Extended-Field Radical Radiotherapy in Advanced Hodgkin’s Disease: Short-Term Results of 2 Randomized Clinical Trials

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Summary

The 2 clinical trials described herein were initiated in 1962 with the following objectives: (a) to determine whether intensive prophylactic irradiation of apparently uninvolved lymph node regions adjacent to clinically involved regions in patients with regionally localized Hodgkin’s disease increases the duration of remission and of survival; (b) to determine whether potentially curative doses of radiation given to patients with generalized Hodgkin’s disease are more effective than palliative doses, as measured by length of remission and/or survival; (c) to accumulate additional information on the natural history of Hodgkin’s disease in patients whose clinical stage was, in all instances, determined with the aid of lymphangiography and other special diagnostic procedures; (d) to evaluate the tolerance of normal tissues in patients treated with extended-field, high-dose radiations.

Patients who met the defined eligibility criteria were assigned to alternative treatment groups at random after an extensive diagnostic evaluation, which included lymphangiography, open bone marrow biopsy, and a battery of liver function tests, as well as other, more routine procedures in all cases. All patients were carefully examined at serial intervals, following completion of the defined radiotherapeutic program. Follow-up intervals are not yet long enough to permit evaluation of comparative survival in the various treatment groups. However, it is clear that extended-field megavoltage radiotherapy to doses in the range of 4000 rads, given at the rate of about 1000 rads/week, is surprisingly well tolerated; there have been virtually no major complications, and most of the observed hematologic, respiratory, neurologic, and endocrine complications have been relatively mild and transient in nature.

Introduction

The clinical trials which are the subject of this preliminary report evolved from an earlier study (5). They were initiated in 1962 with the following objectives: (a) to determine whether intensive prophylactic irradiation of apparently uninvolved lymph node regions adjacent to clinically involved regions in patients with regionally localized Hodgkin’s disease increases the duration of remission and of survival; (b) to determine whether potentially curative doses of radiation given to patients with generalized Hodgkin’s disease are more effective than palliative doses, as measured by length of remission and/or survival; (c) to accumulate additional information on the natural history of Hodgkin’s disease in patients whose clinical stage was, in all instances, determined with the aid of lymphangiography and other special diagnostic procedures; (d) to evaluate the tolerance of normal tissues in patients treated with extended-field, high-dose radiations. The protocols for these clinical trials have been previously described (6); accordingly, only the essential features are reviewed here.3

Eligibility

The following criteria have been applied in establishing eligibility of patients for admission into the study: biopsy diagnosis of Hodgkin’s disease confirmed by at least 2 different pathologists; no previous treatment other than biopsy; clinical evidence of disease limited to lymphoid structures (nodes, spleen); no other malignant neoplasm or other life-threatening disease; consent of patient or guardian and referring physician. A number of cases, because of prior treatment or other reasons, have been treated radically with the same technic as was used in Protocol II; observations on these cases are also included in this report, although these cases will be excluded from our statistical analyses. To date, a total of 69 cases have been found ineligible. The reasons for exclusion (multiple in some instances) were: prior treatment, 38; Stage IV disease, 18; commitment to referring physician, 11; refusal on religious or other grounds, 7; old age and miscellaneous, 5.

Clinical Evaluation

All cases, including those ultimately found ineligible for the study for any reason, have been subjected to a rigorous clinical study. This included a history and physical examination, with careful mapping and measurement of clinically involved lymph nodes, spleen, liver, and other palpable disease; complete blood count; open biopsy of iliac crest bone marrow; liver function tests, including bromsulphthalein retention, alkaline phosphatase, lactate dehydrogenase, bilirubin, and serum glutamic oxalidate

1 These investigations have been supported by Grant CA 05838 from the National Cancer Institute, NIH. An earlier report was presented at a symposium on Hodgkin’s disease held on February 15, 1965, at the Hôpital Saint-Louis, Paris, France, and will appear in French translation in a forthcoming issue of the Nouvelle Revue Française d’Hématologie.

2 A limited number of mimeographed copies of the complete protocols are available to interested individuals by written application to the authors.
Extended-Field Radical Radiotherapy

TABLE 1
LYMPHOMA STUDY: DEFINITION OF STAGES

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No detectable disease (excisional biopsy)</td>
</tr>
<tr>
<td>I</td>
<td>Disease limited to a single lymph node</td>
</tr>
<tr>
<td>II</td>
<td>At least 2 distinct abnormal lymph nodes, limited to above or below the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Disease in lymphoid structures (nodes and/or spleen) above and below the diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Involvement of bone marrow, liver, bone, skin, lung parenchyma, pleura, central nervous system, or viscera other than lymph nodes, Waldeyer’s ring, and spleen</td>
</tr>
</tbody>
</table>

and glutamic pyruvic transaminases, supplemented by needle or open biopsy of the liver in cases with hepatic enlargement or abnormal tests; radiographic examination of the chest, gastrointestinal tract, and skeleton; lymphangiography in all cases, with optional inferior vena cavaography and intravenous urography (2, 3, 7); and tests for cutaneous anergy to natural and chemical delayed hypersensitivity antigens (1).

Clinical Classification

A 4-stage clinical classification of the extent of disease has been utilized (Table 1). Initially, liver involvement was included in Stage III; however, since severe hepatic injury has subsequently been observed as the result of liver irradiation (4), liver involvement is now assigned to Stage IV.

Treatment Options

Protocol I. Patients with regionally localized disease (Stages 0, I, or II-B) were randomly assigned to 1 of 2 groups and treated either with intensive radiotherapy directed to the locally involved regions only or to extended fields, covering the adjacent, apparently uninvolved lymph node chains in addition (Charts 1, 2).

Protocol II. Patients with generalized Hodgkin's disease (Stage III-A or -B) were randomly assigned to 1 of 2 groups and treated either palliatively or radically (Chart 3). Very recently, as experience revealed that extended-field radical treatment in Stage III disease is reasonably well tolerated, it was decided that continued randomization of new Stage III cases to the palliative dose series was no longer justifiable. The cases already entered in this closed control group will, of course, continue to be followed and treated palliatively, as indicated.

New manifestations of disease, after the initial course of treatment, have been treated in accordance with the nature of the clinical problem presented; in most instances, generalized or visceral disease has been treated with chemotherapy and localized new disease with radiotherapy. However, patients in Protocol I, who were initially treated with local fields only, if they later presented a clinical problem suitable for radiotherapy, were rerandomized either to palliative or to radical radiotherapeutic dose groups.

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Lymphoma Study

Plan "A"

4000 rads to known tumor only

Plan "B"

4000 rads to known tumor
3000-3500 rads to adjacent areas

Treatment Plans for Stages 0, I or II

Chart 2. Same as for Chart 1, except that the hypothetical sites of apparent involvement are in the inguinal and iliac or lower paraaortic nodes.

Lymphoma Study

Plan "A"

1500 rads to known tumor only

Plan "B"

3500-4000 rads to known tumor
3000-3500 rads to adjacent areas

Treatment Plans for Stage III


and/or 3rd region is then treated to approximately 1500 rads, following which treatment is carried to completion in the initial field and then in the other fields (alternating technic, Chart 5).

Clinical Observations

A total of 37 protocol and nonprotocol patients have received extended-field radical treatment to date. In 24 of these, a dose of 3500 rads or more was successfully delivered to the mantle, paraaortic, pelvic, and in some instances, splenic fields; in 7 others, 1 or more of these fields received less than 3500 rads because of leukopenia; and in 6 young female patients with no detectable subdiaphragmatic disease, the pelvic fields were electively omitted to spare ovarian function and fertility.

Complications

Although the extended-field treatment of Protocol I and the radical treatment of Protocol II necessitate treatment of a very large fraction of the total active bone marrow in the adult human, there have been no deaths due to hematopoietic injury. Only 1 patient has required hospitalization for blood transfusion, and
CHART 5. Same as for Chart 4, except that in this instance extensive disease in multiple regions required interruption of treatment in 1 area in order to proceed with partial treatment to a 2nd area, followed by resumption and completion of treatment in the initial area, etc. (alternating technic).

CHART 6. Same as for Chart 4, to indicate hematologic responses in an elderly patient treated with extended-field megavoltage radiotherapy.
there have been no septicemias or other significant manifestations of decreased resistance to infection. Body weight has usually remained essentially unchanged throughout the course of treatment, and nausea, vomiting, and diarrhea have been readily controlled by medication and have not necessitated interruption or termination of treatment.

HEMATOLOGIC. Hematologic observations on a number of representative cases are presented in Charts 4–8, in which the extent of disease is indicated schematically in black, and the duration of treatment and dose to each treatment region are indicated by horizontal bars plotted against time as the abscissa. It will be seen that the WBC usually remained in the range of 2000–3000, even in elderly patients (Chart 6), though occasionally, and usually transiently, WBC's descended to approximately 1000. In most cases, there was prompt return of the WBC to the normal range; a few exhibited a persistent mild leukopenia of approximately 3500–4000. The platelet count usually remained above 100,000, though in a few instances counts descended to the range of 25,000–50,000. The platelet count also returned to the normal range in most instances; a small number of patients have a persistent mild thrombocytopenia in the range of 100,000–150,000. Packed cell volume (PCV) was rarely affected early in the course of treatment, but tended to fall slightly near the end of treatment, followed by a return to normal levels. Severe anemia has been noted only in rare instances.

NEUROLOGIC. Seven patients have noted mild, transient numbness and/or tingling in the fingers and toes, accentuated by flexing the neck (Lhermite's sign), presumably attributable to a transient cervical or dorsal myelopathy. There has been no paralysis. Recently, the mantle treatment technic has been modified to extend the midline posterior shield down to cover the dorsal spinal cord after a dose of 2000 rads has been delivered to the mediastinum.

CARDIOPULMONARY, MEDIASTINAL. Transient esophagitis has often been noted during the latter part of the mantle treatment and may persist for a few weeks thereafter. Approximately 1/3 of patient experience a dry, irritating cough during the 1st 3 or 4 months following completion of the mantle field, often associated with slight exaggeration of pulmonary vascular markings on chest radiographs, indicative of paramediastinal radiation pneumonitis. However, the sharp collimation of the linear accelerator X-ray beam and careful attention to periodic field reshaping have minimized this hazard, and symptoms attributable to pulmonary reaction have, in almost all instances, been transient and mild. Three patients have exhibited a transient acute pericarditis within the 1st 6–12 months after treatment. There have been no chronic cardiac or pulmonary complications to date.

HEPATIC. The syndrome of radiation hepatitis resulting from external irradiation of the entire liver to doses in excess of 3000–4000 rads has been described elsewhere (4). Recently a patient in Protocol 1, with disease initially confined to the iliac and paraortic nodes, developed extension of disease in the liver and spleen which was treated with radiotherapy. Although treatment to the liver area was discontinued after a total dose of only 2700 rads, progressive and ultimately fatal radiation hepatitis developed in this case. It is concluded that the liver cannot tolerate the dose levels of external radiotherapy which are required to sterilize Hodgkin's disease, and accordingly, liver involvement is now considered an indication of Stage IV disease; such patients are excluded from both protocols.

RENAL. Great care has been taken to shield the kidneys when abdominal fields are employed. One patient with a horseshoe kidney necessarily received radiotherapy over the isthmus of the horseshoe in the region of the clinically involved nodes. There have been no instances of radiation nephritis to date.

ENDOCRINE. Three patients have developed evidence of hypothyroidism with myxedema, appearing within 1–2 years after completion of treatment. It is of interest that this complication was not observed in a series of patients treated with the mantle technic prior to the use of lymphangiography. It is therefore postulated that the chronic absorption of organic iodine from the opacified lymph nodes may have prevented regeneration of the irradiated thyroid and thus have contributed to the development of myxedema. One other patient has recently exhibited a more complex disturbance of thyroid function, which is still being evaluated.

GASTROINTESTINAL. There have been no significant complications.

INFECTIOUS. There has been no unusual susceptibility to bacterial infection. However, several patients have developed herpes zoster, which in some instances has been of unusual severity. To date, there is no indication that this complication is associated with a more unfavorable prognosis, as has been suggested in other studies (8).
CHART 8. Same as Chart 7, but note that this patient, who developed recrudescence of disease in the liver and required chemotherapy, was able to tolerate such therapy quite well, despite the high doses of prior radiotherapy.

**Duration of Remission and Survival.**

Results to date in Protocol I are summarized in Chart 9 and for Protocol II in Chart 10. Results in the nonprotocol cases treated by the radical technic of Protol II are indicated in Chart 11. In each protocol, patients have been paired in the sequence in which they were randomly assigned to the 2 treatment groups, and the time scale is indicated in months extending laterally in each direction from the center line.

In Protocol I, 8 of 19 patients in the local treatment group have exhibited 1 or more extensions of disease (Chart 9); of these, 6 have been treated intensively with radiotherapy to the new areas of involvement, with apparent control to date in 5 and death in 1; the remaining 2 cases (1 now deceased) have been treated with chemotherapy. Four of 18 patients in the extended-field group of Protocol I have exhibited extensions of disease, of which 1 has been treated, apparently successfully, with additional radiotherapy, 2 with chemotherapy, and 1, now deceased, with both modalities.

In Protocol II, there have been numerous recurrences and extensions in the palliatively treated group, as expected, and 3 of these 15 cases have died of Hodgkin's disease (Chart 10). In the radically treated group, 1 patient with liver involvement developed recurrence in the liver after 2950 rads; 2 other cases have exhibited extension to the bone marrow approximately 18 months after the start of radiotherapy; and a recent case, with Stage III Hodgkin's sarcoma, had an incomplete regression of his massive mediastinal adenopathy after 4000 rads and soon thereafter developed multiple extensions and recurrences elsewhere. All 4 cases are now receiving chemotherapy. Patients who have required subsequent radiotherapy or chemotherapy for extensions of disease have tolerated such additional treatment reasonably well and have responded satisfactorily in the majority of instances (Chart 8). There have been no deaths to date in the radically treated group. If the radically treated nonprotocol cases (Chart 11) are considered together with the radical treatment group of Protocol II, 13 of 24 Stage III cases thus treated remain free of clinical manifestations of disease, 9 of them for 12-35 months since the initiation of treatment. In the radically treated cases, a distinct difference in the course of patients with and without constitutional symptoms initially appears to be emerging. Of 13 Stage III-B patients, with constitutional symptoms, 8 have developed extensions of disease to date, whereas only 3 of 11 Stage III-A patients have had a later manifestation of active disease.

It is concluded that radical treatment of advanced Stage II and Stage III cases is remarkably well tolerated. Although the results of such treatment appear encouraging, it must be emphasized that the observation period is too short and the number of cases too small to permit any conclusions to be drawn at this time concerning the relative efficacy of this plan of treatment.
CHART 9. Treatment results to date in Protocol I. Details are discussed in the text.

<table>
<thead>
<tr>
<th>Hodgkin's Disease, Stages I, II, L-I Protocol</th>
<th></th>
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<tbody>
<tr>
<td>Free of disease</td>
<td>Radiation therapy</td>
<td>Disease evident</td>
</tr>
<tr>
<td>Pul-a</td>
<td>Fri-a</td>
<td>Hur-a</td>
</tr>
<tr>
<td>Phi-IIa</td>
<td>Sev-IIa</td>
<td>Fra-IIb</td>
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CHART 10. Treatment results to date in Protocol II. Details are discussed in the text.

<table>
<thead>
<tr>
<th>Hodgkin's Disease, Stage III - L-II Protocol</th>
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<th></th>
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<tr>
<td>Free of disease</td>
<td>Radiation therapy</td>
<td>Disease evident</td>
</tr>
<tr>
<td>Pul-a</td>
<td>Fri-a</td>
<td>Hur-a</td>
</tr>
<tr>
<td>CII-b</td>
<td>Bau-b</td>
<td>Spa-a</td>
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</table>
### Prior R & Courses

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of admission</th>
<th>Responses after Stanford R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bub-b</td>
<td>2600</td>
<td>No Spl R, Spl Liv</td>
</tr>
<tr>
<td>Ruf-b</td>
<td>10 mg/wbc x 4</td>
<td>E, Radial</td>
</tr>
<tr>
<td>All-a</td>
<td>biopsy</td>
<td>No Spl R</td>
</tr>
<tr>
<td>Par-b</td>
<td>X-ray</td>
<td>Spl Liv</td>
</tr>
<tr>
<td>Fer-b</td>
<td>L1</td>
<td>Spl Liv, Vel 10 mg</td>
</tr>
<tr>
<td>Ret-o</td>
<td>no Rx</td>
<td>E</td>
</tr>
<tr>
<td>Obr-o</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>Tas-o</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>Mac-b</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>Wil-a</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>Arm-a</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>Coe-b</td>
<td></td>
<td>E</td>
</tr>
</tbody>
</table>

### Hodgkin's Disease - Stage III A & B

- Non-Protocol cases, Radial Radiation
- Disease evident, Radiation therapy
- E = Extension, R = Recurrence

### References


**Fig. 1.** Field localization and confirmatory treatment port films for megavoltage radiotherapy of the "mantle" field, encompassing the mediastinal, hilar, supraclavicular and cervical, and axillary lymph node distributions in continuity. In patients with initially large mediastinal masses, the width of the mediastinal treatment field is narrowed by periodic reshaping of the pulmonary lead shields as regression of the mediastinal mass progresses.

**Fig. 2.** Localization and megavoltage radiotherapy treatment port films for the paraaortic lymph node distribution. In some instances, lymphangiography is helpful in delineating variations in contour of the field which are required to encompass enlarged nodes.

**Fig. 3.** Localization and megavoltage radiotherapy port films for the iliac, inguinal, and femoral node distributions.

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