Eur J Cancer Clin Oncol, Vol. 24, No. 11, pp. 1771–1777, 1988.
Printed in Great Britain

0277-5379/88$3.00 + 0.00
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Influence of Therapy on Local Control and Survival in Stage I and II Intermediate and High Grade Non-Hodgkin's Lymphoma

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Abstract—*In a consecutive series of* 113 *patients with localized (Stage I and II) intermediate and high grade non-Hodgkin's lymphoma we have retrospectively analysed patterns of survival and relapse in relation to presenting features and therapy. Two patients were treated by complete surgical excision. Seventy-two were treated by radiotherapy (RT),* 19 *by chemotherapy (CT) and* 20 *by combined CT and RT. A number of different chemotherapy combinations were employed. Overall survival for Stage I patients was* 68.3% *at* 5 *years and* 65.5% *at* 10 *years; for Stage II patients it was* 61.2% *at* 5 *years and* 52.2% *at* 10 *years. Recurrence-free survival for Stage I patients was* 51.4% *at* 5 *years and* 42.1% *at* 10 *years; for Stage II patients it was* 46.2% *at both* 5 *and* 10 *years. Local control by radiation was achieved in* 59/72 (82%) *patients treated with less than* 40 Gy *and* 19/20 (95%) *treated with* 40 Gy *or more. There was no advantage for extended field irradiation when compared with involved field. Eleven of* 19 (58%) *patients treated by CT alone achieved complete response (CR). For patients responding completely to CT there was no clear advantage for irradiation of originally involved bulky sites. For patients with Stage II and bulky Stage I disease there was a significant* (P = 0.05) *improvement in recurrence-free survival (RFS) and a trend* (P = 0.192) *towards improved overall survival for patients treated by CT alone or together with RT compared with RT alone. Independent variables identified by multivariate analysis were age, with better survival for younger patients* (P = 0.034) *and histopathological group, with better survival for DPDL compared with DH* (P = 0.015).

INTRODUCTION

RADIOTHERAPY (RT) is effective for the local control of Stage I and II intermediate and high grade non-Hodgkin's lymphoma (NHL) [1–5]. Although a substantial proportion are cured, relapse occurs in more than 50% of patients, usually outside the irradiated area. Although many relapsed patients are treated effectively by chemotherapy (CT), a proportion of patients relapse with rapidly progressive disease which responds poorly to CT [6].

Following intensive clinico-pathological staging, the majority of patients with apparently localized intermediate and high grade NHL are found to have widespread disease [7]. The results of treatment with CT for advanced intermediate and high grade NHL have shown a significant improvement in recent years [8–10]. Since the majority of patients with clinically localized disease have subclinical disseminated disease, treatment with combination CT has been advocated for patients with intermediate and high grade Stage I and II NHL [11]. In addition pretreatment with CT might improve local control with RT and diminish the extent of the radiation field.

We have reviewed a series of patients treated over a 10 year period, and have analysed response to RT and CT and relapse pattern following therapy. Using a multivariate analysis we have identified prognostic factors for overall survival.

PATIENTS AND METHODS

Between January 1974 and December 1983 113 patients (male: 64, female: 49) aged 6–77 (mean age 55.8) with localized (Stage I and II) intermediate and high grade NHL were referred for treatment to the Department of Clinical Oncology, Edinburgh.

For all patients in this study staging investigations included clinical examination, chest X-ray, marrow aspirate, and either lymphogram, computed tomography abdominal scan or laparotomy. Details of

Accepted 5 July 1988.
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Table 1. *Stage and disease site*

	Stage I	Stage II
Nodal		
Above diaphragm	12	10
Below diaphragm	4	15
Total	16	25
Extranodal		
Gastrointestinal	10	17
Waldeyer's ring	12	4
Thyroid	11	2
Breast	2	2
Bone	4	—
Testis	2	1
Skin	3	—
Orbit	1	—
Thymus	1	—
Total	46	26

stage [12] and disease site are given in Table 1. Forty-one patients (36%) presented with nodal and 72 (64%) with extranodal disease. There were 62 patients with Stage I disease and 51 with Stage II. Only seven patients (6%) had B symptoms.

Pathology

Histology was classified into histopathological groups according to the Rappaport system [13]. Sixty-three patients had intermediate grade histology [58 diffuse poorly differentiated lymphocytic (DPDL) and five diffuse mixed (DM)]. Forty-eight patients had high grade diffuse histiocytic (DH) histology. There were no patients with Burkitt's lymphoma or lymphoblastic lymphoma, probably because of the relatively small numbers in each stage and histopathological group. For two patients, histology was unclassified.

Disease bulk

Assessment of diease bulk at presentation was based on recorded measurements, descriptions of laparotomy findings or pathology specimens. Patients with a nodal or extranodal mass $\geq$5 cm diameter were considered to have bulky disease. In other studies 10 cm diameter masses have been classified as bulky.

Primary treatment

Two patients with Stage I disease (one thyroid and one gastrointestinal) were treated by complete surgical excision. Of the remainder 72 were treated by RT, 19 by CT and 20 by combined RT and CT. Treatment decisions were made by a number of clinicians. The choices of chemotherapy combination and extent of radiation field were made by individual clinicians. There was a tendency for more intensive chemotherapy combinations to be employed for younger fitter patients with more extensive disease. Some patients were treated with combined modality therapy because of a poor response to the initial treatment modality.

(a) *Radiotherapy*. The majority of patients were treated with 4–9 MeV irradiation employing various dose-fractionation regimes. In order to examine the influence of radiation dose on local tumour control, a cumulative radiation effect (CRE) formula [14] was used to calculate the equivalent dose in 2 Gy daily fractions (10 Gy/week). Involved field irradiation was used for 41 patients and extended field for 38. Thirteen patients with gastrointestinal presentation were treated with wide field abdominal RT.

(b) *Chemotherapy*. Various chemotherapy combinations were employed and these are listed in Table 2. Twenty-two patients (56%) were treated with four or five drug adriamycin-containing combinations.

Response criteria

Complete response (CR) was defined as complete disappearance of all clinically detectable disease. Partial response (PR) was defined as a decrease of 50% or more in the size of the products of maximum perpendicular diameters of all measurable lesions, without the appearance of any new lesions with a minimum duration of 1 month.

Statistical methods

Survival was calculated from the date of first treatment. All survival rates are actuarial. Survival was calculated using the life-table method and survival rates compared using the log-rank test [15]. Patients dying from intercurrent disease were counted as lost to follow-up at time of death.

In order to identify factors of prognostic importance, a multivariate analysis of survival data was performed using a proportional hazards model [16].

Table 2. *Chemotherapy combinations*

Cyclophosphamide, adriamycin, vincristine, prednisolone (CHOP)	19
Cyclophosphamide, vincristine, procarbazine, prednisolone (COPP)	6
Cyclophosphamide, vincristine, prednisolone (COP)	7
Bleomycin, adriamycin, cyclophosphamide, vincristine, prednisolone (BACOP)	3
Cyclophosphamide	1
Chlorambucil	1
Chlorambucil, prednisolone	1
Melphalan, vincristine, prednisolone	1

RESULTS

The median duration of follow-up was 40 months (range 2–12 years).

(a) *Survival*

There were 39 deaths due to lymphoma and 10 due to intercurrent disease. The survival rate was 64.9% at 5 years and 59.9% at 10 years.

Survival and recurrence-free survival (RFS) for all patients are shown in Figs. 1 and 2. Five and 10 year survival and RFS are given in Table 3.

The survival rate at 5 years was 70.4% for patients aged less than 60 compared with 59.5% for those aged 60 or more ($P = 0.253$). Survival was significantly better for patients responding completely to primary therapy ($P = 0.001$).

Survival and RFS were similar for patients treated by CT alone or together with RT compared with those treated by RT alone. However, for patients with Stage II or bulky Stage I disease there was a significant ($P = 0.05$) improvement in RFS (Fig. 3) and a trend ($P = 0.192$) towards improved overall survival (Fig. 4) for patients treated by CT± RT compared with those treated by RT alone. Survival and RFS for patients with Stage II and bulky Stage I disease treated by CT ± RT are given in Table 4.

Survival and RFS were better for patients with DPDL pathology than those with DM or DH but the

Table 3. Survival and recurrence-free rates

		Survival(%)		RFS(%)	
	Stage	5 years	10 years	5 years	10 years
All	I	68.3	65.5	51.4	42.1
patients	II	61.2	52.2	46.2	46.2
RT	I	67.6	67.6	51.5	47.9
alone	II	55.8	43.4	35.0	35.0

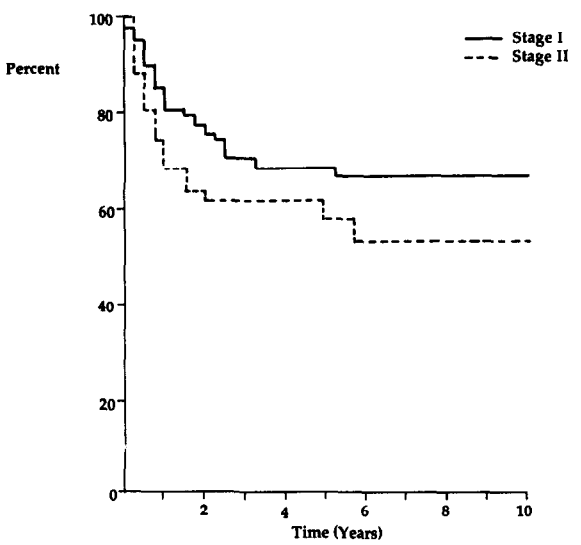

Fig. 1. Overall survival.

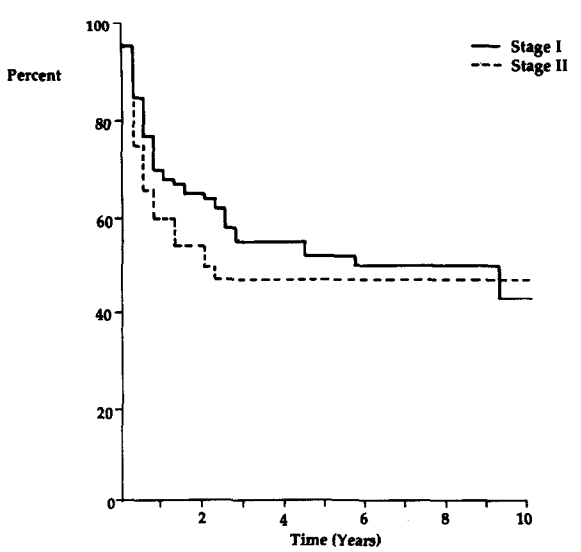

Fig. 2. Recurrence-free survival.

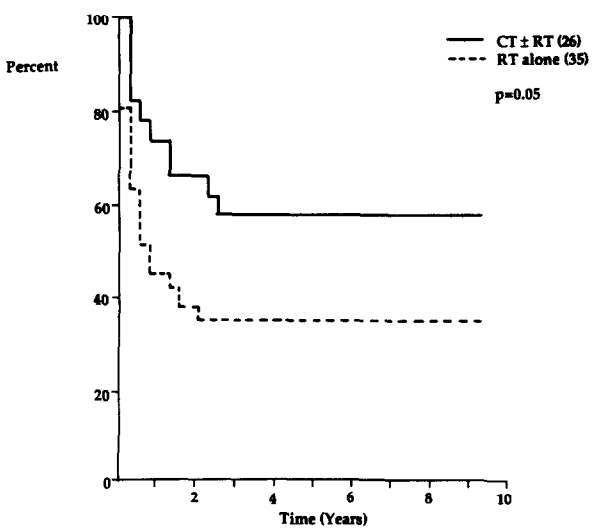

Fig. 3. Stage II/bulky Stage I: recurrence-free survival.

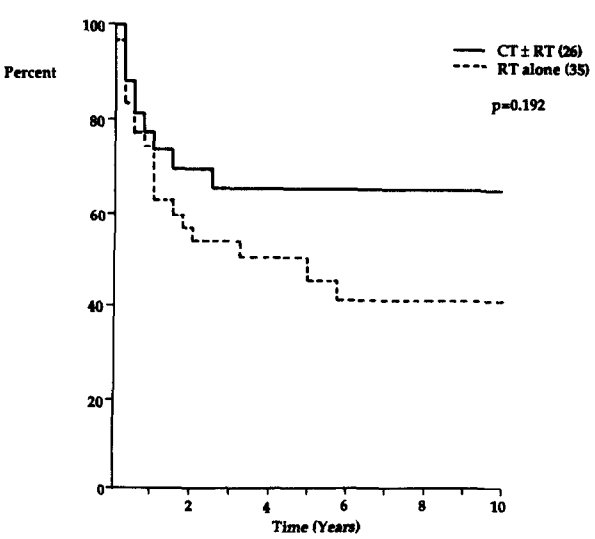

Fig. 4. Stage II/bulky Stage I: overall survival.

Table 4. Stage II and bulky Stage I—survival and recurrence-free rates following CT ± RT or RT

Stage		5 year survival (%) (No. of patients) CT ± RT	RT	P	5 year RFS (%) (No. of patients) CR ± RT	RT	P
Bulky	I	71.4% (7)	56.9% (20)	0.553	71.4% (7)	48.8% (20)	0.288
	II	66.7% (24)	55.8% (27)	0.324	57.9% (24)	35.0% (27)	0.089

difference just failed to reach statistical significance [$P = 0.082$ for survival (Fig. 5) and $P = 0.088$ for RFS].

(b) *Response to radiotherapy*

Ninety-two patients were treated by RT, either alone or together with CT. Lasting local tumour control was achieved in 78/92 (85%) patients. The relationship between local control, disease bulk and radiation dose is given in Table 5. Of 14 patients who failed to achieve local control, 13 had received a dose less than 40 Gy and nine of these had bulky disease.

The relapse pattern according to disease bulk for patients treated by RT alone is given in Fig. 6. Information on relapse site was available for 71 of the 72 patients. Thirty-seven (52%) patients relapsed and 29 (78%) of the relapses occurred outside the irradiated area. Thirty patients were treated with involved field RT alone. The relapse pattern is given in Table 6. No patient relapsed in a contiguous nodal site only. Recurrence-free survival rates were similar for patients treated with involved field compared with extended field RT ($P = 0.457$).

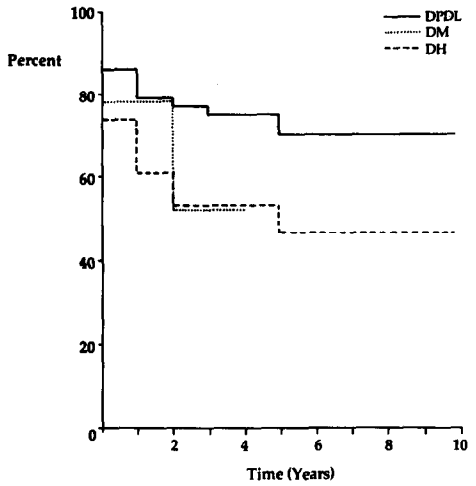

Fig. 5. Pathology: overall survival.

(c) *Response to chemotherapy*

Of the 19 patients treated by CT alone, 11 (58%) achieved CR, one failed to respond, two had disease progression and five were not asessable. Of the 11 patients achieving CR only one had relapsed. This occurred in an originally involved site, the bulk of which was not assessable.

(d) *Multivariate analysis*

The variables included in the proportional hazards model were age, sex, histopathological group, primary site, stage, CT intensity, extent of radiation field and extent of surgical resection. Independent variables of prognostic significance were age, with better survival for younger patients ($P = 0.034$) and histopathological group, with better survival for DPDL compared with DH ($P = 0.015$).

DISCUSSION

The results of this study provide further confirmation of the potential of RT for the local control of localized (Stage I and II) intermediate and high grade NHL, which may be curative in a proportion of patients. However, as in other series [4–6] the relapse rate was unacceptably high with more than

Table 5. Radiotherapy—local control

Dose (Gy)	Disease bulk: Non-bulky	Bulky	Unknown bulk
<40	11/13 (85%)	31/40 (77.5%)	17/19 (89%)
≥40	6/6 (100%)	7/7 (100%)	6/7 (86%)

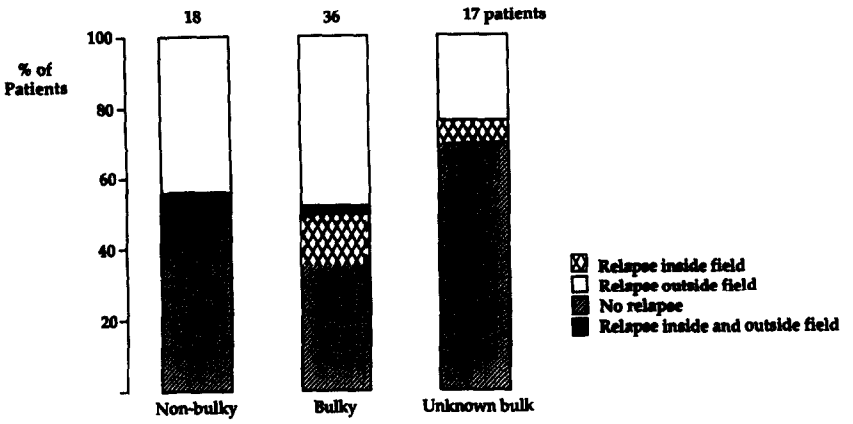

Fig. 6. Radiotherapy alone—relapse pattern.

Table 6. Relapse pattern following involved field radiotherapy alone

	Nodal	Extranodal
Relapse site		
In-field	1	0
Contiguous + distant nodal	1	0
Distant nodal	0	1
Extranodal	3	7
No relapse	6	11
Total	11	19

50% of patients relapsing after treatment with RT alone. For Stage I patients treated by RT alone RFS was 51.5% at 5 years and 47.9% at 10 years. For Stage II patients treated by RT alone the RFS was 35.0% at both 5 and 10 years.

In this series 29 of 37 (78%) relapses following RT alone occurred in unirradiated sites. Following intensive clinico–pathological staging, truly localized NHL is uncommon[7]. In the present series local control by radiotherapy was achieved in 85% of patients. The majority of relapses occurred at distant sites indicating the presence of subclinical disease at the time of local RT.

The increased use of intensive combination CT has resulted in improved survival for patients with advanced intermediate and high grade NHL. Complete regression rates in excess of 60% have been reported [8–10]. The presence of subclinical disseminated disease in the majority of patients with apparently localized disease provides the rationale for treatment with CT [11].

In the present series, treatment decisions were made by a number of clinicians. It is likely that some patients were selected for treatment with combined CT and RT following a poor response to the initial single treatment modality. In addition, it is possible that some patients were selected for treatment by CT because of more aggressive or extensive disease. Despite this, for patients with Stage II and bulky Stage I NHL there was a significant improvement in recurrence-free survival (RFS) and a trend towards improved overall survival for patients treated with CT alone or together with RT compared with those treated by RT alone—this trend was seen in both major histopathological groups. Similar results have been reported by Mauch *et al.* [17] who reported a significant improvement in survival for patients with diffuse undifferentiated (DU) and diffuse histiocytic (DH) Stage I and II NHL treated by combination CT compared with those treated by RT alone.

In a randomized trial [18] Monfardini *et al.* demonstrated a significant improvement in RFS and a trend towards improved overall survival for patients with diffuse histology Stage I and II NHL treated by regional RT followed by CT with COP compared with regional RT alone. It is likely that the use of more intensive multi-drug regimes would result in a greater improvement in overall survival.

In the present series only 19 patients were treated by CT alone. Of these, 11 (58%) achieved CR, and only one has relapsed, with recurrence in an originally involved site, suggesting that following CR to CT, irradiation of bulky sites at presentation is probably not necessary. However the number of patients treated by CT alone in this series was small. Mauch *et al.* [17] reported a significant improvement in RFS and survival for patients treated by combined CT and RT compared with CT alone. In another study [19] of patients with Stage I and II NHL of unfavourable histology, there was no clear advantage for combined CT and RT compared with CT alone. Twenty-eight patients were treated by CHOP, and in five patients with disease relapse, two occurred at distant sites and three in originally involved areas. Of 17 patients treated by combined CHOP and RT there were two relapses within the irradiated field. A randomized trial compared CT alone with CT followed by RT to sites of original bulk disease could be of value in establishing the role of adjuvant RT following CR to CT.

In our series 78/92 (85%) achieved lasting local control after RT or CT/RT. The majority of local failures were seen in patients with bulky (≥ 5 cm diameter) masses treated with a radiation dose <40 Gy, and it appears that a dose of 40 Gy or greater is necessary to control masses ≥5 cm diameter. From another study [6] it appears that some patients require a dose of 60 Gy to achieve control.

In our series 30 patients were treated by involved field RT alone, and only one patient has relapsed in a contiguous nodal site and distant nodal sites. No patient has relapsed in a contiguous nodal site alone. Recurrence-free rates were similar for patients treated by extended field compared with involved field RT. Unlike Hodgkin's disease, patients with localized NHL treated by RT alone frequently relapse in distant nodal or extranodal sites and do not appear to benefit from extended field RT.

The multivariate analysis identified age and histopathological group as independent variables of prognostic significance. It is possible that the better survival for patients with DPDL compared with DH histology is due to the use of older chemotherapy combinations such as COP and CHOP for the majority of patients with high grade NHL (DH). There was no significant difference in survival for nodal compared with extranodal presentations. In an analysis of a larger number of patients [5], stage and disease bulk were identified as additional variables of prognostic significance. Using these variables it has been possible to identify prognostic groups of patients with a low chance of long term RFS following RT alone, who benefit from the early use of CT.

In conclusion, based on the results of this and other studies, we recommend treatment with chemotherapy for patients with Stage I and II intermediate and high grade NHL. Following CR to chemotherapy there is no clear advantage for adjuvant RT. For patients who are elderly or cannot tolerate aggressive chemotherapy, RT offers the potential for local disease control. A dose of 40 Gy or more is required for control of masses 5 cm diameter or greater. There is no advantage for extended compared with involved field RT.

Acknowledgements—We thank the physicians and surgeons in the area for referring the patients and clinical oncologists in the department for allowing us to include their patients in this study. We are grateful to the Imperial Cancer Research Fund for financial support and to Miss Audrey Keegan for typing the manuscript.

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