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Relapse and late complications in early-stage Hodgkin's disease patients with mediastinal involvement treated with radiotherapy alone or plus one cycle of ABVD

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ABSTRACT

Background and Objectives. **Patients affected by Hodgkin's disease (HD) in pathologic stage IA-IIA have a strong possibility of remission and long-term survival when treated with radiotherapy to extended fields. However, 20-30% of cases relapse in the five years following treatment and consequently need further therapy. This study examines the occurrence of relapse and other complications in patients with pathologic stage IIA Hodgkin's disease and mediastinal involvement treated in different ways: radiotherapy alone vs radiotherapy plus one cycle of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD).**

Design and Methods. **Our series consisted of 73 HD patients with mediastinal involvement treated by the Department of Radiation Oncology and the Hematology Department of "La Sapienza" University of Rome from 1983 to 1989. The patients were randomized into two groups according to their initial treatment. The first group contained 37 patients treated, initially, with supradiaphragmatic radiotherapy and para-aortic irradiation (STNI); the second group was made up of 36 patients treated, initially, with supradiaphragmatic radiotherapy and para-aortic irradiation (STNI) combined with one course of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). For 28 (38%) of the patients, the follow-up period was longer than 10 years. The average follow-up period was 114 months (range 22-174 months). Overall survival and relapse-free survival were assessed using the Kaplan and Meier method, while differences were tested by the log-rank test.**

Results. **We recorded twelve cases of relapse after initial treatment. The period of time which elapsed between the end of treatment and the evidence of relapse ranged from 6 to 51 months, with an average of 22 months. Ten relapses occurred in the STNI group and two in the ABVD / STNI group. No statistically significant differences emerged between the two groups in the overall survival analysis but did in the relapse-free survival analysis ($p<0.01$). In the group treated with ABVD and STNI one patient developed acute non-lymphocytic leukemia and another patient treated at the age of 44 developed primary breast cancer. X-ray-related asymptomatic pulmonary fibrosis was observed in 12 patients: 10 cases in the STNI and ABVD group and 2 cases in the group treated with RT alone. The other sequelae of combined CT / RT treatment in our study were thyroid dysfunction (2 cases, hypothyroidism), whereas the sequela of RT treatment was cardiac disease (2 cases).**

Interpretation and Conclusions. **We conclude that one cycle of ABVD and radiotherapy in early-stage HD patients with mediastinal involvement may reduce the risk of relapse. Morever, the combination of low-toxicity CT and RT, administered preferably to limited fields, in patients who have not undergone laparotomy could be a valid alternative to current treatment for early-stage HD. However, additional data and a longer follow-up are mandatory in order to evaluate late toxicity and the potential risk of treatment.**

Key words: chemotherapy, early-stage, Hodgkin's disease, radiotherapy

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The optimal treatment for the early stages of Hodgkin's disease (HD) is still a matter of controversy.

As far back as 1902 Pusey,[1] followed by Gilbert[2] and Peters,[3] reported the possibility of treating the early stages of HD with radiotherapy (RT). Since the 1960s, thanks to the introduction of laparotomy staging and the use of large doses of radiation to extended fields, Kaplan *et al.*[4] were able to shown that the early stages of HD can be cured with RT alone. In the last few years, many studies[5-8] have shown, however, that 20-30% of patients treated with RT are subject to relapse in the five years following treatment. As a result,

researchers have directed their efforts towards finding better therapeutic methods: some authors[9-11] have reported good results with chemotherapy (CT) alone, even in the early stages of the disease; others[12, 13] used RT or CT, finding that RT gave better results; yet others[14-21] have used a combination of RT and CT in the early stages. The aim of all researchers has been to reduce the morbidity associated with laparotomy staging, to lessen the amount of irradiation used, and to improve relapse-free survival. As a result, some authors[22-24] have considered it necessary to identify a subgroup of early-stage patients with unfavorable prognostic factors [>3 affected sites, mediastinal involvement, erythrocyte sedimentation rate (ESR) >30, histology, age] in whom a more aggressive therapeutic method is justifiable. In this study, the only unfavorable prognostic factor taken into consideration was mediastinal involvement. The aim of our work was to analyze the occurrence of relapse and long-term complications in a group of HD patients in pathologic stage IIA, with mediastinal involvement, treated with two different methods: either supradiaphragmatic radiotherapy and para-aortic irradiation (STNI) or STNI combined with a course of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD).

Design and Methods

Patient population

Between 1983 and 1989, 73 HD patients with supradiaphragmatic and mediastinal involvement (with a mediastinal mass size less than one third of the maximum thoracic diameter, < 0.33 ratio) were treated at the Institute of Radiology in the Department of Radiation Oncology of "La Sapienza" University of Rome with the collaboration of the Hematology Department.

The diagnosis of HD was made using the Rye classification and the patients were staged according to the Ann-Arbor classification. Clinical staging procedures included complete history, a thorough physical examination, complete hematologic and biochemical screening, a bone marrow core-needle biopsy, differential blood counts, chest X-rays and tomography, ultrasound of the abdomen and chest and abdominal computed tomography. In addition, all patients underwent exploratory laparotomy and splenectomy, biopsies of selected lymph nodes in the para-aortic, splenic hilar, mesenteric and porta hepatis regions, and wedge biopsies of each lobe of the liver. Radiation therapy was administered using a 6 MV linear accelerator as follows: a total dose of 4,400 (10 Gy/wk in five fractions) to involved areas, 4,000 cGy to the mediastinum, 3,600 cGy to uninvolved areas. A 3-4 week rest period was allowed between the mantle-field and para-aortic treatment. Radiotherapy consisted in mantle- field and para-aortic irradiation (STNI). The upper and lower field limits were at the inferior margin of the mandible and at the level of T_{10}-T_{11}, respectively. Anterior-posterior (AP) and posterior-anterior (PA) 2:1-weighted fields were employed. Individualized blocks for the larynx (only in the AP field), the cervical spinal cord (only in the PA field), the lungs, and the head of the humerus (in both AP and PA fields) were added. After an exposure of 15 Gy, a small block shielding the left lateral portion of the heart was inserted. The lumbar bar for the para-aortic nodes included an L_4 vertebral inferior margin. An appropriate skin gap from the inferior tattoos of the mantle field was left.

Patients received one cycle of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) prior to RT. The ABVD regimen was administered as adriamycin (25 mg/m^2 i.v. on days 1 and 14), bleomycin (10 mg/m^2 i.v. on days 1 and 14), vinblastine (6 mg/m^2 i.v. on days 1 and 14) and dacarbazine (375 mg/m^2 i.v. on days 1 and 14).

The patients were randomized into two groups according to their initial treatment:

i) the first group contained 37 (51%) patients treated, initially, with STNI alone;

ii) the second group was made up of 36 (49%) patients who received, at the onset of the disease, STNI and one course of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) prior to RT.

The patients' clinical characteristics are shown in Table 1.

Statistical analysis

Cumulative probabilities of suffering a relapse and survival curves were estimated actuarially from the date of diagnosis by the Kaplan and Meier method.[25] Comparisons were made using the log-rank test.[26]

Results

The relation of initial therapy (RT alone or combined CT/RT) to the occurrence of relapse and long-term complications was assessed.

Overall survival results at 10 years are similar for the two groups: 97% for the RT group and 92% for the CT/RT group (p >0.1, Figure 1). On the other hand, relapse-free survival results at 10 years show a statistically significant difference: 73% for the RT group and 94% for the CT/RT group (p<0.01, Figure 2).

In our series of patients, there was no connection between sex, age, high ESR, histology and a greater risk of relapse, but an analysis of the number of sites involved (< 3) shows statistical significance (p<0.05, Figure 3).

Among the 73 patients, in an average follow-up of 114 months (maximum follow-up time: 174 months), 12 had a relapse between 6 and 51 months (average: 22 months) after initial treatment. Of these 12 patients (16%), 10 (83%) had been treated with STNI and 2 (17%) with ABVD and STNI; 5 were males and 7 females and their ages ranged from 17 to 59 years (average: 28 years).

Patterns of relapse differed greatly in the two treat-

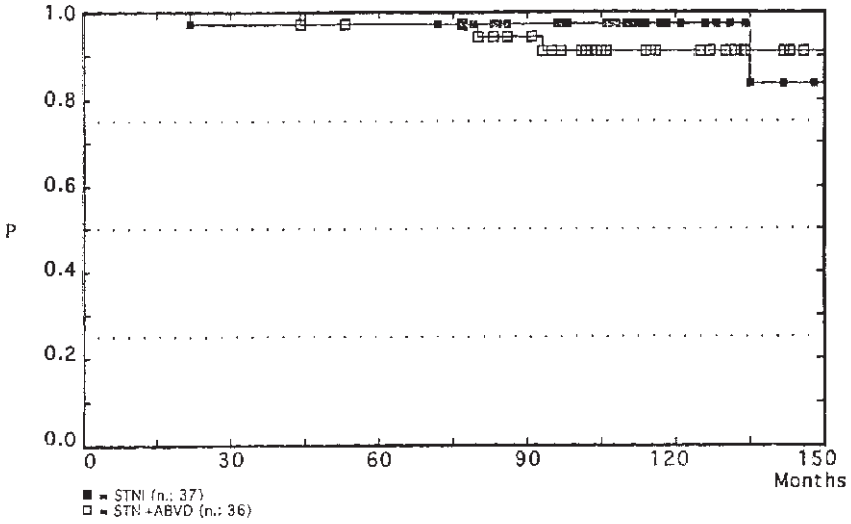

Figure 1. Actuarial overall survival for 73 patients treated with radiotherapy alone or with one cycle of ABVD plus radiotherapy.

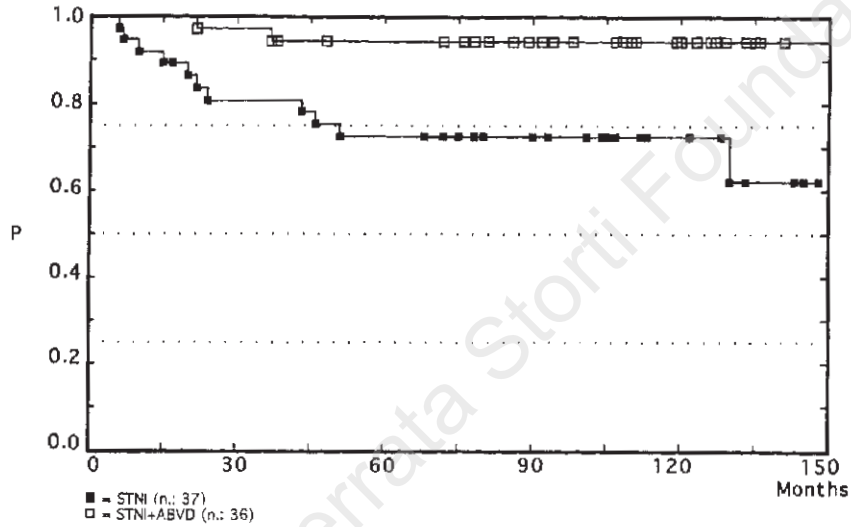

Figure 2. Actuarial relapse free survival for 73 patients treated with radiotherapy alone or with one cycle of ABVD plus radiotherapy.

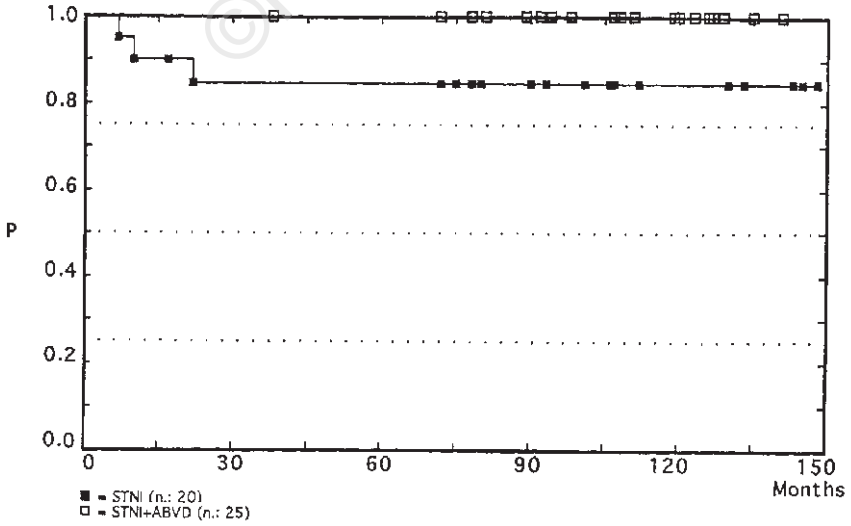

Figure 3. Actuarial overall survival according to number of sites involved (≤ 3).

Table 1. Clinical characteristics of patients.

Characteristics	Therapeutic option (No. of patients) STNI	ABVD+STNI	Total
Total patients	37	36	73
Sex			
male	12	13	25
female	25	23	48
Age in years, median (range)	29 (17-59)	26 (18-48)	28 (17-59)
Histology			
nodular sclerosis	24	29	53
mixed cellularity	11	5	16
lymphocyte predominance	1	-	1
lymphocyte depletion	1	1	2
unclassified	-	1	1
ESR			
<40 mm/hr	26	20	46
>40 mm/hr	11	16	27
No. of sites involved			
≤ 3	20	25	45
> 3	17	11	28
Average follow-up (months) (range)	114 (22-159)	114.5 (44-174)	114 (22-174)

Abbreviations. STNI: subtotal nodal irradiation; ABVD: adriamycin, bleomycin, vinblastine and dacarbazine; ESR: erythrocyte sedimentation rate.

ment groups (Table 2).

In the group treated with STNI alone, our data shows that relapse occurred in previously irradiated areas in 3 cases, in both previously irradiated areas and in areas which had not been irradiated in 3 cases and in areas which had not been irradiated in 4 cases. Four of the 10 cases of relapse in the RT group appeared in the pelvic or iliac nodes. Pelvic relapse was identified by a physical examination, the erythrocyte sedimentation rate and an abdominal CT scan. Parenchymal extension (lung) was present in one of the 10 patients in the RT group and in one of the 2 patients in the combined treatment group. In the group treated with ABVD and STNI, the other relapse involved the bone.

The occurrence of long-term complications is shown in Table 3. In the group treated with ABVD and STNI one patient developed acute non-lymphocytic leukemia (ANLL) after 35 months and died as a result; another patient treated at the age of 44 developed primary breast cancer after 25 months.

X-ray-related asymptomatic pulmonary fibrosis was observed in 12 patients: 10 cases in the STNI and ABVD group and 2 cases in the group treated with RT alone. The other sequelae of combined CT/RT treatment in our study were thyroid dysfunction (2 cases, hypothyroidism) whereas the sequela of RT treatment was cardiac disease (2 cases). Laparotomy staging was complicated in 3 cases by small bowel obstruction.

The patients who relapsed were treated with 6 alternating ABVD/mechlorethamine, vincristine, procarbazine and prednisone (MOPP) courses and all obtained complete remission.

Discussion

In this study, we focused our attention on the occurrence of relapse and long-term complications in HD IIA patients in relation to the treatment they received RT alone or RT combined with one cycle of ABVD.

At 10 years, we found, in line with the findings of

Table 2. Analysis of relapse.

Case	Age*	Sex	Histology	Treatment at onset of HD and relation of sites of relapse to previously irradiated fields	Time elapsed between first therapy and occurrence of relapse (in months)	Site of relapse	Therapy for relapse	Status
1	18	F	NS	ABVD+STNI (outside)	37	bone	ABVD/MOPP	dead
2	33	M	MC	ABVD+STNI (outside)	22	lung	ABVD/MOPP	dead
3	29	F	NS	STNI (inside)	51	axillary node	ABVD/MOPP	alive, NED
4	59	F	NS	STNI (inside)	20	axillary node	ABVD/MOPP	alive, NED
5	24	M	NS	STNI (inside and outside)	6	mediastinum, bone	ABVD/MOPP	alive, NED
6	17	M	MC	STNI (inside)	10	cervical and supraclavicular nodes	ABVD/MOPP	alive, NED
7	51	M	NS	STNI (outside)	24	iliac and inguinal nodes	ABVD/MOPP	alive, NED
8	27	F	NS	STNI (outside)	43	iliac and inguinal nodes	ABVD/MOPP	alive, NED
9	50	F	LP	STNI (inside and outside)	22	para-aortic, iliac, and inguinal nodes	ABVD/MOPP	alive, NED
10	39	F	NS	STNI (inside and outside)	46	para-aortic node, ilio-psoas muscle, and bone	ABVD/MOPP	alive, NED
11	22	M	NS	STNI (outside)	15	iliac node	ABVD/MOPP	alive, NED
12	23	F	NS	STNI (outside)	7	lung	ABVD/MOPP	alive, NED

**Age at HD diagnosis. Abbreviations: HD: Hodgkin's disease; NS: nodular sclerosis; ABVD: adriamycin, bleomycin, vinblastine, and dacarbazine; STNI: sub-total nodal irradiation; MOPP: mechlorethamine, vincristine, procarbazine and prednisone; MC: mixed cellularity; NED: no evidence of disease; LP: lymphocytic predominance.*

Table 3. Summary of results.

	Total
Assessable patients	73
CR	72
Failures	1
Relapses	12
Alive, free of disease	69
Alive with SPC	1 (ST)
Complications	
thyroid dysfunction	2
cardiac disease	2
pulmonary disease	12
gonadal toxicity	3
digestive complications	2
Deaths caused by HD	2
Deaths caused by SPC	1 (ANLL)
Deaths from other causes	1
Type of relapse	
true	4
lymph nodal extensions	5
disseminations	3
Time of relapse (months)	
> 12	9
≤ 12	3

Abbreviations. CR: complete remission; SPC: second primary cancer; ST: solid tumor; ANLL: acute non-lymphoid leukemia.

other authors,[27-32] that there is a higher risk of relapse after RT alone than after CT plus RT: in our study, treatment with RT alone led to a relapse-free survival rate of 73%, whereas combined CT/RT treatment led to a relapse-free survival rate of 94%. In fact, in the papers published over the last ten to fifteen years on the occurrence of relapse in HD patients treated with RT alone, the relapse-free survival rate at 10 years ranges from 65.8%[27] to 86%.[8, 30]

Our results agree from those obtained by Willet *et al.,*[33] who reported a satisfactory relapse-free survival rate of 75% at 5 years in patients with < 0.33 mediastinal involvement, treated with RT alone, although, it is difficult to compare the results of the two studies because of differences in the patients' clinical characteristics and in the types of treatment administered.

Ten of the 12 patients in our study who relapsed had received RT alone and most relapses after RT occurred within 2 years of treatment (7 out 10). Moreover, four patients treated with RT alone relapsed in an area (iliac and pelvic nodes) which had not been irradiated and that would have been treated using inverted Y.

It would seem both from our results and the results of other studies[34, 35] that the use of a small dose of CT before irradiation in patients with mediastinal involvement is sufficient to eliminate microscopic foci of disease present outside irradiated areas.

Recently, Horning *et al.*[35-37] compared RT treatment to treatment consisting in 6 cycles of vinblastine, bleomycin and methotrexate (VBM) followed by regional irradiation in clinically staged I-IIA HD patients. The results of their study confirm better long-term results as far as regards complete remission in the group of patients who received VBM and regional RT, coupled with a decrease in long-term toxicity.

In our study no case of second primary cancer appeared in the group treated with RT alone, whereas 2 cases of second primary cancer appeared in patients treated with one cycle of ABVD and RT. The first case was breast cancer and the second case was ANLL. This second case is significant since it is one of the few of its kind reported in literature.[38, 39] It does not seem that the ANLL was caused by RT, since radiation-induced leukemia generally occurs after a period of time exceeding 5 years, while in our patient it occurred after 35 months. Valagussa *et al.*[40] have reported that ABVD is not associated with the occurrence of ANLL even when combined with radiation. In research carried out by the Cancer Institute in Milan,[41,42] only one case of ANLL was recorded after ABVD+RT treatment, with a cumulative risk of 0.7% (at 15 years), compared with a risk of 9.5% (at 15 years) in patients treated with MOPP+RT (p=0.04). Although several studies have already examined factors associated with the risk of second neoplasm in patients treated for HD,[43,44,45] further investigations are needed to clarify the occurrence of ANLL after ABVD+RT.

As regards other illnesses more frequently observed in our patients, pulmonary sequelae occurred in 12 patients: 10 cases (83%) appeared in the group which received ABVD and RT and 2 cases (17%) in the group which received RT alone.

It should be remembered that the entity of lung damage[46] depends on various factors such as the total dose of RT received, how it is distributed over time, the size of the field of irradiation and the use of chemotherapy regimens containing bleomycin, as our study also shows.

The fact that the majority of cases of pulmonary fibrosis occurred in the ABVD plus RT group confirms the harmful synergistic effects of irradiation and bleomycin (present in the ABVD regimen) on the pulmonary parenchyma. However, all 12 cases were diagnosed as having chronic restrictive fibrosis by chest X-rays within three months of the end of therapy. In all cases the abnormalities of pulmonary damage were asymptomatic and did not require additional therapy.

The observation in other studies[6,7,43,44] that sex, age, high ESR and histology are associated with a greater risk of relapse has been a cause for concern.

To conclude, it is our view that a cycle of ABVD prior to RT is of great value in the subgroup of HD patients with mediastinal involvement. It is also possible that other subgroups with the greatest relapse

risk factors could benefit from this treatment.

All in all, the combination of low-toxicity CT and RT, administered preferably to limited fields, in patients who have not undergone laparotomy could be a valid alternative to current treatment for early-stage HD. In conclusion, one course of ABVD before irradiation in cases with positive mediastinal involvement significantly reduced the incidence of relapses in this series versus the control ($p<0.01$). These results must be confirmed in studies with larger cohorts of patients.

Contributions and Acknowledgments

RME was responsible for the conception of the study, its design, ethical approval, funding, direct supervision, recruitment and day-to-day contact with participants, data handling and interpretation, and for the organization of the group. APA was responsible for the conception of the study, its design, ethical approval, funding, direct supervision, recruitment and day-to-day contact with participants, data handling and interpretation. VD, MFO and VT contributed to the execution of the study. MS was responsible for statistical analysis and contributed to the execution of the study. FM was responsible for the organization of the group. The first author had the most important role in the study. The 2nd, 3rd, 4th, 5th and 6th authors are listed in alphabetical order. The first and seventh authors carried out the role of supervising the working group.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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References

1. Pusey WA. Cases of sarcoma and of Hodgkin's disease treated by exposures to X-rays: a preliminary report. JAMA 1902; 38:166-9.
2. Gilbert R. Radiotherapy in Hodgkin's disease (malignant granulomatosis): anatomic and clinical foundations, governing principles, results. AJR 1939; 41:198-241.
3. Peters MV. A study of survivals in Hodgkin's disease treated radiologically. AJR 1950; 63:299-311.
4. Kaplan HS. Hodgkin's disease. 2nd ed. Cambridge, Mass.: Harvard University Press, 1980.
5. Rosenberg S, Kaplan H. The evolution and summary results of the Stanford randomized clinical trials of the management of Hodgkin's disease: 1962-1984. Int J Radiat Oncol Biol Phys 1985; 11:5-22.
6. Tubiana M, Henry-Amar M, Carde P, et al. Toward comprehensive management tailored to prognostic factors of patients with clinical stage I and II in Hodgkin's disease. The EORTC Lymphoma Group Clinical Trials: 1964-1987. Blood 1989; 73:47-56.
7. Mauch P, Tarbell N, Weinstein H, et al. Stage I and IIA supradiaphragmatic Hodgkin's disease: prognostic factors in surgically staged patients treated with mantle and paraaortic irradiation. J Clin Oncol 1988; 6:1576-83.
8. Hartsell WF, Sarin P, Recine DC, et al. Long-term results of curative irradiation in pathologically staged IA and IIA Hodgkin's disease. Radiology 1993; 186:565-8.
9. Pavlovsky S, Maschio M, Santarelli M, et al. Randomized trial of chemotherapy versus chemotherapy plus radiotherapy for stage I-II Hodgkin's disease. J Natl Cancer Inst 1988; 80:1466-73.
10. Olweny CLM, Katongole-Mbidde E, Kiive C, et al. Childhood Hodgkin's disease in Uganda: a 10-year experience. Cancer 1978; 42:789-92.
11. Ekert H, Waters KD, Smith PJ, et al. Treatment with MOPP or ChlVPP chemotherapy only for all stages of childhood Hodgkin's disease. J Clin Oncol 1988; 6: 1845-50.
12. Longo DL, Glatstein E, Duffey PL, et al. Radiation therapy versus combination chemotherapy in the treatment of early-stage Hodgkin's disease: seven-year results of a prospective randomized trial. J Clin Oncol 1991; 9:906-17.
13. Biti GP, Cimino G, Cartoni C, et al. Extended-field radiotherapy is superior to MOPP chemotherapy for the treatment of pathologic stage I-IIA Hodgkin's disease: eight-year update of an Italian prospective randomized study. J Clin Oncol 1992; 10:378-82.
14. Noordijk EM, Carde P, Mandard AM, et al. Preliminary results of the EORTC-GMPC controlled clinical trial H7 in early-stage Hodgkin's disease. Ann Oncol 1994; 5 (Suppl 2):107-12.
15. Bonfante V, Santoro A, Viviani S, et al. Early stage Hodgkin's disease: Ten-year results of a non-randomized study with radiotherapy alone or combined with MOPP. Eur J Cancer 1993; 1:24-9.
16. Nissen NI, Nordentoft AM. Radiotherapy versus combined modality treatment of stage I and II Hodgkin's disease. Cancer Treat Rep 1982; 66:799-803.
17. Brusamolino E, Lazzarino M, Orlandi E, et al. Early-stage Hodgkin's disease: long-term results with radiotherapy alone or combined radiotherapy and chemotherapy. Ann Oncol 1994; 5 (Suppl 2):101-6.
18. Koziner B, Myers J, Cirrincione C, et al. Treatment of stage I and II Hodgkin's disease with three different therapeutic modalities. Am J Med 1986; 80:1067-78.
19. Straus DJ, Yahalom J, Gaynor J, et al. Four cycles of chemotherapy and regional radiation therapy for clinical early-stage and intermediate stage Hodgkin's disease. Cancer 1992; 69:1052-60.
20. Andrieu JM, Dana M, Desprez-Curely JF, Jacquillat C, Weil M. MOPP chemotherapy plus irradiation for Hodgkin's disease, stages IA to IIB: long-term results of the prospective trial H72 (1972-1976, 334 patients). Hematol Oncol 1985; 3:219-31.
21. Anselmo AP, Bove M, Cartoni C, et al. Combined modality (ABVD plus radiotherapy) versus radiotherapy in the management of early stage (IIA) Hodgkin's disease with mediastinal involvement. Haematologica 1992; 77:177-9.
22. Tubiana M, Henry-Amar M, Van Der Werf Messing G, et al. A multivariate analysis of prognostic factors in early stage Hodgkin's disease. Int J Radiat Oncol Biol Phys 1985; 11:23-30.
23. Mauch P, Goodman R, Hellman S. The significance of mediastinal involvement in early stage Hodgkin's disease. Cancer 1978; 42:1039-45.
24. Carde P, Hagenbeek A, Hayat M, et al. Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early-stage Hodgkin's disease: the H6 twin randomized trials from the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group. J Clin Oncol 1993; 11:2258-72.
25. Kaplan EL, Meier P. Nonparametric estimation from

incomplete observations. J Am Stat Ass 1958; 53:457-81.
26. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. Br J Can 1977; 35:1-39.
27. Gospodarowicz MK, Sutcliffe SB, Bergsagel DE, Chua T for the Princess Margaret Hospital Lymphoma Group. Radiation therapy in clinical stage I and II Hodgkin's disease. Eur J Cancer 1992; 11:1841-6.
28. Sullivan JW, Cooper JS. Optimal treatment of early-stage Hodgkin's disease. Radiology 1993; 186:312-3.
29. Lee CKK, Aeppli DM, Bloomfield CD, Levitt SH. Curative radiotherapy for laparotomy-staged IA, IIA, IIIA Hodgkin's disease: an evaluation of the gains achieved with radical radiotherapy. Int Radiat Oncol Biol Phys 1990; 19:547-59.
30. Wassermann TH, Trenkner DA, Fineberg B, Kucik N. Cure of early-stage Hodgkin's disease with subtotal nodal irradiation. Cancer 1991; 68:1208-15.
31. Shore T, Nelson N, Weinerman B. A meta-analysis of stage I and II Hodgkin's disease. Cancer 1990; 65: 1155-60.
32. Zagars G, Rubin P. Hodgkin's disease stages IA and IIA. A long-term follow-up study on the gains achieved by modern therapy. Cancer 1985; 56:1905-12.
33. Willett CG, Linggood RM, Meyer J, et al. Results of treatment of stage IA and IIA Hodgkin's disease. Cancer 1987; 59:1107-11.
34. Glimelius B, Kalkner M, Enblad G, et al. Treatment of early and intermediate stages of supradiaphragmatic Hodgkin's disease: the Swedish National Care Programme Experience. Ann Oncol 1994; 5:809-16.
35. Horning SJ, Hoppe RT, Mason J, et al. Stanford-Kaiser Permanent G1 Study for clinical stage I to IIA Hodgkin's disease: subtotal lymphoid irradiation versus vinblastine, methotrexate, and bleomycin chemotherapy and regional Irradiation. J Clin Oncol 1997; 15:1736-44.
36. Bates NP, Williams MV, Bessel EM, Vaughan Hudson G, Vaughan Hudson B. Efficacy and toxicity of vinblastine, bleomycin, and methotrexate with involved-field radiotherapy in clinical stage IA and IIA Hodgkin's disease: a British National Lymphoma Investigation Pilot Study. J Clin Oncol 1994; 12:288-96.
37. Gobbi PG, Pieresca C, Frassoldati A, et al. Vinblastine, bleomycin, and methotrexate chemotherapy plus extended-field radiotherapy in early, favorable presenting, clinically staged Hodgkin's patients: the Gruppo Italiano per lo Studio dei Linfomi Experience. J Clin Oncol 1996; 14:527-33.
38. Amadori S, Papa G, Anselmo AP, Fidani P, Mandelli F. Acute promyelocytic leukemia following ABVD (doxorubicin, vinblastine, and dacarbazine) and radiotherapy for Hodgkin's disease. Cancer Treat Rep 1983; 67:603-4.
39. Yahalom J, Voss R, Leizerowitt R, Fuks ZVI, Polliack A. Secondary treatment on Hodgkin's disease: Ultrastructural and cytogenetic data in two cases with a review of the literature. Am J Clin Pathol 1983; 80: 231-6.
40. Valagussa P, Santoro A, Fossati-Bellani F, Franchi F, Banfi A, Bonadonna G. Absence of treatment-induced second neoplasm after ABVD in Hodgkin's disease. Blood 1982; 59:488-94.
41. Valagussa P. Second neoplasm following treatment of Hodgkin's disease. Curr Opin Oncol 1993; 5:805-11.
42. Valagussa P, Bonadonna G. Hodgkin's disease and the risk of acute leukemia in successfully treated patients. Haematologica 1998; 83:769-70.
43. Maurizi Enrici R, Anselmo AP, Osti MF, et al. Analysis of the risk of solid tumor following Hodgkin's disease. Haematologica 1997; 82:57-63.
44. Maurizi Enrici R, Anselmo AP, Iacari V, et al. The risk of non-Hodgkin's lymphoma after Hodgkin's disease, with special reference to splenic treatment. Haematologica 1998; 83:636-44.
45. Brusamolino E, Anselmo AP, Klersy C, et al. The risk of acute leukemia in patients treated for Hodgkin's disease is significantly higher after combined modality programs than after chemotherapy alone and is correlated with the extent of radiotherapy and type and duration of chemotherapy: a case-control study. Haematologica 1998; 83:812-23.
46. Loasses A, Maurizi Enrici R. Pneumopatia da radiazioni. Nostra esperienza nel trattamento del morbo di Hodgkin con campo sagomato a mantellina. Rad Med 1984; 70:520-7.
47. Hoppe R, Coleman C, Cox R, Rosenberg S, Kaplan H. The management of stage I-II Hodgkin's disease with irradiation alone or combined modality: the Stanford experience. Blood 1982; 59:455-65.
48. Specht L, Nordentoft A, Cold S, Clausen N, Nissen N. Tumor burden as the most important prognostic factor in early stage Hodgkin's disease. Relations to other prognostic factors and implications for choice of treatment. Cancer 1988; 61:1719-27.