Acta Radiologica Oncology 24 (1985) Fasc. 2

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PROGNOSTIC FACTORS IN STAGE I AND II NON-HODGKIN'S LYMPHOMA OF WALDEYER'S RING

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Abstract

Sixty-nine stage I and II patients treated for non-Hodgkin's lymphoma of Waldeyer's ring were retrospectively analysed. Diffuse histiocytic lymphoma (Rappaport's classification) was the most common histology (67%). Staging without laparotomy revealed 31 patients in stage I and 38 in stage II. Sixty-five patients received radiation therapy against involved or extended fields. In 43 patients adjuvant chemotherapy with single or multiple agents was given and 4 patients received only chemotherapy. A relapse occurred in 34 (49%) patients. The 5-year relapse-free survival was 67 per cent and 36 per cent in stage I and stage II, respectively. Radiation doses of 50 Gy gave no recurrence within treated volumes. However, since relapse below the clavicles and especially below the diaphragm was common, the radiation doses did not seem important for reduction of the overall failure rate. In stage II, patients with a single neck node less than 5 cm in diameter seemed to have a better prognosis than patients with large or multiple neck nodes. In this non-randomized study adjuvant chemotherapy seemed to reduce the risk of relapse, especially in stage II patients.

Non-Hodgkin's lymphoma (NHL) of Waldeyer's ring (WR) is rather rare and implies several problems. Firstly, most of the published treatment results concern radiation therapy alone (1, 5, 19) and the role of chemotherapy is not yet properly assessed. Secondly, the treatment results are often not separated from those in NHL of other sites and the results in stage I and II patients are often reported together (2, 6, 11, 15). Thirdly, prognostic factors for NHL of Waldeyer's ring have not been well defined. Clinically useful histologic classifications were not used in some series (16, 18). Furthermore, the small numbers of patients in the literature have often excluded meaningful conclusions.

In this report, a rather large series of early stage NHL of Waldeyer's ring treated during the past 15 years is presented. Reflecting the gradual change in treatment policy during this period, the patients were treated in several different ways. This offered an opportunity to compare results of different types of treatment.

Material and Methods

Available pathologic slides from the lymphoma patients seen during the past 15 years at the radiology department were reviewed by one of us (A.M.) and 79 cases of WR-NHL were identified. For the histologic classification RAPPAPORT's system was applied (14). The term "histiocytic" has thus been used in this report despite the fact that later investigations have shown that most of these tumours have a lymphopoietic origin and that newer classification systems are biologically and semantically more adequate (4, 10). Clinical staging was done according to the Ann Arbor system. Staging procedures included physical examination, complete blood counts, peripheral blood chemistry, and chest radiography. Bipedal lymphangiography and ^{67}Ga scanning have recently become routine procedures and therefore have been performed only in one-third of the pa-

Accepted for publication 3 September 1984.

tients, with a positive result in about 10 per cent. No staging laparotomy was performed. After these examinations, 31 patients were classified as stage I, 38 as stage II, 7 as stage III, and 3 as stage IV. If the 10 per cent positive findings by lymphography and ^{67}Ga had been applicable also for the remaining patients, only a further 4 to 5 patients would have been upstaged to stage III or IV. The age of the 69 stage I and II patients ranged from 10 to 81 years, with a mean of 52.2 years and a median of 55 years. Thirty-nine patients were men, and 30 were women.

As disclosed later, the nodal state in stage II appeared to have prognostic significance. The stage II patients were therefore retrospectively divided into two groups. Patients with a single palpable node with a diameter of less than 5 cm were classified as stage II with minimum nodal involvement (stage II min.); there were 10 such patients. Patients with a single node of 5 cm or more (10 patients), small multiple nodes (10 patients), or multiple and large nodes (8 patients), were classified as stage II with advanced nodal involvement (stage II adv.).

With the exception of one patient who had involvement of bilateral cervical and axillary nodes, all stage II patients had nodal involvement above the clavicles only.

All except 4 patients received radiation therapy with 6 MV roentgen rays against involved or extended fields. Involved fields covered only the regions with known involvement. Extended fields covered also at least the nearest non-involved lymph node region(s). The largest field used was a mini-mantle field, which covered Waldeyer's ring, both sides of the neck and axillae, and the upper mediastinum. All stage I patients were treated with extended fields, which also included the lower cervical nodes and in some cases the supraclavicular fossae. Of the stage II patients, 12 were treated with involved fields, and 23 with extended fields. For most patients, conventional fractionation with 2 Gy per day was used. Total radiation doses ranged from 16 to 60 Gy with a median of 40 Gy.

Chemotherapy was given in addition to radiation therapy to 43 stage I and II patients. Single agent chemotherapy was most frequently used, and was given to 26 patients. Bleomycin (BLM) was used for 10 stage I patients and 13 stage II patients with total doses ranging from 15 to 375 mg with a median of 105 mg. Two patients received 5FU, and one cyclophosphamide (CYC) alone. Combination therapy was given to 17 patients, most frequently BLM, CYC, vincristine (VCR) and prednisolone (PSL). When combination chemotherapy was given, the doses of the agents were usually less than those recommended for advanced stage NHL.

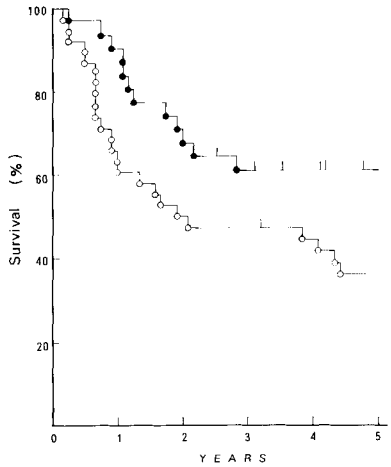

Fig. 1. Survival according to stage. Five-year survival: Stage I (●) 61 per cent, stage II (○) 36 per cent. $p<0.05$.

Four patients were treated with chemotherapy alone. One stage I and two stage II patients received BLM alone with total doses of 300, 300, and 420 mg, respectively. Another stage II patient had combination chemotherapy with BLM, 5FU and mitomycin C.

All patients were followed for a minimum of 3 years or until death. No patients were lost to follow-up. The first relapse site was unknown in only one patient. The site of the first relapse was classified as local, in-field nodal, contiguous nodal (nodal failure outside the radiation field, but which could have been covered with a mini-mantle field), or distant (nodes or other organs).

Survival and relapse-free survival curves were calculated according to KAPLAN & MEIER (7). GEHAN's (3) modification of the generalized Wilcoxon test was employed to evaluate differences in survival curves. For calculation of relapse-free survival curves, patients in complete remission who died of other causes were included as alive and free of disease at the latest follow-up. The method of WALKER & DUNCAN (17) was used for multivariate regression analysis.

Results

Survival for the stage I and II patients at 5 years was 61 and 36 per cent, respectively ($p<0.05$; Fig. 1). Ten (32%) of the 31 stage I patients and 24 (63%) of the 38 stage II patients relapsed. Four (40%) of

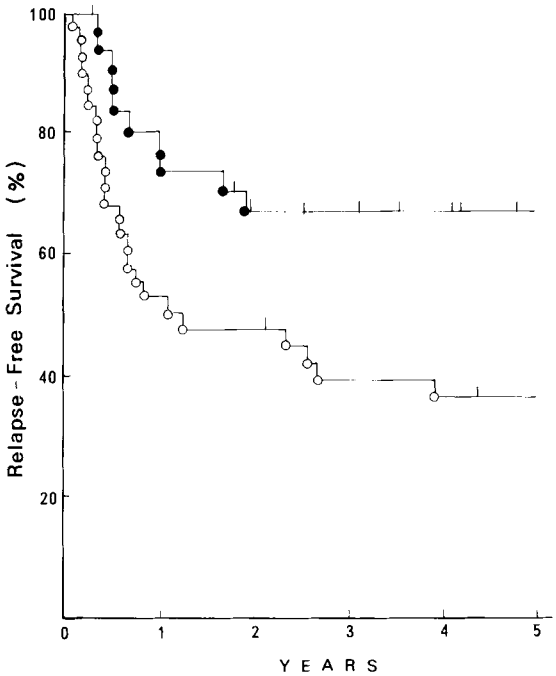

Fig. 2. Relapse-free survival according to stage. Five-year survival: Stage I (●) 67 per cent, stage II (○) 36 per cent. $p<0.02$.

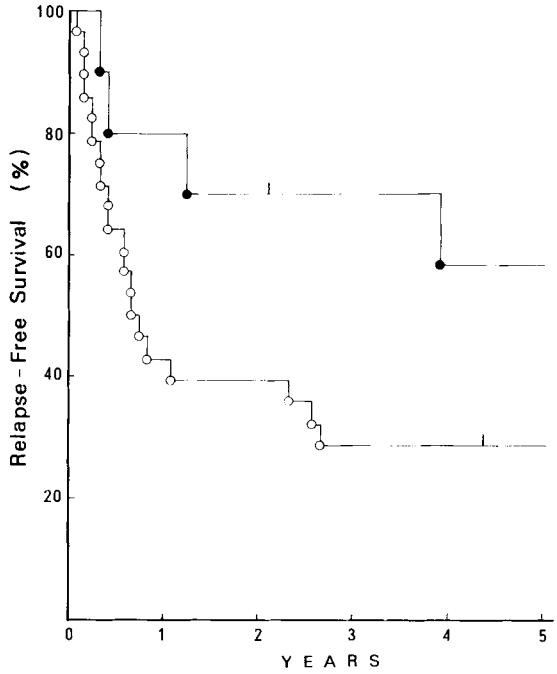

Fig. 3. Relapse-free survival of stage II patients according to nodal state. Five-year survival: Node <5 cm (●) 58 per cent, node >5 cm or multiple (○) 29 per cent. $0.05<p<0.06$.

Table 1

Site of first relapse

Treatment	No. at risk	Site of first relapse					Total with relapse	
		Primary	In-field	Contiguous	Distant	Unknown	No.	Per cent
Stage I								
Irradiation	8	1	1	2 (2)	1 (1)	–	4	50
Irradiation and chemotherapy	22	2 (2)	2	–	3 (1)	–	5	23
Chemotherapy	1	–	1 (1)**	–	–	–	1	100
Stage II								
Irradiation	14	2	3	4	9 (5)	–	10	71
Irradiation and chemotherapy	21	1 (1)	4 (1)	3	7 (3)	1	11	52
Chemotherapy	3	2	3 (1)**	–	1	–	3	100
Total	69	8 (3)	14 (3)	9 (2)	21 (10)	1	34	49

* Numbers in parentheses indicate isolated failures.

** Although irradiation was not given, cervical relapses are listed in this column.

the 10 stage II min. patients and 20 (71%) of the 28 stage II adv. patients relapsed. Of the total 34 (49%) relapses in stage I and II, 30 (88%) occurred within 2 years and 33 (97%) within 3 years. Only one relapsing patient was successfully salvaged, while the other patients died fairly soon after the relapse. The following analyses are therefore limited to relapse-free survival.

Relapse-free survival for the stage I and II patients at 5 years was 67 and 36 per cent, respectively ($p<0.02$; Fig. 2). Stage II min. patients had a better 5-year relapse-free survival rate (58%) than stage II adv. patients (29%; Fig. 3), with an almost significant difference ($0.05<p<0.06$).

The site of the first relapse is shown in Table 1, according to stage and treatment. Distant relapses

Table 2

Histology (Rappaport's classification) versus relapse

Histology	No. with relapse/ No. at risk (per cent)			
	Stage I		Stage II	
Diffuse histiocytic	7/24 (29)		16/22 (73)	
Diffuse lymphocytic poorly differentiated	2/4		4/6	
Diffuse mixed	1/1	3/7 (43)	3/7	8/14 (57)
Diffuse undifferentiated	0/2		1/1	
Diffuse lymphocytic well differentiated	–		0/1	
Nodular histiocytic	–		0/1	
Total	10/31 (32)		24/38 (63)	

Table 3

Site of origin versus relapse

Site of origin	No. with relapse/ No. at risk (per cent)	
	Stage I	Stage II
Tonsil	7/21 (33)	19/30 (63)
Nasopharynx	1/5	0/1
Base of tongue or hypopharynx	0/1	1/2
More than one site*	2/4	4/5
Total	10/31 (32)	24/38 (63)

* Patients with tumours extending to the adjacent site(s) or patients with bilateral tonsillar involvement.

Table 4

Relapse within radiation fields versus radiation dose

Radiation dose (Gy)	No. with relapse/No. at risk (per cent)
<30	3/8 (38)
≤30–40	6/20 (30)
≤40–50	4/21 (19)
≤50≤	0/15 (0)
Total	13/64 (20)*

* Excluding one patient with unknown relapse site.

were most common (21/69 or 30%). Eighteen patients relapsed at only one site, which in 10 cases was distant. Of the 10 patients with distant relapse alone, most had failures below the diaphragm; only one patient had an isolated relapse in the mediastinum. All 4 patients treated with chemotherapy alone relapsed. Of the 65 patients treated with irradiation, 5 stage I and 4 stage II patients relapsed without distant spread. Of these 9 patients, one stage II patient developed relapse in one axilla with concomitant local and cervical recurrence. The other 8 patients had a relapse above the clavicles.

Relapse rates according to histology and stage appear in Table 2. Diffuse histiocytic lymphoma was the most common histologic type and only 2 cases showed favorable histology (diffuse lymphocytic, well differentiated or nodular histiocytic). From this table, a prognostic significance with RAPPAPORT's classification is not apparent for WR-NHL.

Table 3 shows relapse rates according to site of origin within Waldeyer's ring, and stage. WR-NHL originated most frequently in the tonsillar fossa. Nine patients had original tumours involving more than one site within Waldeyer's ring. Patients with tumours involving one site other than the tonsil seemed to have a better prognosis than the other patients.

Patients receiving 50 Gy or more did not relapse within the radiation fields, whereas 13 (27%) of 49 patients treated with less than 50 Gy had a local or regional relapse (Table 4).

For defining prognostic factors affecting the overall relapse rate a multivariate regression analysis was made in the 65 patients treated with irradiation. Tested variables were sex, age, site of origin within Waldeyer's ring, nodal state, radiation dose, number of chemotherapeutic agents, and histology (Table 5). The results indicated that the nodal state was the single most important prognostic variable. Addition of chemotherapy and site of origin seemed also to be important.

Stage I patients who had received adjuvant chemotherapy showed a higher 5-year relapse-free survival rate than those treated with irradiation alone (76% vs. 50%), although the difference was not statistically significant ($p<0.2$). In stage II patients, adjuvant chemotherapy also increased the 5-year relapse-free survival compared with irradiation alone (48% vs. 27%, $p<0.1$). Chemotherapy seemed to be of particular benefit in stage II adv. patients: the 5-year relapse-free survival was 44 per cent for combined therapy, and 10 per cent for radiation therapy alone ($0.05<p<0.06$; Fig. 4).

To judge from the multivariate regression analysis (Table 6) adjuvant multiple drug treatment improved

Table 5

Regression model relating relapse to overall time

Variable	Regression coefficient	p-value (two-tailed)
Intercept	2.6686	–
Sex (1=female)	−0.2218	*
Age (years)	0.0019	*
Original site (1=tonsil)	−0.4269	*
Original site (1=one site other than tonsil)	−1.7389	0.2
Nodal state (1=negative neck)	−1.7772	0.01
Nodal state (1=single and <5 cm)	−2.0972	0.05
Radiation dose (1=50 Gy or more)	−0.5966	*
No. of chemotherapeutic agents (1=one)	−0.9584	0.2
No. of chemotherapeutic agents (1=2 or more)	−1.5768	0.1
Histology (1=other than diffuse histiocytic lymphoma)	−0.8502	0.3

* $p>0.4$.

Table 6

Relapse versus number of chemotherapeutic agents in 65 patients given irradiation

No. of agents	No. with relapse/No. at risk (per cent)		
	Stage I	Stage II min.	Stage II adv.
0	4/8 (50)	1/4 (25)	9/10 (90)
1	4/11 (36)	2/5 (40)	5/10 (50)
≥2	1/11 (9)	–	4/6 (67)
Total	9/30 (30)	3/9 (33)	18/26 (69)

the prognosis more than signle drug treatment. However, even single agent chemotherapy appeared to improve the results. Thus 9 of 10 stage II avd. patients with irradiation alone relapsed compared with only 5 of 10 who received adjuvant single agent chemotherapy. The 5 surviving patients without relapse had received BLM alone with total doses of 30, 60, 75 and 135 mg and 5FU alone with a total dose of 5250 mg.

Xerostomia was the most frequent complication from the radiation treatment. One patient died of chemotherapy-related pneumonia. Another patient developed radiation myelitis after a dose of 50 Gy in the cervical spinal cord given with conventional fractionation.

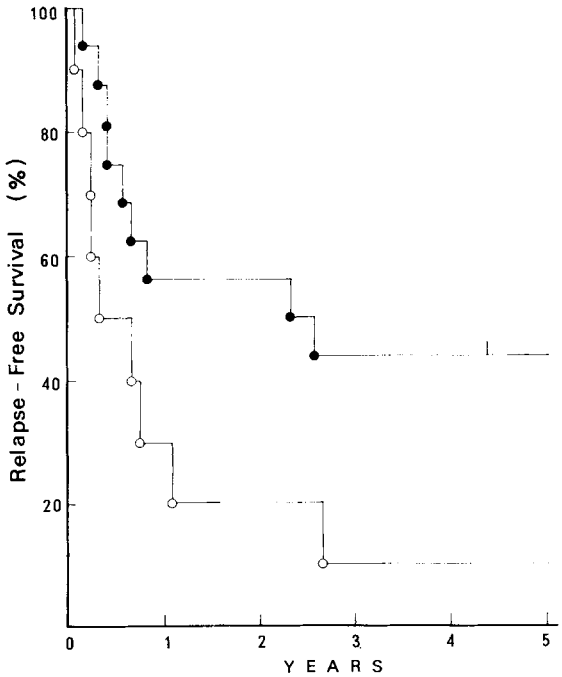

Fig. 4. Relapse-free survival in the stage II patients with an advanced nodal state according to treatment. Five-year survival: Irradiation and adjuvant chemotherapy (●) 44 per cent, irradiation alone (○) 10 per cent. $0.05<p<0.06$.

Discussion

This analysis indicated that the presence of bulky or multiple cervical nodes was the single most important prognostic factor for WR-NHL without distant spread. Other studies have also revealed the prognostic significance of the nodal state (1, 5, 16, 18), without however showing a relation between the extent of cervical node involvement and prognosis. In the present study patients with a single neck node had a similar prognosis to that in stage I patients, but this observation was based on a rather small number of cases.

Several authors have reported an increased relapse-free survival rate after radiation therapy combined with chemotherapy, compared with radiation therapy alone, in localized NHL of diffuse histology (8, 9, 12, 13). However, it is still not possible to evaluate the exact role of chemotherapy in early WR-NHL, from the literature. In the present series adjuvant chemotherapy seemed to be of benefit in patients with stage I and II WR-NHL, most of whom had a so-called unfavorable diffuse histology. Although combination chemotherapy seemed to be more efficacious than single agent chemotherapy, the latter appeared to benefit some patients. Considering that many patients with WR-NHL are elderly,

certain medical conditions may still justify the use of adjuvant single agent chemotherpy.

Although radiation doses of 50 Gy or more produced no in-field relapses the radiation doses were not prognostically important, according to the multivariate analysis. Nevertheless, the radiation technique should not be neglected, and in the present series a significant number of marginal failures occurred. We therefore recommend that all nodal regions above the clavicles except the submental, and most posterior cervical nodes should be included in the radiation fields in most patients with stage I and II WR-NHL. The axillae and the mediastinum can be spared from irradiation, since involvement of these regions at the first relapse is relatively rare. This policy concurs with the opinion of some other authors (6, 11, 18, 19).

The investigation thus suggested that both the extension of cervical node involvement and adjuvant chemotherapy had prognostic importance in stage I and II WR-NHL. However, the observations must be evaluated with caution, due to the retrospective non-randomized character of the study and the small number of cases in some subgroups. Further investigation is warranted, for confirmation.

It is also possible that after more effective chemotherapy, the identified prognostic factors may lose their significance. Recently, we have employed CHOP chemotherapy (adriamycin, vincristine, cyclophosphamide, prednisolone) for most stage I and II patients, as well as radiation therapy. There has been no relapse at the time of writing, but the number of patients is small and the follow-up period is still short.

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