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Treatment of early-stage Hodgkin's disease with four cycles of ABVD followed by adjuvant radiotherapy: analysis of efficacy and long-term toxicity

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ABSTRACT

***Background and Objectives*. The use of combined modality therapy in early-stage Hodgkin's disease can spare staging laparotomy and reduces the risk of relapse compared to radiation alone. This paper reports on the efficacy and long-term events of a combined modality approach consisting of a brief course of chemotherapy followed by adjuvant radiotherapy, without laparotomy, in early-stage Hodgkin's disease.**

***Design and Methods.* This study included 78 patients with Hodgkin's disease (20 in stage I and 58 in stage II); 60% had mediastinal enlargement (12% had bulky disease) and 5% had subdiaphragmatic disease. Their median age was 33 years (range: 15-64) and median follow-up 60 months. The treatment program consisted of four cycles of ABVD followed by adjuvant radiation to involved sites (43 patients) or involved and contiguous sites of disease (35 patients); radiation doses ranged from 30 to 36 Gy to uninvolved and involved sites, respectively; bulky disease received up to 44 Gy. Gonadal function in women was assessed by hormonal tests and evaluation of menses; young men were given the opportunity to have their semen cryopreserved.**

***Results*. The treatment program was completed in a median of 6.2 months (range: 5-10). The complete remission rate was 88% after 4 courses of ABVD and 98.7% after adjuvant RT. The 5-year relapse-free survival was 97% and overall survival 98%; three patients died, one of disease progression and two of small cell lung carcinoma. Long-term events included three cases of pulmonary fibrosis with symptomatic interstitial disease, one case of dilated cardiomyopathy with cardiac failure (all had received mediastinal radiation) and four cases of dysthyroidism. Fertility was preserved in young women, with three subsequent normal pregnancies. Second neoplasms included two small cell lung carcinomas and one breast carcinoma.**

***Intepretation and Conclusions.* In early-stage Hodgkin's disease, four cycles of ABVD followed by adjuvant radiotherapy produced a 5-year overall survival of 98%. Prolonged monitoring for therapy-related long-term complications is mandatory in these potentially curable patients.**

Key words: Hodgkin's disease, early-stage, combined modality therapy, ABVD, long-term toxiciy

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Radiation therapy (RT) has conventionally been the primary treatment modality in surgically staged early Hodgkin's disease (HD); this approach can result in long-term disease-free survival in about 75% of patients.[1-3] In the effort to cure the 25% of patients failing after RT alone, many Institutions have evaluated the effect of adding chemotherapy (CT) to radiation therapy (combined modality treatment). The addition of CT to RT significantly reduces the risk of failure, without however a significant improvement in survival compared to that achieved by RT alone.[4–9] The combined modality approach can spare staging laparotomy and splenectomy and permits the cumulative dose of RT to be reduced thus lowering its toxicity. No advantages have been demonstrated in the combined modality approach for extended-field versus involved-field RT.[10,11] In the past, the most widely CT used in combination with RT was the MOPP regimen; this combination was abandoned after demonstration in advanced stages of disease that ABVD plus RT was superior to MOPP plus RT, at significantly lower gonadal cost and leukemogenic risk.[12-14] Excellent cure rates have been achieved in early-stage HD, without laparotomy, utilizing the VBM (vinblastine, bleomycin, methotrexate) protocol, with adjuvant extended-field radiotherapy[15] or regional irradiation.[16] To minimize acute and long-term toxicity in early-stage Hodgkin's disease, a strategy consisting of a brief course of non-leukemogenic and gonadal-sparing CT and limited adjuvant RT, without surgical staging, is being explored. The Vancouver group utilized two cycles of various CT regimens including VECABOP (vinblastine, etoposide, cyclophosphamide, doxorubicin, bleomycin, vincristine and pred-

nisone), COPP/ABVD or ABVD followed by involved-field RT,[17] while other groups[10,18] evaluated extended or involved-field irradiation after four cycles of ABVD. Our previous experience in early-stage Hodgkin's disease[9] indicated an advantage in terms of longer disease-free survival and lower long-term toxicity in favor of the combined modality approach compared to RT alone. Therefore, in this setting of patients, in 1990 we started a combined modality program consisting of brief chemotherapy (four cycles of ABVD) followed by adjuvant RT. The subgroup of early-stage HD patients with an unfavorable prognosis, defined by the presence of systemic symptoms, was excluded from this study, while a minority with borderline bulky disease were included. This paper reports on the efficacy and long-term events of the program.

Design and Methods

Patient characteristics

This study includes 78 consecutive previously untreated patients with a histologic diagnosis of Hodgkin's disease according to Lukes and Collins, in early clinical stage (stage I or II according to Ann Arbor criteria, without systemic symptoms). Patients were admitted to and treated in the Division of Hematology, Policlinico San Matteo IRCCS, Pavia from 1990 to 1996. Clinical staging procedures were performed according to the Cotwolds meeting criteria.[19] Clinical staging included a complete history, physical examination, routine laboratory tests with hemogram, lactate-dehydrogenase (LDH), β_2-microglobulin, liver and renal function tests, postero-anterior and lateral chest X-rays, chest and abdominal computerized tomography; chest and abdomen magnetic nuclear resonance and gallium-67 thoracic scan were done when tomography was inconclusive. Unilateral bone marrow biopsy was performed in all cases and laparotomy in 7 cases (9%); 4 of them had subdiaphragmatic disease. Table 1 illustrates the main characteristics of the study population. The median age was 33 years (range: 15-64); the most frequent histology was nodular sclerosis (60%) while both lymphocyte predominance and mixed cellularity accounted for 18% of the total. Most patients were in clinical stage II (74%); the mediastinum was enlarged in 60% of cases, with borderline bulky dimensions in 13% of the total. Restaging procedures were performed at the end of CT and after completion of adjuvant RT. All patients were regularly followed-up every 4 months for the first 3 years and annually thereafter; up to this analysis, the median follow-up of the entire series is 60 months (range: 36-120).

Table 1. Patient characteristics.

Characteristics	*No. of patients*	*%*
Total	78	
Men	38	48
Women	40	52
Age (years)		
< 20	13	17
20-40	46	59
> 40	19	24
Histology		
LP	14	18
NS	47	60
MC	14	18
Unclassifiable	3	4
Stage		
I	20	26
II	58	74
Mediastinal enlargement	47	60
Mediastinal bulky disease	10	13
Subdiaphragmatic disease	4	5
Laparotomy with splenectomy	7	9
ESR > 50 mm/hr	7	9

ESR= erythrocyte sedimentation rate; LP= lymphocyte predominance; MC= mixed cellularity; NS= nodular sclerosis.

Therapy

The treatment program consisted of 4 cycles of ABVD chemotherapy followed by megavoltage radiotherapy as adjuvant treatment. The ABVD regimen was administered as originally described by Bonadonna *et al.*;[20] the use of hematopoietic growth factors was not required. Two additional cycles of the same regimen were given to five patients showing only a partial response after the 4 cycles of ABVD. Radiotherapy was delivered through a megavoltage linear accelerator with standard techniques, within 30-60 days from the end of CT; the dose amounted to 1.8-2 Gy per day for 5 days a week, with lung, heart and spinal marrow protection. Table 2 illustrates the radiation dose according to stage and irradiated volumes; 45% of patients were given less than 36 Gy, 28% a dose comprised between 36 and 40 Gy, while only 27% received more than 40 Gy. Involved-field (IF) RT was designed to include only the sites initially involved, while extended-field (EF) RT included adjacent uninvolved sites, as well. The EF modality was adopted in 35 cases (45% of the total) treated before 1994, while the IF modality was adopted in 43 (55%) patients treated thereafter. Extended-field RT consisted of mantle radiation in 23 patients (29% of the total), of mantle with lumbo-aortic node radiation (extended mantle) in 8 patients (10%) and inverted Y radiation in 4 patients (5% of the total). Involved-field RT consisted of medi-

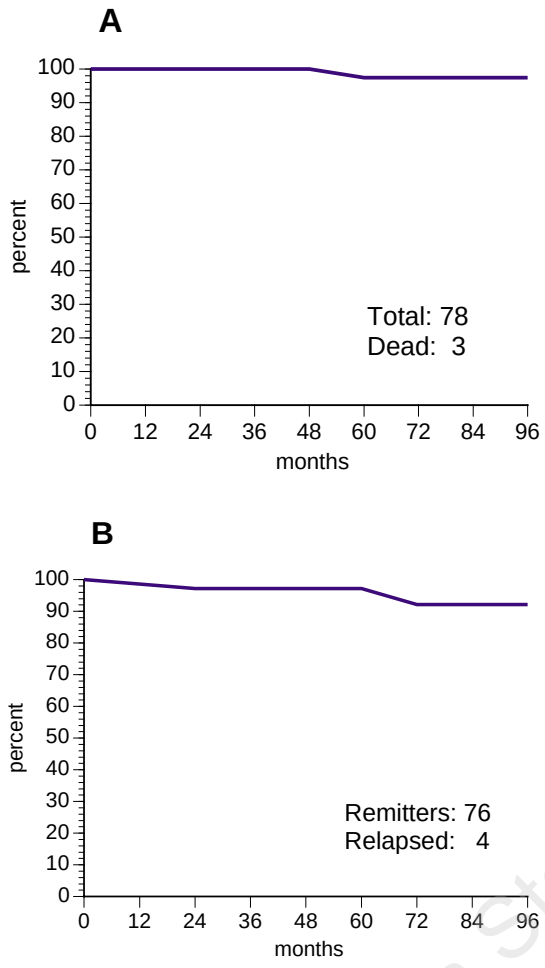

Figure 1. A: overall survival curve. B: relapse-free survival curve.

astinal radiation in 25 patients (32% of the total) and of a single non-mediastinal node radiation in 18 patients (23% of the total).

Evaluation of response and of toxicity

Complete response was defined by a complete regression of all measurable lesions and by the disappearance of all subjective and objective evidence of disease. The toxicity of therapy was measured according to the standard *Eastern Cooperative Oncology Group* (ECOG) criteria.[21] Potential pulmonary toxicity of the ABVD or of the adjuvant RT was assessed through the evaluation of pulmonary symptoms, through radiographic analysis and pulmonary function tests including spirometric evaluation of forced vital capacity (FVC) and forced expiratory volume and measurement of single-breath carbon monoxide diffusing capacity (DLCO). Gonadal function was assessed in women by evaluation of menses and hormonal tests; fertile women were given an estrogen-progesterone combination or a GnRH analog for ovarian protection; semen analysis before therapy was carried out in 10 male patients; 6 of them had their semen cryopreserved. Cardiac function was evaluated by two-dimensional echography and measurement of left ventricular ejection fraction (LVEF) at the end of the program; thyroid function was periodically evaluated as well.

Table 2. Radiation dose according to stage and volumes.

Characteristics	*No. of patients*			
	Total	*< 36Gy*	*36-40 Gy*	*> 40Gy*
Stage				
I	20	11	4	5
II	58	24	18	16
Radiation volumes				
IF	43	29	6	8
EF	35	6	16	13
Enlarged mediastinum	47	23	13	11
Total	78	35 (45%)	22 (28%)	21 (27%)

IF = involved-field RT; EF = extended-field RT.

Statistics

Overall survival (OS) was calculated from the date of diagnosis to the last follow-up or death; relapse-free survival (RFS) was calculated from the date of the assessed complete response to the last follow-up or to relapse. The actuarial OS and RFS were calculated using the product-limit method of Kaplan-Meier.[22]

Results

Efficacy

The response to chemotherapy was evaluable in 76 patients; one patient was lost to follow-up and one was evaluated only at the end of the combined modality program. A complete response (CR) after 4 cycles of ABVD was achieved in 67 patients (88%) and a partial response was achieved in 9 patients (12%). All nine partial responders had mediastinal involvement at diagnosis (3 of them had bulky disease) and 8 had stage II disease; five patients with partial response after 4 ABVD cycles received 2 additional cycles of CT before RT. The evaluation at the end of program indicated that 76 of 77 evaluable patients (98.7%) had achieved a complete remission with the combined modality treatment; the single patient resistant to the ABVR+RT program achieved a sustained CR with myeloablative CT followed by peripheral blood

progenitor cell (PBPC) infusion. So far, in a median follow-up of 60 months, four patients have relapsed after disease-free intervals of 4, 14, 75 and 77 months. The 5-year relapse-free survival was 97%; the RFS curve is illustrated in Figure 1. All relapses occurred in nodal sites; in three cases, relapses occurred in previously irradiated sites of disease (in 3 of 4 cases IF-RT had been utilized). Salvage treatment consisted of RT alone in a single case relapsing in a non-irradiated area, of MOPP chemotherapy in one case and of high-dose chemotherapy followed by infusion of autologous PBPC in two cases. The 5-year overall survival (OS) of the entire series is 98% (Figure 1). So far, 3 patients have died; the causes of death were disease progression in one case, and lung carcinoma in two cases; both cases had been treated with supradiaphragmatic extended-field RT and developed a small cell lung carcinoma 36 and 48 months after the end of therapy.

Toxicity

Acute toxicity was mostly hematologic; however, no episodes of severe neutropenia and/or thrombocytopenia occurred, nor were acute life-threatening complications registered. Table 3 illustrates the non-hematologic toxicity of the combined modality program. Asymptomatic pulmonary toxicity consisted of radiographic findings of interstitial infiltrates following CT+RT, with no correlation with respiratory symptoms. Symptomatic pulmonary toxicity developed in 3 cases (4% of the total); all had been treated with mantle RT with a total dose of 40, 40 and 44 Gy. Symptoms developed 2, 5 and 6 months after the end of RT, respectively, and included exertional dyspnea and cough. Radiographic findings consisted of interstitial infiltrates and post-attinic fibrosis; pulmonary function tests showed a reduction greater than 15% of the forced expiratory volume in all 3 cases, with a marked reduction of DLCO in one case. In all cases, the symptoms subsided within 12 months, without a significant impairment of the patients' functional status. The median time from the end of therapy to pulmonary late events was 11 months. Symptomatic cardiac toxicity developed in a single case 60 months after the end of treatment and consisted of dilated cardiomyopathy with a marked reduction of LVEF (< 40%). The patient had been given extended mantle RT at the dose of 42 Gy and developed a reversible cardiogenic pulmonary edema. Asymptomatic cardiac toxicity consisted of asymptomatic electrocardiogram alterations in 3 cases; in 2 cases, the alterations consisted of a partial bundle branch block, while in a single case, signs of mild pericarditis were demonstrated; this last case had been given a total radiation dose of 42 Gy to the mediastinum. The median time from the end of therapy to any cardiac event was 24 months. Hypothyroidism developed in 3 cases and hyperthyroidism in a single case; all cases with subsequent dysthyroidism had been given extended-field RT (in 3 of 4 patients, the total RT dose was higher than 40 Gy). The median time from the end of therapy to dysthyroidism was 40 months. Transient amenorrhea was observed in 12 out of 36 (33%) women in reproductive age (< 45 years); no cases of permanent amenorrhea were registered in women younger than 25 years (17 women). Hormonal alterations, either amenorrhea or precocious menopause, were documented in 16 women. Five pregnancies were registered after the completion of treatment; a 34-year old woman had two spontaneous abortions before giving birth to a healthy baby; the two other pregnancies occurred in women aged 19 and 27 years and had a favorable outcome. Irreversible azoospermia was registed in only one of 10 cases examined; this patient, aged 31, had been treated with 6 cycles of ABVD (for residual disease after 4 cycles) and inverted Y radiation (40 Gy) for the presence of subdiaphragmatic disease. Myelopathy developed in a single case who had received 40 Gy of RT to the mediastinum; the same patient (a woman aged 26) developed renal toxicity after lumbo-aortic radiation (40 Gy), with eventual chronic renal failure.

Table 3. Non-hematologic toxicity.

Type of toxicity	*No. of patients*	*%*
Pulmonary		
asymptomatic	12	15
symptomatic	3	4
Cardiac		
asymptomatic	3	4
symptomatic	1	1
Thyroid		
hypothyroidism	3	4
hyperthyroidism	1	1
Irreversible azoospermia	1/10	10
Transient amenorrhea	12/36	33
Myelopathy	1	1
Nephropathy	1	1

Secondary neoplasms

Secondary neoplasms developed in 3 cases and consisted of small cell lung carcinoma in 2 cases and breast carcinoma in a single case. The intervals from the end of therapy to the secondary tumors were 34, 36 and 48 months. All three cases had been given mediastinal radiation at the dose of 36 Gy (breast cancer), 44

Table 4. Brief CT and adjuvant RT in early-stage Hodgkin's disease.

	INT Milan (ref #10)	*Vancouver (ref #17)*	*Stanford (ref #16)*	*GISL (ref#15)*	*Pavia (this study)*
Stage	IA, IB, IIA	IA, IIA	IA, IIA	IA, IIA	IA, IIA
No. of patients	114	120	35	50	78
Median follow-up	38 mos	40 mos	48 mos	38 mos	60 mos
Type of CT	ABVD	COPP/ABV or ABVD	VBM	VBM	ABVD
No. of cycles	4	2	2	6	4
Type of RT	IF vs EF	EF	IF	EF	IF or EF
RFS (%)	94	100	98°	89	95
OS %	100	96	100	100	96

°Freedom from disease progression; GISL= Gruppo Italiano per lo Studio dei Linfomi; INT= Istituto Nazionale Tumori; OS= overall survival; RFS= relapse-free survival.

and 46 Gy, respectively. The lung carcinoma was fatal in both cases, whereas the patient with breast carcinoma underwent quadrantectomy with axillary node dissection and adjuvant RT and is alive and well 55 months after surgery.

Discussion

The main concern in treating a curable disease such as Hodgkin's disease must be to minimize therapy-related morbidity and long-term toxicity, without jeopardizing the final outcome. That was attempted in this study by avoiding staging laparotomy, choosing a non-mutagenic CT regimen and by reducing the cumulative dose of both CT and RT. As far as efficacy is concerned, the results of this study demonstrate that a brief course of CT with four cycles of ABVD followed by adjuvant radiotherapy, without laparotomy, can produce a cure rate higher than 95% in early-stage Hodgkin's disease. The efficacy of our program compares favorably with that reported from other Institutions using a combined modality approach in early-stage Hodgkin's disease.[4-10,15-17] Of particular interest is the comparison with other recent programs based, as our own, on a strategy of brief duration chemotherapy followed by adjuvant irradiation (Table 4). In two studies (Milan and Pavia), CT consisted of four cycles of the standard ABVD regimen, in the Vancouver experience, CT consisted of two cycles of ABVD or of alternating COPP/ABV, while in the Stanford and GISL experiences, the CT consisted of the VBM regimen (vinblastine, bleomycin, methotrexate). The Milan study included randomization to involved versus extended field RT after CT; no difference was observed between the two forms of irradiation. The Vancouver and GISL groups utilized extended RT after CT, while in the Stanford experience only IF-RT was given. In our experience, the criteria for the extent of RT changed over time; EF-RT was given before 1993, while IF-RT was adopted thereafter. All available data make clear that brief CT, either with ABVD or VBM, followed by regional irradiation is highly effective in curing early-stage Hodgkin's disease. The toxicity of our program was very limited; some problems of pulmonary, cardiac or thyroid dysfunction did, nonetheless, occur. A major concern about potential pulmonary toxicity derives from the combined use of both bleomycin and thoracic RT. In our experience, respiratory symptoms developed in 4% of patients; all of them had been given extended field irradiation (mantle RT); pulmonary symptoms generally subsided within 4 months, without leaving a significant impairment of respiratory functional status. In the Memorial Hospital experience,[23] ABVD chemotherapy induced pulmonary toxicity that required bleomycin dose modification in 23% of patients and fatal pulmonary toxicity in about 2%. The addition of mantle or mediastinal RT to ABVD resulted in a further decrease in the forced vital capacity (FVC) and in an increase in the incidence of radiographic changes but did not significantly affect the functional status of patients. Decreases in FVC and DLCO have been documented in a prospective analysis from Stanford University[24] after regimens of therapy consisting of bleomycin containing CT alone (VBM: vinblastine, bleomycin, methotrexate), of RT alone including mediastinal irradiation or of a combined modality therapy including bleomycin and mediastinal RT. In this analysis, mantle RT was the only significant treatment variable predictive of FVC and DLCO decline in the first 15 months after treatment; this decline was temporary and recovered generally within 36 months from the end of radiotherapy. In an Italian co-operative experience,[15] the major toxicity after VBM and extended RT was pulmonary; a regression analysis

demonstrated a significant relation to the amount of RT delivered but not to the relative dose of bleomycin, to the dose-intensity of the three drugs or to patient age. All studies comparing involved field and extended field irradiation after CT[10,18] demonstrated the equal efficacy of the two modalities and a German study showed no relevant dose-effect for radiotherapy in the range between 20 Gy and 40 Gy after 4 cycles of modern polychemotherapy.[11] Therefore, limited RT after brief CT may spare substantial toxicity and should be considered the most cost-effective strategy in early-stage Hodgkin's disease.

Cardiovascular complications of mantle irradiation represent the second most frequent cause of treatment-related mortality in Hodgkin's disease.[25,26] Mediastinal radiation of 40 to 45 Gy increases the risk of death from coronary artery and other cardiac disease; this risk increases within 5 years of irradiation and is particularly relevant in children and adolescents. Anthracyclines enhance the risk of cardiac morbidity in patients given combined modality therapy; in this respect, it is of relevance that the Vancouver experience utilized only two cycles of anthracycline-containing CT and it would be of utmost importance in future trials to try to determine the minimal effective dose of both CT and RT. With the doses currently used in combined modality programs, the cardiac risk is limited but not absent; in our experience, only one patient showed symptomatic toxicity, while a minority experienced asymptomatic events consisting of mild pericarditis (one case) or partial bundle branch block. Thyroid dysfunction represents one of the problems requiring evaluation during the follow-up of patients treated with radiotherapy for Hodgkin's disease. The Stanford University experience indicated a 47% cumulative probability of hypothyroidism,[27] with a risk varying according to sex (in women the risk is 1.6 times that in men) and age (decreasing after 20 years). In our experience, alterations of thyroid function developed in four patients (5% of the total); all of them had been given extended-field radiation and 3 had received a RT dose higher than 40 Gy. The limited RT dose we administered to the cervical lymph nodes areas in comparison with that reported in the original Stanford experience[27] may account for the difference in the incidence of thyroid complications. The occurrence of a second malignancy is the most serious consequence of therapy for Hodgkin's disease.[28-30] In a large co-operative case-control study,[14] we demonstrated that the risk of subsequent leukemia is significantly higher in patients treated with alkylating agents and procarbazine (MOPP regimen) and in patients given combined modality programs with extensive radiotherapy. Besides, in our previous experience,[31] the use of splenectomy and the number of courses of MOPP were demonstrated, in a multivariate analysis, to be the most significant risk factors for development of subsequent leukemia. Therefore, in this study, we avoided splenectomy, utilized the ABVD chemotherapy which has proved to be exempt from leukemogenic risk,[13,14] and limited the extent and the dose of RT. No cases of secondary leukemia have occurred in this series, so far. The risk of subsequent solid tumors in HD is mostly attributed to prior irradiation;[30,32,33] and approximately two thirds of subsequent tumors arise within or at the edge of RT fields. Lung and breast carcinomas are of particular epidemiological relevance among metachronous tumors in HD.[30,34-36] For lung cancer, a direct relationship has been demonstrated between risk and dose to the previously irradiated lung segments; a positive smoking history significantly increases this risk.[37] In our series, two of three subsequent neoplasms were lung carcinoma; both developed in a previously irradiated area. The excess risk of breast carcinoma in HD is restricted to women irradiated before the age of 30; the maximum cumulative risk has been observed among women irradiated in the second decade of life, with a 34% actuarial predicted incidence of breast cancer 25 years after RT.[38] In view of the direct relationship between dose of RT and risk of subsequent solid tumors, it is mandatory to limit the dose and the extension of RT as much as possible to avoid this severe complication.

A brief course of CT without alkylating agents and procarbazine limits the risk of sterility; transient azoospermia has been documented in only 14% of men aged ≤ 45 years treated with 4 cycles of ABVD for early-stage HD; in only 4% did the azoospermia persist after 36 months from the end of therapy.[39] In our program, irreversible azoospermia was documented in one patient of 10 examined; this patient had been given inverted Y RT after 6 cycles of ABVD.

The use of ABVD can spare gonadal toxicity in women, as well;[40] no cases of permanent amenorrhea have been observed after 4 cycles of ABVD among women younger than 35 years.[39] In our experience, no cases of permanent amenorrhea were registered in women younger than 25 years and fertility was preserved allowing three women to give birth to normal babies.

Contributions and Acknowledgments

EB was responsible for clinical assessment and treatment of patients, data registration and interpretation and writing of the paper; FL was responsible for the database; EO, CA, FP, CBa, GP, AB, PF and Ma were all involved in the assessment and treatment of the patients. EB, ML

and CBe were responsible for the conception and design of the study. All authors particpiated in data analysis and were actively involved in the discussion of results. The order of the names of the authors is based on the relevance of their contribution, with PF being the head of the Servizio di Radioterapia Oncologica, ML the head of the Divisione di Ematologia, IRCCS Policlinico S. Matteo di Pavia and CBe the Chairman of the Istituto di Ematologia, Università di Pavia, Italy.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- The results of this study demonstrate that brief CT with four cycles of ABVD followed by adjuvant radiotherapy, without laparotomy, can produce a cure rate higher than 95% in early-stage Hodgkin's disease.
- The use of the ABVD regimen reduces gonadal toxicity and the risk of subsequent leukemia or myelodysplasia.
- Potential cardiovascular, pulmonary and thyroid toxicity must be carefully monitored; their risk should be further lowered by reducing the cumulative dose of anthracycline, bleomycin and radiotherapy.
- Long-term follow-up is warranted because of the potential risk of subsequent solid tumors.

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