Acta Radiologica Oncology 19 (1980) Fasc. 3

FROM THE FONDATION BERGONIÉ, CANCER CENTER, F-33076 BORDEAUX, FRANCE.

HODGKIN'S DISEASE, CLINICAL STAGES I AND II

Results of radical irradiation with or without chemotherapy

B. HŒRNI, H. EGHBALI, M. DURAND, A. DE MASCAREL, D. MARÉE, G. HŒRNI-SIMON, P. RICHAUD, J. CHAUVERGNE and C. LAGARDE

The introduction of lymphography in the staging of Hodgkin's disease has individualized stages I and II with lymph node involvement on only one side of the diaphragm. In 1965, the Paris Symposium regulated radical radiation therapy for these stages. Thereafter, patients were submitted to this type of therapy. The results show that about half of the patients were cured. The failures can be attributed to the fact that complete remission had not been induced or that patients had recurrent disease. These failures prompted the Stanford Group to perform exploratory laparotomy with splenectomy in order to obtain a more precise surgical staging and to extend the field of irradiation in certain patients (KADIN et coll. 1971). Nevertheless, even with surgical staging, the percentage of failures after enlarged irradiation remained important. Therefore, it seemed useful to attempt a management associating radiation therapy and adjuvant chemotherapy (ROSENBERG & KAPLAN 1975, ROSENBERG et coll. 1978). The drawback of this solution is that patients with an overall good prognosis are submitted to surgical staging and long heavy treatments which are not without certain complications. The authors are presently attempting to decrease the burden of this medical management, which is not easy, particularly if laparotomy is to be avoided (BERNADOU et coll. 1978, Editorial, Lancet II 1978).

The failures of radical irradiation used alone have prompted also other groups, such as EORTC (1972) and this institute to use adjauvant chemotherapy initially, without surgical staging. Previously, preliminary results have been reported (LAGARDE et coll. 1975), and now the results of 10 years of follow-up are reported.

Material and Methods

Between January 1965 and October 1976, 190 patients with suggested Hodgkin's disease, clinical stages I and II, were treated at this institute. Histologic slides were reviewed in 1976 for all cases and the diagnosis of Hodgkin's disease was confirmed for 177 patients only.

Seven other patients were excluded from the present analysis because they had not been irradiated: 2 were treated before the Symposium of Paris held in February 1965; 4 (between 69 and 85 years) because their general condition was poor due to age or another disease; one refused treatment. Six of these 7 patients died; one is alive and disease-free after secondary irradiation. Thus, 170 patients who had received radical irradiation according to the same procedures during the considered period remain for analysis.

All these patients were seen at this institute at the time of diagnosis or soon after and none had been treated previously. All diagnoses were established by biopsy, and Hodgkin's disease was classified ac-

Submitted for publication 3 September 1979.

Table 1

Main prognostic criteria

	Type of treatment		
	Irradiation alone	Chemotherapy + irradiation	Chemotherapy + irradiation + chemotherapy
Total	42	24	104
Male/female	21/21	13/11	71/33
Age			
<40	27	16	71
40–60	8	2	26
>60	7	6	7
Histologic type			
I	5	5	30
II	20	13	50
III	15	3	23
IV	2	3	1
Clinical stage			
I	9	6	31
II	33	18	73
Mediastinal involvement	12	12	65
Infra-diaphragmatic disease	2	3	8
General symptoms (B)	5	8	26
Extranodal involvement (E)	1	3	11
Tumor diameter > 5 cm	7	10	55
Good prognosis	7	0	31

cording to international nomenclature (LUKES et coll. 1966). All patients underwent clinical radiologic and biologic examinations according to the lines of the Rye Symposium (1966) with chest radiography, tomography of the mediastinum, bilateral lymphography from the foot, and usual hematologic and biochemical blood tests. No surgical staging procedures were performed; diagnostic laparotomy was performed in 3 patients only. All cases were thus classified in a clinical staging; stage I: one area involved, stage II: two or more lymphatic areas involved on only one side of the diaphragm. The main prognostic criteria issued from these pretherapeutic examinations appear in Table 1, along with their distribution following the three treatment regimens. On the whole, 2 groups of patients are distinguished according to the data issued from the EORTC-H1 trial (TUBIANA et coll. 1979): (1) So-called patients with good prognosis fulfilling all the following criteria: less than 40 years old, lymphoid predominance or nodular sclerosis at microscopy, stages I or II with mediastinal involvement, no systemic symptoms (A), no extra-nodal (E) involvement. (2) So-called patients with poor prognosis with one or more of the opposite criteria.

Treatment regimens were as follows. Initially, all patients were treated with radical irradiation only (R). After having observed many early failures with this treatment (1968) it was decided to submit patients with poor prognosis to an initial chemotherapy, followed by the same radical irradiation (C + R). Later on, the treatment was reinforced as follows: patients with particularly poor prognosis (especially those with bulky tumors) were given several courses of chemotherapy before irradiation; secondly, patients in complete remission received one further course of consolidation chemotherapy; lastly, since this sandwich chemotherapy + irradiation + chemotherapy (C + R + C) was well tolerated and gave improved results in patients with poor prognosis, it was decided to submit all patients to this combined therapy (HŒRNI et coll. 1977). All treatments were given in a controlled, but not randomized, manner. The details of the different types of treatment given in each group of patients appear in Table 2.

Table 2

Treatments

	Type of treatment		
	Irradiation alone	Chemotherapy + irradiation	Chemotherapy + irradiation + chemotherapy
Total number of patients	42	24	104
Irradiation			
Localized	5	1	5
Mantle	26	8	9
Mantle+lumbo-aortic	8	12	82
Inverted Y	2	3	8
Splenic	0	0	0
Booster	1	1	3
Chemotherapy			
1 course before irradiation	0	24	93
2–3 courses before irradiation	0	0	5
4–6 courses before irradiation	0	0	6
1 course after irradiation	0	0	100

Table 3

Results

	Type of treatment		
	Irradiation alone	Chemotherapy + irradiation	Chemotherapy + irradiation + chemotherapy
Total number of patients	42	24	104
Initial complete remissions	34	22	100
Initial failures	8	2	4
Relapses*	14	7	5
Irradiated area	1	3	2
Marginal extension	3	1	3
Lymph nodes	9	1	1
Visceral	1	3	2
Persistent complete remissions	20	13	95

* A few patients had two types of relapses.

Almost all patients received irradiation with ^{60}Co at the dose of 35 Gy to 40 Gy in 3.5 to 4 weeks, with a weekly dose of 10 Gy (2 Gy per day × 5 days); 40 Gy were given in the involved regions, 35 Gy in the adjacent areas. Because of 2 cases of myelitis during the first months and years following the treatment, after 1968 the spinal cord was protected with a 1.5 cm wide shield for the posterior field when the dose was higher than 20 Gy. It appears that this shield significantly decreases the dose absorbed by the spinal cord but the dose to the mediastinal lymph nodes is only slightly decreased. However, this decrease has not yet been exactly calculated. Lumbo-aortic regions and mantle fields were more frequently irradiated in the C + R + C regimen (Table 2). Except for 4 elderly patients and one pregnant woman, mantle + lumbo-aortic regions were irradiated at the same time.

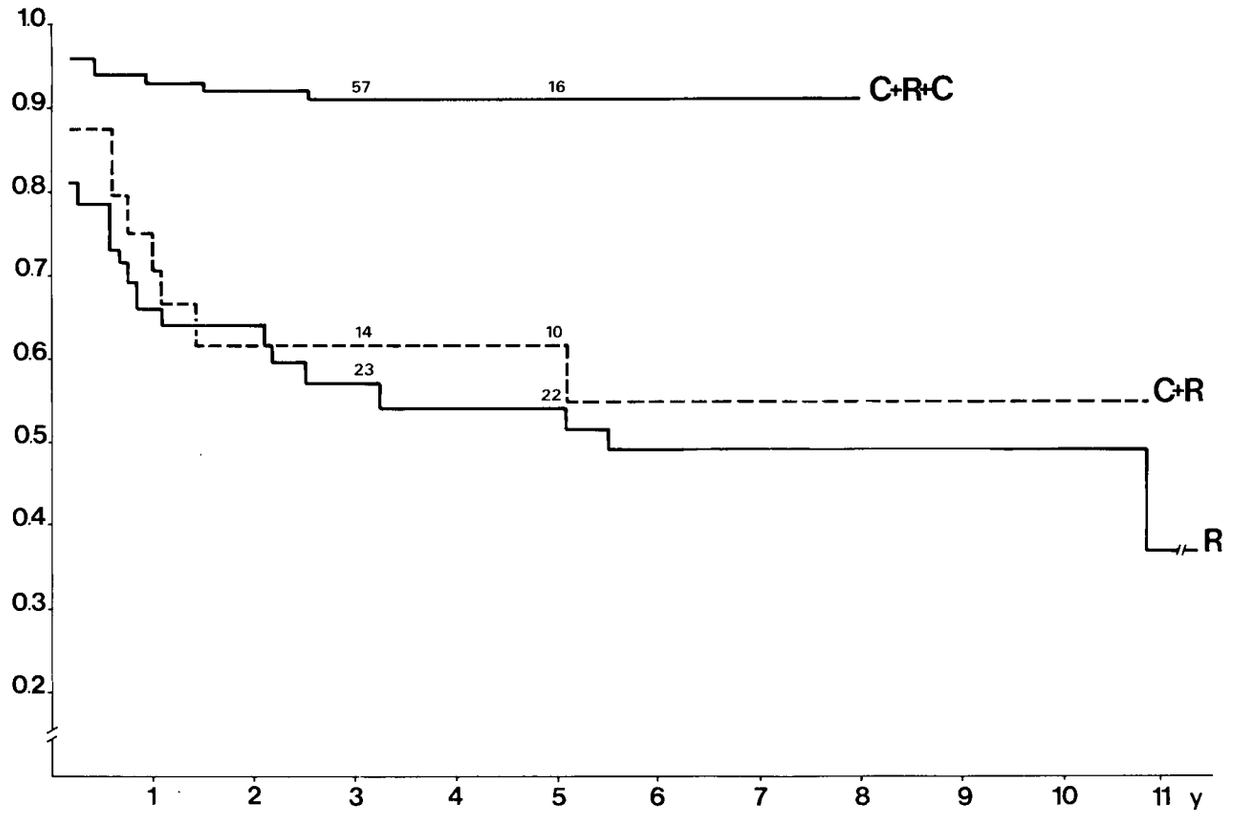

Fig. 1. Actuarial recurrence-free survival (a few patients in complete remission died of intercurrent disease). R = irradiation alone. C + R = chemotherapy + irradiation. C + R + C = chemotherapy + irradiation + chemotherapy.

Chemotherapy was usually an association of cyclophosphamide (200 mg every other day) + vinblastine (10 mg per week) + procarbazine (300 mg per day) + methylprednisolone, given according to a previously published schedule (CHAUVERGNE et coll. 1973); the treatment was discontinued as soon as the patient's leukocyte count dropped to 2×10^9 l usually before the 21st day; thus the treatment was usually shorter for the consolidation course than for the induction course. Most patients submitted to this schedule required hospitalization. Patients with bulky tumors who had received several courses of chemotherapy did not receive the treatment mentioned, which is too poorly tolerated when repeated more than two times; they received the well-known MOPP schedule (DE VITA et coll. 1970).

Radiation therapy was initiated in all patients immediately after the end of the initial 15 to 20 day course of chemotherapy. A rest period of one month was inserted between the end of irradiation and the beginning of the consolidation chemotherapy; the average duration of this rest period was 33 days (for 5 patients chemotherapy could not be repeated until two months later as the leukocyte count was not satisfactory after only a one month rest period).

No maintenance treatment was given after irradiation or consolidation chemotherapy administered as described. Thus the overall treatment was brief: one month when irradiation was given alone (R); 6 to 7 weeks when chemotherapy + irradiation were administered (C + R); about 3 months for patients given chemotherapy + irradiation + chemotherapy (C+R+C).

In case of relapse, patients were restaged and treated according to the best currently available treatment.

Except for one patient who was lost to follow-up, all were followed up until their death or until the first months of 1978. The follow-up period is thus more than one year for all patients. All data were collected during May 1978. They were transcribed on a standard form for each patient. Survivals were calculated according to the actuarial method and significance according to the log-rank test (PETO et

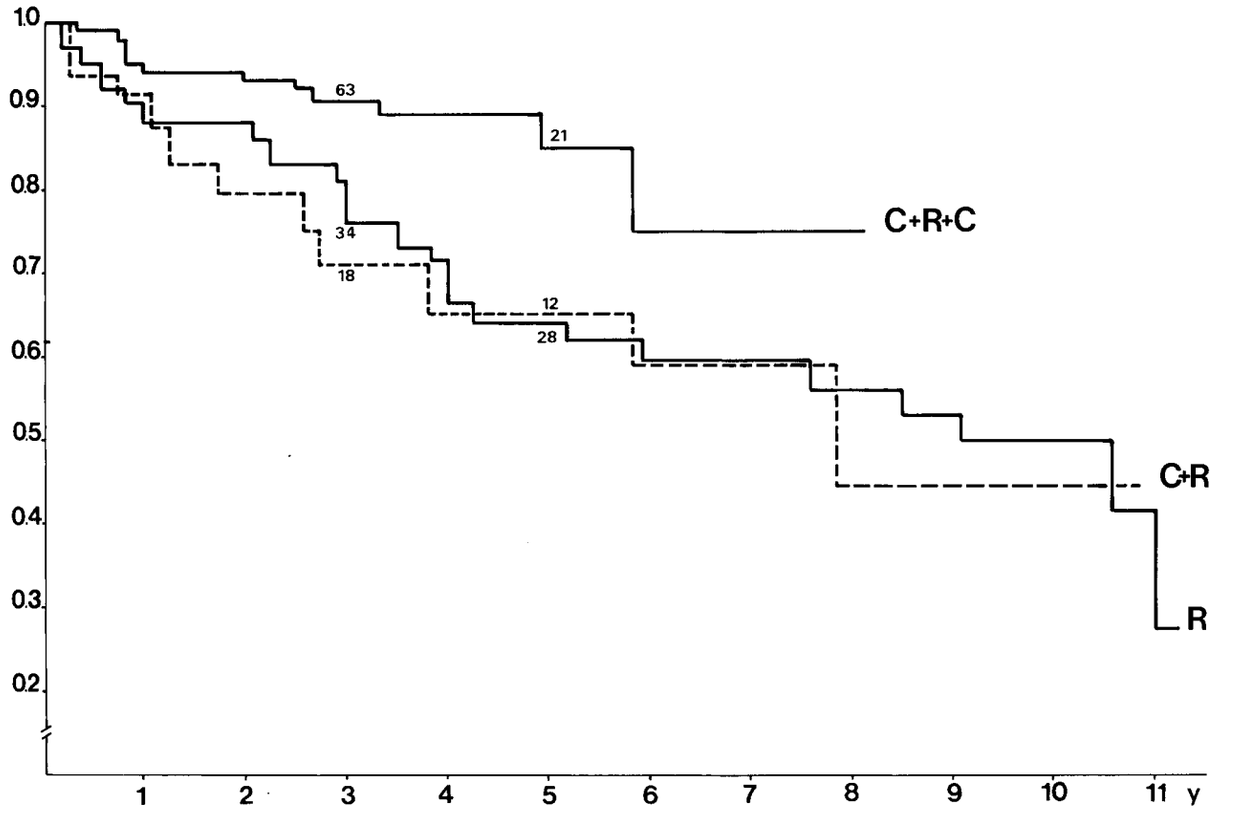

Fig. 2. Actuarial crude survival. Symbols as in Fig. 1.

coll. 1977). Crude survival is considered from the time of diagnosis. Disease-free survival is considered from the last day of radiation therapy.

Results

Complete remission was obtained in 34 of 42 patients given irradiation alone, and in 122 of 128 patients given initial chemotherapy followed by irradiation. This significant difference ($p < 0.01$) appears in Fig. 1, along with the actuarial curve of complete remission or recurrence-free survival (a few patients in complete remission died of intercurrent disease). This figure shows that patients given irradiation alone have a plateau after 6 years (except for one patient who relapsed at 11 years). The disease-free survival of so-called patients with poor prognosis initially given chemotherapy followed by irradiation is quite the same. The curve of patients treated with a sandwich schedule (C + R + C) is very different: no relapse occurred beyond 3 years and 57 patients have exceeded this period; the plateau is above 90 per cent (at 0.9087 exactly); it can thus be expected that 90 per cent of these patients are cured.

The types of relapses are shown in Table 3. All types of relapses are reduced in patients given combined treatments; however, relapses in distant lymph nodes are particularly frequent in patients treated with irradiation alone. The decrease in this latter type of relapse may be due to the fact that the lumbo-aortic area was irradiated more often in the combined regimen. If patients with good prognosis and poor prognosis are considered separately, in the first group 2 failures of 7 R patients occurred and none of the 31 C + R + C patients; in the second group, 21 failures of 35 R patients, 9 failures of 24 C + R patients, and 9 failures of 73 C + R + C patients occurred.

A few patients who did not respond or who relapsed obtained complete remission by another treatment and remained in complete remission with a follow-up of 2 years or more: 4 of 22 failure R patients, 1 of 9 C + R patients and 3 of 9 C + R + C patients. Thus, it appears that it is rare to cure a patient after a primary failure or a relapse.

Table 4

Course and survival

	Type of treatment		
	Irradiation alone	Chemotherapy + irradiation	Chemotherapy + irradiation + chemotherapy
Total number of patients	42	24	104
Total cumulative follow-up (months)	3 139	1 364	4 587
Intercurrent diseases			
Herpes zoster	7	6	21
Other infections	1	1	9
Therapeutic complications	5*	1**	6***
Second malignancy	2	1	6
Hemolytic anemia	1	1	1
Miscellaneous	3	0	7
Normal pregnancies	5	0	4
Deaths			
From Hodgkin's disease	17	6	5
Therapeutic complication	2	1	1
Second malignancy	2	0	4
Other	2	2	2

* 2 myelitis, 3 fibrosis of brachial plexus, 1 hypothyroidism.
** Femoral osteonecrosis.
*** 5 transitory bone marrow aplasia, 1 intestinal complication, 1 pneumothorax.

Survivals appear in Fig. 2. These are uncorrected survivals including all causes of death (which are detailed in Table 4). These results are poorer than those for recurrence-free survivals. About three fourths of the patients (28/40) with primary failures or relapses died; this proportion is slightly lower in patients who had been treated with a combined treatment (11/18) than in those who had been initially treated with irradiation alone (17/22); however, this could be due to a shorter follow-up period for patients given chemotherapy. It is striking that while Hodgkin's disease is the first cause of death in patients given irradiation alone (17/23), it accounts for only 5 of 12 deaths in patients who received sandwich treatment. Among other causes of death, a second malignancy has a prominent place.

No immediate serious complication due to treatment was observed. The detailed hematologic tolerance of the sandwich regimen was presented elsewhere (EGHBALI et coll. 1978). Some severe delayed and eventually lethal complications were observed in the three groups of patients (Table 3). In 2 patients myelitis occurred after irradiation performed without protection of the spinal cord (HENRY et coll. 1971). In the sandwich regimen, 5 patients developed a severe bone marrow aplasia at the end of the last course of chemotherapy, but they recovered without complication (2 of them without antibiotics) within 10 days.

Table 4 shows other pathologic conditions observed in these patients. Herpes zoster was the most frequent infection; however, it was not more frequent in patients given chemotherapy than in patients without chemotherapy (AUBERTIN et coll. 1978). On the contrary, other infections seemed to be more frequent in the third group of patients, but this may be due to a longer period of follow-up; the only infection related to management of Hodgkin's disease was a pneumococcal septicemia supervening in a 15-year-old boy who had undergone laparotomy and splenectomy because of suggested relapse 2 years after initial treatment. Out of the therapeutic complications, 4 were lethal (2 post-irradiation myelitis, 1 bone marrow aplasia following the treatment of a relapse, and the septicemia mentioned). A second malignancy was observed 9 times in 8

Table 5

Nine secondary malignancies

Type of treatment	Type of malignancy	Delay between treatment and second malignancy	Localization in an irradiated region	Sex and age
Irradiation alone	Esophageal carcinoma	9½ years	Yes	F 36
	Esophageal carcinoma	8 years	Yes	M 74
Chemotherapy + irradiation	Skin carcinoma	2½ years	No	F 77
Chemotherapy + irradiation + chemotherapy	Acute myeloblastic leukemia	5½ years	—	M 35
	Laryngeal carcinoma	2 years	No	M 54
	Bronchial carcinoma	3 years	Yes	
	Osteogenic sarcoma	5 years	Yes	M 18
	Ovarian immunoblastosarcoma	8 months	No	F 19
	Bronchial small cell carcinoma	2 years	Yes	M 26

patients: 5 carcinomas seem to be unrelated to treatment: one esophageal in an elderly alcoholic patient; one double (larynx + lung) in a heavy smoker; one skin carcinoma in an elderly patient, and one immuno-blastosarcoma supervening only 8 months after the initial diagnosis of Hodgkin's disease (Table 5). Such secondary non-Hodgkin's lymphomas were recently reported, but always after an interval of over 5 years (KRIKORIAN et coll. 1979). The other malignant tumors may result from the treatment given for Hodgkin's disease: they were more frequent in the third group of patients. Three malignant tumors may be related to the treatment among the 104 C + R + C patients or more accurately among the 95 patients apparently cured from Hodgkin's disease after C + R + C treatment; two of them occurred in an irradiated area (bronchial carcinoma and clavicle osteosarcoma).

Discussion

It is difficult to compare the results obtained with the three therapeutic regimens since they were not randomized. Moreover, patients had been allocated to the second regimen (C + R) because of the presence of poor prognosis criteria. The first group of patients received irradiation alone and the results in this group are comparable to results obtained in other somewhat old series of patients who had been staged only by radiologic and clinical procedures and irradiated in the same manner (EASSON 1966, KAPLAN 1966). It is more difficult to compare the results of the C + R + C regimen with other recent series because most of these series include patients after surgical staging. However, the results obtained with this regimen seem valuable and should thus be considered when the best therapy in a similar type of patients is discussed. Similar results were obtained without laparotomy and extended radiation therapy but only for patients with clinical stage I A and II A (GRIFFIN et coll. 1977), or with a longer period of chemotherapy (ANDRIEU et coll. 1979).

The C + R + C regimen is fairly well tolerated considering it is somewhat heavy. Hospitalization is usually required during chemotherapy, but the overall treatment is quite brief. Large mantle and lumbo-aortic irradiation can be given at the same time, immediately after the first course of chemotherapy, without any major complication. The hematologic effects of this regimen have been detailed elsewhere (EGHBALI et coll.). No deaths directly related to the initial treatment occurred. The only serious complication is second malignancy, observed after association of chemotherapy and irradiation, as noted in other series (ARSENEAU et coll. 1977, BRODY et coll. 1977). In comparison with other series, the overall management is also lightened, since neither surgical staging, nor maintenance chemotherapy are needed. Moreover, the spleens of these patients

were not surgically removed or irradiated and no unfavorable consequences were observed.

Thus it seems difficult to improve the results. About 5 per cent (6/128) of the patients were initially resistant to treatment (both chemotherapy and radiation therapy) and were unable to obtain complete remission. Moreover, 5 per cent of the patients (5/104) relapsed; since relapses are varied, it is difficult to propose any preventive therapeutic measure. Only 4 of 18 patients initially treated by C +R or C+R+C, with initial or secondary failures, had been treated subsequently more heavily and are now without evidence of disease and apparently cured. Therefore, it must be pointed out that these rather good results are obtained with a heavy but brief treatment which does not require surgical staging, removal or irradiation of the spleen, or long-term chemotherapy.

However, second malignancies appear with a low but threatening frequency. Some of them are certainly favored by the association of chemotherapy and irradiation. It is therefore necessary to try to alleviate the therapeutic regimen. It has been suggested that the radiation doses could by reduced; after chemotherapy 15 to 20 Gy might be sufficient (PROSNITZ 1976). The suppression of chemotherapy would be particularly useful in young male patients because this treatment is often responsible for azoospermia (CHAPMAN et coll. 1979). This endeavor is necessary at least in patients with good prognosis. In this latter group no failures occurred in 31 patients given the C + R + C treatment and very few failures in other patients more lightly treated. However, even in this category of patients with good prognosis, the percentage of relapses observed in the H1 trial after radical irradiation with or without vinblastine maintenance chemotherapy was slightly more than 25 per cent (TUBIANA et coll.). There are reasons for reluctance in exposing patients to relapse, since the possibilities of cure after relapse, although not negligible, are small (WELLER et coll. 1976, DE VITA 1977). One way is to submit patients with good prognosis to exploratory laparotomy so that a more accurate prognostic evaluation could be obtained; this is currently being done by the Radiotherapy-Chemotherapy Group of the EORTC. Another way is rather to reduce the irradiated fields; such a randomized trial is now underway in the Pierre-et-Marie-Curie Group in France.

In summary, the results show that it is possible to give these patients a heavy but short treatment without surgical staging and splenectomy or splenic irradiation and without long-term chemotherapy, and to obtain about 90 per cent of cure. However, the treatment is still to be lightened, mainly for patients with good prognosis, in order to reduce the occurrence of complications, mainly second malignancy.

SUMMARY

From 1965 to 1976, 170 patients with Hodgkin's disease, clinical stages I or II, were treated with radical irradiation. A first group of 42 patients was treated with irradiation alone, a second group of 24 patients received one course of chemotherapy followed by irradiation, and a third group of 104 patients was treated with a sandwich regimen including chemotherapy + irradiation + chemotherapy. Although the treatments were not randomized, the comparison of the results shows a striking improvement in the group submitted to the C + R + C regimen: in this group the plateau of disease-free survival was 90 per cent. This result was obtained after treatment for about 3 months without surgical staging or maintenance chemotherapy. However, this treatment may favor some complications, mainly the development of a second malignancy; these risks may be decreased by reducing the treatment in patients with good prognosis.

The article was presented in part at the XVIth Congress of the International Society of Hematology, Paris 1978.

Request for reprints: Professor B. Hœrni, Fondation Bergonié, 180, rue de Saint-Genès, F-33076 Bordeaux Cedex, France.

REFERENCES

ANDRIEU J. M., BAYLE-WEISGERBER C., BOIRON M., BRIÈRE J. F., CLOT P., DANA M., JACQUILLAT C., KATZ M. and TEILLET F.: Chemotherapy-radiotherapy sequence in the management of Hodgkin's disease. Results of a clinical trial. Europ. J. Cancer 15 (1979), 153.

ARSENEAU J. C., CANELLOS G. P., JOHNSON R. and DE VITA V. T.: Risk of new cancers in patients with Hodgkin's disease. Cancer 40 (1977), 1912.

AUBERTIN J., LACUT J. Y., HŒRNI B. and DURAND M.: Opportunistic infections in cancer patients. Vol. 1. Masson, New York 1978.

BERNADOU A., BLANC C. M., JAMES J. M., DAO C., ZITTOUN R. et BILSKI-PASQUIER G.: Maladie de Hodgkin. Valeur des critères dits de prognostic et de l'association radio-chimiothérapique dans les stades lymphoïdes localisés (I et II). 94 malades laparotomisés. Nouv. Presse méd. 7 (1978), 807.

BRODY R. S., SCHOTTENFELD D. and REID A.: Multiple primary cancer risk after therapy for Hodgkin's disease. Cancer 40 (1977), 1917.

CHAPMAN R. M., SUTCLIFFE S. B., REES L. H., EDWARDS

C. R. W. and MALPAS J. S.: Cyclical combination chemotherapy and gonadal function. Retrospective study in males. Lancet I (1979), 285.

CHAUVERGNE J., HŒRNI B., HŒRNI-SIMON G., DURAND M. et LAGARDE C.: *Chimiothérapie de la maladie de* Hodgkin associant procarbazine, vinblastine, cyclophosphamide et méthyl-prednisolone. Analyse d'un série de 124 cures. Z. Krebforsch. 80 (1973), 179.

DE VITA V. T. JR: Hodgkin's disease. The salvage of radiation treatment failures. Int. J. Radiat. Oncol. Biol. Phys. 2 (1977), 1035.

— SERPICK A. A. and CARBONE P. P.: Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann. intern. Med. 73 (1970), 881.

EASSON E. C.: Long-term results of radical radiotherapy in Hodgkin's disease. Cancer Res. 26 (1966), 1244.

Editorial: Staging laparotomy for Hodgkin's disease. Reassessment. Lancet II (1978), 875.

EGHBALI H., HŒRNI-SIMON G., DURAND M., CHAUVERGNE J., TOUCHARD J. and HŒRNI B.: Hodgkin's disease treated by chemotherapy and large field irradiation. Hematologic effects. Acta radiol. Oncology 17 (1978), 289.

EORTC Radiotherapy/Chemotherapy Group: A randomized study of irradiation and vinblastine in stages I and II of Hodgkin's disease. Preliminary results. Europ. J. Cancer 8 (1972), 353.

GRIFFIN T., GERDES A., PARKER R., TAYLOR E., HAFERMAN M., TAYLOR W. and TESH D.: Are pelvic irradiation and routine staging laparotomy necessary in clinically stages I_A and II_A Hodgkin's disease? Cancer 40 (1977), 2914.

HENRY P., CASTAINGS G., HŒRNI B. et TOUCHARD J.: La myélopathie progressive post-radiothérapique tardive. J. Neurol. Sci. 14 (1971), 325.

HŒRNI B., CHAUVERGNE J. and LAGARDE C.: The strategy of treatment of Hodgkin's disease. *In:* Recent result in cancer research, Vol. 62, p. 110. Edited by G. Mathé. Springer, Berlin 1977.

KADIN M. E., GLATSTEIN E. and DORFMAN R. F.: Clinicopathological studies of 117 untreated patients subjected to laparotomy for the staging of Hodgkin's disease. Cancer 27 (1971), 1277.

KAPLAN H. S.: Long-term results of palliative and radical radiotherapy of Hodgkin's disease. Cancer Res. 26 (1966), 1250.

KRIKORIAN J. G., BURKE J. S., ROSENBERG S. A. and KAPLAN H. S.: Occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's disease. New Engl. J. Med. 300 (1979), 452.

LAGARDE C., CHAUVERGNE J., DURAND M., HŒRNI B., HŒRNI-SIMON G. et TOUCHARD J.: Intérêt d'une chimiothérapie complémentaire de la radiothérapie dans les stades I et II de la maladie de Hodgkin. Bull. Cancer 62 (1975), 1.

LUKES R. J., CRAVER L. F., HALL T. C., RAPPAPORT H. and RUBEN P.: Report of the nomenclature committee. Cancer Res. 26 (1966), 1311.

PETO R., PIKE M. C., ARMITAGE P., BRESLOW N. E., COX D. R., HOWARD S. V., MANTEL N., MCPHERSON K., PETO J. and SMITH P. G.: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Brit. J. Cancer 35 (1977), 1.

PROSNITZ L. R.: Radiation doses following intensive chemotherapy in the treatment of Hodgkin's disease. Int. J. Radiat. Oncol. Biol. Phys. 1 (1976), 803.

ROSENBERG R. A. and KAPLAN H. S.: The management of stages I and II of Hodgkin's disease with combined radiotherapy and chemotherapy. Cancer 35 (1975), 55.

— — GLATSTEIN E. J. and PORTLOCK C. S.: Combined modality therapy of Hodgkin's disease. A report on the Stanford trials. Cancer 42 (1978), 991.

Symposium: Obstacles in the control of Hodgkin's disease. Cancer Res. 26 (1966), 1046.

Symposium: La radiothérapie de la maladie de Hodgkin. Nouv. Rev. franç. Hémat. 6 (1966), 1.

TUBIANA M., HENRY-AMAR M., HAYAT M., BREUR K., VAN DER WERE-MESSING B. and BURGES M.: Long-term results of the EORTC randomized study of irradiation and vinblastine in clinical stages I and II of Hodgkin's disease. Europ. J. Cancer 15 (1979), 645.

WELLER S. A., GLATSTEIN E. J., KAPLAN H. S. and ROSENBERG S. A.: Initial relapses in previously treated Hodgkin's disease. I. Results of second treatment. Cancer 37 (1976), 2840.