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Long-term Results of the E.O.R.T.C. Randomized Study of Irradiation and Vinblastine in Clinical Stages I and II of Hodgkin's Disease

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Abstract—*Two hundred and ninety five patients with clinical stages* I *and* II *of Hodgkin's disease were randomized between* 1964 *and* 1970 *for a controlled clinical trial. The patients were staged after clinical and radiological examination. No laparotomy was performed. Radiotherapy was carried out using the mantle field or inverted Y technique. The patients were assigned at random to two groups: (a) no further treatment, and (b) a weekly injection of vinblastine for* 2 yr. *Fourteen hospital centers participated:* 6 *in France*, 5 *in Holland and* 3 *in Belgium.*

The proportion of relapse-free patients is significantly higher amongst those who received long-term adjuvant chemotherapy. The incidence of relapses in liver, spleen, lung and irradiated areas does not differ between the two groups, but the incidence of relapse in non-irradiated lymph node areas is significantly higher in the group of patients who did not receive chemotherapy. This suggests that only small aggregates of neoplastic cells, which were not visible at pretreatment lymphangiogram, were sterilised by the chemotherapy.

No significant difference in survival between the two groups was observed.

A few prognostic factors significantly influence the rates of relapse and survival. For patients with good prognostic indicators, the incidence of relapses was low and not reduced significantly by adjuvant chemotherapy.

INTRODUCTION

SINCE the early sixties, a combination of radiotherapy and chemotherapy was considered for clinical stages I and II of Hodgkin's disease in the hope of compounding the advantages of these two techniques. The first trials mainly demonstrated that such an association was feasible [1, 2]. The results, however, were open to criticism because most of the radiotherapeutic techniques were not satisfactory (either too low doses applied or too limited irradiated areas). In addition, chemotherapy was not administered in the optimal fashion. Moreover, in some of these studies, no control group was provided to allow for an objective evaluation of the results.

In 1964 a controlled clinical trial was undertaken by the radiotherapy–chemotherapy group of the E.O.R.T.C. The basic idea was to apply extended radiotherapy at high doses to see if long term chemotherapy with one drug, vinblastine, would add to such treatment. The preliminary results have been previously reported [3–6] and their therapeutic implications discussed. The

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follow-up for most of the patients is now longer than 10 yr; the aims of this paper are to report the long term results and to show how the analysis of these results has lead to new trials designed to achieve a better relationship between the aggressiveness of the treatment and the severity of the disease.

MATERIALS AND METHODS

Patients

The protocol of this trial has been previously reported [3] and therefore we will only summarize it briefly. Patients were included in the trial if the following conditions were met: (a) the diagnosis was confirmed by biopsy examination; (b) the patient had not received previous treatment for this disease. The patients were staged after careful clinical and radiological examination that included an ilio-lumbar lymphangiogram, a chest roentgenogram and, if necessary, a tomography of the mediastinum and tests of liver function. No laparotomy was performed. Radiotherapy was carried out by telecobalt or megavoltage therapy, using the mantle field or the inverted Y technique. Areas of demonstrable disease as well as adjacent or intervening areas containing lymph nodes located on the same side of the diaphragm were irradiated at a dose of 4000 rad in a 4 week period. No irradiation was carried out on the other side of the diaphragm. For example, in the case of supradiaphragmatic involvement, the para-aortic lymph nodes were not irradiated. Four weeks after the end of irradiation, the patients in complete remission were randomly assigned to two groups: (a) no further treatment and (b) a weekly injection of vinblastine for 2 yr. The trial, began in 1964, ended in March 1971. Fourteen hospital centers participated in it: 6 in France, 5 in Holland and 3 in Belgium.*

During this period, 295 patients were included in the study. Fifty six per cent of the patients with Hodgkin's disease treated in the Co-operative Centres during this period, i.e., 387, were within the criteria for inclusion and received radiotherapy treatment as defined in the protocol. Among the 387 patients, 23% were not randomized because they were not in complete remission 6 weeks after the end of radiotherapy, due to an ESR above 25 mm or a non-normalised mediastinum. Many of these patients were later found to have reached a complete remission.

The slides of all patients were reviewed by the histology review committee† in 1971. They were again reviewed blindly in 1976 since the criteria for the various histological subtypes of Hodgkin's disease had slightly evolved in the mean time [7, 8]. Seven patients were retrospectively excluded from the trial since the histological diagnosis of Hodgkin's disease appeared dubious during the histological review. All lymphography were read by a radiological review committee.† About 5% of the lymphography of the patients with supradiaphragmatic disease were considered as probably involved by the review committee. In view of this small percentage, those patients were not excluded. The data were computed at Villejuif.

RESULTS

Two hundred and ninety five patients were randomized. As previously mentioned, 7 patients were later excluded. Breakdown of patients for each centre and according to the treatment is shown in Table 1. The 2 therapeutic groups were compared on the basis of age distribution, sex, presence or absence of systemic symptoms, erythrocyte sedimentation rate (ESR), stage and histology, and no difference was observed [3]. Table 2 shows that the pattern of presentation is also similar in the 2 groups.

Relapse

Analysis of the results was carried out from all the follow-up forms completed every 6 months. The proportions of relapse-free patients within the two groups were calculated by the actuarial method. There is a significant difference in favour of the group which re-

*The chairmen of this co-operative group have been: M. Tubiana (1964–1967), K. Breur (1967–1969), B. van der Werf-Messing (1969–1972), J. Henry (1973–1975), J. Abbatucci (1975–1977), M. Brugers (1977–). The statisticians have been M. Hayat and M. Henry-Amar.

Co-operative Centres have been, in France: C. A. C. Bordeaux (C. Lagarde), C. A. C. Caen (S. Abbatucci), Lyon (J. Papillon, L. Revol), Paris: Hôtel-Dieu (J. Bousser, R. Zittoun), C. A. C. Rouen (H. Piguet), Villejuif (G. Mathé, M. Tubiana, J. L. Amiel). In Belgium: Brussels Institut Jules Bordet (J. Henry), Liège (R. Lemaire), Louvain (A. Wambersie). In Holland: Amsterdam (K. Breur, M. Burgers), Leiden (P. Thomas), Nijmegen (C. Haanen), Rotterdam (B. van der Werf Messing, W. G. Stenfert-Kroese).

†The members of the histology review committee: R. Gérard-Marchant, J. van Unnik; and of the lymphography review committee: R. W. Kropholler, J. D. Picard, P. Markovits, J. L. Chassard.

Table 1. Number of patients included by each Co-operating Center

	RT	RT+C	Total
Amsterdam	20	17	37
Nijmegen	3	1	4
Rotterdam	46	41	87
Leiden	12	13	25
The Hague	1	—	1
Brussels (I.J.B.)	5	6	11
Louvain	1	—	1
Liège	3	3	6
Lyon	5	5	10
Bordeaux	3	1	4
Caen	7	6	13
Paris (Hôtel-Dieu)	10	11	21
Villejuif (I.G.R.)	35	32	67
Rouen	1	—	1
Total	152	136	288

ceived chemotherapy (Fig. 1). The difference increases slowly after the fourth year. This is due to the fact that there is no late relapse in the group treated by adjuvant chemotherapy whereas 4 relapses have been observed in the group treated by radiotherapy alone after the fifth year (two, 6 yr after treatment, one 8 yr and one 9 yr). 58% of the patients treated by radiotherapy alone have relapsed but only 37% of those treated by combination therapy. Since chemotherapy was discontinued at the end of a two year period, it should be concluded that it had been able to control permanently some of the neoplastic foci.

In both therapeutic groups the mean time interval between randomization and relapse was 23 months. Ninety per cent of the relapses occured during the first 4 yr. Three patterns of relapses have been distinguished: (a) relapse in the irradiated lymphatic area; (b) extension in a non-irradiated lymphatic area; (c) extra nodal relapse (Table 3).

The incidence of relapses in irradiated areas is low in the 2 groups and only slightly smaller in the group treated by combination therapy. On the other hand, the incidence of relapses in non-irradiated nodal areas is much higher in the "radiotherapy" group than in the radiotherapy–chemotherapy group: 42 relapses out of 152 patients in the group treated by radiotherapy, vs 20 out of 136 in the group treated by combination therapy. This suggests that chemotherapy is effective on small tumor sites that are not detected by palpation or by lymphography, since, in this series, the extensions occurred mainly in para-aortic lymph nodes. The incidence of extra-nodal or systemic relapses does not differ in the groups and is relatively high.

Eight of the 56 patients in whom one axillary area had not been irradiated had relapses in this unirradiated area on the same side of the diaphragm. However, the total percentage of relapses in a non irradiated lymph node area is the same, i.e., 20%, whether the patients were treated by a complete or an incomplete mantle field. Two types of recurrences were differentiated: true recurrences and marginal recurrences probably due to an underdosage at the margin of the field. However, out of the 4 patients with marginal recurrences, 3 died within 2–4 yr after relapse.

Among the patients treated by adjuvant chemotherapy, the incidence of relapse was higher for those patients who had discontinued chemotherapy before the eighteenth month (15 out of 35 patients, i.e., 43%) than in the patients who had completed their course of chemotherapy (31%) but with no difference in survival.

Table 2. Description of the patients included in the trial

		CS I		CS II		Total	
		Med 0	Med +	Med 0	Med +		
Above the diaph.	RT	53 (37%)	11 (8%)	35 (24%)	46 (31%)	145	NS
	RT+C	60 (46%)	6 (5%)	25 (19%)	39 (30%)	130	
Below the diaph.	RT	2		5		7	
	RT+C	3		3		6	

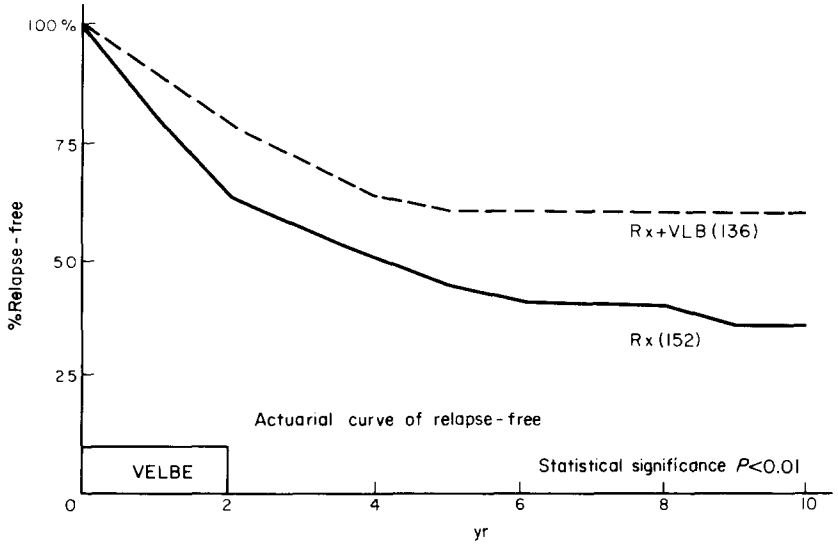

Fig. 1. Comparison between the rates of relapse-free patients (actuarial) in the 2 therapeutic groups (with or without long term chemotherapy).

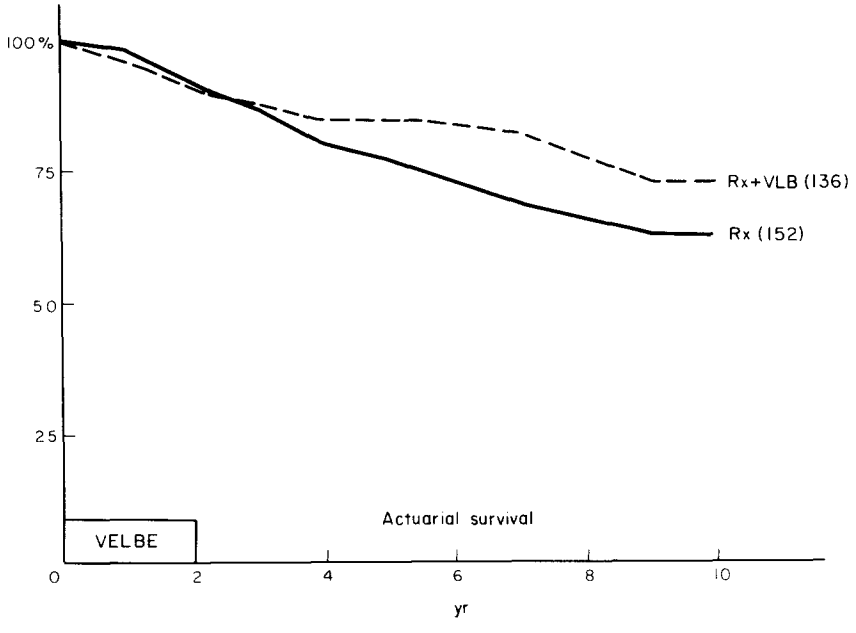

Fig. 2. Survival rate (actuarial) in the 2 groups of patients.

Survival

In spite of the significant difference in the percentage of relapse free patients, the survival rate does not differ significantly ($P = 0.12$). At 10 yr, it is 0.70 ± 0.05 (S.D.) in the group treated by adjuvant chemotherapy vs 0.60 ± 0.04 (S.D.) in the radiotherapy group (Fig. 2). The number of deaths during first relapse is similar in the 2 groups, and the survival rate after relapse is not significantly influenced by the initial therapy (Table 4). Of those patients who are again in complete

Table 3. Relapses in the two therapeutic groups

	RT	RT+C	Total
Patients at risk	152	136	288
Recurrences in an irradiated area	17 (11%)	8 (6%)	25
Relapses in a non irradiated lymph node area	42 (28%)	20 (15%)	62
Extra nodal relapse	29 (19%)	22 (16%)	51
Total of relapses	88 (58%)	50 (37%)	Statistical significance: $P<0.01$
Deaths	47 (30%)	32 (23%)	

Table 4. Outcome of patients after relapse

≧3 yr of follow-up after first recurrence	RT	RT+C	Total
Patients at risk	82	49	131
Patients relapse free since the first relapse	25 (30%)	12 (24%)	37
Patients having relapsed	48 (59%)	26 (53%)	74
Death occuring during the first relapse	9 (11%)	11 (23%)	20

remission after the first relapse, about two-thirds in each treatment group and for each type of relapse experienced a second relapse. Comparison of the survival rates after first relapse in the two groups (Fig. 3) shows that a long follow-up is required for an assessment of the percentage of cure after relapse as at even 6 yr after the first relapse, no plateau is yet observed.

The mean time interval between the first and the second relapses is hardly different in the two groups: 18 months for patients initially treated by radiotherapy alone and 16 months for those having been randomized in the group radiotherapy + chemotherapy. For the deceased patients the mean time interval between first relapse and death is 27.4 ± 3.3 months (m ± S.D.) for the group treated by radiotherapy alone and 24.9 ± 4.6 months for the group treated by combination therapy. However for those patients who die during the first three years after the first relapse, the time interval between relapse and death is shorter in the group treated by combination therapy (10.9 ± 1.7 months versus 19.6 ± 1.8 months for the group treated by radiotherapy alone ($P<0.01$).

Forty-seven per cent of the patients survive 6 yr after the occurrence of the relapse. The survival rate after relapse is not influenced by the type of relapse (Fig. 4). During the first years after relapse, it is slightly lower for the patients with visceral relapse, but later the difference vanishes.

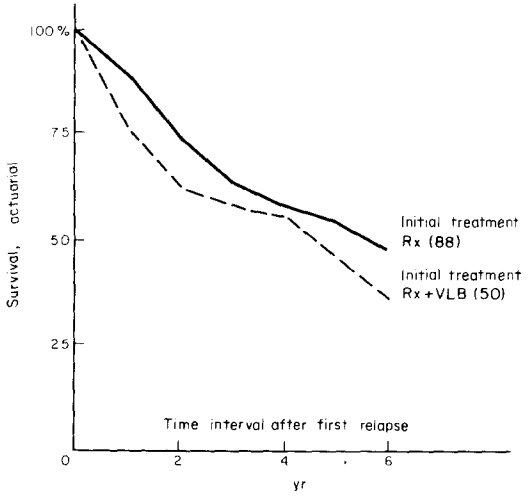

Fig. 3. Survival rate after first relapse for patients initially treated either by radiotherapy or by radiotherapy + chemotherapy.

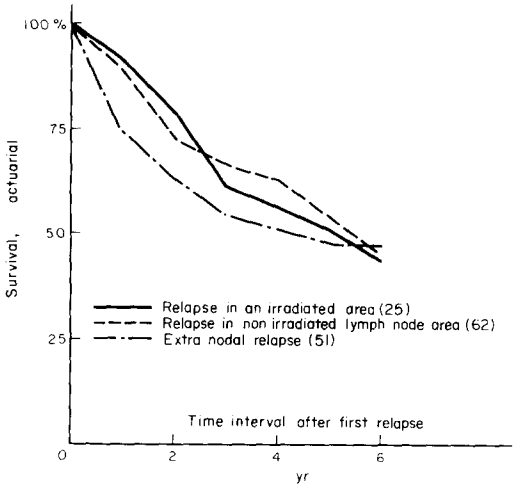

Fig. 4. Survival rate after first relapse for patients with various types of relapse or recurrence.

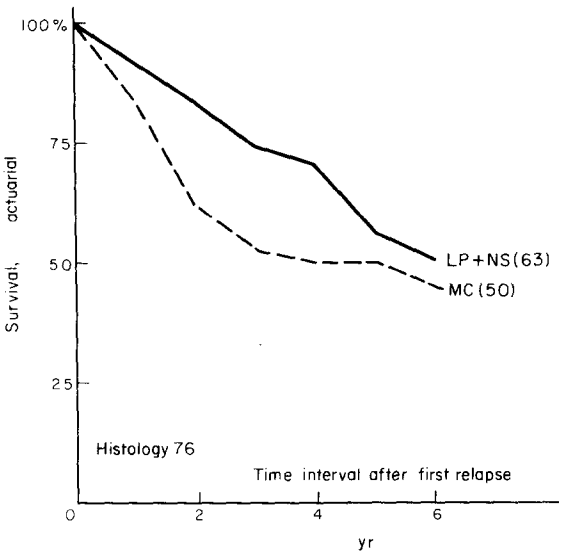

Fig. 5. Survival after first relapse for patients either with a LP or NS histological subtype or with a MC histological subtype (1976 *review*).

Table 5. Causes of death

	RT	RT+C
Total number of deaths	47	32
Hodgkin's disease	41	29
Cardiac failure	3	1
Pneumopathia	2	
Secondary malignancy	1	1
Intercurrent cause		1
Alive with secondary malignancy	4	

On the other hand, survival after relapse seems to be influenced by the histological type (Fig. 5) as previously observed [6], but the difference is not statistically significant. A few deaths were due to cardiac failure or pneumopathias (Table 5) which might have been caused by treatment. Secondary malignancies were observed in 6 patients (Table 5): one acute leukemia, one cancer of the oesophagus, of the lung, of the testes, of the parotid gland and of the skin.

Prognostic indicators

Preliminary analysis of the data [6] had already shown the influence of many prognostic factors: histological subtype, age, sex, systemic symptoms, erythrocyte sedimentation rate (ESR), stage, pattern of presentation (presence or absence of mediastinal involvement). These prognostic indicators were studied in the present series.

Histological subtypes

Their prognostic influence was evaluated on the basis of the 1972 and 1976 histologic reviews, both of which based on the Rye classification [7, 8]. The 2 reviews differ slightly (Table 6); for instance, in the 1976 review, none of the patients was included in the lymphocytic depletion (LD) subtype, and some of the patients previously considered with a mixed cellularity (MC) type were included in the nodular sclerosis (NS) type. In spite of those discrepancies, both classifications have a similar prognostic influence. The percentage of patients who are relapse-free or

Table 6. Correlation between the first (1972) and the second reviews (1976) by the histology committee

1972 \ 1976	LP	NS: Cellular phase	NS: Early phase	NS: Mature phase	MC	LD	Total
LP	15 (53%)	1	2	2	8	—	28 (13%)
NS	—	—	6	81	—	—	87 (41%)
MC	2	3	4	14	69 (75%)	—	92 (43%)
LD	—	—	—	3	2	—	5 (32%)
Total	17 (8%)	4 (2%)	12 (6%)	100 (47%)	79 (37%)	—	212
		116 (55%)					

Statistical significance: $P \ll 0.001$.
[C—I 2 test calculated after grouping MC + LD and NS (cellular, early and mature phases).]

surviving is higher for the lymphoid predominance (LP) and the NS types than for the MC type (Fig. 6). After 10 yr, the actuarial survival rate is about 80% for the patients with a good histological type (NS–LP), whereas for patients with a MC type it is only 60% (Fig. 7).

In the 1976 review, among the NS type, three subtypes were differentiated: the cellular phase, the early phase and the mature phase. Four patients were included in the cellular phase and 12 patients in the early phase (Table 6). The incidence of relapse and death is slightly higher in the early than in the mature phase, but the difference is not significant. The incidence of extension in a non-irradiated nodal area is higher in patients with MC type (Table 7).

The percentage of relapse-free patients for the MC type (Fig. 6) is significantly increased

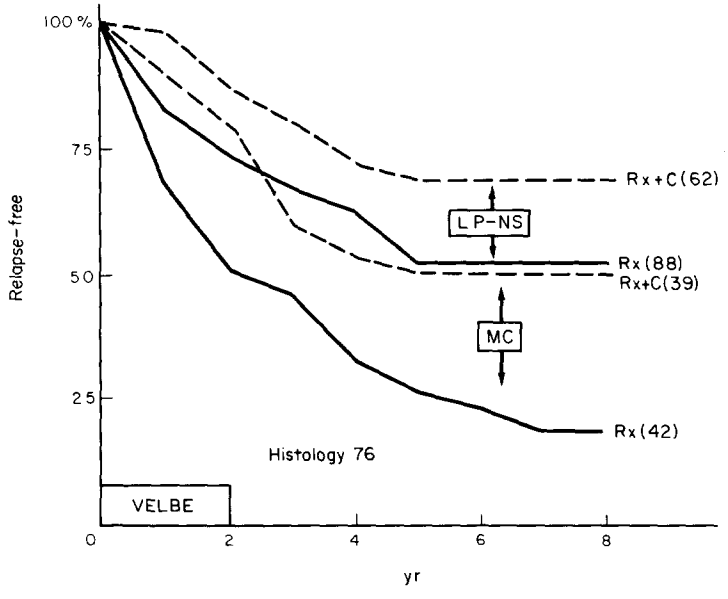

Fig. 6. Proportion of relapse free patients in the 2 therapeutic groups according to histological type.

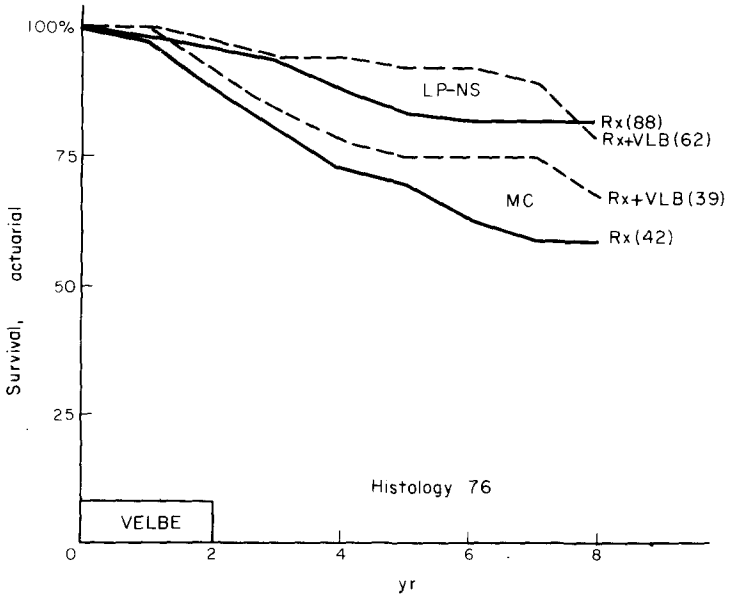

Fig. 7. Survival rate in patients in the 2 therapeutic groups according to histological type.

Table 7. Relapses in the various histological subgroups (1976 review)

	LP+NS		MC+LD	
	RT	RT+C	RT	RT+C
Patients at risk	88	62	41	39
Complete remission	45 (51%)	42 (68%)	10 (24%)	20 (51%)
Relapse in an irradiated area	7 (8%)	2 (3%)	4 (10%)	2 (5%)
Relapses in a non irradiated lymph node area	20 (23%)	10 (16%)	19 (46%)	7 (18%)
Extra nodal relapses	16 (18%)	8 (13%)	8 (20%)	10 (26%)

by adjuvant chemotherapy. In the NS+LP group, chemotherapy has a smaller and not statistically significant beneficial effect on the incidence of relapses. In both histological types, the adjuvant chemotherapy does not significantly improve survival (Fig. 7).

Other prognostic factors

Beside the histological type, six other prognostic indicators were studied: age (less than 40 yr at the onset of the disease or more), sex, clinical stage, pattern of presentation of the disease (presence or absence of mediastinal involvement), presence or absence of systemic symptoms, ESR (≤ 70 mm or > 70 mm during first hour). Systemic symptoms and ESR are strongly correlated and only ESR was analysed in this study.

All those factors are of a prognostic value; however only two of them have a statistically significant effect on the proportion of relapse-free patients: age and ESR. Furthermore, only one of them, age, significantly influences survival. Moreover, most of those various prognostic factors, as well as histology, are correlated [6, 9]. For instance, mediastinal involvement is correlated with age, sex and histology. This is why it is difficult to assess

the independant prognostic significance of each of these parameters. A multiple regression analysis was carried out in a previous paper on preliminary data and demonstrated the significant and independant prognostic influence of histology, age and sex [6]. A multifactorial analysis was carried out on the present data and is reported in another paper [9]. Its results show that only ESR and presence or absence of systemic symptoms are redundant; all the other indicators contribute to the prognosis, but the most important are the histological type and the pattern of presentation (involvement or non-involvement of mediastinum) (Fig. 8).

Taking all of this into account, a group of patients with a good prognosis can be defined: patients of less than 40 yr at first treatment, with a NS or PL histological subtype, and with an ESR of less than 70 mm at 1 hr, clinical stage I or clinical stage II with mediastinum involvement. Figures 9 and 10 and Table 8 compare the incidence of relapse and death either in these patients or in the other patients that is to say the patients with at least one poor prognostic indicator.

The incidence of relapses in irradiated lymph nodes areas is the same in the 2 groups with good or poor prognosis indicators but the incidence of extra nodal relapse and of relapse in non-irradiated lymph nodes is significantly higher in the last group.

Adjuvant chemotherapy decreases the proportion of relapse in all the groups with one, or many, indicator of poor prognosis. For instance, among the patients treated with radiotherapy alone, the proportion of relapse-free patients is significantly smaller for patients without mediastinal involvement than for patients with mediastinal involvement; whereas for patients having received adjuvant chemotherapy, the proportion of relapse-free patients is the same for the 2 patterns of presentation (Fig. 8). But the most important prognostic factor influencing the therapeutic effect of chemotherapy is the histological type.

DISCUSSION

The results obtained show that long-term chemotherapy with one drug is able to sterilize permanently occult lesions in about one third of the patients with subclinical disease. Analysis of the data indicates that the lesions sterilized by chemotherapy are mostly located in non-irradiated lymph node areas.

Lymph nodes are either palpable or visible after lymphography. It is therefore probable that the nodal lesions that had not been detected were small, whereas larger lesions might have remained occult in the spleen or the liver for instance. This suggests that the lesions sterilized by adjuvant chemotherapy were of small size. The absence of late relapses in the group treated by adjuvant chemotherapy and the increase of the difference between the proportion of patients in first remission in time interval after treatment (Fig. 1) confirm that the lesions controlled

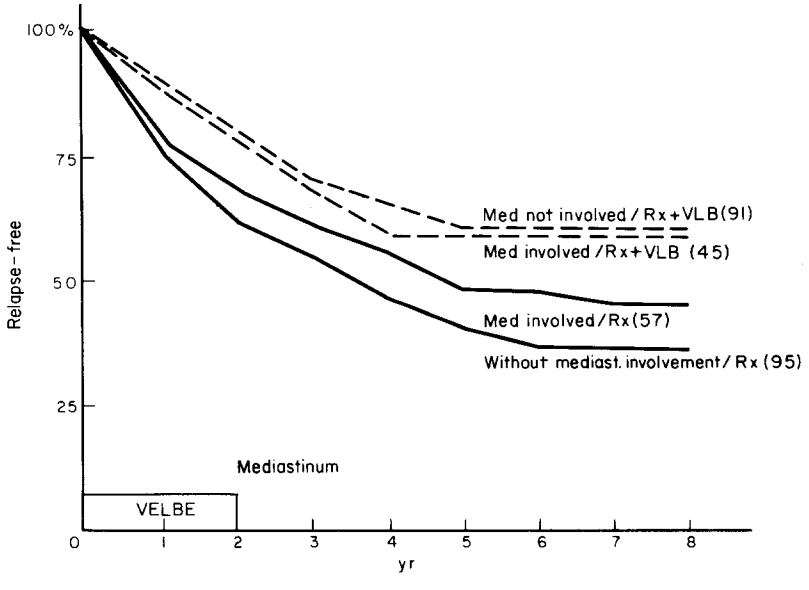

Fig. 8. Proportion of relapse-free patients (actuarial) for patients with or without mediastinal involvement treated by radiotherapy or radiotherapy + chemotherapy.

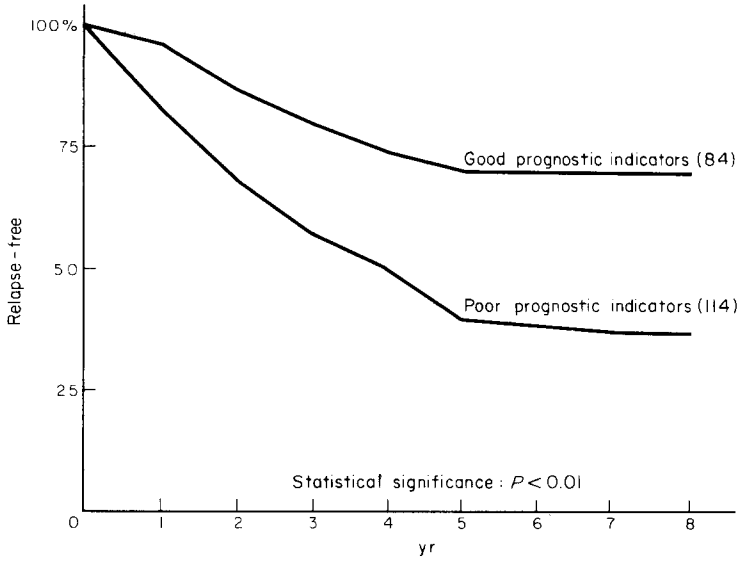

Fig. 9. Proportion of relapse-free patients (actuarial) for patients with good prognostic indicators or with one (or many) poor prognostic indicators.

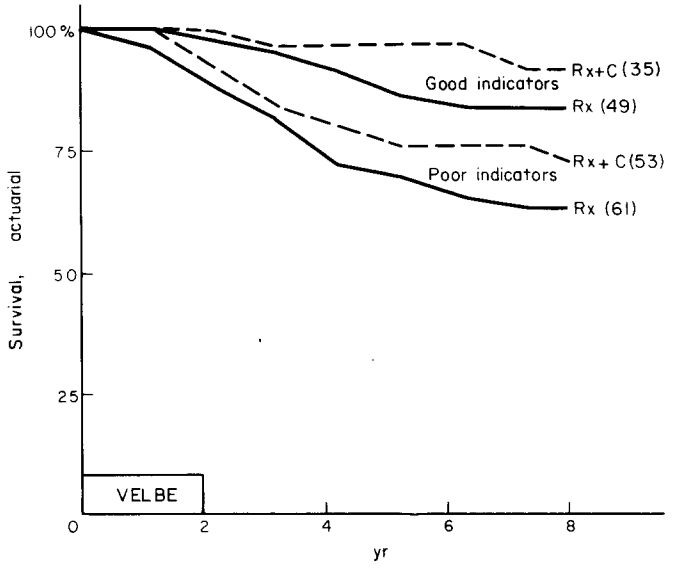

Fig. 10. Survival rate (actuarial) for patients with good prognostic indicators or with one (or many) poor prognostic indicators.

were mostly either of small size or of slow growth rate.

The surprising and apparently paradoxical fact is that, after ten years, survival is not significantly different in the two groups. A few deaths may still occur in the group treated by radiotherapy alone in which late relapses have been observed. Nevertheless it is improbable that the difference between survival rate in the 2 groups will become significant after a longer follow-up. Two hypotheses can be discussed for the interpretation of these data.

The first is that chemotherapy for a relapse is not as well tolerated in patients who have already been treated initially by a 2 yr course of chemotherapy with vinblastine. Therefore, the treatment is less efficient and the number of rescues smaller.

The other possible explanation is that the patients who are not rescued by chemotherapy after relapse and are ultimately dying are comparable in both types of treatment. In other words, patients whose lesions were sterilized by adjuvant chemotherapy would have been rescued after relapse if treated initially by radiotherapy alone and with both types of treatment the patients with the most severe type of disease ultimately die. As seen in Table 4, the proportion of patients

Table 8. Outcome of patients with good or poor prognosis indicators

	Patients with good prognosis indicators			Patients with one (or many) poor prognosis indicators		
	RT	RT+C	Total	RT	RT+C	Total
At risk	49	35	84	61	53	114
Relapses	19	8	27 (32%)	44	24	68 (60%)
Deaths	7	4	11 (13%)	20	14	34 (30%)

Considered good cases are all the patients whose histology has been reviewed in 1976 and who meet the following criteria: histological type LP or NS, age below 40 yr, ESR $\leqq$ 70 mm/hr, CS I or CS II with mediastinal involvement.

Considered poor cases are patients whose histology has been reviewed in 1976 and who do not meet the previous criteria (see Table 9).

Table 9. Breakdown of patients included according to age, sex and histology (76)

Histology		LP	NS	MC	Not reviewed in 1976	Total
Age $\leqq$ 40 yr	Male	10	61	55	16	142
	Female	4	52	12	30	98
Age > 40 yr	Male	2	13	12	8	35
	Female	1	7	2	3	13
Total		17	133	81	57	288

who die after relapse is slightly higher in the group initially treated by combination therapy. It is also higher in the group with poor prognostic indicators (Table 8).

It is therefore difficult to discriminate retrospectively between those 2 explanations, but the second seems more likely.

From a therapeutic point of view, 3 conclusions emerge from these data.

1. The extension rate in non-irradiated lymphatic area and especially in the para-aortic lymph nodes is very high in the group treated by radiotherapy alone. This is why in the following trial (H_2) carried out by the radiotherapy–chemotherapy group of the E.O.R.T.C. from 1971 to 1976, the para-aortic nodes and the spleen were treated in all patients with supradiaphragmatic Hodgkin's disease, CS I or II. This significantly improved both the proportion of relapse-free patients and the survival rate which at 4 yr are respectively 75 and 92%.

2. It would be easy to reduce the incidence of relapse by using a more aggresive initial treatment but this would also increase the therapeutic burden. A few data have underlined the high incidence of secondary cancer in patients with Hodgkin's disease treated by extensive radiotherapy and intensive chemotherapy [10]. Furthermore irreversible damage of the gonads have been observed after such treatments.

On the other hand, some prognostic factors influence both the proportions of relapse-free and surviving patients. This suggests the possibility of some modulation in the treatment taking into account the characteristics of the disease. In particular, chemotherapy by vinblastine had a significant effect only in patients with a poor histological type. Moreover, an aggressive treatment carried out after relapse rescued a large proportion of patients. Since a 10 yr survival rate of about 80% (Fig. 7) was obtained for patients

with NS or LP types treated initially only by radiotherapy, the protocol of the subsequent used chemotherapy only for patients with MC or LD types.

3. Because chemotherapy with one drug, vinblastine, decreased the incidence of relapse in patients with a poor prognosis but was not efficient enough to significantly improve the survival rate, polychemotherapy seems preferable and has been used since the end of 1976.

Could staging laparotomy as introduced by the Stanford group [11] provide guidance for treatment and help to identify a group of patients for whom a minimal treatment would be sufficient? In order to answer this question whose importance was obvious at the end of this trial, another controlled clinical trial (H_2) was carried out by the radiotherapy-chemotherapy group of E.O.R.T.C. from 1971 to 1976. The protocol was the following: all patients with Hodgkin's disease, clinical stages I and II located above the diaphragm, were randomized between either staging laparotomy and splenectomy or no laparotomy. After laparotomy and whatever the results of the pathological study of the spleen and of the biopsy of the para-aortic lymph nodes, an irradiation of the para-aortic lymph nodes was carried out. For those patients without laparotomy, an irradiation of the spleen was also performed. For those patients with mixed cellularity or lymphoid depletion histologic types, chemotherapy was performed systematically whatever the results of the staging laparotomy. This trial had 2 aims: first, to compare splenectomy and splenic irradiation and second, to assess the prognostic significance of the information provided by laparotomy. This is why, in order to get clear answers, all patients received the same treatment without taking into account the results of the splenectomy and of the para-aortic lymph node biopsy. Three hundred and ten patients were included in this co-operative trial and only one patient had a different treatment protocol because the liver biopsy was positive.

The preliminary results of the trial are under analysis and we shall only briefly summarize them. There is no difference in the survival rate or incidence of relapse between the 2 groups: for the patients with a follow-up of 2–6 yr, 7 deaths and 32 relapses out of 110 patients with laparotomy; 9 deaths and 37 relapses out of 111 patients without laparotomy. It should be stressed that for both criteria (relapse-free and survival), splenectomy and spleen irradiation appear to be therapeutically equivalent. Radiotherapy of the spleen causes an irradiation of the upper part of the left kidney. A prospective study carried out at Villejuif has shown that the lesions were not serious and did not influence the overall kidney function [12].

The preliminary data of this trial show that the proportion of relapses and deaths observed in patients with poor prognostic indicators is not, at 4 yr, significantly greater than in patients with good prognostic indicators, conversely to what had been observed in the former H_1 trial. However, the incidence of relapse was smaller in patients with MC+LD histological type than in those patients with NS+LP type with an indicator of poor prognosis (such as age or systemic symptoms) who in this protocol did not receive adjuvant chemotherapy. This observation suggests that they would have benefited from it.

In the laparotomy group, it is interesting to compare patients with or without spleen involvement. Of the 76 patients without spleen involvement, 8 recurrences were located in irradiated areas, one in a non-irradiated lymphatic area and 6 were extra nodal extensions. Of the 34 patients with spleen involvement, the incidence of recurrence in an irradiated area was comparable (5 patients), but the extensions in non irradiated lymphatic area were more numerous (5 patients) and the incidence of extra nodal relapses was slightly increased (6 patients). These data show that spleen involvement has a significant independant prognostic value. They suggest that it is mainly an indicator of lymphatic spread.

On the basis of the data of these two trials, a new trial has been designed whose aim is to better delineate the groups with a favourable or unfavourable prognosis among patients in clinical stages I and II of Hodgkin's disease. In the first group are included the patients with all the following requirements: below 40 yr of age, good histologic subgrouping (LP or NS), ESR below 70 mm/hr and clinical stage I or for clinical stage II, pattern of presentation with mediastinal involvement. All these patients are submitted to diagnostic laparotomy. They remain in the good group only if no involvement of the spleen and/or the para-aortic node is found during laparotomy.

Laparotomy is not performed for the other patients for whom more extensive treatment seems to be required anyway. Hence in this new trial, laparotomy helps select a group of patients with a good prognosis and for whom

a minimal treatment might be sufficient. The other patients are treated by a multiple course of polychemotherapy and/or extended irradiation. It is hoped that this trial will further demonstrate the possibility of avoiding chemotherapy and/or irradiation of the pelvis in half of the young patients. This would significantly reduce damage to the gonads and decrease the genetic burden and the risk of secondary cancer [10].

CONCLUSION

In conclusion, this trial has shown that long term monochemotherapy is able to sterilize occult disease in lymph nodes, in particular para-aortic lymph nodes. However, chances of survival are not significantly improved by adjuvant chemotherapy.

The statistical analysis of these results has helped to distinguish two groups of patients. For those patients with good prognostic indicators, a limited radiotherapy can achieve a high survival rate and thus adjuvant chemotherapy does not appear to be deserved. On the other hand, extensive radiotherapy and/or polychemotherapy appear to be mandatory for patients with one (or many) poor prognostic indicator.

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