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# The addition of radiotherapy to chemotherapy does not improve outcome of early stage Hodgkin's lymphoma patients: a retrospective long-term follow-up analysis of a regional Italian experience

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**Abstract** We retrospectively reviewed 139 stage I–II HL patients who were diagnosed and followed up in an Italian northern region (Liguria) from 1995 to 2007, and who received either chemotherapy (CT) alone (mainly doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVD) or a combined modality treatment (chemotherapy+radiotherapy, CT+RT). The two therapeutic groups were

comparable for clinical and histologic features. Complete remission rate after CT+RT was higher than what was achieved with CT alone (96% vs. 84%, respectively,  $p=0.03$ ). Relapse rate (12%) was the same in both groups and disease-free survival curves were comparable (82% and 83%,  $p=0.47$ ). The overall survival of the two therapeutic groups is comparable. No second tumors have been reported among patients receiving chemotherapy alone, whereas a second neoplasia has been diagnosed in four patients (in two cases possibly radiotherapy related) in the CT+RT group (5%,  $p=0.09$ ). In conclusion, our retrospective study shows that CT+limited RT is an effective and well-tolerated option for early stage Hodgkin's lymphoma, even if the use of RT is associated with a certain risk of developing a second tumor. However, four to six courses of ABVD can lead to similar, optimal, long-term disease control without exposing patients to the risk of a second neoplasia.

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**Keywords** Hodgkin's lymphoma · ABVD · Radiotherapy · Late toxicity · Early stage

## Introduction

The successful treatment of Hodgkin's lymphoma (HL) has been one of the most significant accomplishments in cancer therapy over the last century. Since the introduc-

tion of extended field radiotherapy and MOPP (mustargen, oncovin, procarbazine, and prednisone) combination chemotherapy, more than 60% of patients can be cured [1]. Further progress in prognostic definition has been made over the last decade [2], and several randomized trials compared innovative therapies with an ABVD-based approach [3–6]. Six to eight courses of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) are now considered as the standard treatment for patients with advanced stage HL. On the contrary, the optimal treatment strategy for early stage HL is still the subject of intense debate [1, 7]. Between 1950 and 1980, radiotherapy (RT) was preferentially employed since it was considered a less toxic curative approach than MOPP. Later trials revealed that the risk of relapse in non-irradiated sites was approximately 20–30% and that many of these relapsed patients were rescued by chemotherapy. It therefore became interesting to determine whether combined modality therapy (chemotherapy+radiotherapy, CT+RT) might improve the results as compared to radiotherapy [8–12]. Moreover, the late risk of developing second tumors and coronary heart disease after chest radiotherapy led to reconsider the application of involved or extended field radiotherapy in front line treatment [13–17]. Over the last decade, some trials have explored the possibility of treating HL patients with CT alone [18–20]. There is now increasing evidence that early stage HL patients are likely to be cured by four to six courses of ABVD alone, thus avoiding RT altogether [1, 7, 21].

In order to document the application of these new therapeutic concepts and to verify the outcome of early stage HL patients, we retrospectively reviewed the clinical features, therapy, and long-term outcome of 139 stage I–II HL patients who were diagnosed and followed up in an Italian northern region (Liguria) from 1995 to 2007, and who received either chemotherapy (ABVD) alone or a combined modality treatment (CT+RT).

## Patients and methods

Clinical data were retrospectively collected through the analysis of records of HL patients diagnosed and treated in eight oncology–hematology divisions from 1995 to 2007. Physicians in charge in different hospitals were interviewed to review the charts. The staging procedures included physical exam, total body CT scan, and bone marrow biopsy.

Only stage I and II HL with available follow-up information on response to therapy, long-term outcome, and toxicity were included in the study. Histological type was reassessed according to the current World Health Organization Classification [22]. Bulk disease was defined

as a nodal tumor mass >10 cm. Response to therapy was assessed with physical and radiological imaging (ultrasonography and CT). Only in the last 5 years, 18-FDG PETs have been employed in defining initial stage and response as well.

The median follow-up is 60 months (range 12–175).

Overall survival (OS) was calculated from the beginning of treatment to death by any cause, or to the last follow-up visit. Disease-free survival (DFS) was calculated from the date of the first complete remission to the first relapse. Overall DFS and overall survival (OS) curves were calculated according to the Kaplan and Meier method. Univariate logistic-regression methods were used to evaluate the prognostic importance of various characteristics with respect to complete remission (CR) achievement and overall survival. We considered a two-tailed *p* value of 0.05 or less as statistically significant.

## Patients' features and therapy

Sixty-three patients received chemotherapy alone (CT group) and 76 received an association of CT and radiotherapy (CT+RT group).

**Table 1** Patients' clinical and histological features (all patients)

Patients	139
Male/female	58 (42%)/81 (58%)
Median age (range)	31 (14–79)
Histology	
Nodular sclerosis (NS)	115 (83%)
Type I	24/115 (21%)
Type II	30/115 (26%)
Not specified	61/115 (53%)
Lymphocyte prevalence (PL)	14/139 (10%)
Mixed cellularity (MC)	10/139 (7%)
Presentation	
Above the diaphragm	132 (95%)
Below the diaphragm	7 (5%)
Mediastinal involvement	83 (60%)
Mediastinal bulky	17/83 (20%)
Stage	
I A	13 (9%)
I B	5 (4%)
I E	1 (1%)
II A	71 (50%)
II B	49 (35%)
Hematological parameters	
Median leukocytes x 10 <sup>9</sup> /L (125 pts)	9.150 (4.2–2.7)
Median Hb g/dl (125 pts)	13 (8.4–17)
Median plt x 10 <sup>9</sup> /L (121 pts)	309 (86–574)
Median albumin g/dl (93 pts)	4 (2.1–5.1)
Median LDH U/l (121 pts)	408 (59–1100)
Above normal range	35/121(29%)
Median ESR (in 80 pts)	28 mm/h (2–187)
Median PCR (in 54 pts)	3.4 (0–139)
Median β2 microglobulin mg/l (in 49 pts)	1.8 (0.2–15)

**Table 2** Patients' clinical and histological features according to first line therapy

	First line therapy without radiotherapy (RT) N=63 (45%)	First line therapy including RT N=76 (55%)	p value
Male/female	25 (40%)/38 (60%)	33 (43%)/43 (57%)	0.55
Median age	31	30	
Histology			0.88
LP	7 (11%)	7 (9%)	
NS	52 (83%)	63 (83%)	
MC	4 (6%)	6 (8%)	
Mediastinal involvement	31 (49%)	52 (68%)	0.01
Mediastinal bulky disease	8/31 (26%)	11/52(21%)	0.77
Stage			0.91
I A	6 (10%)	7 (9%)	
I B	2 (3%)	3 (5%)	
I E	–	1 (1%)	
II A	32 (51%)	39 (51%)	
II B	23 (36%)	26 (34%)	
LDH above normal range	11/50 (22%)	24/71 (34%)	0.11

LP lymphocyte predominance, NS nodular sclerosing, MC mixed cellularity

Radiotherapy was started within 1 month of the completion of chemotherapy.

Target volumes for involved-field radiotherapy initially included involved nodal regions, while target volumes for extended field included the mantle field, spleen, and para-aortic nodes. Patients received a median of 30 Gy.

Main clinical, laboratory, and histological features of the whole cohort of patients are reported in Table 1, whereas Table 2 reports relevant prognostic data according to the treatment they received.

As shown in Table 2, the two therapeutic groups were comparable for clinical and histologic features. Mediastinal involvement (not bulky) was more frequent in patients receiving combined therapy.

ABVD was the regimen of choice in the CT group (95%). A median of six courses were given. In the CT+RT group, 53% of patients received ABVD and 42% were given the Stanford V regimen.

## Results

### Response to therapy

Details about type of treatment and response to therapy are reported in Table 3.

Briefly, CR rate after CT+RT was higher than what was achieved with CT alone (96% vs. 86%, respectively,  $p=0.03$ ). Although early application of salvage

**Table 3** Response to therapy

	First line therapy without radiotherapy N=63	First line therapy including RT N=76	p value
Chemotherapy			
ABVD	60/63 (95%)	40/76 (53%)	<0.01
Stanford V	–	32/76 (42%)	<0.01
Other	3/63 (5%)	4/76	0.60
Median N courses	6 (3–6)		
Involved field RT	–	40	<0.01
Extended field RT	–	36	<0.01
CR	54 (86%)	73 (96%)	0.03
PR	9 (14%)	2 (3%)	
NR	–	1 (1%)	
CR after further chemotherapy± HDT	58 (92%)	76 (100%)	0.02

HDT high dose therapy with autologous stem cell rescue

**Table 4** Factors affecting CR rate

	CT CR (%)	CT+RT CR (%)	All patients CR (%)
ABVD 6 courses	A: 33/41 (80%)		
ABVD <6 courses	B: 18/19 (95%)		
Stage I	C: 7/8 (87%)	I: 11/11 (100%)	Q: 18/19 (95%)
Stage II	D: 51/55 (93%)	L: 65/65 (100%)	R: 116/120 (97%)
Mediastinal involvement	E: 25/28 (89%)	M: 52/52 (100%)	S: 73/82 (89%)
No mediastinal involvement	F: 30/32 (94%)	N: 24/24 (100%)	T: 53/57 (93%)
Mediastinal bulky	G: 5/9 (56%)	O: 12/12 (100%)	U: 17/22 (77%)
No mediastinal bulky	H: 16/19 (84%)	P: 40/40 (100%)	V: 109/117 (93%)

Statistical comparison between groups of data: A vs. B  $p=0.14$ ; C vs. D  $p=0.88$ ; E vs. F  $p=0.43$ ; G vs. H  $p=0.12$ ; C vs. I  $p=0.42$ ; D vs. L  $p=0.04$ ; E vs. M  $p=0.04$ ; F vs. N  $p=0.32$ ; G vs. O  $p=0.02$ ; H vs. P  $p=0.03$ ; Q vs. R  $p=0.86$ ; S vs. T  $p=0.31$ ; U vs. V  $p=0.99$

chemotherapy±high dose therapy (HDT) with autologous stem cell rescue to partial responders in the CT group increased the number of complete responses, a statistically significant difference in the final CR rate was still present (92% vs. 100% in CT and CT+RT groups, respectively,  $p=0.02$ ).

Table 4 reports the CR rate according to number of ABVD courses, stage, mediastinal involvement, or bulky disease. Statistical analysis revealed no clinical factors affecting the CR rate in either of the therapeutic groups, or in the cohort as a whole. In stage II patients and in those with mediastinal involvement or mediastinal bulky disease, the combined modality of therapy increased the probability of achieving CR.

#### Outcome, long-term toxicity

Relapse rate (12%) was the same in both groups (Table 5) and DFS curves (Fig. 1) were comparable (83% and 80% in CT and CT+RT groups, respectively,  $p=0.47$ ). All relapses occurred within 38 months. Neither stage (I or II) nor mediastinal bulky disease affected the incidence of relapse (Table 6). Treatments at first relapse are reported in Table 5. There was no statistically significant difference with regards to the complete response rate to salvage therapy between the CT group (71%) and the CT+RT group (43%) ( $p=0.27$ ).

Sixty-one (97%) patients in the first cohort (CT alone) and 73 patients (96%) among those who were initially treated with CT+RT are alive after a median follow-up of 50 and 90 months, respectively. Causes of death, mostly disease related, are reported in Table 7.

Figure 2 shows that overall survival of the two therapeutic groups is comparable. No second tumors have been reported among patients receiving chemotherapy alone, whereas a second neoplasia has been diagnosed in four patients in the CT+RT group (5%,  $p=0.09$ ). The

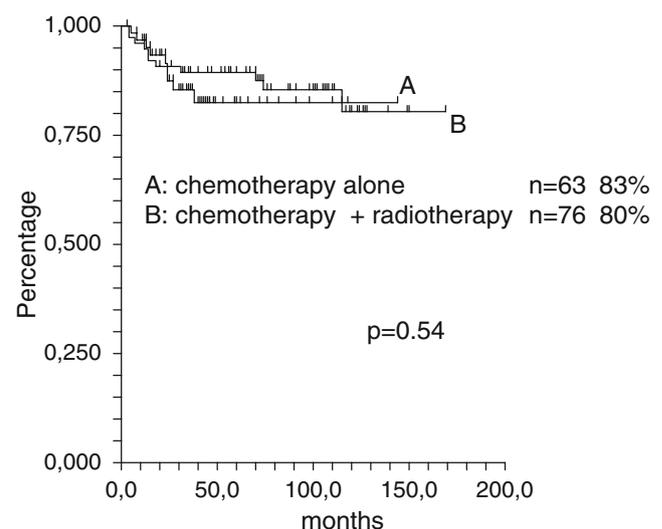
development of a tumor in two cases (breast and lung cancer) is possibly radiotherapy related.

Figure 3 reports the second neoplasia-free survival rates of the CT and CT+RT groups (100% and 92%, respectively,  $p=0.2$ ).

One patient treated with CT+RT developed coronary heart disease.

#### Discussion

The aim of this retrospective study was to review long-term results and toxicity in the management of early stage HL in a regional Italian area (Liguria). We found that the front line therapeutic approach always included chemotherapy, which was followed by radiotherapy in 55% of patients (see Table 7). However, our analysis was not aimed at



**Fig. 1** Stage I–II Hodgkin's lymphoma disease-free survival

**Table 5** Relapse, therapy at relapse

	First line therapy without radiotherapy (RT) <i>N</i> =58 complete responses	First line therapy including RT <i>N</i> =76 complete responses	<i>p</i> value
Relapses	7 (12%)	9 (12%)	0.62
CR length in relapsed patients months	15 (5–38)	14 (4–31)	
Therapy of relapse			
Chemotherapy (CT)+RT	2/7 (28.6%)	2/9 (22%)	0.48
CT	1/7 (14.2%)	3/9 (34%)	
CT+HDT	2/7 (28.6%)	1/9 (11%)	
RT alone	2/7 (28.6%)	1/9 (11%)	
No therapy	–	2 (22%)	
Response to therapy at relapse			
CR	5/7 (71%)	3/7 (43%)	0.28
PR	–	2/7 (28.5%)	
Not evaluated	2/7 (29%)	2/7 (28.5%)	

comparing these therapeutic strategies. This retrospective review of the Ligurian experience confirms the previously reported clinical features and histologic distribution of early stage HL, including the rarity of presentation below the diaphragm (5%) [23]. The only relevant exception to reported data is that females are more frequently affected than males. The longer median follow-up in the CT+RT group is due to the fact that, for a long period of time, CT+RT was considered standard therapy for limited stage HL patients.

Long-term outcome data show that a high cure rate can be achieved with limited side effects in the vast majority of early stage HL patients using either of the therapeutic strategies.

Considering the retrospective, non-randomized nature of this survey, a comparison between the two treatment modalities regarding the efficacy at inducing CR is beyond its aims. Moreover, as many as 36 (42%) patients in the combined modality group did not receive ABVD (Stanford V). Despite these limits, we show that the upfront

combination of CT and involved or extended field RT led to an increased CR rate among stage II patients, in those with mediastinal involvement and mediastinal bulky disease. However, long-term observation showed that omitting radiotherapy did not influence relapse rate or duration of first CR, even in patients with mediastinal involvement or bulky disease. As a matter of fact, both groups showed relapse rates of about 12% and response to salvage treatment was similar.

The administration of ABVD alone as first line therapy is associated with a more frequent and earlier use of HDT compared to the combined modality approach (8 vs 2 patients, respectively).

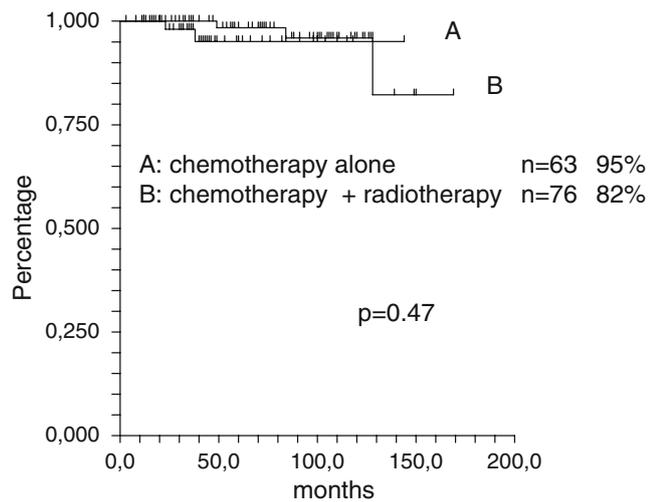
Our study shows that both CT and CT+RT allow us to achieve optimal long-term control of early stage HL, with no statistically significant differences in DFS or in overall survival, as confirmed by a number of recent randomized trials [18–20].

Nonetheless, radiotherapy, especially when administered in extended field has been associated with an

**Table 6** Factors affecting relapse rate

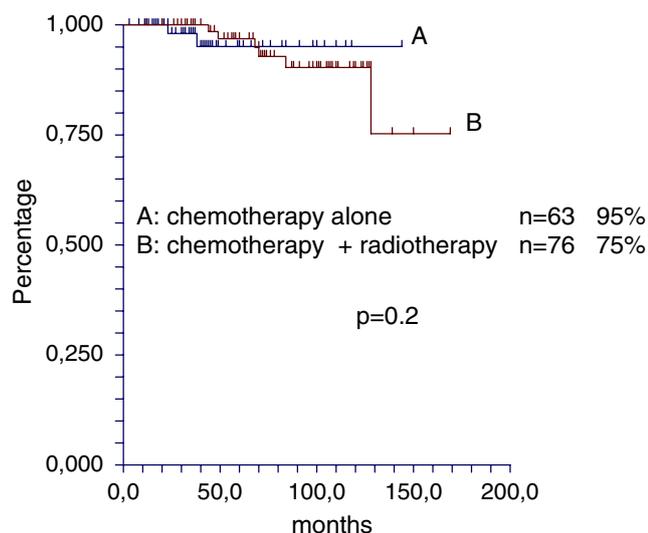
	CT Relapses (%)	CT+RT Relapses (%)	All patients Relapses (%)
Stage I	C: 1/7 (14%)	I: 1/11 (9%)	Q: 2/18 (11%)
Stage II	D: 6/51 (12%)	L: 8/65 (12%)	R: 14/116 (12%)
Mediastinal involvement	E: 5/26 (19%)	M: 3/52 (6%)	S: 8/78 (10%)
No mediastinal involvement	F: 2/32 (6%)	N: 6/24 (25%)	T: 8/56 (14%)
Mediastinal bulky	G: 2/8 (25%)	O: 1/12 (8%)	U: 3/17 (18%)
No mediastinal bulky	H: 5/50 (10%)	P: 2/40 (5%)	V: 13/114 (11%)

Statistical comparison between groups of data: C vs. D  $p=0.80$ ; E vs. F  $p=0.13$ ; G vs. H  $p=0.95$ ; I vs. L  $p=0.61$ ; M vs. N  $p=0.02$ ; O vs. P  $p=0.87$ ; C vs. I  $p=0.64$ ; D vs. L  $p=0.58$ ; E vs. M  $p=0.08$ ; F vs. N  $p=0.06$ ; G vs. O  $p=0.34$ ; H vs. P  $p=0.32$ ; Q vs. R  $p=0.63$ ; S vs. T  $p=0.83$ ; U vs. V  $p=0.87$



**Fig. 2** Stage I–II Hodgkin's lymphoma overall survival

increased risk of second neoplasia [13, 15, 17]. In our series, a second tumor was diagnosed in four patients who had been exposed to RT, even though a clear relationship with RT was only found in two of the cases. No second tumors occurred among the patients who had not been exposed to RT, and despite the increased use of further salvage chemotherapy and HDT, no secondary myelodysplastic syndromes or sAML were observed either. However, there is no statistically significant difference in the second neoplasia-free survival rate in the two therapeutic groups, and the second neoplasia was the cause of death in only one patient. Only one patient who received mediastinal radiotherapy developed coronary disease. However, an increased incidence of delayed heart complications is expected in the future in patients submitted to mediastinal



**Fig. 3** Stage I–II Hodgkin's lymphoma second neoplasia-free survival

**Table 7** Long-term outcome and late toxicities

	First line therapy without radiotherapy (RT) N=63 pts	First line therapy including RT N=76 pts	p value
First CR length, months	33 (7–134)	73 (7–144)	
Patients alive	61 (97%)	73 (96%)	0.59
Patients dead	2 (3%)	3 (4%)	0.59
Overall survival, months	40 (12–144)	87 (12–175)	
Median follow-up	55	98	
Patients with second neoplasia	–	4 (5%)	0.09
Rectum	–	1	
Lung	–	1	
Breast	–	1	
Prostate	–	1	
Coronary heart disease	–	1	
Causes of death			
HL	2	2	
Second neoplasia	–	1	
Patients undergoing salvage HDT	8	2	0.05

radiotherapy, as previously reported [14, 15]. A longer period of observation is needed to reveal small differences in toxicity and non-lymphoma-related mortality. Hoppe showed in fact that the risk of death from Hodgkin's disease is 17% at 15 years of follow-up and increases only slightly thereafter, whereas the risk of death from other causes is also 17% at 15 years, but increases sharply thereafter for at least 25 years [13].

Although quality of life has not been specifically addressed, both initial therapeutic strategies were well tolerated and did not strongly affect quality of life. This may be related to the improved radiotherapy techniques as well as to the use of advanced supportive therapy.

In conclusion, our retrospective study shows that an upfront combination of CT and limited RT is an effective and well-tolerated option for early stage HL because it achieves a very high percentage of long lasting CR, even if the use of RT is associated with a certain risk of developing a second tumor.

Administering four to six courses of ABVD as the first line approach allows us to obtain similar, optimal,

long-term disease control, as indicated by the DFS and overall survival curves without exposing patients to the risk of a second neoplasia. There were no differences in the overall survival and second neoplasia-free survival of CT and CT+RT patients in our study; however, the small number of patients in our cohort may have prevented us from identifying a statistically significant difference. Innovative techniques, such as 3-D radiotherapy or radiotherapy with modulated intensity, may reduce the early and late toxic effects [14, 24–26], although results must be confirmed by controlled studies. Chemotherapy alone proved to be effective and can be used in early stage HL patients when RT is not available or when patients or physicians decide to exclude it from the first line approach.

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