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Results of Radiation Therapy and Implications for the Clinical Staging of Hodgkin's Disease

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Summary

Recent experience has provided the rationale for adoption of more protracted irradiation in the treatment of Hodgkin's disease, thereby minimizing normal tissue reactions and complications without concurrent loss of therapeutic effectiveness. Insistence upon well-tolerated radiation dose schedules is particularly important in light of both the excellent prognosis for many patients and the need for extensive prophylactic irradiation if optimal results are to be achieved. Establishment of the requirement for prophylactic irradiation in a prospective, randomly controlled clinical trial now focuses attention on the subject of defining with maximal precision the extent to which apparently uninvolved areas must be empirically treated. The major handicap in pretreatment diagnostic evaluation at present is the inability to detect minute foci of extranodal dissemination, which bars successful control of disease with irradiation alone. Some possibility of identifying these patients prospectively is provided by either clinicohistological correlations as discussed or by the observation of vascular invasion on the original lymph node biopsy; whereas routine exploratory laparotomy rarely contributes to therapeutic management for clinical presentations above the diaphragm and does not appear warranted in such cases, those selected patients with clinical disease below the diaphragm may often have treatment decisions modified by surgical findings on abdominal exploration.

Introduction

During the first several decades of this century, the marked radioresponsiveness of Hodgkin's disease was repeatedly observed following administration of relatively small radiation doses. The era of modern radiotherapy for Hodgkin's disease awaited the scholarly work of the Swiss radiotherapist René Gilbert (3) in the 1930's. Gilbert recognized the need to achieve not simply temporary regression but "destruction of all the granulomatous foci, deep and superficial, without jeopardizing the general condition of the patient" and condemned the widely accepted practice of delivering serial courses of subtumoricidal treatment. Gilbert also frequently observed patients in whom 2nd manifestations of disease developed "in the immediate vicinity of a field too narrowly irradiated" and stressed the importance of widely treating "the regions patently invaded, as well as regions suspected of invasion." His philosophy of combining intensive irradiation of clinically involved sites with prophylactic irradiation of areas suspected of occult involvement produced an overall doubling of contemporarily reported 5-year survival rates. In more recent years, the "new" radiotherapeutic approaches have in essence reflected a greater appreciation and refined application of these basic principles which were promulgated over 3 decades ago by a physician who not only treated but understood.

Easson (1) emphasized the term "cure" for patients in whom disease is controlled with radiation therapy and documented the ensuing normal life expectancy. Although this optimistic attitude focused attention on the need for aggressive therapy, definition of "proper" treatment for many clinical presentations remained ill defined. In addition, unanimity of opinion is lacking as to the precise dose of radiation required for tumor sterilization as well as the optimal schedule for dose fractionation. Even the fundamental concept of prophylactic irradiation remains debatable, as evidenced by a cooperative clinical trial (13) now in progress in the United States. Nonetheless, several postulates have been or currently are being substantiated, and selection of an individualized approach for each given patient is a goal within realization.

Concept of Tumoricidal Dose

Retrospective analysis has established the inverse relationship between radiation dosage and probability of local recurrence (2, 9, 14, 17). The consistent observation of all investigators has been the nearly predictable tumoricidal effect of tumor doses exceeding 3500 rads. However, the widely held belief that tumor doses of 3500 to 4000 rads must be given within an elapsed time of 3 to 4 weeks for insurance of therapeutic effectiveness is conjectural. Our interpretation of radiation dose-time-response data reported by other authors has been that the dose-time relationship for Hodgkin's disease is not critical, providing the total dose is adequate. This belief stimulated our investigation of more protracted irradiation beginning in 1965, with emphasis on split-course irradiation (11). Administration of 4000-rad tumor doses over an elapsed time of 6 to 8 weeks has not only been highly effective therapeutically but has markedly attenuated the acute and delayed normal tissue reactions. In view of the excellent prognosis now associated with clinically localized or regional Hodgkin's disease, this experience as summarized in Table 1 warrants a reassessment of the rapid treatment schedules presently in vogue and their attendant (despite infrequent) morbid complications.

Concept of Prophylactic Irradiation

Radiation therapy guided by and limited to the *apparent* extent of involvement is often followed by extension of disease to regions which were clinically uninvolved on initial evaluation. Unfortunately, such relapses are frequently not detectable until widespread dissemination has developed, as witnessed by the high mortality rate characteristic for patients experiencing a single extension of disease (Table 2). The inescapable conclusion to be derived from these observations is that the question of "whether or not" prophylactic irradiation is irrelevant. What rather must be established is to what extent prophylactic irradiation of clinically uninvolved areas is required for different clinical presentations to minimize the probability of subsequent extension. Concurrently, there is the obvious constraint that primary treatment does not become excessive with the consequence of unjustified complications or even increased long-term mortality.

Appraisal of prophylactic irradiation in the past has either lacked concurrent controls (*e.g.*, Ref. 15) or failed to confirm a distinct advantage with prophylactic irradiation because the too-limited treatment permitted a significant rate of extension to anatomically noncontiguous regions (*e.g.*, Ref. 10). Recently, the necessity for elective irradiation of uninvolved (clinically) regions has been demonstrated for the first time by a prospective clinical trial performed at the National Cancer Institute (8).

Following random assignment of patients with localized and regional involvement to limited *versus* extensive prophylactic irradiation (Chart 1), the initial observation was a significant ($p < 0.05$) reduction in the incidence of relapse by extension of disease with the latter treatment. The major advantage of prophylactic total nodal irradiation was the consequence of treating unsuspected disease in the retroperitoneal lymph nodes and/or spleen for clinical presentations apparently limited to areas above the diaphragm. In the absence of prophylactic abdominal irradiation for such patients, extension of disease below the diaphragm has been documented in one-third of cases to date (Table 3). The 3 patients with initial involvement limited to the right cervical area who developed extension to retroperitoneal lymph nodes all had lymphangiographic demonstration of thoracic ducts draining into the left subclavian vein. Additional patients treated prophylactically to the lumbar nodes but not the spleen or pelvic nodes developed extension to these latter sites but with lesser frequency than to upper abdominal nodes in the complete absence of abdominal irradiation.

Table 1

Split course irradiation in Hodgkin's disease

Dose was 4000 rads/6 to 7.5 weeks total elapsed time.

No. of patients treated (1965–1969)	62
No. with local recurrence[a]	1
Recurrences/involved fields at risk	1/168
Recurrences/prophylactic fields	0/317

[a] 12/62 patients developed extension to untreated areas without local recurrence.

Table 2

Clinical course after a single relapse following radiotherapy of Stage I and II Hodgkin's disease (treated 1965 to 1969)

No. of patients at risk	137
No. with single relapse	40
No. free of disease after secondary dose with irradiation	8
No. living with disease	15
No. dead from disease	17

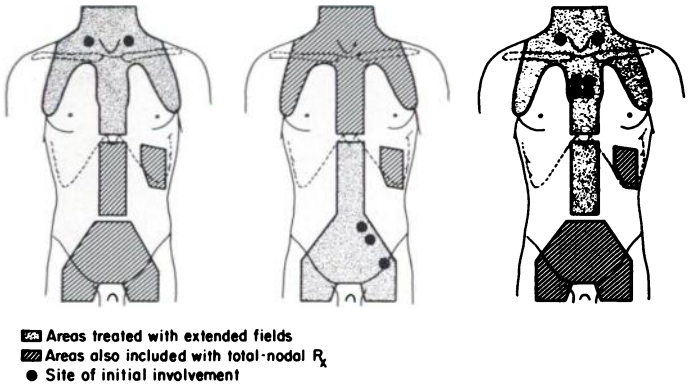

Chart 1. Representative examples of scheme for randomization of Stage I and II patients to extended-field (involved plus anatomically adjacent lymph node areas) *versus* total nodal irradiation.

Table 3

Frequency of extension to upper abdominal lymph nodes correlated with primary sites

Primary sites	Prophylactic therapy[a] Yes	No
Right neck only	0/8	3/12
Left neck only	0/8	3/8
Right and left neck	0/13	5/12
One axilla only	0/4	0/2
Total	0/33	11/34

[a] Prophylactic abdominal irradiation consisting of a minimum of 3000 rads given to the lumbar lymph nodes and spleen.

The decreased incidence of relapse following total nodal irradiation in this randomized comparative study has now become reflected in improved survival for patients with histology other than nodular sclerosis (Chart 2). These results demonstrate that extensive prophylactic therapy not only decreases the risk of extension of disease but also yields improved survival. The overall low relapse rate for Stage I and II patients with nodular sclerosis histology has not permitted recognition of relatively better survival with total nodal irradiation as only 7 of the total 51 patients have had relapse of disease after either extended field or total nodal irradiation. As seen in Chart 3, the often-documented prognostic implication of constitutional symptoms is again observed, with the 5-year survival rates being 98% and 76% for the Stage I-II A and B patients respectively.

This investigation should not be interpreted to imply that total nodal irradiation is required for every clinical

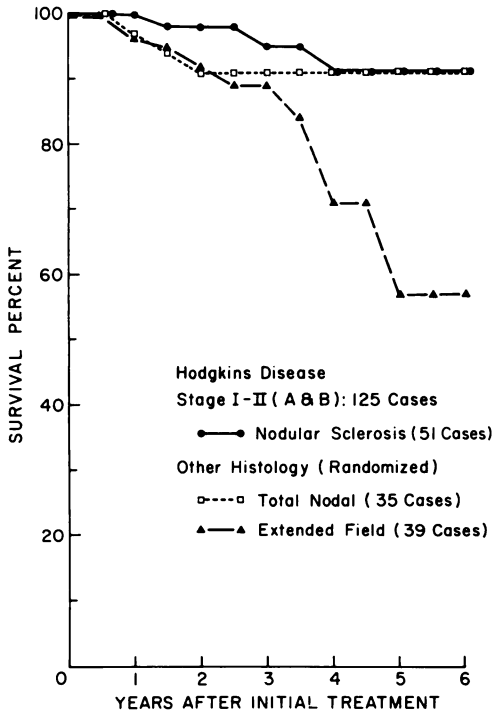

Chart 2. Actuarial survival curves for previously untreated patients with Stage I and II Hodgkin's disease treated from 1965 to 1969. The curve for nodular sclerosis histology combines the results for extended field and total nodal irradiation. Recognition of improved survival with total nodal irradiation was not possible for these latter patients, since 44 of the total 51 nodular sclerosis cases have remained continuously free of disease.

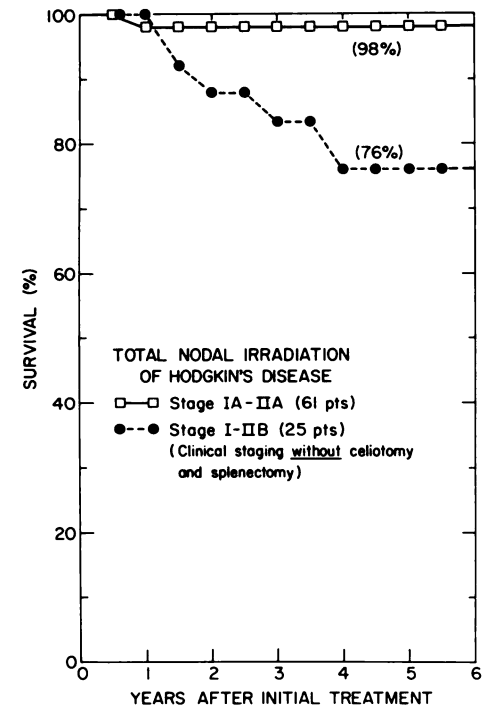

Chart 3. Actuarial survival curves for Stage I and II patients with (B) and without (A) constitutional symptoms. Total nodal irradiation is modified for patients with supradiaphragmatic presentations having nodular sclerosis histology, in which instances prophylactic irradiation of the pelvic and groin areas is deleted.

presentation of disease, irrespective of the primary site(s), presence or absence of constitutional symptoms, histological subclassification, or other factors of prognostic or biological importance. Rather, what is intended for accent is the establishment of the validity for the general concept of prophylactic irradiation.

Initial presentations other than localized or regional lymph node involvement have proven amenable to potentially curative radiotherapy. Patient tolerance to intensive irradiation of all major peripheral and axial lymph node areas (6) has prompted treatment of patients with generalized lymph node involvement (Stage III). The 70% 5-year survival rates reported from the National Cancer Institute and Stanford have been most encouraging for the Stage IIIA patients, whereas less consistent results have been achieved with Stage IIIB cases. Of considerable interest have been the reports of Peters (16) and Musshoff (12) for selected patients with extranodal disease. The excellent prognosis associated with limited extranodal involvement in their experience will stimulate future efforts to define which patients with extranodal involvement remain candidates for curative radiation therapy. At present, it appears justified to conclude that local extracapsular invasion of bones or soft tissues should not be a deterrent to primary management with radiation therapy in the absence of obviously disseminated disease.

Clinical Staging as a Guide to Radiation Therapy

The inadequacy of present techniques for establishing the *true* extent of disease requires emphasis. Not only has physical examination proven unreliable for this purpose but also radiographic studies including lymphography (5) must be recognized as suspect in accuracy. More recently, surgical exploration of the abdomen has been utilized to improve the accuracy of staging (4) but has not yet been shown to be sufficiently reliable to withhold prophylactic abdominal irradiation on the basis of negative surgical findings. However, exploratory laparotomy does appear to be routinely necessary for treatment decision making under specific clinical circumstances. Patients with definite clinical evidence of upper abdominal disease (lumbar lymph nodes or spleen) have a substantial probability of occult spread to lymph nodes outside the usual treatment fields or to the liver (Table 4). The likelihood of administering ineffectual treatment is sufficiently great for these latter patients as to warrant routine surgical exploration of the abdomen unless medically contraindicated.

For patients without clinical evidence of disease below the diaphragm, routine laparotomy would have retrospectively

Table 4

Sites of relapse after therapy for patients presenting with lumbar lymph node involvement[a]

Site of relapse	No. of patients
Continuously free of disease	19
Upper abdominal nodes	4
Liver	5
Extraabdominal sites	7

[a] Involvement demonstrated by grossly abnormal findings on bipedal lymphography.

Table 5

Correlation between clinicohistological staging and development of relapse in extranodal sites

Clinical stage and histology	Extranodal relapse
Stage I to IIIA	
Nodular sclerosis	2/40 (5%)
Lymphocyte predominance	0/26 (0%)
Mixed cellularity	2/25 (8%)
Lymphocyte depletion	1/6 (16%)
Stage I to IIIB	
Nodular sclerosis	2/13 (15%)
Lymphocyte predominance	0/5 (0%)
Mixed cellularity[a]	6/13 (46%)
Lymphocyte depletion[a]	5/5 (100%)

[a] Groups identifiable as having sufficient risk of extranodal relapse to indicate the need for adjuvant chemotherapy despite the absence of obvious dissemination at the time of diagnosis.

contributed to therapeutic management with extreme rarity. The following points summarize the basis for this conclusion.

1. Information is lacking to indicate that negative laparotomy findings are sufficiently reliable to obviate the need for prophylactic irradiation below the diaphragm. Rather, we have observed disease extension to lymph nodes below the diaphragm when prophylactic irradiation was withheld on the basis of negative exploratory laparotomy findings. Similarly, our experience has shown that the abdominal lymph nodes and spleen can be both effectively *and* safely irradiated. Recurrence has not developed in the spleen for 74 consecutive patients receiving prophylactic treatment, and complications such as nephritis and pneumonitis have been avoided with proper field localization techniques.

2. Extension of disease to abdominal lymph nodes outside the standard treatment fields for prophylactic irradiation has not been observed for 124 consecutive patients who presented with supradiaphragmatic involvement only on initial evaluation. Thus, the "marking" of lymph nodes with metallic clips is not an essential contribution to treatment planning unless, as mentioned above, gross involvement is clearly present by lymphangiography or other diagnostic studies.

3. Whereas routine laparotomy will frequently disclose occult involvement of the spleen (4), such microscopic disease does not imply a sufficiently high probability of unsuspected liver involvement to require modification of the treatment when detected. Only 2 of 124 patients with supradiaphragmatic presentations in our series have subsequently developed extension to the liver.

This experience indicates that routine exploratory laparotomy would have infrequently provided information essential for treatment planning and would not have improved the results of radiation therapy for patients with supradiaphragmatic clinical presentations. This assumes, however, an awareness for the need to prophylactically irradiate the upper abdominal lymph nodes and spleen.

A final implication of clinical staging for selection of proper treatment relates to extranodal dissemination of disease as a cause for failure to cure patients with radiation therapy alone (7). With some measure of accuracy, it is now possible to prospectively identify selected patients with a significant risk of unsuspected extranodal dissemination at the time of diagnosis, despite the absence of suggestive clinical findings (Table 5). This type of clinicohistological correlation offers some logical rationale for the use of adjuvant chemotherapy in selected high-risk patients. A similar indication for adjuvant chemotherapy in the early clinical stages of disease may also be afforded by the presence of vascular invasion on the initial lymph node biopsy as reported by Strum *et al.* (18).

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