 88 patients at risk per year, the relapse rate per year from the 5th to the 10th year is 1.1%. Of 40 patients at risk beyond the 10th year in Musshoff's series, none have relapsed.

While all of the above relates to radiotherapy, studies of combination chemotherapy in patients with Stage III and IV Hodgkin's disease have resulted in a decreasing risk of relapse over a 4-year interval which is not significantly different from that of radiotherapy (3). Some 50% of these patients remain in remission at 4 years. Following modern radiotherapy, relapse, if it occurs, almost invariably occurs in nonirradiated sites. In contrast, relapse following chemotherapy occurs in tumor that has been treated. It is possible that the distribution in time of relapses following chemotherapy may differ from those of radiotherapy since the chemotherapeutically treated tumor may behave differently and may possibly be more indolent than nontreated tumor.

In our quest for a definition of cure for Hodgkin's disease, we have arrived at the position that patients who survive relapse free beyond 4 years have at least an 80% chance of cure and those who are relapse free at 10 years have in excess of 90% chance of being cured. The relapse rate from the 4th to the 10th year varies from 5 to 20%, and patients who survive relapse free beyond the 10th year have minimum risk of relapse. An exception to this latter is a study by Chawla *et al.* (1) of patients surviving relapse free beyond 10 years wherein 3 of 23 or a 13% relapse rate occurred. These results would appear to hold not only for Stage I and II disease but, in very preliminary studies, for patients with Stage III and IV disease as well.

Effect of Histopathological Type of Hodgkin's Disease

Another factor that might influence the distribution of relapses following radiotherapy of Stage I and II disease is the histopathological type of disease (Chart 3). In this study by Fuller *et al.* (5), patients with nodular sclerosis and mixed cellularity have a decrease in the risk of recurrence during the 1st 4 years, after which the risk of recurrence is minimal (approximately 5%). For patients with lymphocyte predominance, on the other hand, the risk of recurrence per year remains constant after the 4th year up through the 8th year. This observation is not inconsistent with histopathological observations which suggest that this disease (for cytokinetic, host defense, and other reasons) would be expected to be more indolent. It is also consistent with the fact that lymphocyte depletion results in a very short relapse-free interval (Chart 3). Thus in Fuller's series, while only 13 of 134 (10%) patients have lymphocyte predominance, fully 5 of the 13 patients who relapsed after the 4th year had lymphocyte predominance. Clearly, it may be possible to sharpen markedly our definition for cure of

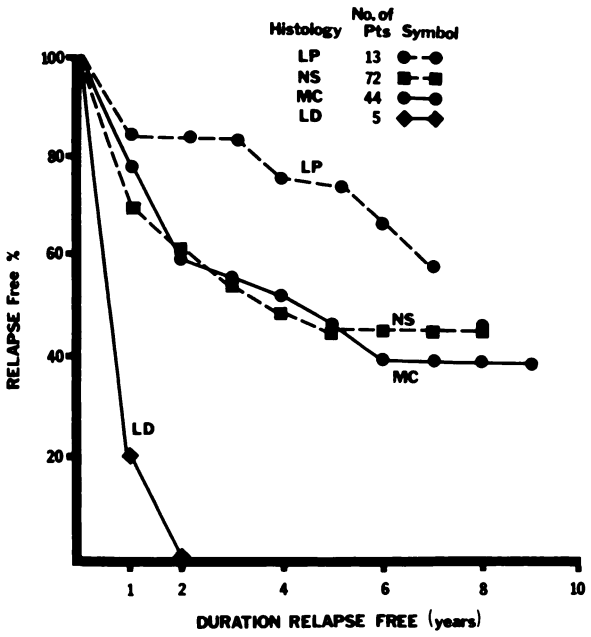

Chart 3. Stage I and II of Hodgkin's disease (relapse-free interval by pathology classification). The curves stopped when there were <5 patients available for analysis. *LP*, lymphocyte predominance; *NS*, nodular sclerosis; *MC*, mixed cellularity; *LD*, lymphocyte depletion.

Hodgkin's disease when these and other factors are taken into account.

Discussion

In general, it is well accepted that patients cured of any disease will have an expected remaining survival time equivalent to that of a group of individuals matched as to age, race, sex, and calendar period of observation. To establish patients as "cured" of Hodgkin's disease, one must have adequate follow-up data on carefully staged cases to determine whether or not groups of patients have been cured. Further, it is desirable to predict an approximate percentage of patients that will be cured as early as possible after initial treatment. One of the difficulties in preparing this paper was that the series of patients given in Table 2 were obtained over a long period of time, different methods and dosages of treatment were involved, methods of staging have improved over the period of observation, and the distribution of patients by histological type in each series was not available. Consequently, only rough estimates of percentage of patients cured could by made by using rather informal weighting of the results from each series of patients.

To predict relative survival curves, Cutler and Heise (2) plot relative survival curves for patients diagnosed during different time periods, say 1940 to 1949, 1950 to 1954, and 1960 to 1964. They proposed the 20-year relative survival rate as a meaningful measure of long-term therapeutic results, and estimates of this figure are obtained by simply extending the relative survival curves for recent time periods so as to make them roughly parallel to those from earlier time periods. Using this technique, for example, they estimate that the 20-year relative survival rate for women with breast cancer is 39% for patients diagnosed from 1960 to 1964 compared with 30% for patients diagnosed from 1940 to 1949. Alternatively, a statistical model could be assumed that characterized the relative survival curve for different time periods. Estimates of parameters of the model could be obtained for data from recent time periods and, assuming that the statistical model remains true, estimates of the relative survival rate could be projected for years after start of treatment well beyond the available data. For patients with Hodgkin's disease, it appears from Chart 2 that the death rate per unit time is decreasing with time and that such curves could be characterized by a Gompertz distribution. This is a 2-parameter distribution, and methods for estimating parameters when data are incomplete have been calculated (6).

Similarly, one could obtain projections of relapse-free interval curves (such as those in Chart 3) by assuming a statistical model and estimating parameters based upon available data. The evidence in Chart 3 and Table 2 indicates a "flattening" of the relapse-free interval curves for patients with Stage I and II disease in the neighborhood of 4 to 5 years after the start of treatment. This type of curve could also be characterized by a Gompertz distribution or perhaps a mixture of exponential distributions. In the latter case, 2 groups of patients would be assumed, 1 group which was subject to a risk of relapse per month to be estimated and a 2nd group which was "cured" so that the risk of relapse per month would be zero. The problem would be to estimate the relapse rate in the patients not cured and the percentage of patients cured.

Of course, separating the deaths occurring into those which could be attributed to Hodgkin's disease and those which could not would also be essential (see Table 1). Further, precise estimates of cure rates can only be obtained from groups of cases that have been carefully staged, classified by histological type, treated in a reasonably homogenous fashion and followed for 3 to 5 years. If one is interested in detecting an increase in the cure rate of 20% at a significance level of 5% with a power of 80%, then approximately 75 patients would be needed in the group.

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