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Early Stage Hodgkin's Disease: Ten-year Results of a Non-randomised Study with Radiotherapy Alone or Combined with MOPP

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From September 1976 to June 1982, 201 consecutive patients with stage I (A and B)-IIA Hodgkin's disease were stratified in two groups according to prognostic factors. The F group included 116 patients with favourable presentation: they were staged with laparotomy and treated with subtotal or total nodal radiotherapy alone. The U group included 85 cases with unfavourable presentation who were staged by laparoscopy and treated with 3MOPP (mechlorethamine, vincristine, procarbazine, prednisone)-radiotherapy-3MOPP. At 10 years the F group showed a freedom from progression (FFP) of 71%, with significant difference between stage I and II (85% vs. 59%; $P=0.003$) and an overall survival of 84%. The results of the U group were: FFP 83%, overall survival 74%, and the findings were not influenced by stage. FFP in patients with bulky vs. not bulky lymphoma was 70% vs. 87% ($P=0.04$). No secondary acute non-lymphocytic leukaemia developed among patients treated with radiotherapy and in continuous complete remission, while acute leukaemia occurred in the F group patients who received salvage chemotherapy (4 of 31 cases) and in the U group (3 of 85 cases). Present results confirm the usefulness of radiotherapy alone in favourable pathological stage IA. All other disease stages will require a different strategy that should consist of radiotherapy combined with short-term effective regimens, such as ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or VBM (vinblastine, bleomycin and methotrexate) to reduce the incidence of MOPP-associated gonadal dysfunction and leukaemogenesis.
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INTRODUCTION

THE STANFORD group first reported that a large majority of patients (75–80%) with pathological stage (PS) IA–IIA Hodgkin's disease could be cured by total or subtotal nodal irradiation [1]. These results were thereafter confirmed by a number of research centres throughout the world. It was also observed that 85% of relapses will occur within 3 years from the completion of irradiation and salvage chemotherapy could probably cure two thirds of relapses [2–6].

Therefore, interest developed in combining radiotherapy and chemotherapy utilising one or two agents. MOPP (mechlorethamine, vincristine, procarbazine, prednisone) was then introduced for selected patient subsets with initial stage Hodgkin's disease but presenting with unfavourable prognostic characteristics as determined by histology, systemic symptoms, extranodal (E) disease, and pulmonary hilus involvement. A highly significant correlation in stages I and II between survival and histological type was reported, the prognosis being significantly better for patients with lymphocytic predominance (LP) and nodular sclerosis (NS) compared to mixed cellularity (MC) and lymphocytic depletion (LD) histology, respectively [7–9]. In addition, systemic symptoms, direct contiguous extranodal and/or pulmonary hilus involvement were also recognised to negatively influence survival [1, 7, 10–14].

Taking these data into account, in 1976 we started a prospective study in consecutive patients with pathological stage (PS) I (A and B) and IIA. The treatment programme was selected according to presence or absence of the above-mentioned prognostic factors. The aims of the study were to confirm the role of radiotherapy alone in patients with favourable presentation and to evaluate the efficacy of a combined treatment in patients with unfavourable prognosis.

PATIENTS AND METHODS

Trial design

From September 1976 to June 1982, patients with clinical stage I (A and B)-IIA Hodgkin's disease were stratified into two groups. The first group included patients with favourable presentation (F group) defined by LP or NS histology and absence of B symptoms, E lesion, and pulmonary hilus involvement. All these patients were pathologically staged with laparotomy and splenectomy. When surgical findings were negative, patients were considered suitable for treatment with primary irradiation alone. The second group with unfavourable presentation (U group) consisted of patients with MC or LD histology or presenting with one or more of the above-mentioned risk factors. These patients were staged by laparoscopy and if the histological examination confirmed the absence of spleen and

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liver involvement, they were treated with combined modality therapy.

Staging procedures

Histological diagnosis of Hodgkin's disease was performed by biopsy of peripheral lymph nodes [10]. Clinical staging consisted of physical examination, complete blood cell count, liver and renal function tests, postero-anterior and lateral chest X-rays, and bypedal lymphangiography. Additional X-rays and radioisotopic studies were performed only in the presence of individual clinical situations.

Pathological staging included two needle bone marrow core biopsies from bilateral posterior iliac crests in all patients, whereas either staging laparotomy or laparoscopy were performed according to the previously mentioned strategy.

Treatment plan

Radiotherapy consisted of subtotal nodal irradiation (STNI) in all patients with supradiaphragmatic Hodgkin's disease, while patients with subdiaphragmatic disease received total nodal irradiation (TNI). Spleen irradiation was performed in all patients not subjected to staging laparotomy with splenectomy. Radiotherapy was delivered through ^{60}Co teletherapy or 6 MeV linear accelerator. Supradiaphragmatic nodal sites were irradiated through an A–P and P–A mantle field tailored to each patient after planning set up at simulator. Check-films were routinely taken at the beginning of treatment and every week. The daily dose was 90 plus 90 cGy, given through both portals. The dose was calculated at midplane corresponding to the centre of both fields. A map of the distribution of the dose to each nodal site was prepared by the physicist in order to arrange and modify fields and blocks during the treatment and to give the scheduled total dose to each site. Five fractions per week were given. Prophylactic irradiation of para-aortic lymphnodes, with or without concomitant spleen irradiation was started at the end of mantle fields. The inferior limit of these tailored A–P and P–A fields was the sacral promontorium. In patients presenting subdiaphragmatic adenopathies only, i.e. those candidated to TNI, treatment was started under the diaphragm and later completed with mantle fields. When administered alone or when combined with MOPP chemotherapy, the doses of radiotherapy were 44 and 35 Gy to involved lymphoid areas and 40 and 30 Gy to the uninvolved areas, respectively. The dose to the spinal cord was carefully monitored and a posterior longitudinal block was positioned when the dose had to exceed 36 Gy to the irradiated volume.

Combined treatment modality was delivered through the sandwich technique, i.e. three cycles of MOPP preceded and followed radiotherapy. Four to six weeks elapsed between chemotherapy and radiotherapy. MOPP was administered at the classical dose schedule designed at the National Cancer Institute [10]. During the delivery of chemotherapy, a dose reduction schedule was planned for all patients showing myelosuppression on the day of drug injection. Doses of mechlorethamine and procarbazine were reduced by 50% when the peripheral leucocyte count ranged from 3999 to 2500/μl and/or the platelet count ranged from 119000 to 75000/μl. In the presence of more severe myelosuppression (leucocyte count < 2500/μl; platelet count < 75000/μl), treatment was delayed until at least half doses of both drugs could be administered. In the presence of severe paresthesias and/or constipation, the dose of vincristine was reduced by 50%; in the presence of adynamic ileus the drug was discontinued.

Table 1. Characteristics of patients

	No. of cases	F group RT No.	(%)	U group 3MOPP/RT/3MOPP No.	(%)
Total evaluable	201	116		85	
Sex					
Males	104	47	(41)	57	(67)
Females	97	69	(59)	28	(33)
Age					
Median		30		37	
(range)	(14–71)	(15–69)		(14–71)	
Histology					
LP	30	25	(22)	5	(6)
NS	116	91	(78)	25	(29)
MC	40			49	(58)
LD	6			6	(7)
Stage					
IA	79	51	(44)	28	(33)
IB	8			8	(9)
IIA	107	65	(56)	42	(49)
IIEA	7			7	(8)
> Three nodal sites	23	8	(7)	15	(18)
Mediastinal involvement	71	40	(34)	31	(36)
Pulm. hilus involvement	26	—		26	(31)
Bulky disease	37	13	(11)	24	(28)

Patients' characteristics

The case series consisted of 202 consecutive patients. Only 1 patient, whose diagnosis at review was changed to non-Hodgkin lymphoma, was considered not evaluable. Of the 201 evaluable patients, 116 belonged to the F group and were treated with radiotherapy alone; 85 of the U group received the combined treatment program. At the time of present analysis, the median follow-up was 10 years. The main patient characteristics are reported in Table 1. Overall, NS and MC were the most frequent histological subsets in both groups of patients.

Besides the unfavourable characteristics required by the study design, other factors having a negative prognostic influence were more frequent in the U group compared with the F group (male sex 67% vs. 41%; median age 37 years vs. 30 years; involvement of more than three nodal areas 18% vs. 7%). Subdiaphragmatic disease was present in 3 and 4 patients of the F and U group, respectively. At the time the study was designed, the presence of bulky disease was not considered among selection criteria since the prognostic relevance of massive adenopathy was documented in studies published after 1977. Thus, the assessment of bulky lymphoma in patients entered into these treatment programs was only retrospectively evaluated on previously recorded clinical data as well as on accurate re-evaluation of X-ray films. As illustrated in Table 1, bulky disease was present in 13 of 116 patients (11%) treated with radiotherapy only and in 24 of 85 (28%) patients also treated with MOPP. In particular, 9 and 19 patients belonging to the F and U group, respectively, presented with bulky mediastinal disease (mass/thoracic ratio >0.33 between the largest transverse diameter of the mediastinal mass and the transverse diameter of the thorax at the level of T5 or T6 on a standing posteroanterior chest radiography), while 1 patient in each treatment group showed bulky retroperitoneal

Table 2. Favourable (F) group (116 patients): 10-year freedom from progression (FFP) and overall survival

	FFP %		Survival %
Total	71		84
Histology			
NS	68		88
LP	79		72
Stage			
I	85	$P=0.003$	83
II	59		85
≤ 3 Nodal sites	70		85
> 3 Nodal sites	87		75
Mediastinal involvement	60		90
Bulky disease	77		85
Non-bulky disease	70		77

Table 3. Unfavourable (U) group (85 patients): 10-year freedom from progression (FFP) and overall survival

	FFP %		Survival %
Total	83		74
Histology			
NS	75		80
Others	86		71
Stage			
I	82		66
II	83		79
≤ 3 Nodal sites	83		75
> 3 Nodal sites	79		67
Mediastinal involvement	73		81
Mediastinal + hilus involvement	70		81
Bulky disease	70	$P=0.04$	74
Non-bulky disease	87		75

lymphoma. The other patients presented with bulky disease at the level of superficial nodes.

Statistical analysis

Freedom from first progression (FFP), overall survival (all causes of deaths), and freedom from tumour mortality (FTM, or deaths due to disease progression alone) were computed by the life-table method starting from the date of starting treatment. The statistical analysis of observed differences was assessed by log–rank test [15].

RESULTS

Radiotherapy alone

Complete remission (CR) was achieved in 114 of 116 (98%) patients. At 10 years, 71% of cases are in first CR (Table 2). The majority of failures (25 of 33) were documented within the first 3 years from starting irradiation and only one patient relapsed beyond the fifth year. The likelihood of durable remission was significantly influenced only by stage (Fig. 1). In fact, 85% of stage I patients were continuously disease-free at 10 years compared with 59% of stage II cases ($P=0.003$). Relapses occurred in nodal sites in 24 cases, in extranodal sites only in 2 cases and in both nodal and extranodal sites in 7 cases. In 19 patients new disease manifestations occurred in irradiated areas and in 3 cases nodal relapses were located at the border of the irradiated fields. Relapses in previously involved areas occurred in 15 of 33 patients.

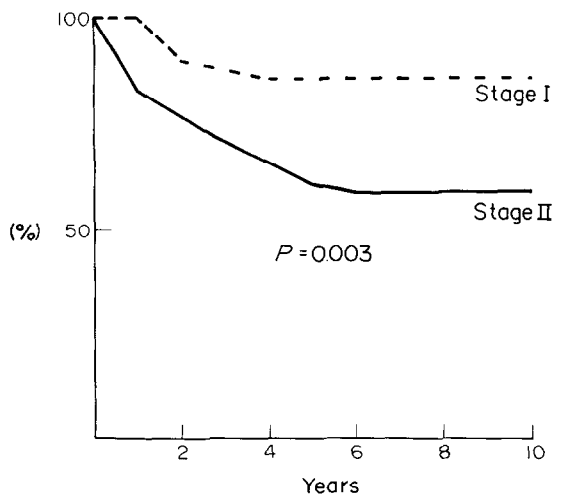

Fig. 1. Freedom from progression after radiotherapy in patients with favourable (F) Hodgkin's disease.

The 10-year overall survival following irradiation was 84% and was not influenced by stage. Among the 19 documented deaths only 2 were directly related to progressive lymphoma; thus, total freedom from tumour mortality was 98% (stage I 100%, stage II 97%).

The most frequent cause of death was represented by second neoplasms which accounted for 11 of 19 cases (see forthcoming paragraph). The remaining patients died of myocardial infarction (2 cases), cerebral stroke (1 case) adrenal insufficiency (1 case), and sepsis (1 case).

Combined modality treatment

Complete remission was achieved in 81 of 85 patients (95%) and the overall 10-year freedom from progression was 83% (Table 3). The majority of failures (8 of 14) were documented within the first 2 years from starting MOPP and only 1 patient presented with new disease manifestations beyond the sixth year.

Stage, histology and number of involved nodal sites (≤3 vs. >3) failed to influence treatment outcome. By contrast, patients presenting with bulky lymphoma had a significantly inferior freedom from progression (70%) compared with patients without massive adenopathy (87%, $P=0.04$). Also in this treatment group most relapses were documented in previously irradiated nodal sites (9 of 14 or 64%), and 6 of them were in previous involved regions. 5 patients relapsed in both nodal and extranodal sites. Overall, 74% of patients remained alive after 10 years. It is worth noting that only 66% of stage I patients were alive vs. 79% with stage II, respectively. Only one third of patients (7 of 22) died of progressive disease; freedom from tumour mortality was 91% for both stage I and II patients. Second neoplasms were the cause of death in 8 of 22 cases, while other patients died of myocardial infarction (1 case), cardiovascular failure (3

Table 4. Results of salvage therapy related to the initial treatment

Salvage therapy	Radiotherapy		3MOPP/RT/3MOPP	
	2nd CR/Total	Median duration in months (range)	2nd CR/Total	Median duration in months (range)
RT	2/2	3, 120	3/3	70 (10–107)
MOPP* with or without RT	8/8	120¶ (12–120)	—	
ABVDD† with or without RT	6/6	120¶ (16–120)	0/3	
MOPP/ABVD with or without RT	13/14	85¶ (8–110)	3/4	36¶ (29–60)
ABVD/CEP‡	2/2	101, 107	2/3	26, 80
POBI§	—		1/1	40

*MOPP: mechlorethamine, vincristine, procarbazine, prednisone.
†ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine.
‡CEP: lomustine, etoposide, prednimustine.
§POBI: prednisone, oncovin, bleomycin, dacarbazine.
¶: Median duration in excess of given figures.
CR = complete remission.

cases), cerebral stroke (1 case), radiation pneumonitis (1 case), and sepsis (1 case).

Treatment compliance

During the first three cycles of MOPP, all patients received more than 80% of the planned dose of all drugs. Radiotherapy could either not be completed or was delivered with frequent delays because of persisting myelosuppression in 12% of patients. Postirradiation chemotherapy was either administered at 50% of the optimal dose or delivered beyond the projected period of time because of prolonged bone marrow suppression in 54% of patients.

Salvage therapy

Types and results of salvage therapy in relation to the initial treatment program are outlined in Table 4. Salvage radiation therapy alone was delivered to patients with relapse limited to nodal areas not previously irradiated; otherwise radiotherapy was utilized in individual clinical situations as consolidation of partial or complete response obtained with salvage chemotherapy. Four chemotherapy regimens were utilised: MOPP; ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); MOPP monthly alternated with ABVD (MOPP/ABVD) or ABVD monthly alternated with CEP (lomustine, etoposide, prednimustine) (ABVD/CEP). Salvage chemotherapy was administered to complete remission plus two additional cycles (minimum of six cycles). Salvage treatment was able to achieve complete remission in 94% of patients initially given irradiation alone (31 of 33 cases) and in 64% of patients treated with combined MOPP and radiotherapy (9 of 14 cases). In 1 patient given primary radiotherapy alone adequate information about salvage treatment was lacking.

Second neoplasms

Twenty-three new cancers (basal cell carcinomas excluded) were documented within 10 years (Table 5). Among 85 patients treated with irradiation alone and in continuous complete remission of their Hodgkin's disease, two high grade non-Hodgkin lymphomas and six solid tumours were observed within a median of 51 months (range 4–103) from starting irradiation. Among 31 patients started on radiotherapy alone who subsequently received salvage chemotherapy including alkylating agents, four acute non-lymphocytic leukaemias and one soft tissue sarcoma were documented. The median time to leukaemia was 55 months from starting irradiation (range 42–83) and 37 months (range 24–53) from starting salvage treatment.

After combined MOPP and radiotherapy, second malignancies developed in 10 patients who were all in first CR. The median time to leukaemia (total, 3 cases) was 56 months (range 22–106) from starting MOPP, whereas the median time to other second cancers was 72 months (range 15–103).

DISCUSSION

The management of PS I (A, B) and IIA Hodgkin's disease remains controversial. In fact, while some investigators advocate staging laparotomy followed by irradiation alone to reduce chemotherapy-related toxicity including the risk of secondary leukaemia [16–18], other suggest avoiding laparotomy and the use of a primary combined approach with the aim to increase the duration of first complete remission [19–23].

Radiation therapy in the treatment of early-stage Hodgkin's disease results in long-term disease free survival in up to 75% of patients [1–6, 14, 16, 18, 22–26]. Differences in technical procedures and radiation delivery equipment can affect the end results. In fact, several studies report considerable variations in

Table 5. Second neoplasms

Second neoplasms	RT	3MOPP/RT/3MOPP
	No	No
Total	13 (5)	10
Acute leukaemia	4 (4)	3
Non-Hodgkin lymphoma	2	1
Lung cancer	3	5
Cancer of rynopharynx	1	—
Cancer of larynx	1	—
Vulvar carcinoma	—	1
Breast cancer	1	—
Soft tissue sarcoma	1 (1)	—

( ) Second neoplasms developing in patients treated with RT plus salvage chemotherapy.

the disease free survival which ranges from 65% to 82% at 10 years. Despite this wide variation, the overall survival at 10 years is generally greater than 85% because of effective salvage chemotherapy.

To improve the therapeutic results of radiotherapy in the early stages of Hodgkin's disease, radiotherapy has been combined with chemotherapy. In general, combined modality treatment results in more durable complete remissions compared with irradiation alone. However, the overall survival differences are small and there is an increased iatrogenic morbidity including secondary acute leukaemia or myelodisplastic syndrome [28–31].

Therefore, chemotherapy alone is the alternative approach that has been pursued. It was thought that if 65% of patients with advanced disease could be cured by combination chemotherapy, this programme when applied to patients with limited disease could exceed the cure rate attained by radiotherapy alone without the morbidity associated to combined modality approach. The results of two trials testing the potential value of chemotherapy alone in early-stage Hodgkin's disease have been recently reported [23, 27]. In these studies patients were randomly assigned to receive either MOPP alone or subtotal nodal irradiation. Cimino *et al.* [27] treated 89 patients with PS I-IIA and noticed CR in more than 90% in both treatment groups with comparable 5-year relapse free (73%) and total survival rate (90%). Most relapses in MOPP-treated patients were documented in previously involved sites while recurrences after radiation therapy showed tendency to occur in uninvolved and unirradiated nodal areas. Moreover, a higher frequency of early relapses was noted in the chemotherapy-treated groups. Likewise Longo *et al.* [23] reported a CR rate >95% for both MOPP and radiotherapy in patients presenting with "central" Hodgkin's disease, i.e. with PS IA, IIA and III_1A. The projected 10-year disease free survival was in favour of patients randomised to receive MOPP (86% vs. 60%; $P=0.0009$) and survival showed a trend favouring chemotherapy (92% vs. 76%; $P=0.051$). However, there were no significant differences between the two arms when patients with massive mediastinal disease or stage III_1A obviously not fit for primary RT were excluded from the analysis. Other reports in the medical literature concerning adult patients with localised disease treated with chemotherapy alone included a few cases given MOPP while no data are available about the use of less toxic combinations [27].

In our study radiotherapy alone resulted in a 10-year FFP and survival of 71% and 84%, respectively. The findings are consistent with those reported by other investigators and confirm that more than 70% of patients with PS IA and IIA can be cured by radiotherapy alone. As reported almost invariably in patients with localised disease treated with irradiation alone, we observed that stage remained the most important predictor of prognosis because only 59% of patients with favourable stage IIA achieved a long-term continuous FFP compared with 85% of patients with PS IA. Although the salvage rate of chemotherapy in relapsed patients was high, it was not always successful. Therefore, while radiotherapy can be considered the curative treatment of choice for patients presenting with favourable stage IA Hodgkin's disease, the strategy involving laparotomy followed by subtotal or total nodal irradiation does not appear to be adequate for patients with stage IIA even in the absence of unfavourable indicators.

In our experience, the combined modality approach for patients with unfavourable early-stage Hodgkin's disease resulted in a 10-year FFP of 83%. There was no difference between stages I and II and only the presence of bulky disease negatively influenced long-term results (70% vs. 87%, $P=0.04$) but the difference in freedom from progression was not translated into an improved overall survival (74% at 10 years). There are two main reasons that can explain this fact. The first is the low effectiveness of salvage chemotherapy in patients relapsing after combined treatment, compared with patients failing after radiotherapy alone. The second reason is the high rate of fatal iatrogenic morbidity, namely, second malignancies, frequently reported when extensive irradiation is associated with alkylating-containing regimens [28–31].

For all these reasons, the best option for early stage patients (e.g. unfavourable stage I presentation and stage IIA) should consist of involved-field radiotherapy combined with short-term chemotherapy devoid of late morbidity such as the ABVD or VBM (vinblastine, bleomycin and methotrexate). ABVD has proved superior to MOPP in randomised trials and did not appear to induce permanent gonadal damage and second leukaemia [29, 32–34]. The other potentially less toxic regimen, i.e. VBM, has not been previously compared to MOPP; however, preliminary results when VBM was combined with involved field radiotherapy vs. extended radiotherapy alone in stages I to IIIA patients appear promising [35]. To further refine combined strategies, besides the use of few cycles of chemotherapy regimens not including alkylating agents, the role of involved versus extended radiotherapy should be fully explored through additional randomised studies [36].

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Prognosis of Lymphoma From a Fine-needle Aspirate

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The prognostic value of S-phase fraction (SPF) determined by flow cytometry from a fine-needle aspirate was investigated in a prospective series of 52 non-Hodgkin lymphomas. The aspirates were drawn either at diagnosis (n = 16) or at lymphoma recurrence (n = 36). Patients with lymphoma with a large SPF (> 10%, n = 24) had only a 21% 3-year survival rate corrected for intercurrent deaths as calculated from the date of aspiration, whereas a smaller SPF was associated with a 71% 3-year survival rate (n = 28, P = 0.0009). SPF size also correlated with Working Formulation grading (P = 0.002). In a multivariate analysis the relative risk of death from lymphomas with a large SPF was 4.01 (1.60–10.1), whereas histological grading, age, and sex had no additional independent prognostic value. SPF determined from a fine needle aspirate had unexpectedly good prognostic value, and the result suggests that the method is of clinical importance.
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INTRODUCTION

HISTOLOGICAL EXAMINATION of excised lymphoma tissue is essential not only for making the distinction between Hodgkin's disease and non-Hodgkin lymphoma, but also for further subtyping of lymphoma to augment selection of treatment and to estimate the biological aggressiveness of lymphoma. Aggressiveness of lymphoma can also be assessed by several techniques other than histology, e.g. by measuring the relative number of cells in the DNA synthesis phase of the cell cycle (the S-phase fraction, SPF) by DNA flow cytometry or image cytomery. The SPF can be determined rapidly by flow cytometry, and both Hodgkin's and non-Hodgkin's lymphomas with a large SPF have been shown to have inferior outcome as compared with lymphomas with a low SPF [1–13]. Unlike the SPF, DNA ploidy appears to have relatively little prognostic value in lymphomas [3–5, 7–19]. A few authors report that the SPF may be superior to histology in predicting survival in lymphoma [5, 6, 9, 20]. These studies have been performed from surgically