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Perspectives in Cancer Research

Survival of Patients with Hodgkin's Disease

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INTRODUCTION

IT IS generally accepted that survivals for patients with Hodgkin's disease have steadily improved from the 1930's up to the present time. However, in 1972, Campos [1] demonstrated that for groups of patients treated aggressively, the survival curves were concave downwards on a semi-log plot, whilte for patients treated previously in a less aggressive manner, the survival curve on a semi-log plot followed a straight line. He contended that this indicated an increasing mortality rate for the aggressively treated when compared with the less aggressively treated patients. In this paper an attempt has been made to examine the justification for the assumption that survivals in Hodgkin's disease have progressively increased with the introduction of more aggressive therapy.

A search of the literature has been made for all articles published from 1930 up to the present time which dealt with survivals in Hodgkin's disease. A critical analysis has been made of this data.

ARTICLES EXCLUDED FROM ANALYSIS

Those articles quoting remission rates only

It was found that patients who had a complete remission following treatment and did not relapse within 5 yr had a 90% chance of being permanently cured [2]. It was found that those patients who relapsed usually had poor survivals. Kaplan contended that it was therefore possible to assess survival by estimating the relapse rate. This has been steadily reducing over the years. However, of those patients who relapse, approximately 15% will again go into remission on treatment and have long survivals [3]. The remission rate can therefore only be taken as an indication of survival if we know that this 15% remains constant. Unfortunately, there is no information about this in the literature. An indication that increased remission rates may not mean longer survivals is given by results of several clinical trials [4–6] where the relapse free survival rates were significantly different, but the overall survival rates showed no significant difference.

Those articles quoting only mean or median survivals

It has often been said that the mean or median survival has improved recently and is still improving. However, to calculate the mean all the patients must be dead, and to calculate the median, at least half the patients must be dead. It was difficult to ascertain from the literature whether these criteria were observed in the articles where mean or median survivals were quoted.

Those articles quoting only changes in survival stage by stage with historical controls or compared with groups from other centres

It was noticed that the overall results were not comparable due to different patterns of referral to different centres. An attempt was made to overcome this problem by quoting survivals stage by stage. Survivals when considered stage by stage seem to have improved dramatically over the years. However, unless precisely the same staging is employed the results are meaningless, since refinement in staging tends to make survival for each stage appear better when no real improvement has taken place [7].

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ANALYSIS OF REMAINING ARTICLES

The remaining articles may be divided into three groups.

Those quoting non-randomised studies

Claiming increased survivals.

Claiming no increase in survivals.

Those quoting randomised clinical trials

Those claiming increased survivals following more aggressive therapy

Non-randomized studies

Claiming increased survivals. Medinger and Craver [8] attempted to show that whole body irradiation for Hodgkin's disease improved survival. However, they compared their figures with those of Nathanson and Welch [9] who gave a 5-yr survival of 23% against Medinger and Craver's figure of 32%. The Christie Hospital figures employing relatively small-field therapy were 30–35%.

Peters attempted to show that the use of larger X-ray fields in the treatment of Hodgkin's disease yielded improved survivals. Two series were reported. In the first [10], the numbers were small and the differences in survival insignificant. In the second [11], a larger group of patients was divided into those that had small-field and those that had large-field irradiation. It was found that the latter sub-group had longer survivals. However, there was no indication why some patients had small-field and others had large-field irradiation.

Cook *et al.* [12] attempted to show that survivals had improved over the previous years. The 5-yr survivals were:

1929–34 36.1%
1941–46 37.9%
1947–52 38.4% out of 116 cases.

During the period 1941–46, patients were treated by X-ray therapy only, except in 12 cases where nitrogen mustard was used for recurrent disease. During the period 1947–52 most of the patients had X-ray therapy and adjuvant nitrogen mustard. They attempted to show that this improved results. However, the only survival figures stated were those at 5 yr and there is no significant difference.

As recently as 1971, Aisenberg and Goldman [13] wrote that there was no definite evidence that chemotherapy prolonged life. They attempted to show that it did so by comparing survivals of two groups of patients treated over consecutive periods. The earlier group received mustine only, while the latter group received mustine, vinblastine and procarbazine. They claimed that the indications remained constant, viz.—systemic disease too extensive for X-ray therapy. Only the survivals of those patients receiving chemotherapy were compared. A remarkable improvement in survival was said to have been produced by the combination of drugs. However, it is possible that the authors' faith in the value of chemotherapy increased with time, and it would therefore have been used earlier and more extensively in the second group and the survivals of this group would therefore appear to be better. An indication that this occurred is given by the fact that 55 patients were accumulated in 11 yr in the early group and 48 patients were accumulated in 6 yr 2 months in the later group. It is significant that the survivals of all the patients in the two treatment periods were not compared.

DeVita [14] claimed that combination chemotherapy gave more than 60% survival at 6 yr. This was said to be better than single agents in the past. However, the group having combination chemotherapy was not defined. He claimed that prolongation in survival occurs when the proportion of significant responses is more than 50%, and the duration of these responses is significantly prolonged. There was no evidence in his paper to support this and no reference for this statement.

Responders to chemotherapy lived longer than non-responders [15]. However, responders to chemotherapy had disease significantly longer prior to first administration of chemotherapy than non-responders. Those patients who had a longer pre-treatment interval, and presented with apparently early disease, had longer survivals after the start of treatment [16]. It would therefore appear that responders to chemotherapy are those with disease which is less aggressive and therefore compatible with longer survivals.

Claiming no increase in survivals. Gellhorn and Collins [17] compared the survivals of 67 patients treated by X-ray therapy and nitrogen mustard with 65 consecutive cases treated by radiotherapy alone. They found no difference between the two groups. This was confirmed by Osgood [18] who analysed their figures independently.

Shimkin *et al.* [19] found no difference in survival since nitrogen mustard had been available.

In 1966, Karnofsky [20] wrote, "There is

no evidence that chemotherapy, while suppressing the disease for several years in most cases, has an important influence on the underlying process or in prolonging survival time".

Randomised clinical trials

In 1958, a controlled trial was undertaken to compare X-ray therapy with X-ray therapy and adjuvant mustine. There was no difference in survivals [21].

In 1973, Kaplan and Rosenberg [22] reported a trial of extended field vs involved field irradiation. There was no significant difference in survival in any group, although in stages 1B and 2B the differences were almost significant $P=0.0511$. The numbers in these latter groups were, however, small, 10 patients on one side and 11 on the other. Total nodal irradiation and splenectomy produced no difference in survivals.

Adjuvant MOPP chemotherapy made no difference to survivals.

Total nodal irradiation and MOPP made no difference to survivals.

Total nodal irradiation and X-ray therapy to the liver + colloidal radioactive gold + MOPP made no difference to survivals.

In 1975 the result of a controlled trial was reported [23] comparing limited field X-ray therapy and MOPP chemotherapy with extended field X-ray therapy alone for Hodgkin's disease stages 1, 2 and 3A. There was no difference in survivals.

Carbone and Spurr [24] found that for stages 3 and 4 there was no difference in survivals between those treated with cyclophosphamide and those treated with vinblastine. There was no difference in survival after intermittent re-induction of chemotherapy. The authors were unable to say whether chemotherapy was better than no chemotherapy when survival alone was considered.

A controlled trial of extended field X-ray therapy vs extended field X-ray therapy with adjuvant vinblastine showed no significant differences in survival for stages 1 and 2A and B [4].

Claiming increased survivals following more aggressive therapy

A reference curve was drawn by Osgood [19] from data previously published [25, 26]. Survival curves, drawn from data produced by Vera Peters [10], Medinger and Craver [8] and Smetana and Cohen [27], were all significantly better than Osgood's reference curve. However, the 5-yr survival for the group published by Nice and Stestrom [25] was 25.2% and the 5-yr survival of Bethell *et al.* was only 19.3% [26].

This latter group of patients was accumulated between 1934 and 1944. The 5-yr survival for 319 patients registered at the Christie Hospital 1934–49 was 30.5%. Radiotherapy techniques were essentially similar in the group of Bethell *et al.* and in the Christie Hospital group. Surgery for early Hodgkin's disease was an acceptable form of treatment at least until 1966 in the U.S.A. [28], and it is likely that many radiotherapy centres were deprived of early cases by the surgeons. This might account for the poor survivals from many American groups of patients treated by radiotherapy. It is therefore not surprising that Osgood was able to find series of patients whose survival was significantly better than his reference curve.

The Christie Hospital survival data remained constant from 1934–59 [29] (Table 1).

Table 1. *Christie Hospital survivals, showing little change over the period* 1934–1959

	No.	5 yr (%)	10 yr (%)	15 yr (%)
Generalized				
1934–49	216	19.6	13.4	12.6
1934–54	466	18.4	11.3	
1934–59	489	18.9		
Localized				
1934–49	103	53.5	44.1	38.9
1934–54	220	55.3	43.2	
1934–59	375	56.5		

The overall 5-yr survival over the period 1934–59 was 30–35%. The Christie Hospital figures from 1968–71 show an overall 5-yr survival of 42%. However, in the early series 26.5 patients/year were treated. In the later series 97.5 patients/year received treatment for Hodgkin's disease. The relative proportions of early to late cases were similar in the two groups. However, in view of the large differences in referrals per year, the differences in survival cannot be accepted as necessarily significant.

In 1966, Vera Peters [30] compared her results with those from the Christie Hospital (Table 2). She claimed that her slightly better survival figures were the result of large field X-ray therapy. However, the 5-yr survival at the Christie Hospital, 1934–59, ranged from

Table 2. Comparison of Christie Hospital and Toronto survival rates

	No.	5 yr (%)	10 yr (%)	15 yr (%)
Christie 1934–54	686	30	22	21
Toronto 1928–54	319	40	26	20

30–35%. The 5-yr survival of 42% at the Christie Hospital 1968–71 was obtained using modest size X-ray fields.

In 1966, Musshoff and Boutis [31] claimed an actuarial 5-yr survival, for those patients treated before 1964, of 48%. This was subsequently amended to 42% [32]. They claimed an actuarial 10-yr survival of 28.7% and a 15-yr survival of 21.2%. The distribution of early to late cases was similar to the Christie Hospital data.

In 1973 Musshoff [32] appeared to demonstrate that using extended field X-ray therapy to a dose of 4000 rad in 4 weeks had increased the 5-yr survival from 42% (before 1964) to 66% (1964–1969). However, the survival curves are similar over the first 3-yr but no patients appear to die in the recent series over the subsequent 3-yr. This can only mean that the numbers of patients available for analysis in the recent series after 3-yr were too small to produce a meaningful survival curve. In fact if the recent survival curve forms a straight line continuous with the survival curve of the first 3-yr, as would be expected on a log survival curve, there would be little difference between the recent and the less recent groups.

In 1966 Kaplan [33] published an overall 5-yr survival figure of 48.8%. This was for patients treated 1948–64 and was an actuarial 5-yr survival. Confidence intervals were not quoted. The 10-yr survival of 24.4% was not appreciably different from the Manchester and Toronto figures.

In 1969 Kaplan [2] reported a series of patients treated by large field irradiation to the relatively high dose of 4000 rad in 4 weeks. The overall 5-yr survival was 73%. However, many patients had not been followed up for 5-yr and an actuarial analysis had been done. In Kaplan's series there were 40% clinically staged late cases (old Manchester staging). In the Manchester series (1968–70) the 5-yr survival rate was 42%, but there were 55% clinically staged late cases. Kaplan's good survival rates may therefore be accounted for by a paucity of late cases combined with the inherent inaccuracy of an actuarial analysis.

In 1976, Aisenberg and Qazi [34] reported survivals of patients with Hodgkin's disease treated over three separate periods.

1948–64 34% 5-yr survival
1965–68 65% 5-yr survival
1969–73 87% 5-yr survival

Patients over 65-yr of age were excluded from the analysis.

The proportion of patients distributed among the four stages was said to be similar for the three periods of time considered. However, many of the patients from the latter period had staging laparotomies. This would indicate that if clinical staging alone was used, the latter group would be shown to contain a larger proportion of early cases than the middle group, thus accounting for their better survivals.

The reduced risk of recurrence in those patients who were staged 1 or 2 by laparotomy, compared to those who were clinically staged, closely approximated to the 24% chance of uncovering unexpected lymphoma. This indicates that more aggressive treatment given to these patients did not affect survival.

In 1975 Kaplan and Rosenberg [35] claimed an overall 81.3% 5-yr survival and 50% 10-yr survival. They indicated that these were patients whose survivals had been presented in earlier papers: 1973 [5]—this was a series of clinical trials showing no increase in survival using more aggressive therapy. 1975—5-yr survivals of 92% and 88% were quoted [23]. An actuarial analysis had been done since the longest follow-up was 64 months, and stage 4 cases had been excluded from the analysis.

CONCLUSIONS

There is no doubt that disease-free survival has been extended by more aggressive methods of treatment. However, claims that overall survival has improved is open to dispute.

The author has searched the literature for reports of controlled trials, where patients have been randomised to receive one of two treatments. No statistically significant difference in survival has been reported.

Several papers have been published claiming increased overall survivals, but these have not been controlled studies and the validity of their conclusions is doubtful.

However, no further evidence could be found in the literature to support Campos's contention that aggressively treated patients actually had poorer survivals than those treated less aggressively.

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