



Retrospective Evaluation of Patients Diagnosed with Stage I-II Supradiaphragmatic Presentation Hodgkin's Lymphoma: Treatment Effect and Late-side Effect

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Abstract

Objective: The long-term treatment outcomes of patients with Hodgkin's lymphoma are important, as such patients have increased lifespans. Treatment options must be evaluated particularly for secondary malignancy risk and heart health.

Methods: We retrospective re-evaluated a total of 113 patients (all) who had received radiotherapy and/or chemotherapy for stage I-II disease out of 320 patients with Hodgkin's lymphoma who presented to and were treated at the Okmeydanı Training and Research Hospital Radiation Oncology Clinic between January 1974 and December 1997, and who then continued regular follow-up. I this period, only anterior mantle and anterior-posterior mantle treatment and/or chemotherapy, were evaluated for long-term side effects and efficacy.

Results: We compared 42 patients who had received only anterior radiotherapy (group 1) and 71 patients who had received anteroposterior radiotherapy (group 2). Recurrence was detected in 15 patients in group 1 and in 20 patients in group 2. Six patients in group 1 and 16 patients in group 2 died. The 5-year survival rate for group 1 and group 2 was 77.18% and 71.33%, respectively, and the respective 10-year survival rates were 70.8% and 67.16%. The secondary malignancies detected were lung cancer (3 patients), hemangiosarcoma (1 patient), larynx carcinoma (1 patient), neurofibromatosis (1 patient), and thyroid carcinoma (1 patient).

Conclusion: We discuss the patients' quality of life in addition to the possible late adverse effects of the treatments given the increased curability and survival in Hodgkin's lymphoma. The aim is to minimize the treatment-related adverse effects, given patients' longer life expectancy. For this reason, it is currently being tried to improve the quality of life and survival by reducing the risk of organs and heart doses in terms of secondary cancer such as lung and breast, ischemic heart disease by different methods such as anterior field radiotherapy. But still, giving up smoking and increasing physical activities must be recommended, particularly against lung cancer and ischemic heart disease.

Keywords: Hodgkin's lymphoma, anterior field radiotherapy, chemotherapy, secondary malignancy, ischemic heart disease

INTRODUCTION

Hodgkin's lymphoma has successfully been treated in our clinic with radiotherapy devices since the 1970s. The use of chemotherapy and radiotherapy has yielded better survival results. However, patients with long-term life expectancy develop various adverse effects, particularly cardiovascular disease, and treatment-associated secondary malignancies.

The Dutch researchers Schaapveld et al. (1) reported the secondary cancer risks of patients they had treated between 1965 and 2000. Van Nimwegen et al. (2) reported the association between radiotherapy and coronary arterial diseases in 1965-1995. Milgrom et al. (3) compared anterior field radiation and anteroposterior radiation for decreasing cardiac and secondary malignancy risk. Heart doses measured better in only anterior field radiation, and breast and lung doses measured lower



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in anteroposterior radiation. The authors indicated that the anterior field may be preferred mainly in anterior mediastinal and neck involvement, but that more studies are required.

Long term side effects of treatments have been questioned, especially in Hodgkin's lymphoma, which is nowadays considered a cure disease. As can be seen from the above studies, ischemic heart disease and second cancer that may develop years after Hodgkin's lymphoma treatment. To reduce these risks different radiotherapy techniques are applied according to the location of the disease. For this purpose, in three studies in 2017 ASTRO, it was predicted that only anterior field or antero-posterior radiation technique could reduce these side effects in the long term. In our clinic, only anterior field or anterior posterior radiotherapy was applied for a period. We retrospectively reviewed all patients (113 patient) who had been treated with Hodgkin's disease for a period of time with these treatment techniques and investigated the long-term efficacy and side effects of these methods.

In light of the above information, we re-evaluated a total of 113 patients who had received radiotherapy and/or chemotherapy for stage I-II disease out of 320 patients with Hodgkin's lymphoma who presented to and were treated at the Okmeydanı Training and Research Hospital Radiation Oncology Clinic between January 1974 and December 1997, and who then continued regular follow-up. Forty two patients (group 1) had been treated with only anterior field radiation using 8-MV photon bolus and/or treatment was completed using electron therapy in case of the presence of missing dose in the superficial lymph nodes; 71 patients (group 2) had been treated with anteroposterior field radiation. The patients were retrospectively investigated for secondary malignancies, cardiac diseases, and to compare the two radiotherapy methods in addition to evaluating general supradiaphragmatic stage I-II Hodgkin's lymphoma.

METHODS

We retrospective re-evaluated a total of 113 patients (all) who had received radiotherapy and/or chemotherapy for stage I-II disease out of 320 patients with Hodgkin's lymphoma who presented to and were treated at the Okmeydanı Training and Research Hospital Radiation Oncology Clinic between January 1974 and December 1997, and who then continued regular follow-up. In this period, our radiotherapy technique used which only anterior mantle and anterior-posterior mantle treatment with and/or chemotherapy, were evaluated for long-term side effects and efficacy. For a better evaluation of the follow-up, 10-year results were given primarily in these patients. We investigated the distribution characteristics, staging and treatment methods,

recurrence regions and rates, survival times in accordance with group, and treatment type in detail, second malignancies and ischemic heart disease. Only anterior field mantle using bolus with 8-MV photon to 42 patients (group 1), while 71 patients (group 2) received anterior posterior field mantle 8-MV photon therapy.

If there is a lack of dose from the anterior area, it is completed by electron boost. Mean radiotherapy doses is 36 Gy/180-200 cGy daily.

Given the retrospective design of the study, informed consent and ethics committee approval were not obtained. This article complies with the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association Declaration of Helsinki.

Statistical Analysis

Patient data collected in the scope of the study were analyzed with the SPSS for Windows 21.0 package program. For discrete data, frequency and percentage were given as descriptive values. Kaplan-Meier method was used for survival analysis. "Chi-square test" was used to compare two discrete groups. Results were considered statistically significant when p value was less than 0.05.

The Kaplan-Meier method was used for survival analysis, and significance was evaluated using the chi-square test (4).

RESULTS

For the years we included in the study, the shortest patient follow-up was 36 months and the longest was 285 months. But long-term follow-up is 581 months and median overall survival (OS) was 30 years. Pretreatment patient and tumor characteristics are presented in Table 1. The disease free survival for group 1 patients with a complete response at 10 years were 62% [95% confidence interval (CI): 58-66], for group 2 patients were 60% (95% CI: 56-64). Progression free survival at 10 years for group 1 was 59% (95% CI: 55-63), group 2 was 58% (95% CI: 54-62). The median age in group 1 and group 2 was 33 years and 34 years, respectively. Distribution of the statistical analysis are showed Table 2. Rates of chemotherapy administration by stages is presented in Table 3.

The secondary malignancies detected were lung cancer (3 patients), hemangiosarcoma (1 patient), larynx carcinoma (1 patient), neurofibromatosis (1 patient), and thyroid carcinoma (1 patient). Breast cancer and ischemic heart disease were not detected during the study period.

Kaplan-Meier survival curve for all patients is shown in Figure 1.

In group 1, the 5-year and 10-year survival rate was 77.18% (95% CI: 73-81) and 70.88% (95% 66-75), respectively. Kaplan-Meier survival curve for group 1 is shown in Figure 2.

In group 2, the 5-year and 10-year survival rate was 71.33% (95% 67-76) and 67% (95% 63-71), respectively. Kaplan-Meier survival curve for group 1 is shown in Figure 3.

All groups 30 years survival 60% (95% CI: 56-64) (group 1 61.5%, group 2 58.5%).

Characteristics	n	%
Group		
Group 1	42	37.2
Group 2	71	62.8
Gender		
Male	63	55.8
Female	50	44.2
Histology		
L. rich	28	24.8
Nodular	32	28.3
Mixed	50	44.2
L. poor	3	2.7
Stage		
IA	26	23.0
IB	8	7.1
IIA	34	30.1
IIB	45	39.8
Subtotal nodal irradiation		
Positive	40	35.4
Negative	73	64.6
Recurrence		
Yes	35	31.0
No	78	69.0
Mortality		
Alive	91	80.5
Deceased	22	19.5

No statistical difference was detected for both groups.

Statistical note: In addition, the detailed mean and median survival values of the subgroups were not included for this disease, which was cured in parallel with current developments since it was beyond the primary purpose of the study.

Gender	Group 1		Group 2		p value
Male	24	57.1	39	54.9	0.843*
Female	18	42.9	32	45.1	
p value	0.235**		0.189**		
Histology					
L. rich	8	19.0	20	28.2	0.177**
Nodular	10	23.8	22	31.0	
Mixed	23	54.8	27	38.0	
L. poor	1	2.4	2	2.8	
p value	0.192**		0.345**		
Stage					
IA	11	26.2	15	21.1	0.106**
IB	2	4.8	6	8.5	
IIA	14	33.3	20	28.2	
IIB	15	35.7	30	42.3	
p value	0.155**		0.148**		
Subtotal nodal irradiation					
Negative	25	59.5	48	67.6	0.655*
Positive	17	40.5	23	32.4	
Recurrence					
No	27	64.3	51	71.8	0.554*
Yes	15	35.7	20	28.2	
Recurrence, specify					
No	27	64.3	51	71.8	0.349**
Internal	2	4.8	11	15.5	
External	13	31.0	9	12.7	
Survival					
Alive	36	85.7	55	77.5	0.285*
Deceased	6	14.3	16	22.5	

*Fisher exact test, **Pearson chi-square test

Group 1	IA		IB		IIA		IIB		p value
Did not receive	8	72.7			10	71.4			0.000*
Received	3	27.3	2	100	4	28.6	15	100.0	
Group 2	IA		IB		IIA		IIB		p value
Did not receive	13	86.7	3	50.0	7	35.0	1	3.3	0.000*
Received	2	13.3	3	50.0	13	65.0	29	96.7	

*p<0.05; Pearson chi-square

DISCUSSION

This study with long-term results showed that the risk of ischemic heart disease, second solid cancer risks did not change profound among patients with Hodgkin's lymphoma who were treated.

In the present study, the male:female ratio was 1.26, which is statistically compatible with the rate of 1.26 in the literature (5,6).

Here, the median age was 34 years; however, it is 26 years in the literature. This inconsistency stems from the transfer of pediatric patients to another center for treatment.

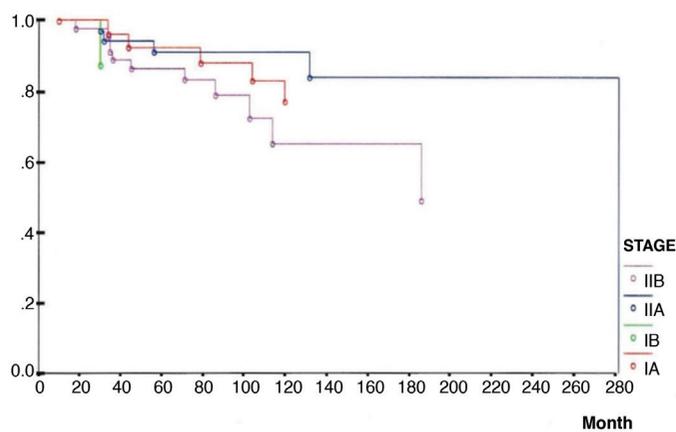


Figure 1. Kaplan-Meier survival curve for all patients

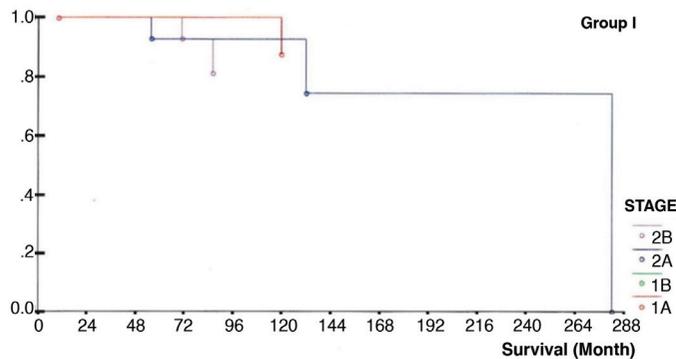


Figure 2. Kaplan-Meier survival curve for group I

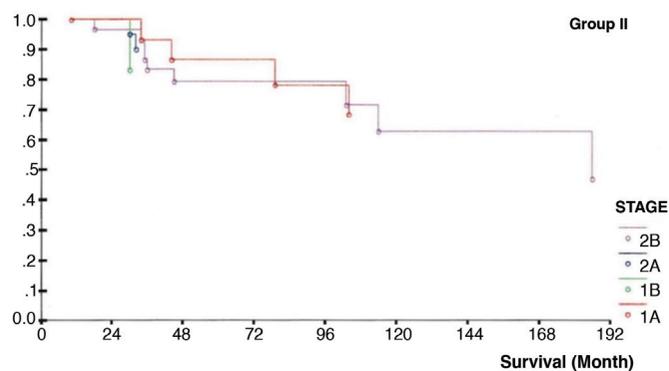


Figure 3. Kaplan-Meier survival curve for group II

There was a greater proportion of an obvious mixed type histology in the patients included in our study; however, nodular sclerosing histology was the most frequently detected histologic type in the literature (5,7). One reason is that cases that did not fit the other histologic types tended to be included in the mixed type. The most important reason is that, compared with the other histologic types, etiologic association between the mixed type with infection agents is more frequently detected in Turkey as compared the developing countries. In particular, the development of this histologic type has been attributed to Epstein-Barr virus infection (5,8-12).

In the present series, both groups had similar survival rates. The 5-year survival rate for stage IA and stage IIA disease in group 1 was 83.3% and 68.1%, respectively; the respective 10-year survival rates were 77.78% and 58.92%, respectively. In group 2, the 5-year survival rates were 90% and 61.9%, respectively, and that for 10-year survival was 89.74% and 67.6%, respectively. These results are statistically compatible with the literature, and we suggest that the difference between the 5-year and 10-year survival is due to the recognition of the total 5 patients as exitus from both groups after initially presenting as controls in the first 5 years; however, they then did not show up in the controls.

In group 1, the 5-year survival rate for stage IB and stage IIB disease was 100% and 81.47%, respectively, and that for 10-year survival was 100% and 76.47%, respectively. In group 2, the 5-year survival rate was 83.3% and 84.46%, respectively, and that for 10-year survival was 81.62% and 47.45%, respectively. There is no difference in disease-free survival and OS between both radiotherapy techniques.

Secondary malignancies may be detected in the long-term follow-up of Hodgkin's lymphoma, including in particular leukemia, non-Hodgkin's lymphoma, and solid tumors. The risk of leukemia and lung cancer is increased 3-7 years after treatment in patients who receive an alkylene agent and procarbazine (mechlorethamine, vincristine, procarbazine, prednisone) (13,14). Secondary solid tumors are more frequently detected due to radiotherapy (14), and generally develop after 7-10 years. The most frequently detected malignancies are lung, breast, and gastrointestinal malignancies (15-17).

In the present series, secondary primary tumors were detected in the form of 3 lung carcinomas in both groups (group 1, 2 patient; group 2, 1 patients), hemangiosarcoma in 1 patient (group 2), larynx carcinoma in 1 patient (group 1), neurofibromatosis in 1 patient (group 2), and thyroid carcinoma in 1 patient (group 1). Interestingly, we detected

no breast cancer during our study period, which is suggested to be associated mainly with the procarbazine chemotherapy administered in that period (18-26). However, long-term follow-up after the study detected breast cancer in 1 patient, and heart attack due to coronary artery disease in 2 patients. The death of the younger patient was associated with the disease.

CONCLUSION

We discuss the patients' quality of life in addition to the possible late adverse effects of the treatments given the increased curability and survival in Hodgkin's lymphoma. The aim is to minimize the treatment-related adverse effects, given patients' longer life expectancy. For this reason, it is currently being tried to improve the quality of life and survival by reducing the risk of organs and heart doses in terms of secondary cancer such as lung and breast, ischemic heart disease by different methods such as anterior field radiotherapy. Treatment fields must be minimized as far as possible with guidelines using current modern radiotherapy techniques.

In our study, the incidence of ischemic heart disease, especially in patients with anterior mediastinal localized Hodgkin lymphoma, can be a protective factor for single anterior field radiotherapy. However, attention should be paid in terms of breast cancer in women. Anterior-posterior radiotherapy can also be used in patients at risk of lung cancer, since fields receiving high volumetric doses will decrease. But still, giving up smoking and increasing physical activities must be recommended, particularly against lung cancer and ischemic heart disease. Patients receiving treatment for Hodgkin's lymphoma must have regular heart and breast controls.

Ethics

Ethics Committee Approval: This article complies with the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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