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Early and intermediate stage Hodgkin's lymphoma – report from the Swedish National Care Programme

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Abstract: In Sweden a National Care Programme provides treatment principles for Hodgkin's lymphoma (HL) since 1985, for early and intermediate stages often less extensive than international recommendations. The purpose is to evaluate long-term results of these principles. A total of 308 patients (167 men and 141 women), 17–59 yr old (median 31), diagnosed during 1985–92, pathological stage (PS) I-III$_1$A and I-IIB and clinical stage (CS) I-IIA, mean follow-up 8.8 yr, were studied. Staging laparotomy was recommended in CS IIA. Recommended treatment was mantle or mini-mantle radiotherapy (RT) alone in CS IA, and PS I-IIA and subtotal nodal irradiation in PS III$_1$A if the disease was not bulky. Patients in PS I-IIA and III$_1$A with bulky disease, and PS I-IIB received one cycle of mechlorethamine, vincristine, prednisone, procarbazine/doxorubicin, bleomycin, vinblastine, lacarbazine (MOPP/ABVD) before irradiation. The remaining patients received three to four cycles of MOPP/ABVD with RT to bulky disease. Relapse-free (RFS), Hodgkin specific (HLS), and overall survival (OS) at 10 yr were 74%, 92% and 85%. In the individual stages, RFS ranged from 53% (PSIII$_1$A) to 90% (PS IA). RFS ($P = 0.006$), HLS, and OS were significantly better in patients treated with chemotherapy compared with those treated with RT alone, especially in patients with bulky disease ($P = 0.0005$). The international prognostic score did not provide any prognostic information. The OS rates are in agreement with results from international centres during that time. The recommended treatment was sufficient to produce the desired results of $<$20–30% recurrences, except in PS III$_1$A. Most relapses could be salvaged. Patients with risk factors treated with one MOPP/ABVD and RT had an excellent outcome, superior to those without risk factors treated with RT alone. These results favour the trend to treat early and intermediate stages with a short course of chemotherapy followed by limited RT.

Daniel Molin[1], Gunilla Enblad[1], Anita Gustavsson[2], Tor Ekman[3], Martin Erlanson[4], Eva Haapaniemi[5], Bengt Glimelius[1]

Department of Oncology, [1]Uppsala, [2]Lund, [3]Gothenburg, [4]Umeå, and [5]Linköping, Sweden for the Swedish Lymphoma Study Group

Key words: Hodgkin's lymphoma; treatment; prognosis; early stage; intermediate stage

Correspondence: Daniel Molin, Department of Oncology, Radiology, and Clinical Immunology, Section of Oncology, Rudbeck Laboratory, University Hospital, SE-751 85 Uppsala, Sweden
Tel: +46(0)18-6110213
Fax: +46(0)18-4713432
e-mail: daniel.molin@onkologi.uu.se

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Hodgkin's lymphoma (HL) in early and intermediate stages is today characterised by a favourable prognosis and at least 80% of younger patients are cured (1, 2). However, the treatment involves a risk of both acute and late side-effects, particularly secondary malignancies, and lung and cardiac dysfunction in patients treated with mantle radiotherapy (RT) (3–7). The risk of these late events is particularly important in young patients with a long life expectancy. In Sweden, therapy is based on a National Care Programme for HL since 1985 (8). According to the programme the treatment was less extensive than internationally recommended for the early and intermediate stages at that time. The recommended treatment principles also considered prognostic subgroups. Patients with low risk disease were treated with locally extended field RT only, and patients with high-risk disease were treated with a short course (one cycle of MOPP/ABVD) of chemotherapy, followed by RT. The model with a short course of chemotherapy followed by RT had been used at certain centres in the early 1980s, and is now introduced by many large co-operative groups, but the long-term results have not been studied.

When the programme was designed the aim was to have no more than 20–30% recurrences in any group together with a high probability to salvage the patients with a recurrence. An early evaluation after mean 5 yr of follow-up has been made for patients diagnosed during the years 1985–89 (9). The conclusion of that evaluation was that the treatment results were favourable and fulfilled the objectives of the Care Programme.

The aim of this study was to evaluate the treatment results after a longer follow-up of this relatively limited and tailored treatment in a large unselected population-based material. Furthermore, our aim was to study secondary tumours in different treatment groups. Another objective was to evaluate whether the international prognostic score (IPS) (10), originally designed for advanced stages, adds prognostic information concerning early and intermediate stages. If the IPS is not applicable there is a need for other prognostic factors to help further tailoring of the treatment. In one study, IPS had a moderate predictive value in intermediate stage disease (11).

Patients and methods

Patients

Since 1985 all new patients with HL in five of six health care regions in Sweden have been reported to a National Care Programme. The National Care Programme database is regularly updated against the Swedish Cancer Registry. During the years 1985–92, 1055 patients were reported, of whom 308 (29%) were between 17 and 59 yr of age in clinical (CS) or pathological stage (PS) IA, CS + PS IIA, PS IB, PS IIB or PS III_1A, and had supradiaphragmatic involvement. The median age was 31 yr, 167 (54%) patients were men and 141 (46%) women. Seventy-six (25%) tumours had mixed cellularity (MC), 179 (58%) nodular sclerosis (NS), 40 (13%) lymphocyte predominant (LP), 4 (1%) lymphocyte depleted (LD) histology, and nine (3%) were unclassifiable. The diagnoses were made by the regional haematopathologist according to the Rye-classification (12) and no re-evaluations have been made for the purpose of this study. The median follow-up for living patients is 9.3 yr (range 0.3–15.3 yr).

Staging

The staging was made according to the Ann Arbor system (13). The recommended clinical staging procedures involved clinical history, physical examination, ear, nose, and throat examination, where biopsies were made if there were any suspicious findings, laboratory investigations and bone marrow biopsy. Radiological investigations consisted of a chest X-ray, a chest computed tomography (CT) or magnetic resonance imaging (MRI) in cases of known mediastinal disease or NS histology. Both an ultrasonic examination of the abdomen, and CT and/or MRI/lymphogram were recommended if none of the techniques clearly showed HL involvement or disease was morphologically verified. However, lymphogram was abandoned during the time of the study.

Staging laparotomy with splenectomy was not recommended in stage IA if both CT and ultrasonic examination of the abdomen showed similar results. In stage IIA laparotomy was recommended and full chemotherapy (see below) given if laparotomy was not made. In stages IB and IIB laparotomy could be avoided if the patient was given full cytostatic treatment. Stage III was an indication for laparotomy if no unambiguous concordance between CT or MRT and ultrasound existed, or if morphological verification could not be obtained. If splenectomy was performed, pneumococcal vaccination was recommended.

The IPS was used as described (10). Parameters in the IPS are serum albumin level (< 40 g/L), blood haemoglobin level (< 105 g/L), sex (male), age (≥ 45 yr), stage (IV), leukocytosis (WBC $\geq 15 \times 10^9$/L), and lymphocytopenia (0.6×10^9 /L or $< 8\%$ of WBC). All parameters were available in 169 patients, six were available in 85, five in 10, four in one, and only three in 43 patients. Patients with six or seven parameters ($n = 254$, 82%) were included in the analyses. Laboratory values were not originally recorded in the case record forms, and have been collected retrospectively.

Treatment, dose and intensity

Primary treatment according to stage was, as follows:

Stage IA: Mantle RT, 40 Gy with 1.75–2.0 Gy daily with a split of 2–3 wk after 24 Gy, alone, except in cases of upper neck presentation only, where the RT could be restricted to mini-mantle,or, in cases of bulky mediastinal disease, preceded by one cycle of MOPP/ABVD.

Stage IB: If laparotomy was performed (PS IB) one cycle of MOPP/ABVD followed by mantle RT was recommended. If no laparotomy was made (CS IB) the recommendation was three to four cycles of MOPP/ABVD with subsequent involved field (IF)-RT (30 Gy), if the disease was initially bulky.

Stage IIA: Mantle RT alone was recommended, except in the cases with bulky mediastinal disease, whom received one cycle of MOPP/ABVD prior to

the RT, or where laparotomy was not performed (CS IIA), where three to four cycles of MOPP/ABVD ± IF-RT was recommended.

Stage IIB: If laparotomy with splenectomy was made (PS IIB), one cycle of MOPP/ABVD followed by mantle treatment was recommended and if this was not made (CS IIB), full chemotherapy, followed by IF-RT if initially bulky mediastinal disease was recommended.

PS III_1A: Subtotal nodal irradiation (STNI) was recommended, either alone or preceded by one cycle of chemotherapy. In case of bulky disease 1 cycle of MOPP/ABVD followed by STNI was given.

Complete remission (CR) was defined as disappearance of all known disease, and continuous complete remission (CCR) as no signs of disease at the last control. Undetermined CR (CRu) means that the patient is probably in CR but a radiologic abnormality remains. In the analyses, CRu was counted as CR.

Statistical methods

All statistical analyses were made utilising the Statistica 6.0 software (StatSoft, Tulsa, OK, USA). HL-specific survival, overall survival (OS), and relapse-free survival (RFS) were analysed with Kaplan–Meier graphs and the log rank significance test. In the analyses of HL-specific survival patients who died without HL were censored and patients who died with HL were not censored, and thus considered to have died of HL, irrespective of the actual cause of death. When analysing RFS, patients in CCR at follow-up were censored and patients with relapse were not censored at the time of the relapse. Patients who never reached CR (or CRu) were not censored and their time of follow-up was zero in the RFS analysis. Differences in proportions were evaluated with the chi-square test or Fisher exact test, if the frequency in any group was too small (<5) to use chi-square test. Concerning IPS the patients were divided into four groups: no risk factor, one, two, and three or more. The proportional Cox hazards regression model was used to compare the importance of different prognostic variables.

Results

Overall results

Overall 304 (99%) patients reached CR (or CRu) after treatment. Out of these 74 (24%) have experienced one or more relapses. The probability of living relapse-free at 5 yr was 80% and at 10 yr 74% (Fig. 1). Eighteen (6%) patients have died from or with HL and overall 44 (14%) patients have died irrespective of cause. The probability of dying from or with HL within 10 yr was 8% (Fig. 1). The overall probability of dying within 10 yr was 15%.

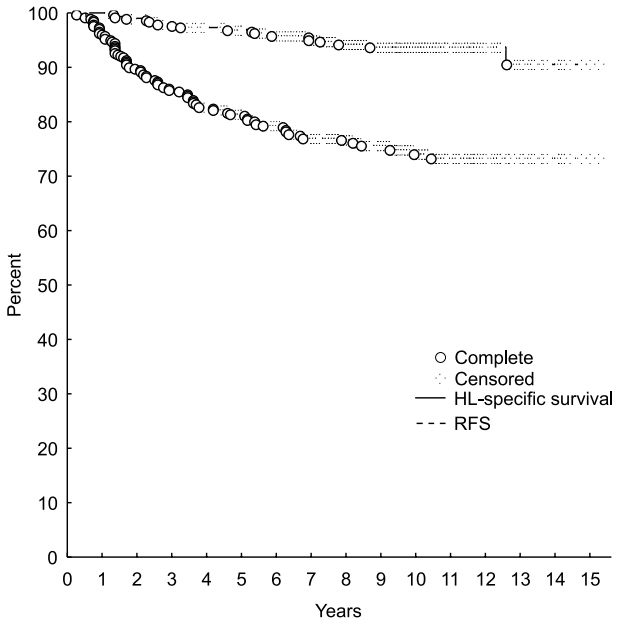

Fig. 1. Relapse-free (RFS) and HL-specific survival (HLS) for all patients ($n = 308$).

Results according to stage

In the individual stages the results at 10 yr was: PS IA RFS 90%, HLS 95%, and OS 90%, CS IA RFS 64%, HLS 92%, and OS 82%, PS IIA RFS 80%, HLS 94%, and OS 78%, CS IIA RFS 75%, HLS 88%, and OS 82%, PS IIB RFS 80%, HLS 94%, and OS 79%, and PS III_1A RFS 53%, HLS 90%, and OS 71%, respectively. Treatment results in CS + PS IA are given in Table 1 and those in the other stages in Table 2.

Results according to treatment

In total 205 (67%) patients were treated with RT alone. At 10 yr the RFS was 65%, the HL-specific survival 91%, and the OS 77%. Fifty-nine (19%) patients were treated with one cylce of MOPP/ABVD followed by RT, and at 10 yr the RFS was 95%, the HL-specific survival 98%, and the OS 98%. Three to four cycles of MOPP/ABVD ± RT was given to 38 (12%) patients, and at 10 yr the RFS was 72%, the HL-specific survival 91%, and the OS 82%. Results according to treatment in the different stages are given in Tables 1 and 2.

The outcome depending on whether the guidelines of the Care Programme were followed or not, is given in Table 3. Patients treated with a short

Table 1. Treatment results in CS + PS IA, according to treatment

	Total	Number of patients (%) R1	R2	Dead, HL
RT alone				
PS IA	21	2 (10)	0	1 (5)
CS IA	100	30 (30)	5 (5)	7 (7)
CS + PS IA	121	32 (26)	5 (4)	8 (7)
Non-bulky	110	28 (25)	5 (5)	7 (6)
Bulky[a]	11	4 (36)	0	1 (9)
Mantle field	85	25 (29)	3 (4)	5 (6)
Mini-mantle	21	3 (14)	1 (5)	0
Reduced CT + RT				
CS + PS IA, bulky	7	0	0	0
Full CT ± RT				
CS + PS IA	2	1 (50)	0	0
Total, IA				
All	131	33 (25)	5 (4)	8 (6)

R1 = first recurrence, R2 = second recurrence, RT = radiotherapy, CT = chemotherapy.
[a] Patients treated violating the recommendations.

Table 2. Treatment results in stages IB-III$_1$A

	Total	Number of patients (%) R1	R2	Dead, HL
PS IIA				
All	90	18 (20)	3 (3)	4 (4)
Non-bulky, RT alone	55	13 (24)	2 (4)	3 (5)
Bulky, RT alone[a]	9	5 (56)	1 (11)	1 (11)
Bulky, reduced CT + RT	22	0	0	0
Two sites	66	12 (18)	0	2 (3)
Greater than two sites	24	6 (25)	3 (13)	2 (8)
CS IIA				
All	46	10 (22)	7 (15)	3 (7)
Reduced CT + RT	8	0	0	0
Full CT ± RT	23	4 (17)	4 (17)	1 (4)
RT alone[a]	13	5 (38)	2 (15)	2 (15)
Two sites	29	5 (17)	3 (10)	1 (3)
Greater than two sites	17	5 (29)	4 (24)	2 (12)
PS IB				
RT alone[a]	1	0	0	0
PS IIB				
All	18	3 (17)	0	1 (6)
Reduced CT + RT	14	2 (14)	0	1 (7)
RT alone[a]	3	1 (33)	0	0
Full CT ± RT	1	0	0	0
Two sites	9	2 (22)	0	1 (11)
Greater than two sites	9	1 (11)	0	0
PS III$_1$A				
All	22	10 (45)	5 (23)	2 (9)
Non-bulky, RT alone	3	3 (100)	1 (33)	0
Bulky, RT alone[a]	1	1 (100)	0	0
Non-bulky, reduced CT + RT	4	1 (25)	1 (25)	0
Bulky, reduced CT + RT	2	0	0	0
Full CT ± RT	12	5 (42)	3 (25)	2 (17)
All patients	308	74 (24)	20 (6)	18 (6)

R1 = first recurrence, R2 = second recurrence, RT = radiotherapy, CT = chemotherapy.
[a] Patients treated violating the recommendations.

course of chemotherapy followed by RT had a significantly better RFS ($P = 0.0003$) and OS ($P = 0.004$) compared with those treated with RT alone. Also when patients treated with RT alone were compared with all patients treated with chemotherapy (including those treated with a long course of chemotherapy) the differences remained ($P = 0.006$ and $P = 0.04$, respectively) (Fig. 2).

Table 3. Treatment results depending on whether the guidelines have been followed or not

	Treated in accordance	Total	Number of patients (%) R1	R2	Dead, HL
All patients					
Only RT	Yes	162	45 (28)	9 (6)	10 (6%)
Reduced CT + RT	Yes	48	3 (6)	1 (2)	1 (2)
Full CT ± RT	Yes	23	4 (17)	4 (17)	1 (4)
Not according	No	75	22 (29)	6 (8)	6 (8)
Bulky disease					
Reduced CT + RT	Yes	36	2 (6)	0	1 (3)
Full CT ± RT	Yes	16	2 (13)	2 (13)	1 (6)
Not according	No	35	12 (34)	3 (9)	3 (9)

R1 = first recurrence, R2 = second recurrence, RT = radiotherapy, CT = chemotherapy.

Risk factors

Patients with bulky disease did not have a worse RFS in the whole material (Fig. 3A). However, RFS was significantly worse in patients with bulky disease treated with RT alone, violating the recommendations, compared with chemotherapy + RT (Fig. 3B). HL-specific survival tended to be worse (91% vs. 94% at 10 yr, $P = 0.5$) and

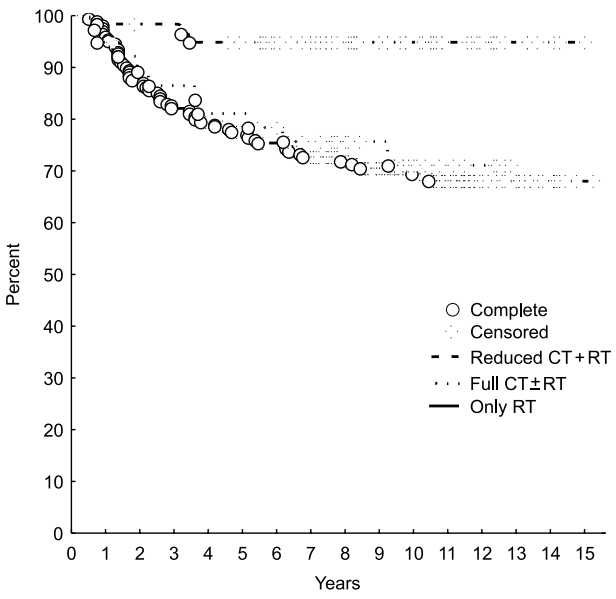

Fig. 2. Relapse-free survival, according to treatment [only radiotherapy (RT) vs. reduced chemotherapy (CT) + RT $P = 0.0003$, only RT vs. full CT ± RT $P = 0.8$]. Also the difference between only RT and all CT is statistically significant, $P = 0.006$.

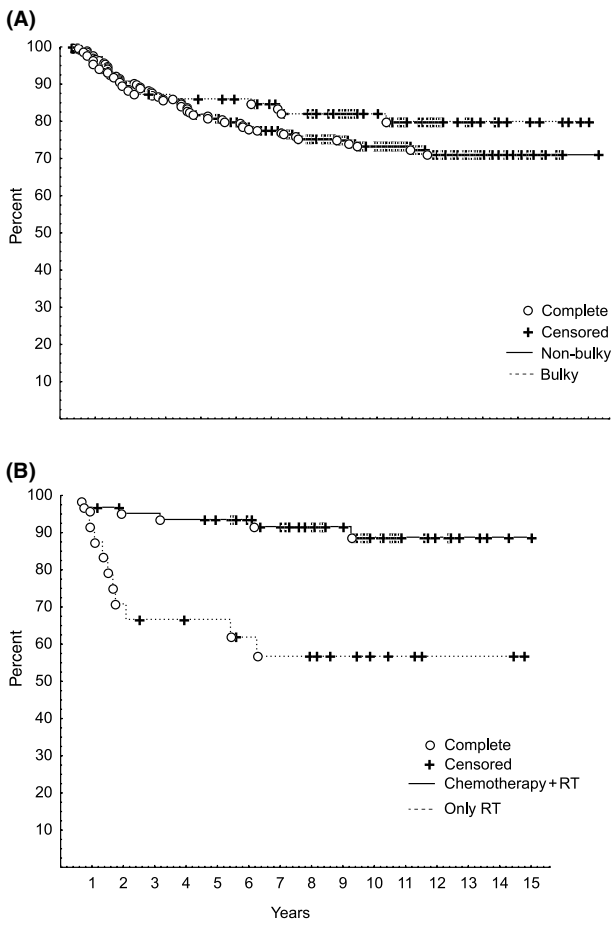

Fig. 3. (A) Relapse-free survival in bulky vs. non-bulky disease ($P = 0.2$). (B) Relapse-free survival in bulky disease, according to treatment: combined treatment vs. only radiotherapy ($P = 0.0005$).

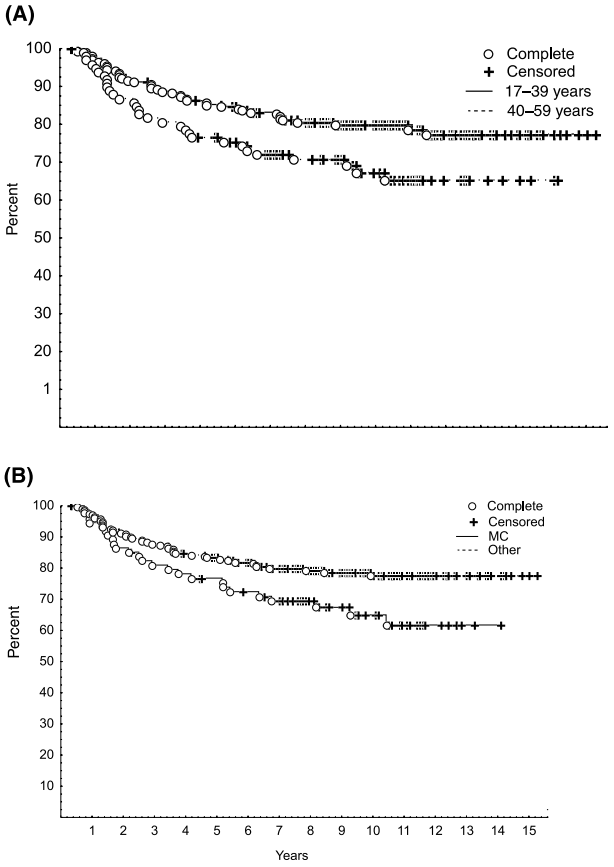

Fig. 4. Relapse-free survival, in (A) younger (< 40 yr) vs. older (40–60 yr) patients ($P = 0.03$), and (B) in MC histology vs. other histologies ($P = 0.02$).

OS was significantly worse (70% vs. 90% at 10 yr, $P = 0.04$) in patients with bulky disease treated with RT alone compared with the patients treated with chemotherapy ± RT. Patients above 40 yr had a significantly worse RFS (Fig. 4A), HLS (87% vs. 95% at 10 yr, $P = 0.03$), and OS (62% vs. 90% at 10 yr, $P < 0.01$) than the younger patients. In this material 22% of the patients under the age of 40 had MC histology, compared with 31% of the patients in the age group 40 and above ($P = 0.09$). Patients with MC had a worse RFS than the other histologies (Fig. 4B). The IPS did not have any impact on relapse or HL-related death frequency (Table 4). In univariate analyses, histology, age, ESR, and stage ($PSIII_1A$ vs. the others) significantly affected the RFS, but not sex, B-Hb, or bulky disease. In a multivariate analysis, only stage and MC histology significantly affected the relapse rate. However, if treatment (RT vs. chemotherapy ± RT) was included in the analysis, treatment, stage, and ESR significantly affected the outcome.

Table 4. Treatment results according to the International Prognostic Score (IPS)

		Number of patients (%)		
IPS	Total	R1	R2	Dead, HL
0	65	11 (17)	2 (3)	1 (2)
1	118	30 (25)	8 (7)	5 (4)
2	38	9 (24)	3 (8)	4 (11)
0–2	221	50 (23)	13 (6)	10 (5)
3+	33	7 (21)	1 (3)	3 (9)

R1 = first recurrence, R2 = second recurrence.

Treatment at relapse

In total 74 (24%) patients relapsed a first time, but only 20 (6%) a second time, and 18 (6%) died. First and second relapses in the different stages are given in Tables 1 and 2, and depending on whether the guidelines were followed or not in Table 3.

Sixty (29%) patients relapsed after RT alone. In these cases recommended treatment was chemotherapy if the relapse was within the treated area. If the relapse was outside the treated area, treatment could be radiation if it was localised and there were no signs of systemic disease. In 46 patients

treatment of relapse was reported. Four patients were treated with RT and 42 with chemotherapy. Forty-seven (78%) reached a new CR, 11 (18%) of these suffered a second relapse, and 12 (20%) died.

After one cycle of MOPP/ABVD followed by RT, only three (5%) patients relapsed. Patients relapsing after chemotherapy were recommended chemotherapy, in early relapses (within 1 yr) and for most late relapses the methyl-GAG, iphosphamide, methotrexate, and etoposide (MIME) regimen was used, with or without subsequent high-dose therapy with stem cell support. Two reached a new CR, one suffered a second relapse, and succumbed to HL.

Ten (26%) patients previously treated with full chemotherapy relapsed. Nine (90%) reached a new CR, seven (70%) suffered a second relapse, and three (30%) died.

Late effects and causes of death

Serious late effects are partially illustrated by the OS compared with the HL-specific survival. In total 44 (14%) patients [mean age 42 yr, 28 (64%) over 39 yr] died. In 18 (6%) [mean age 40 yr, 10 (56%) over 39 yr] the cause of death was HL. Of the patients who died, 27 (61%) received either full chemotherapy primarily or chemotherapy at relapse (if reported). This proportion was higher (78%, 14 patients) in those who died from HL than among those who died from other causes (50%, 13 patients). Twenty-six patients [mean age 43 yr, 18 (69%) of them over 39 yr] died without HL. The causes of death in these patients were in eight cases other malignancies (three other lymphomas, three adenocarcinomas, one colon cancer, and one mesothelioma), six serious infections, three myocardial infarctions, one pulmonary embolism, one cerebrovascular lesion, one retroperitoneal bleeding, and one suicide. In four patients the cause of death was missing and in one case it was reported as probably without HL, with no report of autopsy.

Discussion

We report here generally favourable treatment results in patients with early and intermediate stage HL treated according to the Swedish national guidelines, with an overall HL-specific survival rate of 92% and an OS of 85% after 10 yr. As these results contrast favourably with the international perspective, and were obtained in an unselected population-based material, and thus not only for patients eligible for a trial, they show that a limited tailored treatment does not worsen the outcome. The late toxicity was also limited, although more patients died from reasons other than HL. However, follow-up is still too short to reliably evaluate the risks of secondary malignancies and cardiac mortality.

In the original version of the programme the aim was to obtain at the most 20–30% recurrences and this was obtained in all stages, except PS III_1A. The idea was that most of the patients should only receive a comparatively limited treatment (locally extended-field RT) and that patients who relapsed could be rescued with a full course of chemotherapy. The results of the present study show that this aim was achieved, as the survival after relapse following RT was very high and in accordance with the survival after treatment for advanced stages (2, 14, 15). However, patients with risk factors (bulky disease or B-symptoms) initially treated with a short course of chemotherapy and RT had an even better survival than the patients without risk factors treated with RT alone. This result favours the present international trend (2, 15, 16) of treating all patients with early and intermediate stage HL with a short course of chemotherapy followed by RT. The idea may not be that long-term tumour control is substantially increased, but that long-term toxicity will be diminished. The addition of limited chemotherapy can limit the RT volumes, thus potentially limiting long-term toxicity. In the present material patients treated with a short course of chemotherapy usually received mantle RT and, of course, the results cannot be transferred to the present situation using IF-RT. However, some studies have indicated that IF-RT is equally effective as extended field RT when given after a short course of chemotherapy (17–19). When interpreting results of patients treated with chemotherapy vs. those treated with RT alone it must, however, be considered that there could be a bias in the selection of these patients.

In a review of treatment for early-stage HL Josting and Diehl (16) conclude that recent trials have reported excellent results with combined-modality treatment in early stages of HL without risk factors. In the early stages with risk factors (intermediate stage), new chemotherapy regimens may offer the chance of decreasing failure rates and further reducing the radiation. Several studies and researchers have also emphasised that laparotomy can be avoided and the results of the present study are in accordance with those results.

Patients not treated according to the principles in the programme had a worse prognosis, especially patients with bulky disease treated with RT alone. This result stresses the importance of combined therapy for those with bulky disease. Again, the comparison between patients treated according to vs. not according to the guidelines must be interpreted with care because the choice of not treating

according to the guidelines might be due to poor performance status of the patients or other factors indicating a poor prognosis *per se*.

In this study we were not able to detect any prognostic information from the IPS initially developed for advanced stages. The multivariate analyses showed the impact of stage ($PSIII_1A$ vs. the others), ESR, and MC histology. Treatment also affected the outcome if it was included in the analysis, further emphasising the worse outcome in patients treated with RT alone. The worse outcome in patients over the age of 40 is not unexpected (20, 21), but still worth commenting on, as this is not a comparison between younger and elderly patients, over 60 yr with established worse prognosis (2, 22). Patients within different age segments of the younger population with early or intermediate stage HL could gain from separate treatment strategies, although it is not possible to draw any firm conclusions on these results alone. The difference in prognosis could also be secondary to a difference in distribution of histopathological subgroups, with a higher proportion of MC in those over 40 yr of age. MC had a worse outcome in this study, and is known from old staging laparotomy series to carry a higher risk of abdominal involvement (23, 24). Also, these cases were not histopathologically re-evaluated.

Changes have been made in the Swedish recommendations. In Sweden, revisions were made in 1994, and in the Nordic countries, a new treatment protocol has provided updated principles for the treatment since 1999. Staging laparotomy with splenectomy is no longer recommended. Neither is mantle RT or RT alone (except IF-RT in LP histology, stage I + IIA without risk factors) recommended. (S)TNI was abandoned in Sweden in 1984, except for a few patients in $PSIII_1A$. The risk factors described in the new Care Programme for patients with supradiaphragmal presentation are bulky disease, number of involved sites, and erythrocyte sedimentation rate (ESR). The recommended chemotherapy was changed in 1994 from MOPP/ABVD to MOPP/ABV, and in the Nordic programme in 1999 to ABVD. Still there is a need for further research concerning prognostic factors, possibly found in the biology of the disease, i.e. in the role of the tumour cells (25), the cells surrounding the tumour cells and their communication with each other (26–28).

The principles in the programme from 1984 and in the revisions made thereafter are in accordance with the current international trend aimed at minimising the therapy in early stages of HL to diminish late toxicity while retaining high antitumour activity. Most centres now treat patients with short (two or four courses depending upon the number of risk factors) chemotherapy followed by IF-RT. The present study can give an idea of the long-term results of this approach, although mantle fields, rather than IFs, were used in combination with the reduced chemotherapy.

A comparison of the results in the Swedish population with those obtained by international single centres or co-operative groups can be biased in many ways but still worth pursuing for several reasons. It not only provides a quality control of the guidelines and the standard of care but may also yield important information of general interest prior to the design of new trials and new guidelines. In order to diminish the risk of bias, patient selection must be known in detail, i.e. the material must be truly population-based, not excluding any patient. This study fulfils that criterion.

Between 1982 and 1993, i.e. during the same time period as this material was collected, the EORTC Lymphoma Group included patients in early and intermediate stages in two trials, the H6 and H7 trials (2). Six-yr disease-free survival (DFS) varied between 68% (H7 trial, intermediate stage, 6 EBVP + IF-RT) and 92% (H7 trial, early stage, 6 EBVP + IF-RT), and OS between 82% (H7, intermediate stage, 6 EBVP + IF-RT) and 98% (H7, early stage, 6 EBVP + IF-RT). Our results are comparable with those results, although staging and/or treatment were generally more intense in the EORTC trials than recommended in the Swedish guidelines. In the current H9 trial, in co-operation with GELA, the reference treatment for patients without risk factors is 6 EBVP followed by IF-RT (36 Gy), which is compared with 6 EBVP + IF-RT (20 Gy) or no RT. Patients with risk factors are randomised between 6 ABVD, 4 ABVD, or 4 baseline BEACOPP, all followed by IF-RT.

When compared with the results of the German Hodgkin's Lymphoma Study Group (GHSG) in intermediate stages (29) where two cycles of COPP/ABVD were compared with two cycles of COPP/ABV/IMEP followed by extended-field RT (usually STNI), our results are satisfying. In that study, including patients between 1988 and 1993, OS at 7 yr was 88% in both arms, and the 7-yr freedom from treatment failure was 79% with no difference between the two arms.

In a Canadian review of 731 patients with CS I and II HL, treated between 1968 and 1986, the 10-yr OS was 76% and the DFS 65% (30). Our results are superior to those but some of these patients were treated up to 17 yr before the patients in this material. As both the staging and treatment have evolved during the study the results may not be fully comparable. In the Canadian study it was concluded that patients relapsing early (within 4 yr from diagnosis) had a worse prognosis than those

relapsing late. This was not found in our material (data not shown). In our material 52 (70%) of the 74 relapses were early, compared with 171 (83%) of 206 relapses in the Canadian material.

In a population-adjusted clinical epidemiology (PACE) (31) study of patients treated between 1991 and 1993 from the Northern Region Lymphoma Group, UK, results were evaluated according to the SNLG index, including age, CS, lymphocyte count, haemoglobin, and bulky disease in an equation (32–34). In younger patients (15–55 yr) with good index the 5-yr OS was 87%, and with intermediate index 78%. In our material the SNLG index was not calculated.

The British National Lymphoma Investigation (BNLI) compared in a pilot study methotrexate, vinblastine, and prednisolone (MVP) with vinblastine, bleomycin, and methotrexate (VBM); in both cases two cycles of chemotherapy followed by IF-RT and then four cycles of chemotherapy, for patients in CS IA or IIA (35). The patients were treated between 1992 and 1994. In the study the 5-yr survival was 97% for MVP and 93% for VBM. The 5-yr event-free survival rates were 71% and 87%, respectively.

In the Stanford-Kaiser Permanente G1 study for CS I-IIA, VBM and IF-RT (87% freedom from progression after 4 yr) gave a result comparable with that of STNI (92% freedom from progression after 4 yr) (36). The patients were treated between 1988 and 1995. In that paper Horning and co-workers encouraged participation in clinical trials aiming at reducing toxicity while maintaining efficacy in early stage HL, but they did not suggest the use of VBM and IF-RT in routine clinical practice. The idea of combined modality treatment was otherwise introduced early in Stanford, however performed as extended-field RT followed by adjuvant chemotherapy for 6 months (37).

In conclusion, the tailored recommendations regarding staging and treatment presented in the Care Programme fulfilled its aim of producing favourable results, using, in most instances, less extensive investigations and treatment than was internationally recommended when the guidelines were defined and during the course of the recommendations. Most patients who relapsed could also be salvaged with chemotherapy. Patients treated with one course of MOPP/ABVD and RT had an excellent outcome. IPS is not possible to use for further tailoring of treatment in this group of patients, why other prognostic markers must be looked for.

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