

# Evaluating the Survival Rate and the Secondary Malignancies after Treating Hodgkin's Lymphoma Patients with Chemotherapy Regimens

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## ABSTRACT

In this study we surveyed the average survival time of the treated Hodgkin's lymphoma patients and also the side effects and malignancies occurring secondary to the treatment. This is a retrospective study of patients referring to Ahwaz's Shafa hospital in a period of 10 years diagnosed with Hodgkin's lymphoma without any age restriction. After gathering all their data, we calculated their survival rate and the chance for a relapse and the secondary malignancies.

389 patients were included in the study with an average age of 27.5 years old and they had received only chemotherapy regimens. 87.9% of them had been treated by ABVD and 12.1 % by Stanford V regimen. 23.1% of them experienced a relapse and 13.1% of all patients, passed away during the study. Secondary malignancies were observed in 11 cases. An overall mean survival time of 295.31 months was resulted. The secondary malignancies after treating Hodgkin's lymphoma patients are different between chemotherapy regimens and chemotherapy – radiotherapy.

**KEY WORDS:** Hodgkin, Chemotherapy, Survival, Second malignancy

## INTRODUCTION

In the 19th century a unique illness currently known as Hodgkin's Lymphoma was recognized for the first time. By the early years of the next century, this type of lymphoma was differentiated from other diseases with the same symptoms and other lymphadenopathies, by its typical microscopic appearances. About 50 years ago a definite diagnosis and a curative treatment which is initiated

with radiotherapy, followed by multi agent chemotherapy was introduced. Thus, Hodgkin's lymphoma is being sufficiently and accurately diagnosed due to the good understanding of its specific presentations and clinical behaviors.<sup>1</sup>

Distinguishing between its two major branches is of major concern; which are the classic variety including the nodular sclerosis, mixed cellularity, lymphocyte rich or lymphocyte depleted subtypes

and the nodular lymphocyte predominant Hodgkin's lymphoma, a rare subtype seen in approximately 5% of cases.<sup>2</sup>

Hodgkin's lymphoma before finding a reliable treatment was succumbing patients as a fatal illness with its presentations like progressive bulky lymphadenopathies eventually compromising vital organ functions and constitutional symptoms such as, weight loss, cachexia, inanition and death at the end.

Currently chemotherapy regimens and radiotherapy courses cure at least 80% of patients, mostly with the very first line of therapy. Therefore, fortunately, late manifestations of the disease have become more uncommon. However, its recurrence affects a minority of patients.

The most important concern for a clinician is predicting the odds for a relapse. The upside is that the disease relapses soon after completion of primary treatment. More specifically half the recurrences happen within 2 years of primary treatment and up to 90% occur before 5 years. Occurrence of a relapse after 10 years is rare and after 15 years the risk of developing lymphoma is same as its risk in the normal population.<sup>3</sup> As it is obvious from above, after 10 years the major aspect of follow up is assessed for late complications, which is mostly about development of secondary neoplasm.<sup>4-6</sup> Hodgkin's Lymphoma has the highest incidence in two age ranges that are, first between 15 and 34 and the second is after 55, therefore it is one of the most common cancers in young population. Having an available curative therapy makes Hodgkins' lymphoma a cancer with favorable outcomes. Although it has a low incidence and it is mostly curable, its propensity for happening in productive years of life, brings about tons of morbidity and also a significant mortality rate. After childhood cancers and gonadal neoplasms, hodgkin's lymphoma ranks third in the average amount of years lost for a cancer.<sup>7,8</sup>

In this study we tried to survey the average survival time of the treated patients and also assessing the side effects and malignancies occurring secondary to the treatment. In addition in our study we used two types of chemotherapy regimens (ABVD and Stanford) and we compared the survival time in these two treatment groups.

## MATERIALS AND METHODS

In this survey we went through medical documents of patients referring to Shafa oncology and hematology center (in the south west of Iran) from 2002 until the end of the year 2012, diagnosed with hodgkin's lymphoma (diagnosed by the opinion of two pathologists) without any age restriction. These patients had undergone chemotherapy regimens and we gathered their demographic, clinical, histopathology and laboratory data and we also included whether or not that they had have bone marrow involvement and their stage of the disease based on Ann Arbor staging system. Also their response to treatment, recurrence of the disease, secondary malignancies and mortality information was obtained from the documents and any deficiency in the information was fulfilled by a phone call to the patients.

All the patients who had undergone radiotherapy were excluded from the survey as our goal was to determine the effects of the isolated chemotherapy. The follow up period was from 2 months up to 10 years. The first line of the treatment is ABVD regimen but in previous years there were patients treated with Stanford regimen and also for patients with bulky lymphadenopathies radiotherapy had been operated; so we could have a limited comparison between these methods beside our main goals.

## Statistical Analysis

Demographic and clinical characteristics were presented as means and standard deviations for continuous variables, or frequencies and percentages for categorical variables. To depict the distribution of age at diagnosis in this population, a histogram was applied. For estimating the mean survival time of the patients in each treatment group and in the whole sample, Kaplan-Meier method was applied. To investigate the effect of the chemotherapy regimens on survival of the patients, Cox regression model was applied to adjust for the stage of the disease and age. For a better fit of the model, stage variable was recategorized into two categories (stage I or II and stage III or IV) and age was standardized and entered into the model. Variables just with P value less than <0.10 in univariate analysis entered into the multiple Cox

regression model. Hazard ratio with 95% confidence interval was calculated for the model. The proportional hazard (PH) assumption was checked by log-log survival curve. A P value less than 0.05 was considered statistically significant. All analyses were carried out using SPSS for Windows v.16.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

In this survey, 389 patients were studied with a mean age of 27.5 years (standard deviation=15.8 years). Most of the patients were between 20 to 40 years (42.2%) and were in the stage II of their disease (45.0%). As shown in Figure 1, the distribution of age was unimodal in this population. 228 patients (58.6%) were male. Most of the patients were treated by an ABVD regimen (87.9%) and 12.1% by Stanford regimen. Relapse occurred in 90 (23.1%) patients and Fifty one patients (13.1%) passed away during the study time. Secondary malignancies was observed in 11 cases (2.8%) (Table1). Based on Kaplan-Meier estimations, the mean survival time in general was  $295.31 \pm 28.22$  months and this figure was  $207.86 \pm 10.63$  and  $228.65 \pm 39.53$  in ABVD and Stanford treatment groups, respectively. Results of Cox multiple regression model with survival time as a response variable which adjusted for age and stage of the disease indicated a significant hazard ratio of 3.38 (95% CI ; 1.69-6.74) for Stanford regimen compared to ABVD therapy. Also a same model with relapse as the response variable showed that Stanford treatment had 2.2 times (95% CI; 1.26 – 3.86) more hazard for relapse compared to ABVD treatment (Table 2). Patients with a higher stage of the disease had significantly higher risks for relapses (HR=2.39; 95% CI: 1.51-3.76) and older patients had a significantly higher risk of expiration (HR=1.37; 95% CI: 1.04-1.80).

In Figure 2, cumulative survival curves for both treatment methods at the mean of the covariates in a Cox regression model for the time until death was depicted. As shown in this figure, patients in ABVD treatment had more survival time compared to Stanford treatment. In a same way in Figure 3 which compares treatment groups about the time before relapse, a similar pattern was observed. As shown in Figures 4 and 5, Log-log survival curves for checking

the PH assumption for two studied models were almost completely parallel and PH assumption was completely satisfied.

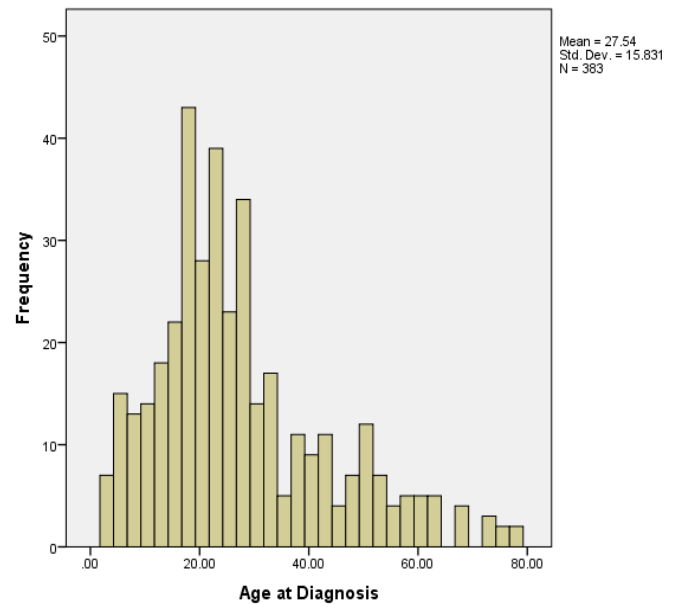


Figure 1: Distribution of age at diagnosis

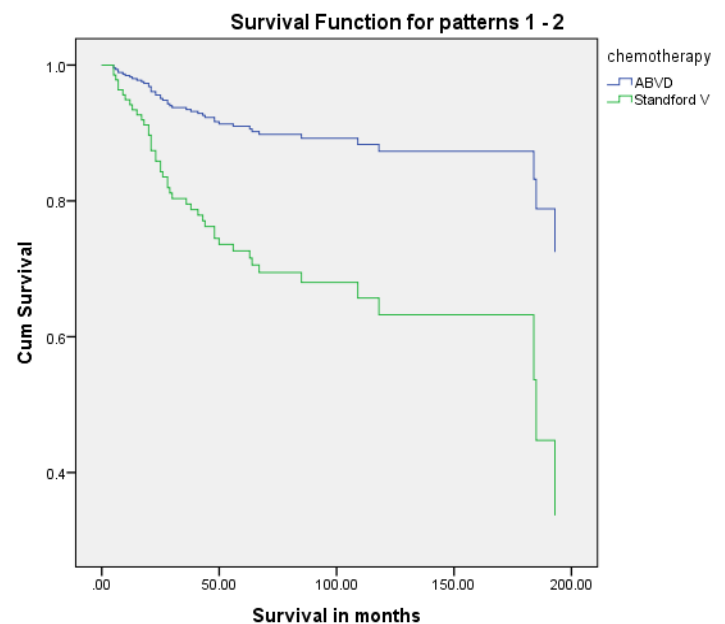


Figure2. Survival curves for survival time for comparing ABVD and Stanford treatments

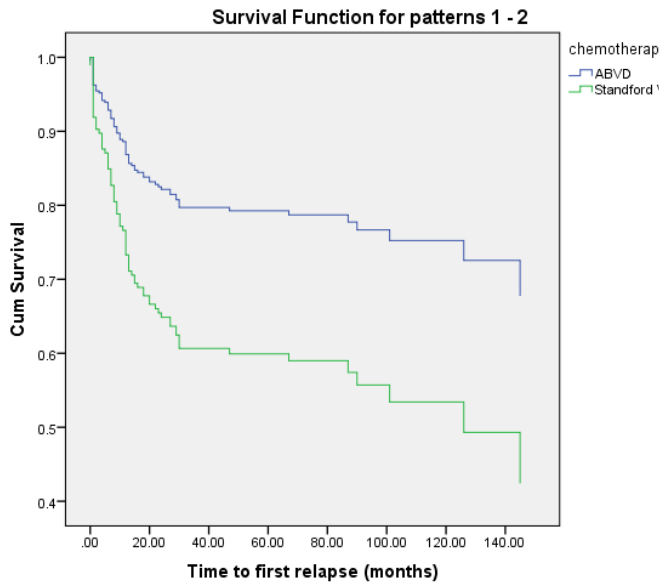


Figure3. Survival curves for relapse time for comparing ABVD and Stanford treatments

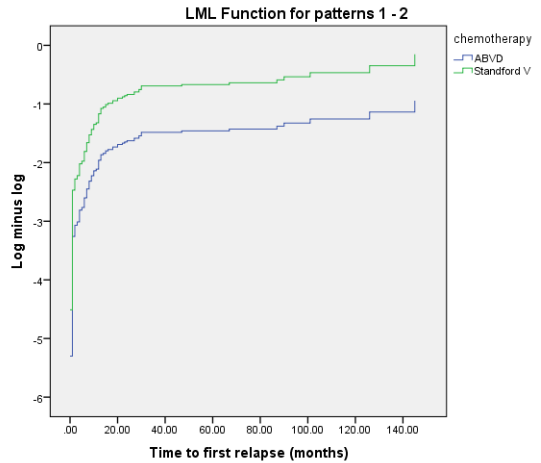


Figure5. Log-log survival curve for checking PH assumption in relapse model

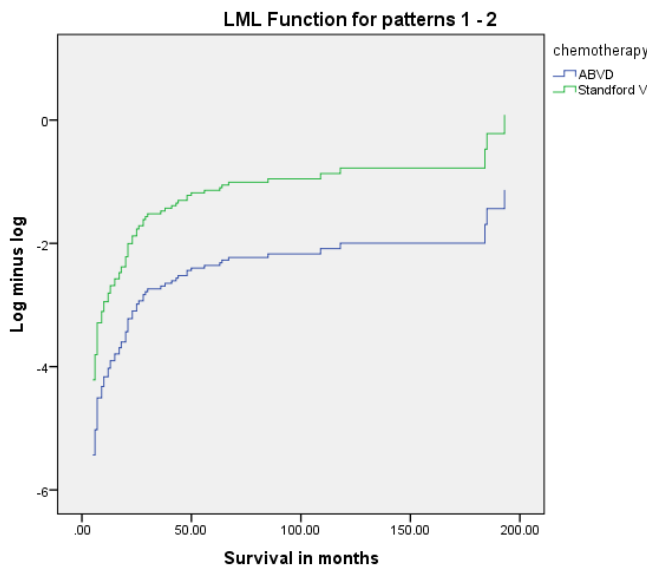


Figure4. Log-log survival curve for checking PH assumption in survival time model

**Table 1: patient's characteristics**

Variables	N (%)
<b>Gender</b>	
Female	161 (41.4)
Male	228 (58.6)
<b>Age, years</b>	
<20	145 (37.3)
20-40	164 (42.2)
>40	80 (20.5)
Mean (SD)	27.5 (15.8)
<b>Stage of Hodgkin's Lymphoma</b>	
I	82 (21.1)
II	175 (45.0)
III	108 (27.8)
IV	24 (6.2)
<b>Chemotherapy</b>	
Stanford V	47 (12.1)
ABVD	342 (87.9)
<b>Relapse</b>	
Yes	90 (23.1)
NO	299 (76.9)
<b>Survival</b>	
Dead	51 (13.1)
Alive	338 (86.9)
<b>Second Malignancy</b>	
Yes	11 (2.8)
NO	378 (97.2)

**Table 2: Multiple Cox proportional hazard model for survival time and time to relapse**

Variables	Survival		Time to relapse	
	HR (95% CI)	P value	HR (95% CI)	P value
Chemotherapy				
Stanford V	3.38 (1.69 – 6.74)	0.001	2.20 (1.26 – 3.86)	0.006
ABVD				
Age, years	1.37 (1.04 – 1.80)	0.025	1.01 (0.80 – 1.27)	0.927
Stage				
III or IV	1.37 (0.73 – 2.60)	0.326	2.39 (1.51 – 3.76)	<0.001
I or II				

## DISCUSSION

Hodgkin's disease is considered as a clonal malignancy of the lymphatic system with a variety of clinical and histopathological manifestations and a higher incidence rate in developing and developed countries with a good progress in its diagnosis and treatment during ages.<sup>9,10</sup> In contrast to the western countries, prevalence of Hodgkin's lymphoma is lower in Asia; therefore there is not enough studies assessing its clinical specifications and outcome of its different treatments. In this study we tried to survey the epidemiological and histopathological features of the disease and also evaluating its recurrence and survival rate besides detecting the secondary malignancies due to chemotherapy. In most of the regions the age spectrum of this disease has a bimodal pattern<sup>10,12</sup> but our study showed a decrease in its incidence after the third decade of life. Like other studies, ours showed the nodular sclerosis as the most prevalent subtype and low and high lymphocyte types as the least prevalent<sup>10,11</sup> in contrast with another study that had taken place in the northwest of Iran, a cold region, introduced the mixed cellularity subtype as the most prevalent.<sup>13</sup> Also in our study all subtypes and generally Hodgkin's lymphoma was more prevalent in men<sup>4,11</sup> than women but similar studies had shown a greater incidence for nodular sclerosis subtype in the female population.<sup>10</sup>

The most prevalent symptom at the point of diagnosis was lymphadenopathies (80.8%) with 66% of it happening in the neck area. In our study extra nodal involvement was about 17% which is similar to the results of studies in neighboring Arab regions; which is in contrast with a study in Turkey, another neighbor country, that showed only 7.9% of this parameter.<sup>10</sup> This difference is most probably due to the effects of race and environment on the Hodgkin's pathogenesis which needs more epidemiological studies in Iran.

Our patients were mostly in the 2nd stage (45%) and 27% in the 3rd stage while in the northwest of Iran, most of the patients (42.7%) were on the 3rd level of their diseases<sup>6</sup> same as the results from similar patients in Turkey that had shown a same result as ours.<sup>10</sup>

Our patients had been mostly referred and diagnosed in March (late winter and early spring) but in the fall (October) we had very few patients.

The survival rate of the patients on the same stage was significantly higher in ABVD group which was expected and is similar to other studies.<sup>12, 15</sup> There are also studies in Italy that the results show a 3% progress of the disease after completion of the ABVD regimen in contrast with no progression at all after Stanford V regimen. With these results in hand, it is logical to follow up our patients treated with regimens other than ABVD for at least 10 years in order to compare their 10 year survival rate.

Recurrence of the disease had happened earlier for the patients treated by Stanford V regimen than the ABVD group and also the interval between remission and the first symptoms of recurrence was getting longer as remission period was extending just like other surveys;<sup>13, 15</sup> But in our recurrence cases after ABVD in our center they hadn't been using the ABVD again so we couldn't compare the second line treatment results with other centers that had used the ABVD for the second line of the treatment as well.<sup>10</sup>

About the side effects of chemotherapy regimens we have two major branches. The first one is disorders that it brings about which are, cardio respiratory disorders, thyroid gland disorders and infections (mostly chronic viral infections). The second type of side effects which are more concerning are malignancies secondary to chemotherapy regimens such as, Acute myeloid leukemia, myelodysplasia, secondary lymphoid leukemia and also the lungs, skin, breast and GI tumors.<sup>15</sup>

Our patients had been only undergoing chemotherapy regimens of ABVD so we could only evaluate them for secondary malignancies; the result showed 11 (2.7%) cases of secondary cancers that all were females. Three of them had breast cancer and others (8 patients) had developed an acute lymphoid leukemia which is different from other similar studies showing breast cancer as the most prevalent secondary malignancy<sup>16</sup> due to the exclusion of patients who had undergone radiotherapy and also since our patients had a lower age range, they were too young to develop a

breast cancer so follow up of patients for a longer period is advised to survey the upcoming secondary malignancies. Unfortunately in our study we didn't dedicate enough attention to the prognosis factors such as ESR and B-symptoms. We could also show that as the age goes higher, the survival rate was decreasing but age wasn't affecting the remission-recurrence interval and the age factor for prognosis of the Hodgkin's lymphoma wasn't matching the results of other similar studies and it requests further evaluations.<sup>11, 14</sup>

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#### Conflict of Interest

The authors declare no conflict of interest.

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