Europ. J. Cancer Vol. 17, pp. 355–363

0014-2964/81/030355-09 $02.00/0

Five-Year Results of the E.O.R.T.C. Randomized Study of Splenectomy and Spleen Irradiation in Clinical Stages I and II of Hodgkin's Disease

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Abstract—*A controlled clinical trial was carried out on patients with clinical stages* I *and* II *of Hodgkin's disease by the E.O.R.T.C. from* 1972 *to* 1976. *Three hundred patients with supradiaphragmatic presentation were assigned at random into two groups, one treated by spleen irradiation, the other by splenectomy. All patients received a mantle field irradiation as well as a para-aortic lymph node irradiation. The actuarial survival rates and relapse-free survival rates at five years were, respectively,* 90 *and* 62% *in the group treated by spleen irradiation and* 90 *and* 67% *in the group splenectomized. The efficiency of the two treatments is therefore identical. In the group submitted to staging laparotomy, all patients received the same treatment without taking into account the results of the splenectomy and of the lymph node biopsy. Of* 107 *patients without spleen or lymph node involvement* 18 *relapsed* (17%); *of* 33 *patients with spleen involvement* 14 *relapsed* (42%). *Relapse in non-irradiated lymph node territories (iliac and inguinal areas) were fifteen-fold more frequent in patients with spleen involvement, whereas extra nodal relapses were about twice as frequent in patients with spleen involvement than in patients without spleen involvement. Patients with mixed cellularity or lymphoid depletion histological types received long term adjuvant chemotherapy either by Vinblastine + Procarbazine or by Vinblastine alone. The* 5*-year relapse rate was* 12% *with both chemotherapeutic regimens.*

INTRODUCTION

FROM 1964 to 1970 the radiotherapy–chemotherapy group of the E.O.R.T.C.** carried out a controlled clinical trial (H_1) on clinical stages (CS) I and II of Hodgkin's disease in order to assess the efficacy of long term adjuvant chemotherapy by weekly injection of Vinblastine after extended radiotherapy delivered to the areas of demonstrable disease as well as to the other lymphatic areas located on the same side of the diaphragm. No irradiation was carried out on the other side of the diaphragm. The results obtained have been published [1]; they demonstrated the usefulness of chemotherapy in some groups of patients but not in all. Furthermore, a high incidence of relapses in non-irradiated lymph node areas was observed, notably in the para-aortic lymph nodes and in the spleen for patients with supradiaphragmatic presentation.

In 1971, on the basis of the preliminary results of this H_1 trial, a second clinical trial (H_2) was designed in which all the previously untreated patients with CS I + II, supradiaphragmatic presentation, received a mantle field irradiation as well as para-aortic lymph node

Accepted 22 August 1980.

**The chairmen of this cooperative group were M. Tubiana (1964–1967). K. Breur (1967–1969), B. van der Werf-Messing (1969–1972), J. Henry (1973–1975), J. Abbatucci (1975–1977), M. Burgers (1977–1980). M. Hayat (1980). The statisticians were M. Hayat and M. Henry-Amar. The sponsors are M. Tubiana and K. Breur.

irradiation. The aim of this H_2 trial was: (a) to compare the therapeutic efficiency of spleen irradiation and of splenectomy, (b) to assess the prognostic significance of the information provided by laparotomy [2]: in order to achieve this goal all patients received the same treatment without taking into account the results of the splenectomy and of the para-aortic lymph node biopsy, except for liver involvement; and (c) to compare for these patients with poor histological subtypes—mixed cellularity (MC) and lymphoid depletion (LD)—the effectiveness of two types of long term chemotherapy: either Vinblastine (VLB) alone or Vinblastine + Procarbazine (PCZ).

This H_2 trial was carried out from 1972 to 1976. The preliminary data have been briefly reported [1] and the aim of this paper is to analyse the results obtained by March 1980, at a time at which the follow-up was longer than 5 years for more than half of the 300 patients included in the trial.

MATERIALS AND METHODS

Prior to randomization, the work-up of patients with supradiaphragmatic disease (CS I+II) included: a complete clinical examination, chest X-ray and, when relevant, tomography of the mediastinum, a bi-pedal ilio-lumbar lymphangiogram, an ESR assay, a bone marrow biopsy and a spleen scan. All patients had a lymph node biopsy to establish the diagnosis.

Patients who, after completion of the work-up, were staged in clinical stages I or II, were assigned at random to two groups: spleen irradiation or staging laparotomy and splenectomy. After laparotomy those patients in pathological stage (P.S.) IV were treated by chemotherapy; in fact only one patient was found to be P.S. IV (liver involvement).

Both groups of patients were treated by mantle field irradiation (4000 rads in 4 weeks plus a booster of 500 rads on areas with slowly regressing bulky mass). Some centers used a ^{60}Co teletherapy unit, others a linear accelerator. Two to four weeks after completion of this irradiation, 4000 rads in 4 weeks were delivered to the para-aortic lymph nodes by an anterior and a posterior field.

For those patients assigned to the spleen irradiation group, the same radiation field comprised both the para-aortic area, the spleen and the spleen hilar nodes. The delineation of the spleen field was helped by the use of a spleen scintigram and/or a spleen X-ray.

Those patients with mixed cellularity (MC) or lymphoid depletion (LD) histological subgroups subsequently received adjuvant chemotherapy. Patients in complete remission and with a blood count enabling them to withstand chemotherapy were randomised into 2 groups which received chemotherapy for 2 years according to the following protocols:

Group H2 C1: Vinblastine each week: 3 mg/m^2 if the WBC is between 2000 and 4000 per μl; 6 mg/m^2 if the WBC is superior to 4000; no VLB if the WBC is inferior to 2000 and wait one week more. Total duration: two years (same as in H_1 protocol).

Group H2 C2: Vinblastine (VLB) for three months as Group 1. Gap of 4 weeks or 1, 2 weeks more if necessary.

Procarbazine (PCZ): 150 mg/m^2/day for 3 weeks if the WBC is superior to 4000 and platelets superior to 150,000 per μl; half dosage when the WBC is between 2000 and 4000 and platelets between 80,000 and 150,000.

PCZ was stopped if the WBC was inferior to 2000 or platelets inferior to 80,000.

After a gap of 4 weeks, or more when necessary, VLB was given again during 3 months and so on during 2 years.

This inclusion in the group receiving chemotherapy was based on the reading of the histologic slides by each cooperating center's histopathology department. Subsequently the slides of all the patients included in the trial were collected and reviewed by the histology review committee (Van Unnik, R. Gérard-Marchant). The present report is based on the data of the histology review committee.

Out of the 310 patients included in the trial, 10 (3%) were excluded as the diagnosis of the review committee was not Hodgkin's disease. Breakdown of the patients for each center and according to the treatment is given in Table 1.* Out of the 300 patients 284 have

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Table 1. Number of patients included in the trial by each cooperating center

	Spleen irradiation			Laparotomy + splenectomy			
	No chemo.	VLB	VLB+PCZ	No chemo.	VLB	VLB+PCZ	Total
Bruxelles	4	2	1	3	—	1	11
Florence	6	1	1	6	—	1	15
Reims	4	—	1	3	2	1	11
Caen	3	—	—	3	1	—	7
Villejuif	31	5	7	26	8	5	82
Nijmegen	5	2	1	6	1	2	17
Rotterdam	29	15	2	23	2	13	84
Amsterdam	23	4	5	20	6	6	64
The Hague	3	—	1	4	—	1	9
Total	108	29	19	94	20	30	300

been read by the review committee, and 194 have been subclassified as lymphoid predominance (LP) or nodular sclerosis (NS). Of them, 37 (19%) had been initially classified MC or LD by the center's histologist and had therefore received chemotherapy.

Ninety patients have been classified MC or LD by the review committee. Of them 31 (34%) had been initially classified LP or NS and had not received adjuvant chemotherapy.

All lymphograms were read by a radiological review committee.* About 2% of the lymphograms were considered as probably involved (1%) or doubtful (1%) by the review committee. In view of this small percentage, those patients were not excluded.

All patients included in the trial were examined at 6 months interval at the treating center. An ESR assay and a chest X-ray were routinely performed. Information was sent to the statistical office. The protocol did not envisage the therapy policy of the relapses and when a relapse was observed the further treatment was left to the decision of the center's physicians.

*The members of the lymphography review committee were R. W. Kropholler, P. Markovits, J. L. Chassard. Feremans and C. Lameer.

Analysis of the data. Survival curves were calculated according to the actuarial method. The Logrank test was used to assess the statistical significance of differences in survival and in disease-free survival.

RESULTS

Comparability of patients

The comparability of the patients included in the two arms of the protocol was studied and no difference between the two groups was observed. Although the difference by sex in the two treatment groups (Table 2) is not statistically significant, a slight imbalance does exist. Hence the influence of sex as a prognostic factor was studied and found to be without significance. The distribution according to age and histological subtypes (Table 3) in the two therapeutic groups (splenectomy or spleen irradiation) are similar.

Table 2. Age and sex distribution for the patients treated by spleen irradiation or by splenectomy

	Age				Sex		
	<15 years	[15–30]	[30–40]	≥40 Y	M	F	
Spleen irradiation	10 (7%)	76 (49%)	35 (22%)	35 (22%)	81 (52%)	75 (48%)	156
Splenectomy	12 (8%)	69 (48%)	26 (18%)	37 (26%)	88 (61%)	56 (39%)	144
Total	22	145	61	72	169	131	300

Also the incidence of mediastinal involvement, systemic symptoms or increased ESR do not differ between the two groups. In males the mean age in the spleen irradiation group and the splenectomy group were 30.9 ± 11.8 and 31.2 ± 12.1 years, respectively. In females they were 31.3 ± 12.9 and 32.2 ± 15.1 years, respectively.

Table 3. Histological types of the patients treated by spleen irradiation or by splenectomy

	LP	NS	MC	LD	
Spleen irradiation	3 (2%)	95 (66%)	45 (31%)	1 (1%)	144
Splenectomy	10 (7%)	86 (61%)	42 (30%)	2 (2%)	140
Total	13	181	87	3	284

Table 4. Correlation between sex and histologic type for the patients included in the trial whose slides were reviewed in 1979 by the histology review committee

	LP–NS	MC–LD	
M	95 (58%)	69 (42%)	164
F	99 (83%)	21 (17%)	120
Total	194	90	284

$P<0.001$.

Table 4 shows that, as in most other series, sex and histologic types were correlated. There was also a very strong correlation between systemic symptoms and ESR (Table 5). Table 6 shows the distribution of histological subtypes in the various stages and presentation patterns. In CS II without mediastinal involvement the ESR was higher in the NS subtype than in the MC subtype but the difference is not statistically significant ($P=0.19$). The NS subtype had the highest incidence of mediastinal involvement.

Tolerance to treatment

Radiotherapy delivering the protocol doses has been well tolerated. No immediate complications have been observed. One death attributed to radiation pneumonitis occurred 2 years after completion of radiotherapy. One post-operative death after laparatomy with splenectomy was observed. Both VLB and VLB+PCZ chemotherapy have been well tolerated.

Table 5. Correlation between systemic symptoms and erythrocyte sedimentation rate prior to treatment

		ESR < 30	30 ⩽ ESR < 70	70 ⩽ ESR	Total	Mean ESR ± S.D.
Systemic symptoms	A	136 (58%)	78 (34%)	18 (8%)	232	28.9 ± 24.8
	B	12 (19%)	27 (43%)	24 (38%)	63	58.3 ± 33.9
Total		148	105	42	295*	$P<0.001$

χ^2, $P<0.001$.

*ESR not assayed: 5 patients.

Table 6. ESR and histological type of the various subgroups of patients with or without initial mediastinal involvement

			LP	NS	MC	LD	Total
CS I	Mediastinum 0	ESR < 70	10 (10%)	39 (40%)	47 (49%)	1 (1%)	97
		ESR ⩾ 70	0	3	0	0	3
	Mediastinum +	ESR < 70	0	6	0	0	6
		ESR ⩾ 70	0	0	0	0	0
CS II	Mediastinum 0	ESR < 70	2 (3%)	41 (56%)	29 (40%)	1 (1%)	73
		ESR ⩾ 70	0	10 (83%)	2 (17%)	0	12
	Mediastinum +	ESR < 70	1 (2%)	58 (91%)	5 (8%)	0	64
		ESR ⩾ 70	0	21 (84%)	3 (12%)	1 (4%)	25

Comparative results of spleen irradiation and splenectomy

Out of 156 patients treated by spleen irradiation, 44 relapses (28%) were observed, vs 33 relapses out of 144 patients treated by splenectomy (23%). The difference is not siginificant (Table 8).

The actuarial survival and relapse-free survival rates at five years were, respectively, 90 and 68% in the group treated by spleen irradiation and 88 and 74% in the group splenectomized. The efficiency of the two treatments is therefore identical (Fig. 1).

The various types of relapses are described in Table 7. Sixteen deaths were recorded in the spleen irradiation group, 12 due to Hodgkin's disease and 4 to intercurrent disease. In the splenectomy group, 15 deaths were observed (9 due to the disease or to its treatment complication, and 6 to ID). The causes of death are given in Table 8.

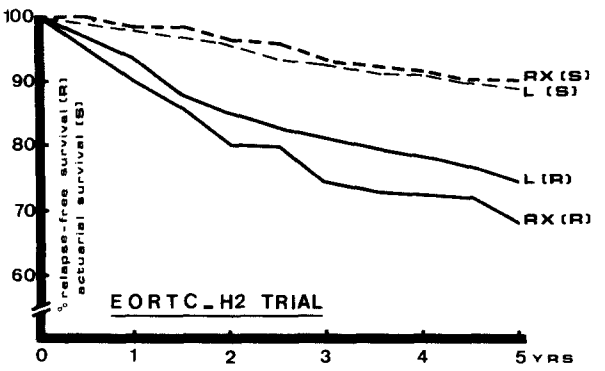

Fig. 1. Actuarial survival (S) and relapse-free survival rate (R) for patients treated either by splenic irradiation(RX) or by laparotomy + splenectomy (L).

Table 7. Results of the trial. Comparison of the two therapeutic groups

	Spleen irradiation	Lap. + splenectomy	Total
Patients at risk	156	144	300
Recurrence in irradiated areas	15 (10%)	13 (9%)	28 (9%)
Relapse in non-irradiated lymphatic areas	10 (6%)	6 (4%)	16 (5%)
Extra nodal relapse	19 (12%)	14 (10%)	33 (11%)
Total	44 (28%)	33 (23%)	77 (25%)
	NS ⟷		
Number of deceased patients	16 (12+4 ID)	15 (9+6 ID)	31

Table 8. Causes of deaths in the two therapeutic groups

	Spleen irradiation			Laparotomy + splenectomy			
	No chemo.	VLB	VLB+PCZ	No chemo.	VLB	VLB+PCZ	Total
Patients at risk	108	29	19	94	20	30	300
Number of relapses	38 (35%)	4 (14%)	2 (11%)	27 (29%)	2 (10%)	4 (13%)	77 (26%)
Death following relapse	10	1	1	6	—	1	19
Deaths for patients in C.R.							
Myocardial infarct.	—	—	—	2	1	1	4
Post-operative	—	—	—	1	—	—	1
Treatment complications	—	—	—	1	—	—	1
Intercurrent disease	1	1	—	1	—	—	3
Unknown	1	1	—	—	1	—	3
Total of deaths	12 (9%)	3 (10%)	1 (3%)	11 (12%)	2 (10%)	2 (7%)	31 (10%)

Results of laparotomy

Staging laparotomy and splenectomy were performed on 144 patients. Of them, 106 were PS I+II and 37 PS III: 16 spleen involvement without lymph nodes involvement, 17 spleen and para-aortic lymph nodes involvement and 4 para-aortic lymph nodes involvement without spleen involvement. Liver involvement was observed in one patient (PS IV).

The incidence of relapse is significantly higher ($P<0.01$) in the patients with spleen involvement: 14 out of 33 patients (42%) versus 18 out of 106 patients without spleen involvement (17%). The type of relapse is given in Table 9. Relapse in unirradiated lymph node territories (iliac and inguinal areas) occurred very seldom in patients without spleen involvement (1 out of 106 patients); its incidence was much greater (more than fifteen-fold) in patients with spleen involvement. Extra nodal relapses were about twice as frequent in patients with spleen involvement than in patients without spleen involvement (6 out of 33 patients versus 8 out of 106).

The time interval between treatment and first relapse was similar in PS I+II and in PS III patients, except for relapse in unirradiated lymph nodes areas. For the latter types of relapse the time interval was only of 9.8±6 months which suggests that the occult disease in iliac or inguinal nodes, although not detected on lymphangiogram and during laparotomy, was already of a fairly large size. The time interval between treatment and relapse in the iliac area was 37 months for the one patient with PS II disease in whom such a relapse occurred (Table 9).

Comparsion of the two chemotherapy regimens

Ninety-eight patients were assigned by a second randomization to chemotherapy either by VLB (49 patients) or by VLB+PCZ (49 patients). No significant difference was observed between the two groups regarding either the relapse incidence, 6 (12%) and 5 (12%), respectively, or the number of deaths, 5 (10%) and 3 (6%), respectively. However, the number of deaths due to intercurrent disease is slightly higher in the VLB group, 4 versus 1 in the PCZ group. The data are presented in Table 8.

Figure 3 shows a relatively high relapse-free survival rate for patients with MC histology indicating the efficacy of the adjuvant chemotherapy given to this group. The incidence of relapses is higher in patients with NS histology who did not receive chemotherapy. However, the survival rates are identical for the three histological groups (Fig. 3).

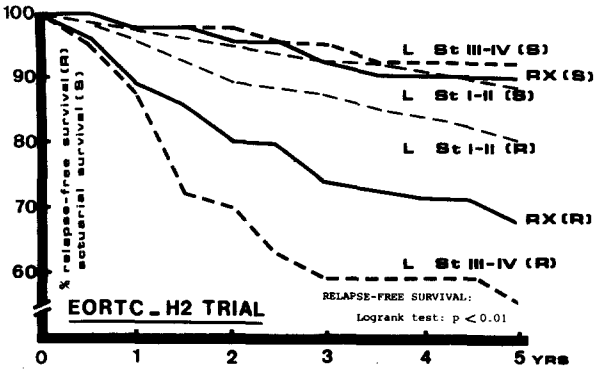

Fig. 2. Actuarial survival (S) and relapse-free survival (R) for patients treated by splenic irradiation (RX) or submitted to laparotomy (L). In the latter group the relapse rate is much higher in the patients with spleen or para-aortic lymph node or liver involvement (P.S. III or IV) than in patients without infradiaphragmatic involvement. However, the survivals are identical in the three subgroups.

Table 9. Prognostic significance of laparotomy findings

	Path. stage I+II	Pathological stage III		
		Total	N+	S+ or N+S+
Patients at risk	106	37	4	33
Recurrence in irradiated area	9 (8%)	4 (10%)	1	3
Relapse in non-irradiated lymph node areas	1 (1%)	5 (13%)	0	5 (15%)
Time interval treatment–relapse	37 mo.	9.8±6.1 mo. range 4–19 mo.		
Extra-nodal relapses	8 (7%)	6 (16%)	0	6 (18%)
Time interval treatment–relapse	22.0±18.6 mo. range 6–60	19.7±10.8 mo. range 5–32		
	S $P<0.01$			
Total relapses	18 (17%) ⟷	15 (39%)	1	14 (42%)
Deaths	11 (10%)	4 (10%)	0	4

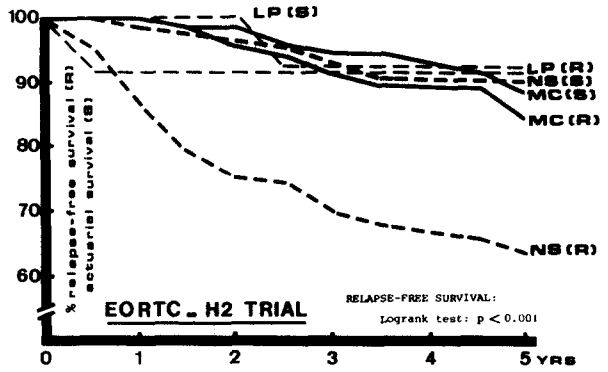

Fig. 3. Actuarial survival (S) or relapse-free survival (R) in the three histological types. The relapse rate is higher in the nodular sclerosis (NS) type. This is due to the fact that patients with NS or LP histological type did not receive adjuvant chemotherapy. However, the survival rates are identical for the three histological subgroups.

Survival rate after relapse

Four years after the occurrence of the relapse the survival rate was about 63% (Fig. 4), only slightly higher than in the relapsed patients of the H_1 trial.

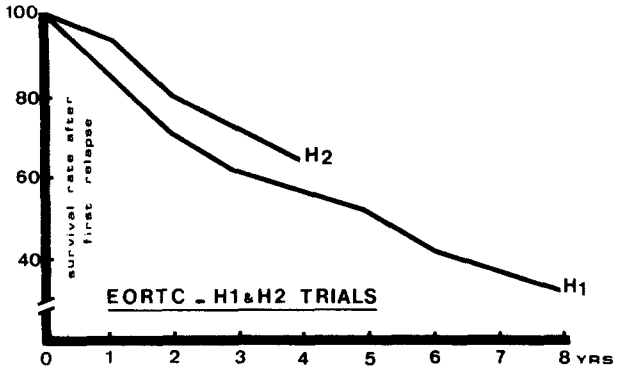

Fig. 4. Survival rates following relapse. No plateau is observed up to five years for the patients included in this trial (H_2). For comparison survival rate after relapse for patients treated from 1964 to 1969 and included in the H_1 E.O.R.T.C. trial.

DISCUSSION

It must be stressed from the onset that the overall results are given for clinical stages (C.S.) and not for pathological stages (P.S.). This is mandatory because we are comparing two groups, one treated by splenic irradiation for which only the clinical stage is available, and the other one for which both C.S. and P.S. are known. Moreover, it should be reminded that the international Ann Arbor staging committee [3] recommended that only C.S. should be used for comparison of various series. Unfortunately this recommendation has often been overlooked, and some papers even mix patients staged with laparotomy (P.S.) and without laparotomy (C.S.) in the same set of data. Such a method can only lead to confusion.

In a previous trial carried out in patients with C.S. I+II Hodgkin's disease, the E.O.R.T.C. H_1 trial, radiotherapy was delivered to the lymphatic areas located on the side of the diaphragm bearing the lesions, and a high incidence of transdiaphragmatic relapses was observed [1]. In order to avoid them, it appeared necessary to treat both the para-aortic lymph nodes and the spleen. The basic idea of the present trial was to compare two modalities of treatment of the spleen: irradiation and splenectomy.

Another aim of the trial was to evaluate the prognostic and therapeutic guidance provided by staging laparotomy which, at the time at which this H_2 trial was initiated, had been recently introduced by the Stanford group [2]. This H_2 trial was therefore designed in order to investigate the significance of laparotomy findings. Let us consider these two points.

Relapse-free survival and survival rates are similar following spleen irradiation or splenectomy. A prospective study carried out at Villejuif [4] showed that spleen irradiation causes some damage to the upper part of the left kidney. But this lesion is well tolerated and has no detectable consequence upon the overall kidney function or the arterial blood pressure even after many years of follow-up.

One post-operative death was observed after splenectomy; nevertheless our data confirm that splenectomy is, by and large, relatively innocuous. However, the number of intercurrent deaths was somewhat higher in the splenectomy group, balancing the number of deaths due to the disease in the irradiated group. Even in 12 children—age ranging from 7 to 15 years—no serious infectious disease was reported following either splenectomy or spleen irradiation. Thus the advantages and drawbacks of the two treatments seem to counterbalance and on the basis of our current data there is no reason to prefer one to the other. However, spleen irradiation should be recommended for patients with a higher surgical risk.

However, our data show that the prognostic information given by the discovery of a spleen involvement is of high significance. In order to ascertain its meaning it was mandatory to deliver an identical treatment whether or not the spleen was involved. This is why in both cases the treatment protocol was the same.

Until now it was often often assumed that spleen involvement was an indicator of blood dissemination and therefore implied a high

risk of extra-nodal occult disease. However, no reliable data has yet been reported because the treatment was more aggressive in cases with spleen involvement. Our data show that in fact this risk is higher, but only twice as great, in patients with spleen involvement than in patients without spleen involvement (Table 9).

But the most interesting and original finding is that spleen involvement is a good indicator of lymphatic spread. In patients with supra-diaphragmatic CS I and II the incidence of relapse in iliac or inguinal node is only 1% for patients without spleen involvement and amounts to 15% in patients with spleen involvement.

Our data show that the prognostic information provided by spleen involvement remains high even in patients who have otherwise good prognostic indicators such as NS histological type, young age, absence of systemic symptoms, etc.

This observation has two clinical implications. The first is that spleen involvement should lead to an aggressive treatment either by chemotherapy or total nodal irradiation. The second is that laparotomy is a useful procedure when one aims at the delineation of a good prognostic group for which the treatment could be minimal. In fact, intensive chemotherapy as well as pelvic irradiation can damage the gonads and cause genetic hazards and staging laparotomy can help to identify a group of patients for whom none of these treatments is necessary.

We have previously reported that the analysis of the H_1 trial [1], and in particular a multivariate study, has shown the existence of a good prognostic group comprising the CS I + II patients with LP or NS histological types, aged between 15 and 40 years, without systemic symptoms or accelerated ESR, and for CS II the patients with mediastinal involvement [1]. For those patients, in the H_1 trial, chemotherapy did not improve the rate of relapse nor the survival. In the H_2 trial only patients with MC + LD histological subtypes received adjuvant chemotherapy, which means that the patients who could have been classified in the poor prognostic group for indicators other than the histological type were treated by radiotherapy alone.

The patients are analysed further in Table 10. Of 163 patients with LP–NS categories and without chemotherapy 58 relapses were recorded (36% of the patients at risk). Out of these 163 patients, 80 had also other good prognostic indicators. Of them 25 relapsed (31%) versus 33 relapses out of 83 patients (40%) with LP–NS histology but poor prognostic indicators. In particular, out of 39 patients with good prognostic indicators who were subjected to laparotomy and treated without chemotherapy, a splenic or a para-aortic involvement was found in 8 patients; of these 5 relapsed (63%), whereas out of the 31

Table 10. *Relapses and deaths in patients who did not receive chemotherapy or who received adjuvant chemotherapy (either VLB or VLB + PCZ)*

		LP–NS	MC–LD	Total
No. chemotherapy		163	26	189
VLB		19 } 31	28 } 64	95
VLB + PCZ		12 }	36 }	
Recurrences in irradiated territory	No chemotherapy	22 (14%)	1	23
	VLB/VLB + PCZ	1	4	5
Relapse in non-irradiated lymph-node areas	No chemotherapy	13 (8%)	—	13
	VLB/VLB + PCZ	1	1	2
Extra-nodal relapse	No chemotherapy	23 (14%)	2	25
	VLB/VLB + PCZ	2	2	4
Total relapses	No chemotherapy	58 (36%) }	3 (12%) } $P<0.02$	61
	VLB/VLB + PCZ	4 (14%) }	7 (12%)	11
Deaths	No chemotherapy	16 (10%)	5 (19%)	21
	VLB/VLB + PCZ	3 (10%)	6 (10%)	9

Table 11. *Percentage of relapses in the two prognostic groups*

Cases with	No chemotherapy	VLB/ VLB+PCZ	
Good prognosis indicators	25/80 (31%)	2/10 (20%)	NS
Poor prognosis indicators	42/120 (35%)	10/88 (11%)	$P<0.001$

patients without infradiaphragmatic involvement only 6 relapsed (19%). These last data confirm the usefulness of laparotomy for the characterization of a good rognostic group for which the treatment may be less aggressive.

It should be underlined that despite these high relapse rates the 5-year survival rate appears to be satisfactory, higher than 85% in all subgroups.

There was a small group of 26 patients with MC–LD histological types originally classified by the treatment center as LP or NS and who did not receive adjuvant chemotherapy. Of these only 12% relapsed.

As compared to those of the H_1 trial, both rate of relapse and survival are significantly improved in this trial and this is mainly due to the treatment of spleen and para-aortic lymph nodes. However, the analysis shows that in the H_2 trial relapse rate is relatively high in both the good and the poor prognostic subgroups which did not receive chemotherapy (Table 9). In both prognostic groups, the incidence of relapse is lower in patients receiving chemotherapy, but the difference is not significant for the patients of the good prognostic group.

Comparison in the laparotomy group of the PS I+II patients and PS III patients shows that most relapses occured in the group with spleen involvement (Table 9). In the group without spleen involvement the rate of relapse is about 17% at 5 years: however, the survival rate is high in both groups which means that the rescue chemotherapy given at the time of relapse achieved a high rate of secondary remission and hopefully of cure.

Acknowledgements—The helpful interest of the physicians of all the cooperating centers is gratefully acknowledged. We wish also to express our thanks to Miss Noëlle Dupouy, data manager, for her technical assistance.

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