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Guest Editorial

Is There a Role for Radiotherapy in Localized Diffuse Lymphomas?

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The choice of initial therapy for patients with non-Hodgkin's lymphomas (NHL) has historically been determined by the extent of disease at diagnosis [10] and by the histologic subtype, as classified according to Rappaport [19]. Patients with extensive disease (Stage III or IV) have generally been treated with systemic chemotherapy, whereas patients with localized disease (Stage I or II) have been treated with radiotherapy. There are exceptions to this generalization. For example, total nodal irradiation (TNI) has been used with some success for highly selected patients with nodular histologies [7]. However, nodular lymphomas are rarely localized at the time of diagnosis [9]. Furthermore, selected patients with nodular lymphocytic lymphomas or diffuse well-differentiated lymphocytic lymphoma (DLWD) may not require any therapy at the time of diagnosis [21]. Thus, the role of radiation therapy for the treatment of most patients with advanced disease is usually limited to palliation. This role for radiotherapy is unlikely to change, in view of the continued improvement in survival for patients treated with systemic chemotherapy.

Although radiation therapy has been regarded as standard therapy for Stages I and II diffuse lymphoma, information regarding alternative treatment options has recently become available. This editorial will review the results of trials of radiation therapy alone, and consider the results of recent trials of adjuvant chemotherapy or chemotherapy alone for the treatment of localized diffuse lymphoma.

Any discussion of localized disease is primarily concerned with diffuse histiocytic lymphoma (DHL), as it is the histologic type most likely to be localized at the time of diagnosis [9] and the type offering the best chance for cure if properly managed. Both localized nodular histiocytic (NH) and nodular mixed (NM) lymphomas probably have the same potential for cure [1, 11, 20].

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There are several unique features of DHL that are fundamental to understanding the results of treatment. First, DHL is a high-growth-fraction tumor with labeling indices as high as 40% in some cases (H Hansen and B Clarkson, personal communication). Clinically, this feature of rapid growth is reflected in the propensity of DHL for early lymphatic and hematogenous dissemination. Indeed, in some series 10%–25% of patients undergoing radiotherapy have developed new disease before radiotherapy was completed [3, 14, 15]. Secondly, there is not a clear-cut dose-response relationship to radiation therapy in DHL, in contrast to other histologic subtypes [6]. For example, failure to achieve local tumor control in DHL occurred in 13 of 38 disease sites (34%) at 4,000–4,200 rads and in 6 of 16 disease sites (38%) at 5,000–6,500 rads. In other lymphoma subtypes, including Hodgkin's disease, there is less than a 5% failure of local control with radiation doses of 4,000 rads or more [6]. Thirdly, improved chemotherapy programs have resulted in cure of 40%–50% of patients with advanced DHL [13, 17, 22, 23]. Finally, if DHL recurs after treatment, 90%–95% of all recurrences are manifest within the first year after treatment [11]. Thus, a comparison of the percentage of patients free of disease at 2 years is an excellent indication of the curative potential of present treatment programs. Accordingly, we collated 2-year disease-free survival and overall survival rates for patients who received radiotherapy alone, combined treatment, and chemotherapy alone in Tables 1–3.

In contrast to Hodgkin's disease, the major impact of the effect of stage on prognosis of DHL is between Stage I (or IE) and Stage II (or IIE) [11]. Thus, the best results of radiotherapy have been observed in patients with quite limited Stage I or IE disease. Radiation therapy for Stage I or IE DHL is curative in 50% of clinically staged patients [5, 11]. When true Stage I disease is better defined with extensive staging techniques, including laparotomy, the results of radiotherapy can be improved (Table 1) [2, 16]. However, systemic chemotherapy employed as the

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Table 1. Treatment of Stage I diffuse histiocytic lymphoma

Reference	Number of patients	Freedom from relapse at 2 years (%)	Survival at 2 years (%)
Clinically staged (radiation alone)			
Jones et al. [11]	13	50	65
Chen et al. [5]	20	55	78
Laparotomy staged (radiation alone)			
Bitran et al. [2]	9	100	100
Levitt et al. [16]	9	100	100
Clinically staged (chemotherapy alone)			
Miller and Jones [18]	4	100	100
	4[a]	100	100
Cabanillas et al. [4]	6	100	100

[a] Received adjuvant radiotherapy after initial chemotherapy

Table 2. Treatment of Stage I and II diffuse histiocytic lymphoma: Results of radiation therapy

Reference	Number of patients	Freedom from relapse at 2 years (%)	Survival at 2 years (%)
Clinically staged series			
Jones et al. [11]	48	40	50
Chen et al. [5]	53	55	65
Landberg et al. [15]	10	40[a]	40[a]
Laparotomy staged series			
Bitran et al. [2]	20	78	71
Glatstein et al. [8]	25[b]	65	70
Bonadonna et al. [3]	15	35[a]	–

[a] Corrected for a 10% failure rate occurring during initial radiotherapy
[b] Included patients with other unfavorable histologies

Table 3. Treatment of Stage I and II diffuse histiocytic lymphoma: Results of chemotherapy

Reference	Number of patients	Freedom from relapse at 2 years (%)	Survival at 2 years (%)
Series using adjuvant chemotherapy			
Bonadonna et al. [3]	15	59[a]	–
Landberg et al. [15]	10	90[a]	90[a]
Glatstein et al. [8]	23[c]	65	50
Series using initial chemotherapy			
Miller and Jones [18]	18[c]	96	100
	10[b]	100	100
Cabanillas et al. [4]	22	82	–

[a] Corrected for a 10% failure rate occurring during initial radiotherapy
[b] Patients were treated with adjuvant radiotherapy following initial chemotherapy
[c] Includes other unfavorable histologies

initial treatment appears to be equally effective, and has the advantage of obviating the need for extensive staging [4, 18].

The rationale for the treatment of Stage II or IIE disease with radiation is even less clear. Survival at 2 years following completion of radiotherapy is reported to be 40%–65%, and relapse-free survival 40%–55%, for clinically staged patients [5, 11, 15]. The results are generally better in surgically staged series (Table 2) [2, 8]. This has not been universal, however, as only 35% of the Milan series treated by radiotherapy are free of disease at 2 years (Table 2) [3]. However, even these survival rates are clearly influenced by patient selection. Selection of patients by age is common when laparotomy is employed, apparently to avoid surgical morbidity. For example, 12 of 65 patients with DHL were excluded from a study by the Chicago group because laparotomy was contraindicated due to advanced age [2]. Patients older than 65 years are regularly excluded from study by the Stanford group [9, 12]. In our experience in Tucson, 45% of all patients with DHL are over 60 years and 25% are over 65 years old.

Patients have also been excluded from several radiotherapy trials because of progressive disease developing during treatment. Both the Milan and the Swedish studies have reported that 10% of patients developed progressive disease while receiving radiotherapy and were therefore excluded from analysis [3, 15]. To place the results from these studies in proper perspective we have reduced the percentage of patients reported free of disease at 2 years by 10% in Tables 2 and 3. The Stanford group has reported that 15 of 27 patients receiving extended-field radiotherapy failed during initial local therapy, thus preventing these patients from completing TNI [14].

In an attempt to improve upon the results of radiation for localized disease, several centers have undertaken trials of radiotherapy followed by chemotherapy (Table 3). The basis for such an approach has already been described. At least two studies report a definite advantage for patients treated with this approach over those receiving radiotherapy alone, but the results are still less than optimal (Table 3) [3, 15]. The third study, conducted at Stanford, failed to demonstrate any benefit from adjuvant chemotherapy, with 65% of both groups of patients free of disease at 2 years (Table 3) [8]. However, in this study patients underwent laparotomy followed by TNI including whole-abdominal radiotherapy. Therefore, most patients did not actually begin chemotherapy until 3–4 months after diagnosis.

There are several probable reasons for the less than optimal results of adjuvant chemotherapy summarized in Tables 2 and 3. First, during the initial local radiotherapy DHL can disseminate and did [3, 14, 15]. Thus, disease outside radiation ports is allowed time to progress during local therapy. Secondly, the chemotherapy regimens used in these trials (primarily cyclophosphamide, vincristine, and prednisone [CVP]) are less effective than adiramycin-cyclophosphamide-based combinations [13, 17, 22, 23]. In view of these facts, adjuvant chemotherapy, if employed, should utilize the more effective chemotherapy regimens. Such a trial is under way in the Southwest Oncology Group.

At the University of Arizona, patients with clinical Stage I and II disease have been treated only with adriamycin-based combination chemotherapy. The initial results have been reported elsewhere [18]. Currently, 17 of 18 (96%) patients remain free of disease (Table 3). The median follow-up is now 26 months (range 3–63 months). An additional ten patients were treated with chemotherapy and adjuvant radiotherapy to sites of bulky disease. All these patients remain free of disease, median follow-up now being 39 months (range 12–87 months). It is of note that five of these patients received only minimal therapy: two courses of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) followed by local irradiation (4,000–5,000 rads). The 28 patients we have now treated have numerous adverse prognostic factors, as detailed elsewhere [18]. These results have recently been confirmed by the MD Anderson group [4]. Eighteen of 22 patients (82%) are currently free of disease with combination chemotherapy alone for Stage I and II DHL (F Cabanillas, personal communication). The results of early aggressive systemic therapy have clearly improved the prognosis for patients with clinically staged II DHL. The role of adjuvant radiotherapy remains to be defined.

The results of the previous studies lead us to believe that radiotherapy is curative only in a small portion of patients with DHL. To define that group of patients who are potentially curable with radiotherapy requires extensive staging, including laparotomy with its attendant morbidity and risks. Such aggressive staging techniques are frequently not appropriate in the older age groups and unfortunately DHL is common in these patients. With clinical rather than surgical staging, patients are at substantial risk of developing progressive or recurrent disease with conventional radiotherapy, thereby lessening their chance of cure.

Initial treatment for localized DHL with systemic chemotherapy, employing regimens of proven optimal efficacy in advanced disease, is curative and obviates the need for extensive staging. Initial chemotherapy for the more aggressive histologic types of NHL appears to be the treatment of choice. The role of radiotherapy as an adjuvant for the treatment of sites of bulky disease remains to be defined.

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