Long-Term Results of Radical Radiotherapy in Hodgkin's Disease

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Summary
A series of 1276 histologically proven cases of Hodgkin's disease is analyzed. The primary treatment was roentgen therapy followed, when systemic symptoms developed, by chemotherapy. All treated cases were followed up for a minimum of 5 years and a maximum of 15 years after treatment. Though the 15-year survival rate of patients with "generalized" lymphadenopathy (with or without systemic symptoms) was poor, very gratifying results were found in those patients whose lymph node involvement at the time of treatment was still localized to 1 single or 2 contiguous anatomic sites. A series of 213 patients diagnosed as having either localized lympho- or reticulosarcoma was also analyzed and found to have survival rates at 5, 10, and 15 years remarkably similar to those with Hodgkin's disease. Yet another series of 493 patients in whom the histologic report, though indicating a malignant lymphoma, was in some way disputatious, enjoyed survival rates not significantly different from the other 2 groups of patients. It seems obvious that, however we may classify malignant lymphoma, the urgent need is to treat the patient radically with X-rays at the earliest opportunity.

Some 10 years after treatment more than 40% of the patients with localized Hodgkin's disease were alive and well, and were shown to have a life expectancy similar to that of the general population of the same age and sex. This indeed provides a valuable definition of definitive cure.

The better prognosis usually claimed for females was substantiated in this series of Hodgkin's patients, but the impact of age on prognosis was found to be confined to females and the difference between the younger and older age groups was highly significant statistically. The implications for further investigation of these extreme categories are obvious.

Introduction
What, it may be asked, is the outcome of a consultation between a pessimistic patient and an equally pessimistic physician? In 1963 Marion Russell and I published a paper entitled "Cure of Hodgkin's Disease (4)." This title was deliberately chosen to catch the eye of the sceptics, and its content was aimed at the pessimists who still regard Hodgkin's disease as a multifocal disease and inevitably fatal. The passage of 2 years since the publication of that paper has allowed us to include a larger number of patients into each category analyzed. This provides increased statistical stability and enhances the validity of the conclusions drawn.

Clinical Material
Between 1934 and 1959 inclusive, we have seen at the Christie Hospital in Manchester a total of 1276 cases of histologically proved Hodgkin's disease in both sexes and at all stages. Two hundred and four of these patients were considered unsuitable for treatment for a variety of reasons—extensive disease, too ill for treatment, or the patient's refusal. Of the remaining 1072 cases, 8 have been lost to follow-up, leaving a total of 1064 patients for statistical analysis.

Staging
At international meetings during the past year or 2 there has been much discussion on the need for an internationally acceptable system of staging or descriptive classification. The application of a modified T.N.M. system (7) is being advocated, and it seems likely that such a scheme will commend itself to workers in this field. There are, however, differences in opinion as to how complex and exhaustive a descriptive classification need be. Some are in favor of recording great detail, including pyelography, venography, and lymphography for all patients. The writer would advocate the simplest possible system consistent with proper therapy, in the interests not only of universal acceptance but of universal application.

However, during the period of 1934–59, and with the patients here analyzed, the staging method was an essentially practical one. Where it proved feasible to treat the patient with radical intent, the clinical stage was considered to be "early" or "localized." Such a staging was applied to a patient whose lymphadenopathy was confined to 1 reasonable volume, such as the neck on 1 or both sides, or 1 side of the neck and its contiguous axilla, or the supraclavicular fossa and the upper mediastinum. Any extension of disease beyond what could be treated in a radical fashion was regarded as "generalized disease."

Treatment
The clinical extent of the disease is important in deciding the therapeutic approach in each case. Where the disease was confined to 1 anatomic lymph node group, it was and still is our practice to attempt to irradiate this substantial region in 1 undivided volume, and to deliver to that volume as high a dosage as it will safely tolerate. For example, where 1 or both sides of the neck are involved, we would normally irradiate from a level above the upper deep cervical lymph node region down to the suprasternal notch or even lower. A rough guide is to attempt to irradiate from 5 or 7 cm beyond the uppermost and lowermost of the palpable lymph nodes in the chain. No attempt was made "prophylactically" to irradiate the clinically uninvolved contiguous lymph node groups. During the period discussed in this paper all of the patients were treated with kilovoltage X-rays, and the level of dosage employed for radical treatment was between 2750 and 2500 rads to field sizes from 20 to 30 cm long.
The total dose was given over a period of 3 weeks with daily fractions 5 times weekly. Such a level of dosage is close to the tolerance limits of the spinal cord, the tolerance of which is a function not only of total dosage but of total length of cord irradiated (2, 3, 5). This dosage is also as much as the patient is usually willing to tolerate, since acute mucosal reactions are unpleasant, and dysphagia can lead to fluid and electrolyte problems. Such reactions are indeed acceptable only in the interests of cure.

Where the disease was widespread and radiation could clearly not be given in substantial dosage to a number of large volumes, the object of treatment became palliative rather than radical. In such cases the volumes irradiated were kept as small as possible, and smaller doses in shorter overall times were employed. Where the patient also had systemic symptoms of pyrexia, anemia or pruritis, chemotherapy in one or another form was also employed.

Analysis of Results

Of the total of 1064 cases available for analysis 375 were categorized as early lymphadenopathies and were therefore treated by radical irradiation. The remaining 689 cases were generalized either in the sense of having widespread lymphadenopathy alone or having, in addition to this, one or more of the signs of systemic disease. Table 1 shows, as one would expect, that the results of treating generalized Hodgkin’s disease are distinctly disappointing. The number of survivors at the 10th and 15th years, however, exceeds 10%, which is much better than many other forms of malignant disease and indeed better than some benign conditions!

Of particular interest, however, are the results achieved following radical treatment of early cases of Hodgkin’s disease. Table 2 shows the total number of 375 patients surviving at 5, 10, and 15 years. The internal statistical consistency for each subgroup is such that when the whole group of 375 cases have matured to the full 15 years it is reasonable to anticipate that their 15-year survival rate will be similar to that of the smaller 1934-49 group. The striking fact is the large numbers of patients who are still alive and free of disease at the 15th year.

In view of the histologic disputation which so commonly surrounds this group of lymphoreticular diseases, it is useful to consider the long-term survival of lymphoreticular sarcoma (lymphosarcoma and reticulum cell sarcoma combined). Their response to irradiation is very similar to that of Hodgkin’s disease and their treatment, in Manchester at any rate, is identical. Table 3 shows the 5-, 10-, and 15-year survival rates from a total of 212 early or localized cases of lymphoreticular sarcoma treated between the years 1933 and 1959 inclusive. Though this is clearly a very mixed group of malignant lymphomas, it will be noted that the internal consistency of the 5-, 10-, and 15-year survival rates for each subgroup is again remarkable and encouraging, and the results of treatment are if anything slightly better than those for Hodgkin’s disease—though the differences are not significant statistically.

A further point of interest is the sex difference in prognosis, for evidence has accumulated to show that females have a distinctly better prognosis than do males for the same stages of the disease. Many writers have confirmed this finding, and Peters (6) has further suggested that age also plays a most significant part, with the younger females having a better prognosis than the older males. Recent data from the Christie Hospital, Manchester, (Table 4) suggest that age does not in fact influence prognosis in males, but in females it is of very considerable significance. This wide difference in the response to treatment between younger and older women calls for urgent investigation.

It is worthy of note that our long survivors were predominantly described as having Hodgkin’s granuloma, not paragranuloma. Indeed those in the latter category did not display a better prognosis than do males for the same stages of the disease. Many writers have confirmed this finding, and Peters (6) has further suggested that age also plays a most significant part, with the younger females having a better prognosis than the older males. Recent data from the Christie Hospital, Manchester, (Table 4) suggest that age does not in fact influence prognosis in males, but in females it is of very considerable significance. This wide difference in the response to treatment between younger and older women calls for urgent investigation.

It is worthy of note that our long survivors were predominantly described as having Hodgkin’s granuloma, not paragranuloma. Indeed those in the latter category did not display a better prognosis, and since the paragranuloma is recognized as being many times commoner in males (whose prognosis is worse than females) the “benign” nature of paragranulomatous Hodgkin’s disease must be seriously questioned. Indeed morphologic consideration alone provides an inadequate guide to prognosis.

All of these foregoing lymphoma patients had their diagnosis confirmed by an unequivocal histologic report, either of Hodgkin’s disease or lymphoreticular sarcoma. During the period of this survey (1933-49), however, we have accumulated a group of patients whose biopsy reports have been in some way equivocal. In all, 493 such patients are available for analysis, and this

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1 Because of the poorer relative biologic efficiency of megavoltage radiation, a correction factor must be applied to convert kilovoltage into megavoltage doses (approximately +500 rads). A further nonlinear (N.B.) increase must also be made for more extended over-all treatment times. (See Ralston Paterson, The Treatment of Malignant Disease by Radiotherapy, London; Edward Arnold, 1963).

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### TABLE 1

<table>
<thead>
<tr>
<th>YEARS</th>
<th>No. treated</th>
<th>AGE-CORRECTED SURVIVAL RATE (%)</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>5 yr</td>
</tr>
<tr>
<td>1934-49</td>
<td>216</td>
<td>19.6</td>
</tr>
<tr>
<td>1934-54</td>
<td>466</td>
<td>18.4</td>
</tr>
<tr>
<td>1934-59</td>
<td>689</td>
<td>18.9</td>
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### TABLE 2

<table>
<thead>
<tr>
<th>YEARS</th>
<th>No. treated</th>
<th>AGE-CORRECTED SURVIVAL RATE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 yr</td>
</tr>
<tr>
<td>1934-49</td>
<td>103</td>
<td>53.5</td>
</tr>
<tr>
<td>1934-54</td>
<td>220</td>
<td>55.3</td>
</tr>
<tr>
<td>1934-59</td>
<td>375</td>
<td>56.5</td>
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### TABLE 3

<table>
<thead>
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<th>YEARS</th>
<th>No. treated</th>
<th>AGE-CORRECTED SURVIVAL RATE (%)</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>5 yr</td>
</tr>
<tr>
<td>1933-49</td>
<td>107</td>
<td>51.6</td>
</tr>
<tr>
<td>1933-54</td>
<td>147</td>
<td>50.6</td>
</tr>
<tr>
<td>1933-59</td>
<td>213</td>
<td>47.9</td>
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TABLE 4
HODGKIN'S DISEASE—LOCALIZED LYMPHADENOPATHY
(375 CASES TREATED 1934-59)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Males</th>
<th>Females</th>
<th>Age-Corrected Survival Rates (5 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>100</td>
<td>47</td>
<td>57.5</td>
</tr>
<tr>
<td>35-54</td>
<td>100</td>
<td>36</td>
<td>53.9</td>
</tr>
<tr>
<td>55 &amp; over</td>
<td>48</td>
<td>44</td>
<td>57.7</td>
</tr>
</tbody>
</table>

* The difference in survival rates between the younger and older age groups in females is highly significant (P = 0.0001).

TABLE 5
COMPARISON OF UNEQUIVOCAL AND EQUIVOCAL GROUPS

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Group</th>
<th>Age-Corrected Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 yr</td>
</tr>
<tr>
<td>Localized</td>
<td>Unequivocal</td>
<td>53.6</td>
</tr>
<tr>
<td></td>
<td>Equivocal</td>
<td>54.9</td>
</tr>
<tr>
<td>Generalized</td>
<td>Unequivocal</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>Equivocal</td>
<td>12.7</td>
</tr>
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</table>

is a sufficiently large group to justify a separate statistical study. A comparison of the survival rates for this group with those for the summated Hodgkin's and lymphoreticular sarcoma patients is shown in Table 5. None of the differences in survival rates is significant statistically. The conclusion seems inescapable that whatever we call these lymphomas, and however much they may appear on morphologic grounds to differ one from the other, their response to radical radiation therapy is remarkably similar, consistent, and encouraging.

The Concept of Cure

The use of the word “cure” raises many difficulties, some real and some semantic. A deficiency disease like diabetes mellitus is incurable, but by replacement therapy it is controllable. Dental decay, on the other hand, can be cured by removal of the teeth. So far as cancer is concerned, we require some different definition. To express the results of treatment in terms of crude survival rates can be most misleading, if only because such a method ignores the fact that a patient aged 70 years has a natural expectation of life very different from another aged only 25. Of all the various methods for evaluating treatment the age-corrected survival rates first suggested by Berkson (1) appealed to us most and were adopted some 15 years ago at the Christie Hospital in Manchester. The logical conclusion of this, however, is implicit in Russell's (4) definition of cure: "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 submit that this is a most practical and realistic interpretation of the difficult word "cure"—and is certainly a most acceptable definition from the patient's point of view! As we showed in 1963 this interpretation of cure can be applied to Hodgkin's disease. Chart 1 shows the survival curve of radically treated localized Hodgkin's disease (based on the same data as those recorded in Table 2), showing how this curve begins to run approximately parallel to that for the normal population of the same sex and age. This disease is so universally judged to be lethal that to claim some 40% of cures for the early cases has met with some resistance. Unfortunately, numbers do not permit a meaningful breakdown into males and females.
but in a few years' time larger numbers of patients will be available for analysis in these terms, and it should then be possible to draw more firm and more interesting statistical conclusions.

Chart 2 (based on the data in Table 3) shows a similar curve for lymphoreticular sarcoma, and once again the high cure rates are most gratifying.

This concept of definitive cure has been applied to many other types of malignant disease. Charts 3 and 4 show 15-year survival curves for squamous carcinoma of the uterine cervix and squamous carcinoma of the skin (many other examples might have been chosen). Though few people would deny that cancer of the cervix or of the skin is entirely curable by radiation therapy, it is curious how the application of the same statistical principle to Hodgkin's disease evokes a powerful emotional resistance.

It is difficult to understand how Hodgkin's disease came to be regarded as so hopeless. I suspect that too many of the earlier published studies of Hodgkin's disease were made by morbid anatomists working backwards in time from the autopsy table! To draw conclusions about survival from a population of dead patients is a singularly fallacious approach to the problem. Medical students are still being taught that Hodgkin's disease is inevitably fatal, but on what evidence this teaching is based I do not know. There is surely an urgent need to teach the teachers.

**Conclusions**

The primary object of this paper is to present statistically valid evidence that patients with Hodgkin's disease are potentially curable provided (a) that they are fortunate enough to have localized lymphadenopathy at the time of treatment, and (b) that they are treated by X-rays to an adequate volume of tissue and to an adequate level of dosage. The significance of the terms “curable,” “localized,” and “adequate volume and dose” is discussed.

A mixed group of patients with lymphoreticular sarcoma, and also a group of patients in whom the histologic picture was equivocal, were found to have survival rates at 5, 10, and 15 years after treatment which were similar to those with Hodgkin's disease.

It is therefore concluded that where a patient is considered to have a malignant lymphoma, and when it is considered to be clinically localized, every effort should be made to irradiate with curative intent. In the light of our present knowledge, histologic disputation should not be allowed to inhibit such radical intentions.

**Acknowledgment**

I am indebted to Marion H. Russell for statistical information and guidance.

**References**

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