Europ. J. Cancer, Vol. 15, pp. 153–161
© Pergamon Press Ltd. 1979. Printed in Great Britain
0014-2964/79/0201-0153 $02.00/0

The Chemotherapy–Radiotherapy Sequence in the Management of Hodgkin's Disease. Results of a Clinical Trial

J. M. ANDRIEU, C. BAYLE-WEISGERBER, M. BOIRON, J. F. BRIERE, Ph. CLOT, M. DANA, Cl. JACQUILLAT, M. KATZ and F. TEILLET

Research Institute for Blood Diseases Hôpital Saint-Louis, Université Paris VII, *France*

Abstract—*One hundred and thirteen patients with clinically supradiaphragmatic Hodgkin's disease were consecutively treated between April* 1972 *and December* 1975 *using a randomized chemotherapy–radiotherapy program* (*H* 72 02). *Both branches of this program had chemotherapy* (*MOPP*) *prior to irradiation; but in the branch* S_1 *laparotomy was performed before chemotherapy and in the branch* S_2, *after chemotherapy. Staging laparotomy* (*trial* S_1) *showed that the rate of initial subdiaphragmatic involvement was around* 45%. *Restaging laparotomy* (*trial* S_2) *performed on patients put into complete remission by* 6 *courses of MOPP therapy showed that* 92% *of the patients were free of subdiaphragmatic involvement. When staging or restaging laparotomy was negative, no subdiaphragmatic irradiation was performed. The rate of survival and disease free survival at* 3 yr *was around* 95%. *This proves that prior chemotherapy is able to sterilize occult subdiaphragmatic involvement of the disease, thereby avoiding in most cases unnecessary subdiaphragmatic irradiation.*

INTRODUCTION

A MAJOR problem in the management of Hodgkin's disease (H.D.) is occult subclinical involvement. This fact was emphasized when initial staging laparotomy became a routine procedure by the high rate of occult subdiaphragmatic (SDG) lymph nodes and spleen involvement [1–4]. Moreover, for patients with H.D., even when apparently confined to lymph nodes, there is a considerable risk of occult visceral involvement, especially when constitutional symptoms are initially present; this is proved by the substantial number of patients who relapsed in extranodal sites after treatment by radiotherapy [5–7]. Since intensive chemotherapy often achieves long term disease-free survival in patients with advanced disease [8, 9], it has seemed reasonable that a combination of radiotherapy and chemotherapy might benefit to most patients in the intermediate or even early stage of the disease. This has been proved by Rosenberg and Kaplan's controlled trial [10]. However, admitting that the combination of chemotherapy and radiotherapy is desirable, two questions arise. Firstly, which of the two therapies must be used first? Preliminary clinical trials (1969–1972) convinced us that initial chemotherapy was more advantageous than initial radiotherapy for the following reasons: (a) both nodal areas and eventual visceral involvement were able to be checked simultaneously; (b) constitutional symptoms were rapidly alleviated; (c) for the majority of patients, apparently complete remission could be obtained after 3–6 courses of chemotherapy [11–13]. The second question is to know whether prior chemotherapy is able to reduce the overall volume of treatment?

In 1972, in order to answer these questions, we designed a randomized clinical trial (H 72 02) for clinically supradiaphragmatic localized H.D. Both branches of the trial included chemotherapy prior to irradiation, but in the branch S_1 laparotomy was undertaken before chemotherapy, and in the branch S_2 after chemotherapy. In both branches, when laparotomy proved that the spleen and para-aortic

Accepted 27 June 1978.
Address for reprints: Dr. Jean-Marie Andrieu, Institut de Recherche sur les Maladies du Sang, Hôpital Saint-Louis, 2, Place du Dr-Fournier 75010-Paris, France.

lymph nodes were free of disease, SDG irradiation was avoided. The aim of this study was to show whether chemotherapy alone was able to cure occult SDG involvement of H.D. This was done by comparing pre- and post-chemotherapy laparotomy findings, and by omitting SDG irradiation once laparotomy had proved that SDG areas were free of histological disease.

MATERIALS AND METHODS

Chemotherapy–radiotherapy programs

From April 1972 to June 1975, 113 consecutive patients with newly diagnosed supradiaphragmatic H.D. were admitted to the Research Institute for Blood Diseases (Saint-Louis Hospital, Paris). Patients were randomized into two study groups. Group S_1 (Fig. 1): patients allocated to this program had a

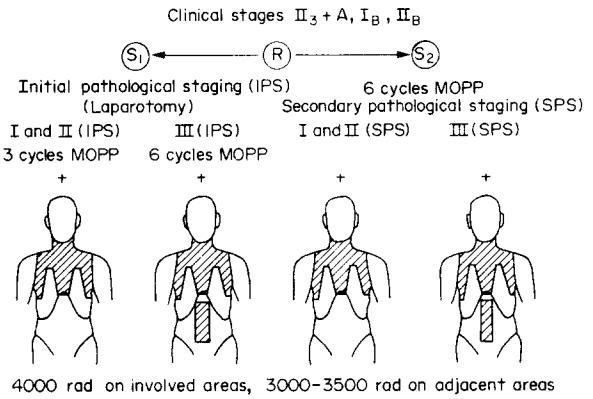

Fig. 1. Schematic representation of clinical H 72 02.

staging laparotomy with a splenectomy. Pathological stages (PS) I or II were assigned to a sub-branch of treatment S_1A: they received 3 monthly courses of combined drug therapy (MOPP, see below), followed 1 month later by supradiaphragmatic irradiation (see below). Patients with stages III (PS) were assigned to the alternative sub-branch, S_1B, consisting of 6 cycles of the same chemotherapeutic association, followed by three monthly injections of vinblastine (6 mg/m^2). Supra- and, after a month of rest, subdiaphragmatic irradiation (see below) were made one month after the completion of the chemotherapy program. Group S_2 (Fig.1): patients assigned to this program initially received 6 chemotherapy courses followed by 3 monthly injections of vinblastine. Two to four weeks later, a laparotomy with splenectomy and biopsy of any palpable lymph nodes was performed for a post-chemotherapy pathological restaging (PRS). Patients without SDG histological involvement were classified as being in stages I or II (PRS) of the disease. They were assigned to the sub-branch S_2A and received supradiaphragmatic irradiation only. Patients who still had SDG involvement were classified in stage III (PRS) and put into the sub-branch S_2B, receiving supra- and subdiaphragmatic irradiation.

Patients' initial evaluation

All patients received a complete physical examination and laboratory work up. The latter included a peripheral blood count, a sedimentation rate, a bone marrow biopsy, and liver and renal function tests. X-ray examinations included chest tomography and bilateral lower limb lymphangiography. For the diagnosis, a lymph node biopsy was performed at the Institute, or the slides were reviewed. The pathological material was classified according to Lukes criteria [14]. Patients were assigned to the study when their initial evaluation indicated supradiaphragmatic clinical stages I B, II B and II_{3+} A according to the Ann Arbor clinical staging classification [15] (II_{3+} means 3 or more nodal areas on the same side of the diaphragm). Included in this study were 4 patients subclassified as "E" because of a single area of extra nodal disease contiguous to an involved lymph node region. Patients below 5 yr and over 65 yr of age were excluded from the study, as well as patients whose initial diagnosis involved thoracotomy and women pregnant at the time of diagnosis.

Chemotherapy

Drugs used were mechlorethamine hydrochloride, vincristine sulfate, procarbazine and prednisone (MOPP). They were administered according to the dosages and schedules described by De Vita *et al.* [16], except for prednisone which was given in cycles, 1, 3 and 5. Patients received 3 or 6 cycles of MOPP, according to the sub-branch to which they had been assigned. After the 6th cycle of MOPP therapy (for patients allocated to a 6 cycles program) patients received 3 monthly courses of vinblastine (6 mg/m^2). Appropriate reductions in drug dosage were made, depending on the peripheral white and platelet counts, on the degree of neurotoxicity and on gastrointestinal reactions. Packed cells were transfused every time hemoglobin concentration was under 8.5 g/dl.

Post-chemotherapy clinical remission status

This was assessed two weeks after the end of the last chemotherapy cycle. Post-chemotherapy complete remission (CTCR) was defined as the absence of all clinical and X-ray evidence of disease. Post-chemotherapy partial remission (CTPR) was defined as the persistence to some extent of clinical or X-ray existence of the disease. Failure was defined by the absence of any noticeable effects of chemotherapy, the increase in the size or number of pathological lymph nodes, or the extension to non lymph nodes areas during chemotherapy. In this case, patients were excluded from the program and allocated to other therapeutic schedules.

Radiotherapy

Supradiaphragmatic irradiation began 1 month after the end of chemotherapy for branch S_1 and 3 weeks after the restaging laparotomy for branch S_2. It was administered with 60 Co teletherapy, by the mantle technique [17]. The initially involved areas received 4000 rad at a dose rate of 1000 rad/week. The adjacent areas received 3000–3500 rad at the same dose rate. A few patients (4/58 in the group S_1 and 3/55 in the group S_2) with upper cervical lymph nodes, and free from mediastinal involvement, received supradiaphragmatic irradiation excluding the mediastinum. SDG irradiation was given only to patients belonging to branches S_1B or S_2B. It was administered, 1 month after completion of supradiaphragmatic irradiation, by an 8 meV linear accelerator to the paraaortic areas, including a splenic pedicle field, but excluding pelvic areas. The dose rate was 1000 rad/week, reaching a total tumor dose of 4000 rad.

Post-treatment status and follow-up

The remission status was reassessed one month after the end of radiotherapy. In cases of post-radiotherapy complete remission (RTCR), no further treatment was given. In partial responders (RTPR) chemotherapy was continued with an association consisting of thiotépa, rufochromomycine, vinblastine, methylhydrazine, prednisone. The follow-up consisted of repeated physical, X-ray, and laboratory examinations every 4 months for the first 2 yr after complete remission and afterwards every 6 months.

Statistical considerations

Actuarial curves of survival and disease free survival were drawn according to Schwartz *et al.* [18].

For all patients entered in the study, survival data were calculated from the date of the patient's first visit to the Research Institute for Blood Diseases. Disease free survival data were calculated from the date of completion of radiotherapy.

RESULTS

Characteristics of the 113 patients beginning therapy are summarized in Table 1.

Table 1. *Patients' characteristics*

		Program S_1	Program S_2
Number of patients		58	55
Clinical Stages	$II_{3+}A$	23	17
	$II_{3+E}A$	2	2
	I B II B	33	35
	II_Eb	—	1
Histology	LP	1	—
	NS	48	43
	ML	7	5
	LD	—	1
	Unclassified	2	6
Sex	Men	30	29
	Women	28	26
Age	Mean	28.4	26.6
	Range	7–49	8–59

Both groups S_1 and S_2 were comparable as to their clinical staging, histological findings, sex and age. Of 58 patients who were randomized in the program S_1, at staging laparotomy, 32 (55%) were free of SDG disease and were assigned to the branch S_1A. One patient died during chemotherapy without evident H.D., 25/32 were in CTCR and 6 in CTPR after 3 chemotherapy cycles. These 31 patients (25 +6) were put under supradiaphragmatic irradiation, after which 29 (25 CTCR and 4 CTPR) were found to be in RTCR, whereas 2 patients in CTPR stayed in RTPR. Out of a total of 32 patients beginning the program S_1A, 29 (91%) were in RTCR. 26/58 patients (45%) of the program S_1 were found to be at stage III PS because of paraaortic and/or spleen involvement, and assigned to program S_1B. After 6 chemotherapy cycles, 16/26 patients (61%) were in CTCR while 7 were in CTPR. Three died during chemotherapy. The 23 patients alive after chemotherapy (16 CTCR +7 CTPR) were allocated to supra-

and subdiaphragmatic irradiation; after irradiation the 16 patients in CTCR were found to be in RTCR, while only 1/7 in CTPR obtained RTCR. Of 26 patients beginning this S_1B program 17 (65%) were in RTCR. 55 patients were randomized to program S_2. After 6 chemotherapy courses, 39 (71%) were in CTCR. Laparotomy performed for pathological restaging (PRS) showed that 36/39 patients were free of SDG histological disease (I or II PRS), and were therefore assigned to S_2A sub-branch. Three out of thirty-nine patients (all with constitutional symptoms) still had spleen or paraaortic nodal involvement (III PRS). They were allocated to S_2B sub-branch. Sixteen out of fifty-five patients were in CTPR, 8 of them were free of SDG disease (I or II PRS), 4 still had SDG involvement (III PRS), and 4 had both SDG and visceral involvement (IV PRS). In this last case, chemotherapy was considered a failure and patients were assigned to other treatment schedules. A total of 51 patients (36 I or II PRS in CTCR, 8 I or II PRS in CTPR, 3 III PRS in CTCR, and 4 III PRS in CTPR) underwent irradiation. After radiotherapy, the 44 patients (36 CTCR +8 CTPR, I or II PRS) assigned to the S_2A sub-branch (supradiaphragmatic irradiation alone), were in RTCR and out of the 7 (3 CTCR, 4 CTPR, III PRS), 4 were in RTCR (3 CTCR +1 CTPR). These results are summarized in Tables 2 and 3.

In the post-chemotherapy complete remission (CTCR) rate, there was no difference between branches S_1 (41/58 = 71%) and S_2 (39/55 = 71%). In the post-radiotherapy complete remission (RTCR) rate there was no statistically significant difference between branches S_1 (46/58 = 79%) and S_2 (48/55 = 87%). Survival and disease free survival curves are shown respectively in Fig. 2 for the S_1A, S_1B and in Fig. 3 for the S_2A and S_2B studies. Figure 4 shows the curves for all patients entered in the study. There were no significant differences either in the rate of survival at 4 yr between group S_1 (93%) and S_2 (96%), or in the disease free survival at 3 yr (S_1 = 97%, S_2 = 99%). Of the patients in RTCR, 3 relapsed, all within 12 months after complete remission. Table 4 synthetizes the duration of each phase of the treatment and the MOPP doses received. Four patients died under chemotherapy (1 of surgical complication during the first course of MOPP; 1 of suspected viral infection after 3 courses of MOPP, 1 of infectious hepatitis during the 6th course of MOPP, and the last of malignant measles after the third course). All these patients belonged to the S_1 treatment group. Apart from these deaths, treatment was easily tolerated. Doses of MOPP therapy were reduced by about a third for 28/113 patients; 17 patients whose hemoglobin was under 8.5 g/dl had to be given transfusions. The total duration of treatment was 5.3 months for the S_1A trial and 15.8 months for the other treatment schedules (S_1B, S_2A, S_2B).

DISCUSSION AND CONCLUSIONS

There have been numerous reports on treatments using chemotherapy–radiotherapy combinations [19–29]. The controlled trial by

Table 2. Post-chemotherapy remission status

Program	Stage	Patients	CTCR*	CTPR†	Death under chemotherapy
S_1A	$II_{3+}A$	14	10	3	1
	I-II B	18	15	3	—
S_1B	III A	11	6	3	2
	III B	15	10	4	1
S_2A	$II_{3+}A$	16	14	2	—
	I-II B	28	22	6	—
S_2B	III A	3	—	3	—
	III B	4	3	1	—
S_2 excluded	IV B	4	—	4	—
Total		113	80	29	4

*CTCR: Post-chemotherapy complete remission.
†CTPR: Post-chemotherapy partial remission.

Table 3. Post-radiotherapy remission status

Program	Stage	Patienrs	RTCR*	RTPR†
S_1A	$II_{3+}A$	14	13	—
	I-II B	18	16	2
S_1B	III A	11	7	2
	III B	15	10	4
S_2A	$II_{3+}A$	16	16	—
	I-II B	28	28	—
S_2B	III A	3	1	2
	III B	4	3	1

*RTCR: Post-radiotherapy complete remission
†RTPR: Post-radiotherapy partial remission.

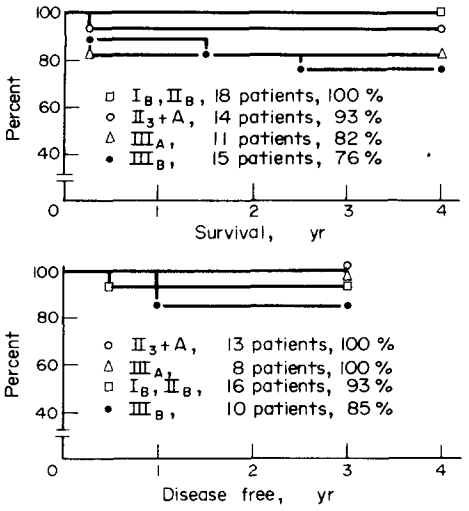

Fig. 2. Results of trial H 72 02 S_1 for stages $II_{3+}A$, I B, II B, III A, III B (PS).

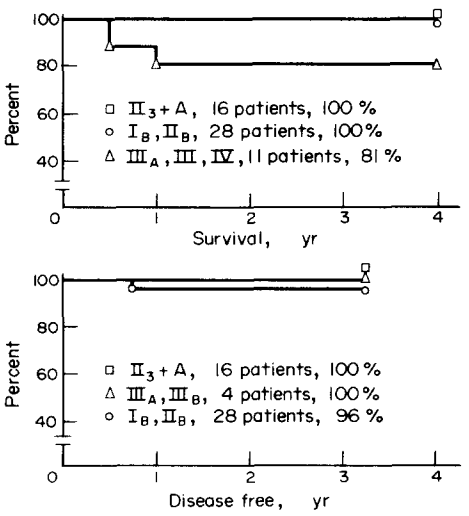

Fig. 3. Results of trial H 72 02 for stages $II_{3+}A$, I B, II B, III A, III B (PRS).

Table 4. Duration and adverse effects of treatment

Program	Patients	CT (months) Range	CT (months) Median	Total dose CT Full	Total dose CT 1/3 Reduced	Death under CT	CT + RT (months) Range	CT + RT (months) Median	Patients transfused
S_1A	32	3–5	3.2	26	6	1	5–7	5.3	3
S_1B	26	8–15	11.6	18	8	3	11–19	16.2	5
S_2A	44	7–13	11.9	33	11	—	12–16	14.1	7
S_2B	7	8–12	10.4	4	3	—	12–20	15.6	2

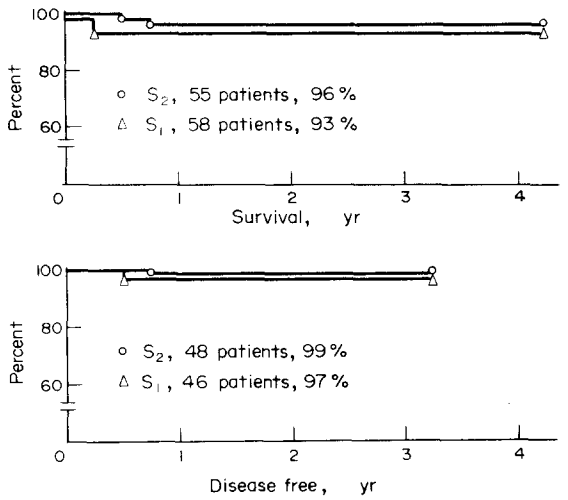

Fig. 4. Survival and disease free survival of all patients of trial H 72 02.

Rosenberg and Kaplan [10], using a 6 cycles MOPP therapy following radiotherapy, has demonstrated the advantages of chemotherapy, by prolonging the radiation induced initial remission of H.D. However, the use of widely spread irradiations and heavy chemotherapy is not without serious iatrogenic disadvantages. Pericardis and lung fibrosis after irradiation are well-known; intestinal complications (subocclusions or occlusions) are liable to follow splenectomy and SDG irradiation. Descriptions have been made of fulminans meningitis and septicemia following splenectomy, especially in children, but also in adults. Moreover, the risk of occurrence of malignant diseases (especially leukemias) well known after irradiation alone and chemotherapy alone, is probably increased when these two therapies are associated.

The clinical trial H 72 02 was designed to observe whether prior chemotherapy was able to sterilize occult SDG involvement, thereby avoiding SDG irradiation. This treatment reduction will entail a possible reduction of iatrogenic complications.

The randomized S_1 branch of treatment was designed (a) to determine the precise percentage of occult SDG involvement in H. D., clinical stages $II_{3+}A$, I B, II B; (b) to establish, in cases of negative laparotomy whether prophylactic lomboaortic irradiation (branch S_1A) could be avoided by prior 3 MOPP therapy. The randomized S_2 branch was planned (a) to correlate the clinical status (CTCR or CTPR) and the histological findings of laparotomy at the end of 6 courses of MOPP; (b) to know, in cases of CTCR and negative laparotomy, whether a long term or definitive sterilization of SDG area could be maintained without the help of SDG irradiation.

Staging laparotomy of the program S_1 showed that 14 of the 25 patients clinically staged as $II_{3+}A$, were free of subdiaphragmatic disease (II A, PS=56%) while 11 had subdiaphragmatic involvement (III A, PS =44%). For the I, II B patients, the proportion of occult subdiaphragmatic involvement was comparable (I, II B PS=18/33 =54.5%, III B, PS=15/33=45.5%).

The study S_1A showed that 3 cycles of MOPP may make SDG irradiation unnecessary. Up to now, the results of this study have not differed from those of the radiotherapy chemotherapy branch of the R_1, K_1, H_2 clinical trials of Rosenberg and Kaplan [10], who used more extended irradiation followed by 6 cycles of MOPP therapy (Fig. 5). The 3 initial cycles of MOPP therapy seemed to abolish the differences between favorable stages A (without systemic

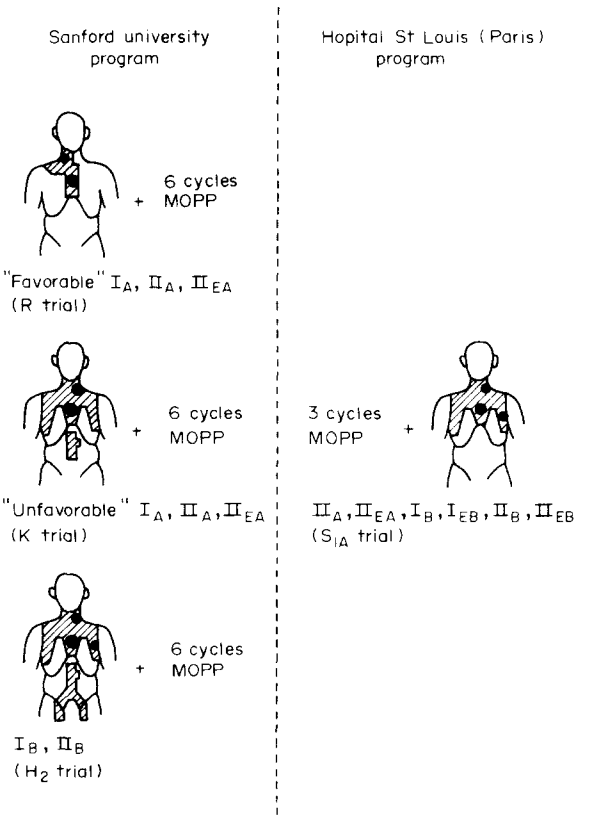

Fig. 5. Schematic representation of Stanford University program (24) and Hôpital Saint-Louis program (trial S_1A) for stages $II_{3+}A$, IIB (PS).

symptoms) and unfavorable stages B (with systemic symptoms). This is shown by the identical percentage of post MOPP complete remissions, (Table 2), the actuarial survival at 4 yr, and the disease-free survival for each

subgroup (Fig. 2). In this group S_1A, 29 patients achieved complete remission, one of them relapsed in extranodal site (lung) after 6 months. For the group S_1B the results were excellent, despite the fact that the prognosis for pathological stages III B is relatively unfavorable. There was no significant difference between stages III A, PS and III B PS for post MOPP complete remission (Table 2), for survival at 4 yr, or for disease-free survival at 3 yr. Moreover, disease-free survivals were not significantly different for subgroups S_1A and S_1B. In the group S_1B, out of the 17 patients in RTCR, one extra nodal (lung) relapse occurred within the first year after RTCR. It must be noted that 4 of the 58 patients randomized into the S_1 program died under chemotherapy from infectious complications. Initial laparotomy may be followed by an immunological break-down which, reinforced by subsequent chemotherapy, may explain these dramatic immunosuppressive complications.

Trial S_2 is of special interest. After chemotherapy, 39/55 patients were in CTCR; in this group, 36/39 patients (92.3%) were found free of SDG disease at restaging laparotomy, while 3/39 still had SDG histological involvement. Table 5 compares, according to initial systemic symptoms, laparotomy findings before chemotherapy (trial S_1) and after CTCR (trial S_2). The percentage of initial SDG involvement is similar for patients "A" and "B" (44.9%), whereas at restaging laparotomy after CTCR, the percentage of SDG involvement is nil for patients staged as "A" (0/14), and 12% for those staged as "B" (3/25). Thus, when chemotherapy is clinically efficient (CTCR), the percentage of SDG sterilization is 100% for "A" patients and 77.9% (54.5–12/54.5) for "B" patients (Table 5).

Table 5. Comparison of laparotomy findings before (trial S_1) and after post chemotherapy complete remission (trial S_2), according to constitutional symptoms

	Staging laparotomy (trial S_1)	Restaging laparotomy after CTCR (trial S_2)	Percentage sterilization by CT of SDG involvement
II A	14/25 (56%)	14/14 (100%)	100%
III A	11/25 (44%)	0/14 (0%)	
I-II B	18/33 (54.5%)	22/25 (88%)	77.9%
III B	15/33 (45.5%)	3/25 (12%)	
II A-II B	32/58 (55.1%)	36/39 (92.3%)	84.9%
III A-III B	26/58 (44.9%)	3/39 (7.7%)	

None of the patients found free of SDG involvement at restaging laparotomy received SDG irradiation. As the 3 relapses occurred in the first year (none of which in this area) we can reasonably conclude that a follow-up of 4 yr can establish that sterilization of SDG area by chemotherapy is probably definitive.

This randomized clinical trial brings out several points: (a) in future, the laparotomy–chemotherapy sequence should be avoided because of major infectious complications, which caused the death of 4 patients; (b) prior chemotherapy, when it entails clinical complete remission, is able to sterilize occult lymph node and splenic involvement in 100% of the "A" patients and around 85% of the "B" patients; (c) this chemotherapy sterilization seems to be definitive; up to the present, no relapse has occurred in the SDG area, either in patients of the S_1 trial (who could be supposed to have a possible infrahistological lymph node involvement) or in patients of the S_2 trial (half of whom initially had occult SDG disease).

In conclusion, the chemotherapy–laparotomy–radiotherapy sequence has proved to be adequate in the treatment of clinically localized supradiaphragmatic H.D. Up to now, the results in terms of survival and disease-free survival are equal if not superior to those obtained with heavier treatment programs [10, 21, 22, 25]. In more than 90% of the patients, post-chemotherapy laparotomy made it possible to suppress SDG irradiation. In the future, it might be possible to avoid laparotomy–splenectomy for all patients without initial constitutional symptoms. Treatment reduced in this way might diminish the risk of iatrogenic complications, without affecting the high rate of cure.

Acknowledgement—We gratefully acknowledge the help of Dr Ann Barrett for reading and correcting the manuscript.

REFERENCES

1. J. L. Amiel, J. Lacour, R. Gérard-Marchant, T. Genin, M. Lemerle, C. Parmentier, M. Schlienger, P. Pouillart, G. Netter, H. Tubiana and G. Mathé, Cent trente-cinq aparotomies et splénectomies pour maladie de Hodgkin. *Bull. Cancer* **58,** 167 (1971).
2. E. Glatstein, S. H. Guernsey, S. A. Rosenberg and H. S. Kaplan, The value of laparotomy and splenectomy in the staging of Hodgkin's disease. *Cancer (Philad.)* **24,** 709 (1969).
3. E. Glatstein, H. W. Trueblood, L. P. Enright, S. A. Rosenberg and H. S. Kaplan, Surgical staging of abdominal involvement in unselected patients with Hodgkin's disease. *Radiology* **97,** 425 (1970).
4. C. Weisgerber, R. Bousquet and F. Teillet, La laparotomie avec splénectomie dans la maladie de Hodgkin. *Nouv. Presse méd.* **4,** 1787 (1978).
5. R. J. Carmel and H. S. Kaplan, Mantle irradiation in Hodgkin's disease. *Cancer (Philad.)* **37,** 2813 (1976).
6. R. E. Johnson, L. B. Thomas and P. Chretien, Correlation between clinicohistologic staging and extranodal relapse in Hodgkin's disease. *Cancer (Philad.)* **25,** 1071 (1970).
7. S. A. Weller, E. Glatstein, H. S. Kaplan and S. A. Rosenberg, Initial relapses in previously treated Hodgkin's disease. *Cancer (Philad.)* **37,** 2840 (1976).
8. E. Frei, J. K. Luce and J. F. Gamble, Combination chemotherapy in advanced Hodgkin's disease. *Ann. int. Med.* **131,** 435 (1973).
9. C. Jacquillat, M. Weil, G. Auclerc, J. P. Desprez-Curely, N. Chelloul, A. Goguel, M. Dana, C. Weisgerber, F. Teillet, V. Izrael, C. Chastang, M. De Heaulme, M. Boiron and J. Bernard, Traitement initial de la maladie de Hodgkin par la polychimiothérapie. *Nouv. Presse méd.* **3,** 2073 (1974).
10. S. A. Rosenberg and A. S. Kaplan, The management of stages I, II and III Hodgkin's disease with combined radiotherapy and chemotherapy. *Cancer (Philad.)* **35,** 55 (1975).
11. V. T. de Vita, A. A. Serpick and P. P. Carbone, Combination drug treatment of Hodgkin's disease. Remission induction, remission duration and survival—an appraisal. *Nat. Cancer Inst. Monogr.* **36,** 373 (1973).
12. J. F. Gamble, L. M. Fuller, E. Ibrahim, J. J. Butler and C. C. Shullenberger, Combined chemotherapy–radiotherapy management of stage III Hodgkin's disease. *Arch. intern. Med.* **131,** 435 (1973).
13. M. R. Moore, S. E. Jones, J. M. Bull, L. A. William and S. A. Rosenberg, MOPP chemotherapy for advanced Hodgkin's disease. Prognostic factors in 81 patients. *Cancer (Philad.)* **32,** 52 (1973).
14. R. J. Lukes, Criteria for involvement of lymph node, bone marrow spleen and liver in Hodgkin's disease. *Cancer Res.* **31,** 1755 (1971).
15. P. P. Carbone, H. S. Kaplan, K. Musshoff, D. W. Smithers and M. Tubiana, Report of the committee on Hodgkin's disease staging classification. *Cancer (Philad.)* **31,** 1860 (1971).
16. V. T. de Vita, A. A. Serpick and P. P. Carbone, Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann. intern. Med.* **73,** 881 (1970).
17. H. S. Kaplan, *Hodgkin's Disease*, Cambridge, Harvard University Press (1972).
18. D. Schwartz, R. Flamant and J. Lellouche, L'Essai Thérapeutique chez l'Homme. Flammarion, Paris (1970).
19. G. Bonnadonna, Clinical trials with intensive chemotherapy and radiotherapy in Hodgkin's disease. *Nat. Cancer Inst. Monogr.* **36,** 403 (1973).
20. B. Hoogstraten, J. F. Holland, S. Kramer and O. J. Glidewell, Combination chemotherapy–radiotherapy for stage III Hodgkin's disease. *Arch. intern. Med.* **131,** 424 (1973).
21. L. E. Kun, V. T. de Vita, R. C. Young and R. E. Johnson, Treatment of Hodgkin's disease using intensive chemotherapy followed by irradiation. *Int. J. Radiat. Oncol. Biol. Phys.* **1,** 619 (1976).
22. R. Goodman, P. Mauch, A. Piro, D. Rosenthal, M. Goldstein, J. Tullis and S. Hellman, Stages II B and III B Hodgkin's disease, results of combined modality treatment. *Cancer (Philad.)* **40,** 84 (1977).

23. M. R. Moore, J. M. Bull, S. E. Jones, S. A. Rosenberg and H. S. Kaplan, Sequential radiotherapy in the treatment of Hodgkin's disease: a progress report. *Ann. intern. Med.* **77,** 1 (1972).
24. J. H. Moxley, V. T. de Vita, K. Brace and E. Frei, Intensive combination chemotherapy and X-irradiation in Hodgkin's disease. *Cancer Res.* **27,** 1258 (1967).
25. M. J. O'Connell, P. H. M. Wiernik, C. B. Kirkland, R. W. Byhardt and W. H. Greene, A combined modality approach to the treatment of Hodgkin's disease. *Cancer (Philad.)* **35,** 1055 (1975).
26. L. R. Prosnitz, L. R. Farber, J. J. Fischer and J. B. Bertino, Low dose radiation therapy and combination chemotherapy in the treatment of advanced Hodgkin's disease. *Radiology* **107,** 187 (1973).
27. K. L. Smith, D. Johnson, O. Hustu, C. Prah, I. Fleming and C. Holton, Concurrent chemotherapy and radiotherapy in the treatment of childhood and adolescent Hodgkin's disease. *Cancer (Philad.)* **33,** 38 (1974).
28. G. Bonadonna, R. Zucali, M. Delena and P. Valagussa, Combined chemotherapy (MOPP or ABVD) -radiotherapy in advanced Hodgkin's disease. *Cancer Treat. Rep.* **61,** 769 (1977).