Substitution of doxorubicin with etoposide in the treatment of lymphomas

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Substitution of Doxorubicin with Etoposide in the Treatment of Lymphomas

GRADUATE THESIS

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List of Abbreviations

aaIPI	age-adjusted International Prognostic Index
ABVD	doxorubicin, bleomycin, vinblastine and dacarbazine
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
GCB	Germinal Center B-Cell
HL	Hodgkin lymphoma
IPI	International Prognostic Index
LDH	lactate dehydrogenase
NHL	Non-Hodgkin lymphoma
PET	Positron-emission tomography
PTCL	peripheral T-cell lymphoma
R-CEOP	Rituximab, cyclophosphamide, etoposodie, vincristine and predisone
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
WHO	World Health Organization

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1. Summary

Title: Substitution of Doxorubicin with Etoposide in the Treatment of Lymphomas

Author: Meredith Olivia Terry

Purpose

This study set out to examine the survival and progression-free outcomes in aggressive lymphoma patients receiving (R)CEOP therapy due to contraindications for anthracycline therapy. Toxicities that developed were also evaluated and reported.

Patients & Methods

Hospital records were searched for patients who received (R)CEOP in >50% of chemotherapy cycles. A total of 44 patients were included from KBC Zagreb, with 33 B cell lymphoma and 11 T cell lymphoma patients. Data was analyzed to evaluate survival, risk factors, and toxicities.

Results

Patients were followed up a median of 30.3 months. The 5 year overall survival rate was approximately 48%, and event-free survival 40%. It was found that elevated LDH at diagnosis and age >70 years are poor prognostic factors, having a statistically significant correlation to poorer overall survival. All other risk and prognostic factors were not found to have a statistically significant impact on survival. The most commonly encountered toxicities were cytopenias and infections (34% and 34%).

Conclusion

(R)CEOP therapy is generally well-tolerated in patients with co-morbidities that preclude traditional anthracycline therapy. Elevated LDH and advanced age are poor prognostic factors for survival. This study found no statistically significant difference according to cell of origin in DLBCL patients and survival outcomes.

Keywords: *diffuse large B-cell lymphoma, CEOP, aggressive lymphoma treatment*

2. Sažetak

Titula: Zamjena doksorubicina etopozidom u liječenju limfoma

Autor: Meredith Olivia Terry

Cilj

Ovo istraživanje ispitalo je ukupno preživljavanje i preživljavanje bez događaja bolesnika s agresivnim limfomima koji su primali (R)CEOP terapiju zbog kontraindikacija za liječenje antraciklinima. Ispitana je i toksičnost ovog protokola.

Bolesnici i metode

Iz bolničkih povijesti bolesti su identificirani bolesnici koji su primali (R)CEOP u >50% ciklusa kemoterapije. U istraživanje je uključeno ukupno 44 bolesnika liječenih u KBC Zagrebu, 33 s B-staničnim i 11 s limfomima T stanice. Na temelju prikupljenih podataka analizirani su preživljavanje, čimbenici rizika i toksičnost.

Rezultati

Medijan praćenja iznosio je 30,3 mjeseci. Petogodišnje preživljavanje iznosilo je 48%, a preživljavanje bez događaja 40%. Povišen LDH pri dijagnozi i dob >70 godina bili su statistički značajni nepovoljni prognostički faktori koji su korelirali s lošijim preživljavanjem. Za sve ostale rizike i prognostičke čimbenike nije utvrđeno da imaju statistički značajan utjecaj na preživljavanje. Najčešće toksičnosti bile su citopenije i infekcije (34% i 34%).

Zaključak

Bolesnici s komorbiditetima koji onemogućavaju uobičajeno liječenje antraciklinima obično dobro podnose (R)CEOP. Povišen LDH i starija dob su prediktori lošijeg ishoda. U ovoj studiji nismo našli da postoji statistički značajna razlika u preživljavanju između bolesnika s DLBCL različitog staničnog porijekla.

Ključne riječi: *difuzni B-velikostanični limfom, CEOP, liječenje agresivnog limfoma*

3. Preface

Introduction

Lymphomas are a group of malignant diseases originating from lymphocytes. These illnesses can have a wide range of presentations, with a multitude of subtypes and prognoses. Even with similar histological findings, the symptoms and aggressiveness of the lymphoma can differ significantly. Several different classification methods have developed over the years, with the most frequently used being that created by the World Health Organization (WHO). Regarding staging, the Ann Arbor system is most common. Patients are also typically evaluated according to various prognostic indices, such as the International Prognostic Index (IPI) for NHL. Treatment depends on the histological subtype and stage, but generally involves application of a chemotherapeutic protocol with or without the addition of surgical intervention or radiotherapy. There are also a wide range of modifications to standard therapy that have been developed and are undergoing research to take into account co-morbidities present in patients, age, and other factors that could affect prognosis. The remainder of this section will go into greater detail explaining the classification and staging of lymphomas, commonly used prognostic indicators, and the therapeutic approach to lymphomas. The focus of this paper is on a specific subset of lymphoma patients with contraindications to a certain chemotherapeutic agent, so information relevant to this focus will also be included, particularly in the section on treatment modalities.

Classification of Lymphomas

Traditionally, lymphomas are divided in two primary categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). These malignancies can also be divided according to cellular origin, with the WHO being based on this distinction (1). The most recently updated WHO classification was published in 2016, and forms the basis of classification for most clinicians. This divides lymphomas into mature B-cell neoplasms, mature T and NK cell neoplasms, Hodgkin lymphoma, histiocytic and dendritic cell

neoplasms, and post-transplantation lymphoproliferative disorders (1). An additional helpful classification is dividing lymphomas into indolent and aggressive based on the behavior of the disease and overall outcomes (2,3).' Yet another descriptive classification is based on initial location of presentation, such as central nervous system (CNS) involvement. A combination of these classification systems is typically used, with the WHO classification forming the backbone and understanding if the lymphoma is indolent or aggressive to guide therapy choice.

Most lymphoma subtypes can be additionally subdivided according to pathological, genetic or other characteristics. The most frequent aggressive lymphoma is diffuse large B-cell lymphoma (DLBCL). Using gene expression profiling this lymphoma can be divided into Germinal Center B-cell (GCB) and non-GCB subtypes. The original study demonstrated that the former has a better prognosis (4–7). Since gene expression profiling is complicated and expensive, it is not appropriate for routine clinical practice. Numerous attempts have been made to replicate this classification using immunohistochemistry (IHC), with Hans' algorithm being used most frequently (4). Despite the fact that the prognostic value of this classification using IHC remains doubtful, the WHO classification asks for routine subtyping of DLBCL tumors into these two categories.

Lymphoma Staging

Staging is a crucial part of the diagnostic procedure in all malignant diseases for several reasons, including therapy selection, predicting prognosis, and stratifying patients for research and quality assessment (8). The Ann Arbor system is used for anatomic staging of lymphomas on a scale of I to IV, with IV being the most advanced and generally having the poorest prognosis. It was originally developed for staging of Hodgkin lymphoma, but has also become generally accepted for non-Hodgkin lymphoma as well (8). A table describing the modified Ann Arbor staging system can be found below in Table ***1***. Tever greater than 38 degrees Celsius, drenching sweats, and weight loss of greater than 10% over a six month period are the so-called "B symptoms."

Table 1: Ann Arbor Staging (8)

Stage	**Features**

I	Involvement of a single lymph node region or lymphoid structure
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E
Additions:	
A	No symptoms
B	Fever (>38º C), drenching sweats, weight loss (10% body weight over 6 months
E (for stages I-III)	Involvement of a single extranodal site contiguous or proximal to known nodal site

Prognostic Indicators

There are several prognostic indices that have been developed to predict outcomes in patients with lymphoma. The most widely used in NHL is the International Prognostic Index (IPI) (9). Five factors are Table ***2***. The age-adjusted index is a simplified version of IPI used to compare patients within the same age group (9). These indices have demonstrated their usefulness in predicting overall outcomes, and are easy to use from a clinical perspective. Factors used in both IPI and aaIPI can be seen below in

included in this index to form a predicted prognosis. These include stage, LDH level, number of extranodal disease sites involved, age, and performance status. The Eastern Cooperative Oncology Group (ECOG) performance status is given below in

Table ***3***.

Table 2: ECOG performance status scale (10)

Grade	Performance Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Table 3: Factors used to determine IPI and aaIPI (9)

Parameter	IPI Score	aaIPI Score
Age > 60 years	1	n/a
ECOG 2-4	1	1
Stage III-IV	1	1
Elevated LDH	1	1
>1 Extranodal site	1	not considered
Interpretation	Low risk: 0-1 Low intermediate risk: 2 High intermediate risk: 3 High risk: 4-5	Low risk: 0 Intermediate risk: 1 High risk: 2-3

These two clinical indices have been widely used, particularly in diffuse large B-cell lymphomas (DLBCL). Other factors can be used for predicting outcome and treatment response in DLBCL, including looking at various pathological subtypes. As previously mentioned, the non-GCB subtype was in some series associated with a poorer outcome. Other molecular markers, such as MYC and BCL2, are under investigation to determine usefulness in providing a prognosis for patients, and will likely play a greater role as additional data on these markers becomes available (11).

In T-cell lymphoma, there is less consensus regarding the most appropriate prognostic index. Besides IPI, different prognostic indices have been proposed for various subtypes of T-cell lymphomas. For peripheral T-cell lymphomas (PTCL), four indices have been used and compared: IPI, Prognostic index for T-cell lymphoma (PIT), International peripheral T-cell lymphoma project score (IPTCLP) and modified Prognostic index for T-cell lymphoma (mPIT) (12,13). It has been found that IPI was best for predicting

complete remission, while IPTCLP was best for predicting overall survival (12). IPTCLP uses age, ECOG performance status, and platelet count as prognostic factors.

IPI is easy to use and widely accepted and is therefore frequently used in all NHL types.

Lymphoma Treatment

As with many malignancies, lymphoma treatment centers on combining various therapeutic modalities to achieve the greatest anti-tumor effect without causing excessive damage to healthy tissues. The basis for most aggressive lymphoma treatment is centered on a combination of several chemotherapeutic drugs. This can be combined with immunotherapy, radiation, surgical interventions, and stem cell transplant, depending on the patient and type of lymphoma being considered, to achieve the best overall outcome. The typical chemotherapeutic protocol for HL is doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) in the United States, while bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) is frequently used in Europe. On the other hand, NHL is typically treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), with or without rituximab depending on the cellular origin of the lymphoma. These regimens form the basis for most lymphoma treatment, with patient factors dictating modifications of these protocols. This paper primarily focuses on NHL patients with cardiac comorbities and contraindications to doxorubicin treatment.

Treating lymphomas in patients with cardiac disease can prove particularly challenging. The primary concern of the CHOP regimen in NHL patients is the cardiotoxicity of the drug doxorubicin, a member of the anthracycline class of chemotherapeutic drugs. Anthracyclines exert their effect through four mechanisms: inhibition of topoisomerase II, intercalation with DNA and subsequent blockage of DNA & RNA synthesis, generation of free radicals, and altering the fluidity and ion transport of cell membranes (14). As mentioned, anthracyclines are cardiotoxic, with both acute and chronic forms of this toxicity present. Several studies have investigated the development of cardiotoxicity in patients with aggressive lymphoma receiving CHOP, and it is well-

documented (15,16). It is therefore inappropriate to prescribe the traditional CHOP regimen to patients with cardiac disease, and alternative regimens have been explored for this patient population.

There are several treatment options that have been investigated in patients with aggressive lymphoma and a contraindication to anthracycline use. These include simply removing doxorubicin from the (R)CHOP protocol, replacing doxorubicin with etoposide, replacing doxorubicin with mitoxantrone, using liposome-encapsulated doxorubicin, substituting procarbazine for doxorubicin, continuously infusing doxorubicin, or using bendamustine-R (17). Replacing doxorubicin with etoposide, with patients then receiving cyclophosphamide, etoposide, vincristine, and prednisone (CEOP), has shown some success (18). Etoposide, although from a different class of chemotherapeutic agents, has a similar primary mechanism of action. It works by inhibiting topoisomerase II, like doxorubicin (14). Due to this effect, it was postulated that this would be an appropriate substitute drug that would ideally lead to similar survival and progression outcomes. Several regional centers have evaluated the effects of substituting etoposide for doxorubicin when doxorubicin is contraindicated, and there have been mixed results (18–20). In some series the non-GCB DLBCL subgroup of patients responded worse to R-CEOP than the GCB subgroup (19). There are therefore many factors to consider when selecting a specific therapeutic regimen for a patient with aggressive lymphoma.

Treatment Outcomes

Overall response to treatment can be classified according to several different criteria. The most widely used was developed by Cheson and was updated in 2008 (21). In general, treatment response can be classified into five primary categories: complete remission, partial remission, stable disease unable to evaluate, and progressive disease or non-responsive (22). This classification is based on imaging such as PET and CT scanning to determine response. In lymphoma patients, response is often evaluated when half of chemotherapy cycles have been administered, and repeated when all cycles are finished.

Table 4: Cheson Criteria for evaluating treatment response (23)

Treatment Outcome	Description
Complete Remission (CR)	• Nodes returned to normal (if GTD >15 mm before therapy, GTD now ≤15 mm; if GTD 11-15 and SA >10 mm before therapy, SA now ≤10 mm) • All (non-nodal) target lesions completely resolved
Partial Remission (PR)	• SPD of target lesions decreased ≥50% from baseline • Spleen and liver nodules regress by 50% in SPD or single lesion in GTD

Progressive Disease (PD)	• SPD increase ≥50% from nadir (smallest value seen during trial)
	• in nodal target lesions overall
	• or in any single nodal target
	  ○ A node with SA <10 mm must grow ≥50 % and to ≥15 x 15 mm or >15 mm
	  ○ A node with SA >10 mm must increase ≥50% in GTD
	• or in non-nodal target lesions overall (e.g . liver/spleen nodules selected as target lesion

Stable Disease (SD)	• not enough shrinkage for PR • not enough growth for PD
Unable to Evaluate (UE)	• One or more lesions cannot be seen ○ This is most commonly caused by inadequate coverage

Treatment Toxicities

Chemotherapeutic regimens have well-documented toxicities. The risk of cardiotoxicity with CHOP-based regimens was outlined above. Cyclophosphamide is typically associated with nausea, vomiting, cytopenias, alopecia, and occasionally cystitis (14). Vincristine has potential adverse effects including neurotoxicity (especially peripheral neuropathy), paralytic ileus, myelosuppression, alopecia, and possibly SIADH (14). Prednisone has a plethora of potential side effects, including metabolic effects like fat redistribution, increased appetite, insomnia, impaired wound healing, muscle wasting, peptic ulcers, and impaired immune response (14). Etoposide is typically associated with nausea, vomiting, hypotension, alopecia, and myelosuppression (14). Rituximab is rarely associated with significant side effects; there is occasionally a transfusion-type reaction including rash development (14). Alopecia, nausea, vomiting, and cytopenia are commonly encountered side effects in patients receiving CHOP or CEOP therapy. Toxicities can be classified and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) developed by the U.S. National Institute of Health (24).

4. Hypothesis

The hypothesis of this study is that (R)CEOP is a valid chemotherapeutic regimen in treating patients with NHL, with good progression-free and overall survival outcomes. It is also predicted that there will not be significant excess toxicity associated with this protocol. Lastly, it is hypothesized that (R)CEOP treatment will have better outcomes in the GCB subtype of DLBCL patients in comparison to the non-GCB subtype.

5. Objectives

The objectives of this study are to examine the progression-free and overall survival of patients with aggressive NHL receiving (R)CEOP therapy. The toxicities of this protocol will also be examined to determine their severity. Finally, since it has been suggested that patients with non-GCB DLBCL fare worse with R-CEOP therapy than those with the GCB subtype, this study sets out to determine if there is a difference in response to R-CEOP therapy between these two subtypes. Additional factors, such as the International Prognostic Index (IPI), will also be considered when looking at treatment outcomes.

6. Patients and Methods

In order to examine the effects of (R)CEOP treatment in lymphoma patients, archival data was collected retrospectively from hospital documentation from 2009 to present. Patients were selected if they received >50% of chemotherapeutic cycles according to CEOP or R-CEOP protocol for de novo B or T cell lymphoma. A total of 44 patients fulfilled these criteria, with 33 B cell and 11 T cell lymphoma patients. One patient received two cycles of R-COP prior to starting R-CEOP, three patients were first started on R-CHOP then converted to R-CEOP, and one patient received CHEOP prior to starting CEOP. Patients received a median of eight cycles of (R)CEOP (range 1-8). Thirteen patients received radiation therapy (30%), and four patients received intrathecal methotrexate (9%).

Descriptive statistics for the patient population can be found in the following section. The statistical analyses were performed using the program Statistica. Kaplan-Meier survival analysis was performed to examine the overall survival and progression-free survival outcomes. Additional log-rank tests have been performed to examine the effect of several variables on outcomes, including LDH, age, gender, IPI score, ECOG status, and cellular origin in DLBCL. These results can also be found in the following section. Toxicities were also examined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (24).

7. Results

Descriptive Statistics

Based on the criteria outlined in the previous section, 44 patients were included in this study. There was roughly equal distribution of male and female patients, with 52% male and 48% female. The median age was 76.5, with patient ages ranging from 58 to 87. The majority of patients were above age 60. Overall, 86% of patients were Stage III or IV, 55% had B symptoms, 77% had extranodal localization, 18% had ECOG status 3 or 4, 57% had elevated LDH, and 66% had IPI score of 3-5. Additionally, 30% of patients also received radiation therapy.

*Table **5*** provides basic descriptive data for patients, including sex and age group. This is then followed by Table 6 and descriptive data for prognostic factors such as stage, ECOG performance status, LDH level, IPI, and aaIPI. Table 7 is specific for DLBCL patients and provides descriptive information regarding GCB vs. non-GCB status in this subgroup. Cell of origin information was obtained for 24 out of 33 (73%) DLBCL patients according to Hans criteria (4). Table 8 describes final outcomes patients achieved.

Table 5: Patient demographics

Variable	**B-cell** *N = 33 (%)*	**T-cell** *N = 11 (%)*
Sex		
Male	15 *(45%)*	8 *(73%)*
Female	18 *(55%)*	3 *(27%)*
Age Group		
≤60	2 *(6%)*	1 *(9%)*
>61	31 *(94%)*	10 *(91%)*

Table 6: Prognostic factors

Variable	B-cell *N = 33 (%)*	T-cell *N = 11 (%)*
Initial Staging		
I	4 *(12%)*	1 *(9%)*
II	0 *(0%)*	1 *(9%)*
III	8 *(24%)*	4 *(36%)*
IV	21 *(64%)*	5 *(45%)*
B Symptoms		
Present	19 *(58%)*	5 *(45%)*
Absent	14 *(42%)*	6 *(55%)*
Extranodal Localization		
Present	28 *(85%)*	6 *(55%)*
Absent	5 *(15%)*	5 *(45%)*
ECOG Status		
1	7 *(21%)*	6 *(55%)*
2	20 *(61%)*	3 *(27%)*
3	6 *(18%)*	2 *(18%)*
4	0 *(0%)*	0 *(0%)*
LDH		
Normal	13 *(39%)*	6 *(55%)*
Elevated	20 *(61%)*	5 *(45%)*
IPI		
1	3 *(9%)*	1 *(9%)*
2	5 *(15%)*	6 *(55%)*
3	7 *(21%)*	2 *(18%)*
4	11 *(33%)*	2 *(18%)*
5	7 *(21%)*	0 *(0%)*
aaIPI		
0	2 *(6%)*	0 *(0%)*
1	4 *(12%)*	8 *(73%)*
2	12 *(36%)*	1 *(9%)*
3	15 *(45%)*	2 *(18%)*

Table 7: Pathohistological subtype of DLBCL

Pathohistological subtype	**N = 33 *(%)***
GCB	11 *(33%)*
non-GCB	13 *(39%)*
Not evaluated	8 *(24%)*

Table 8: Patient outcomes

Variable	**B-cell** *N = 33 (%)*	**T-cell** *N = 11 (%)*
Final response		
Complete remission	17 *(52%)*	5 *(45%)*
Partial remission	6 *(18%)*	2 *(18%)*
Stable disease	1 *(3%)*	1 *(9%)*
Non-responsive	2 *(6%)*	3 *(27%)*
Not evaluated/lost to follow up	7 *(21%)*	0 *(0%)*
Overall survival		
Alive	20 *(61%)*	6 *(55%)*
Dead	13 *(39%)*	5 *(45%)*
Progression-free survival		
No Progression	27 *(82%)*	6 *(55%)*
Progression	6 *(18%)*	5 *(45%)*

Out of a total of 44 patients, 30 (68%) responded to treatment. Of these 30 patients, 22 achieved complete remissions, and 8 achieved partial remission. Two (5%) patients achieved stable disease, 5 (11%) progressed, and 7 (16%) were lost to follow-up or have not yet completed treatment and have therefore not been evaluated. Figure 1 displays this information in graphical format.

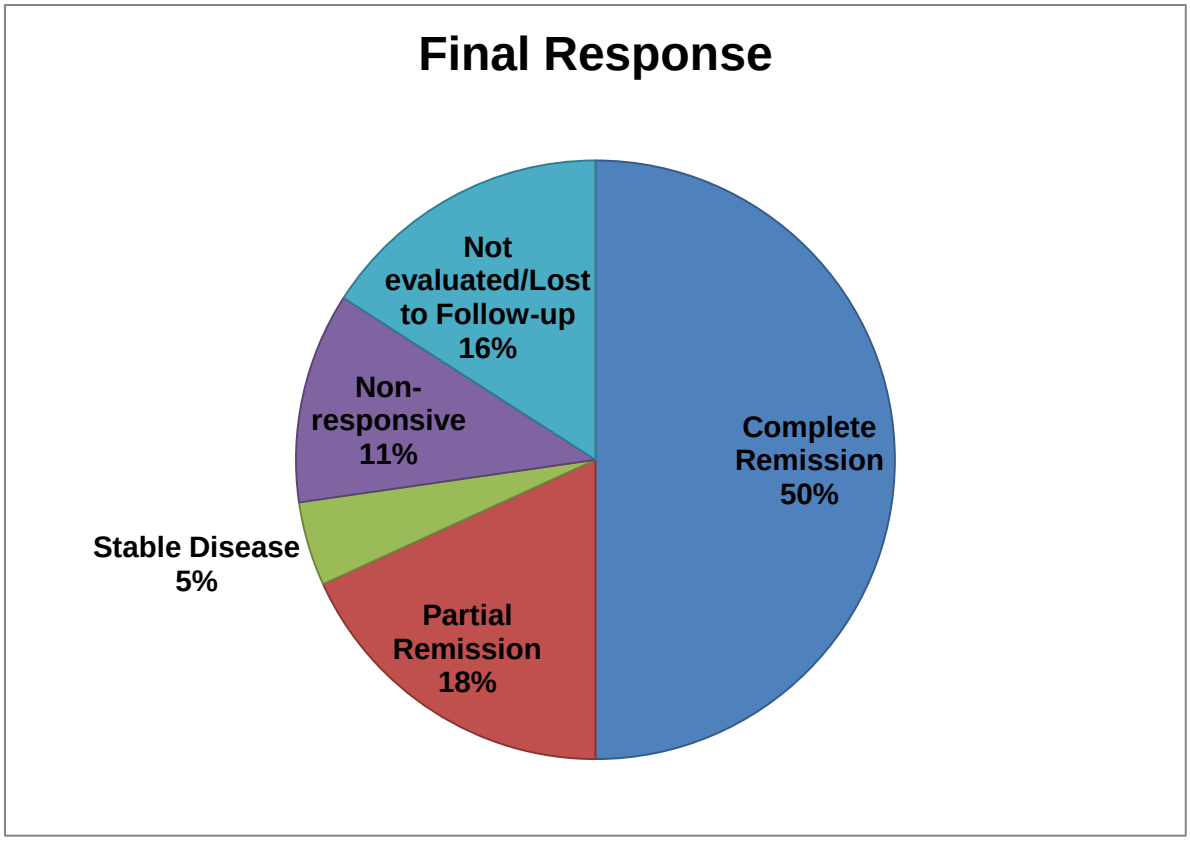

Figure 1: Final response achieved

Survival Analysis & Log-Rank Tests

Median follow-up 30.3 months (The overall survival curves for each of these variables can also be seen below in Figures 4-13.

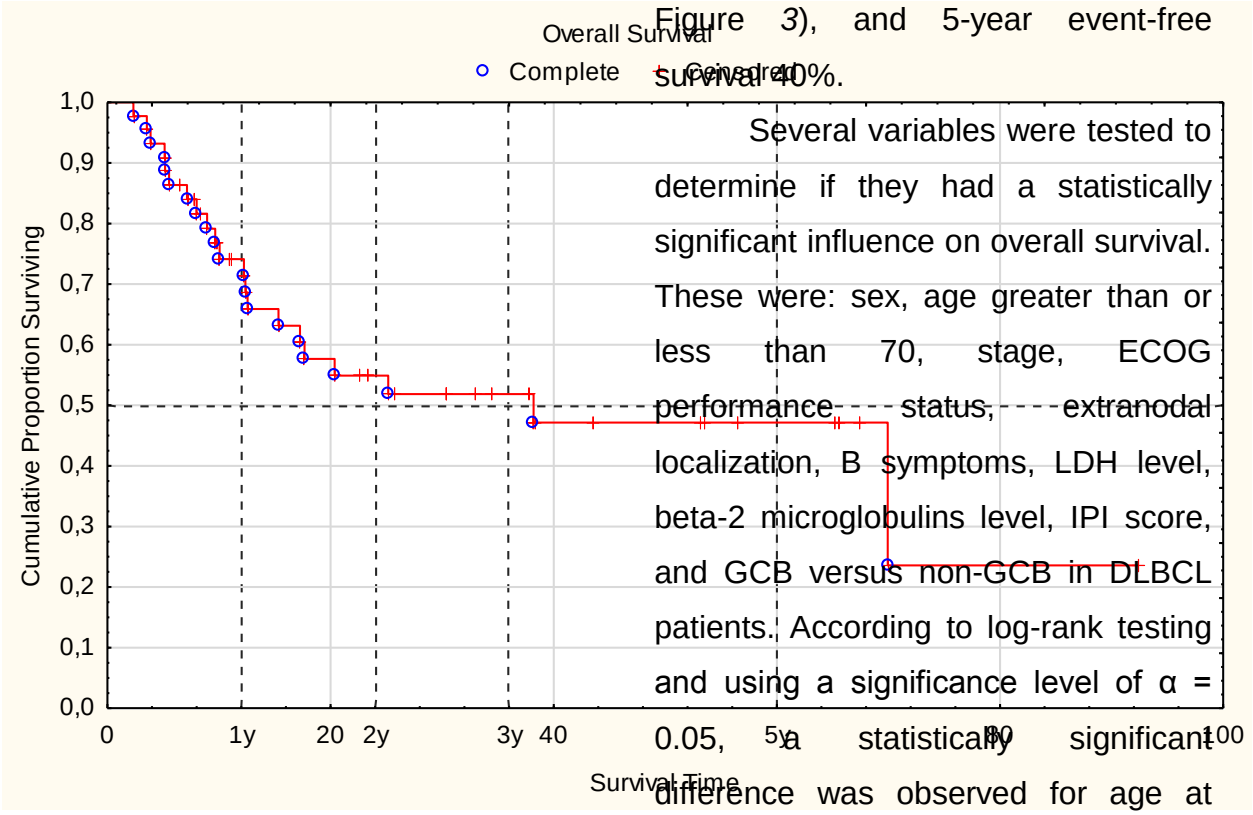

Figure 2), 5-year overall survival rate 48%, median event-free survival 16.6 months (

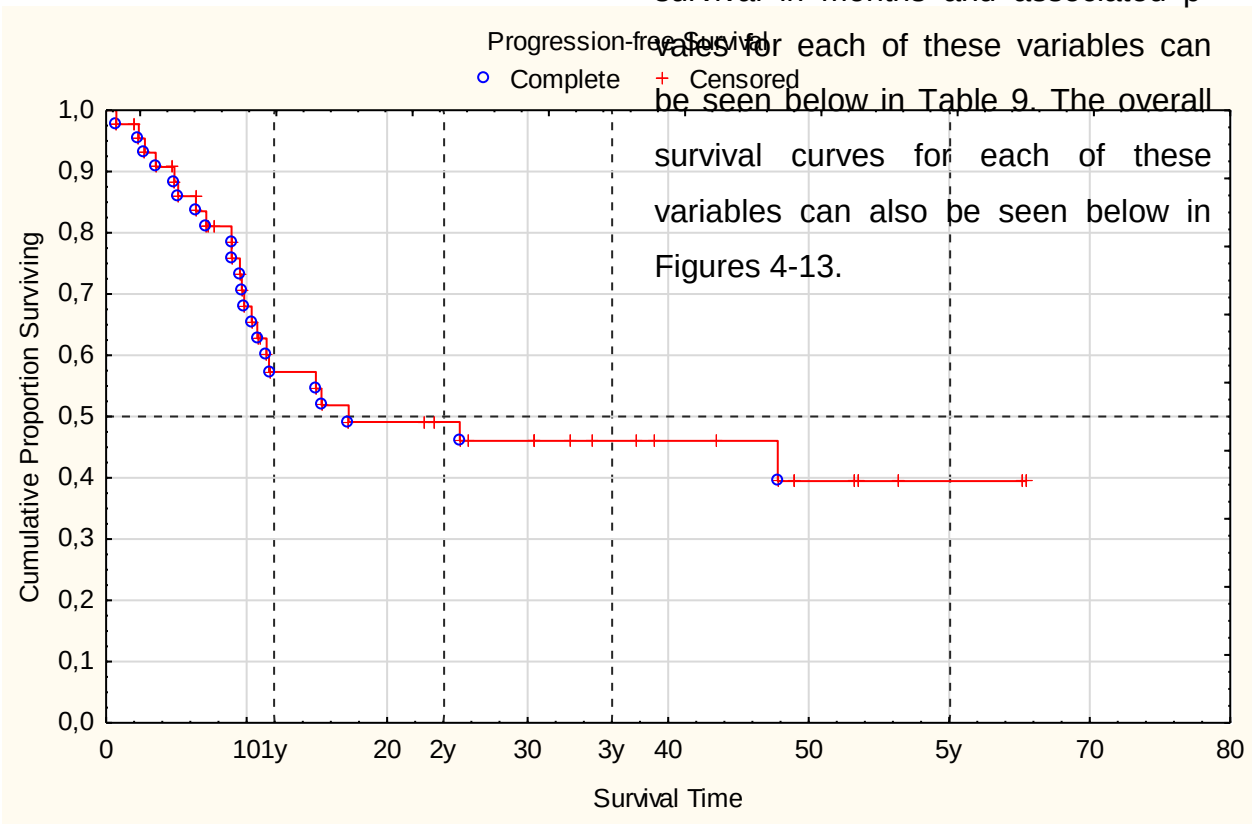

Figure *3*), and 5-year event-free survival 40%.

Several variables were tested to determine if they had a statistically significant influence on overall survival. These were: sex, age greater than or less than 70, stage, ECOG performance status, extranodal localization, B symptoms, LDH level, beta-2 microglobulins level, IPI score, and GCB versus non-GCB in DLBCL patients. According to log-rank testing and using a significance level of α = 0.05, a statistically significant difference was observed for age at diagnosis (p = 0.04726) and for LDH level (p = 0.02706). The median survival in months and associated p-values for each of these variables can be seen below in Table 9. The overall survival curves for each of these variables can also be seen below in Figures 4-13.

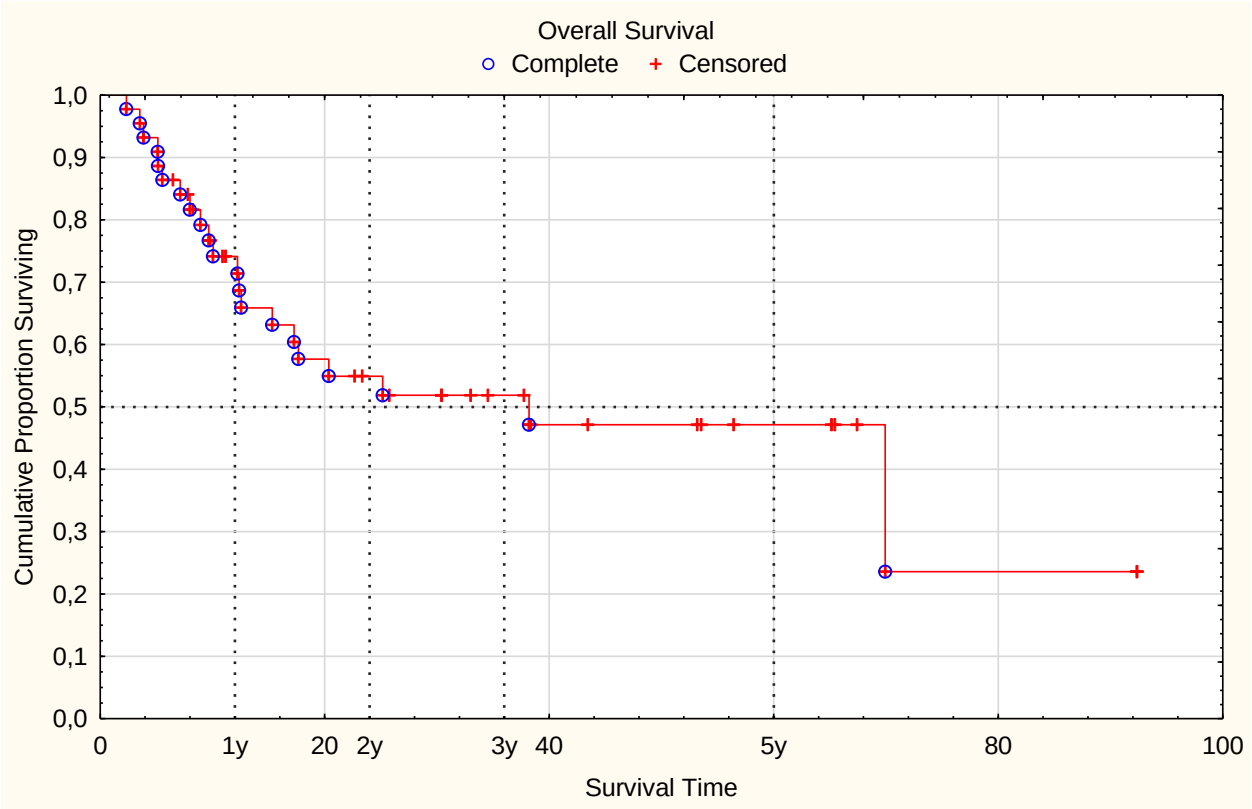

Figure 2: Kaplan Meier overall survival analysis

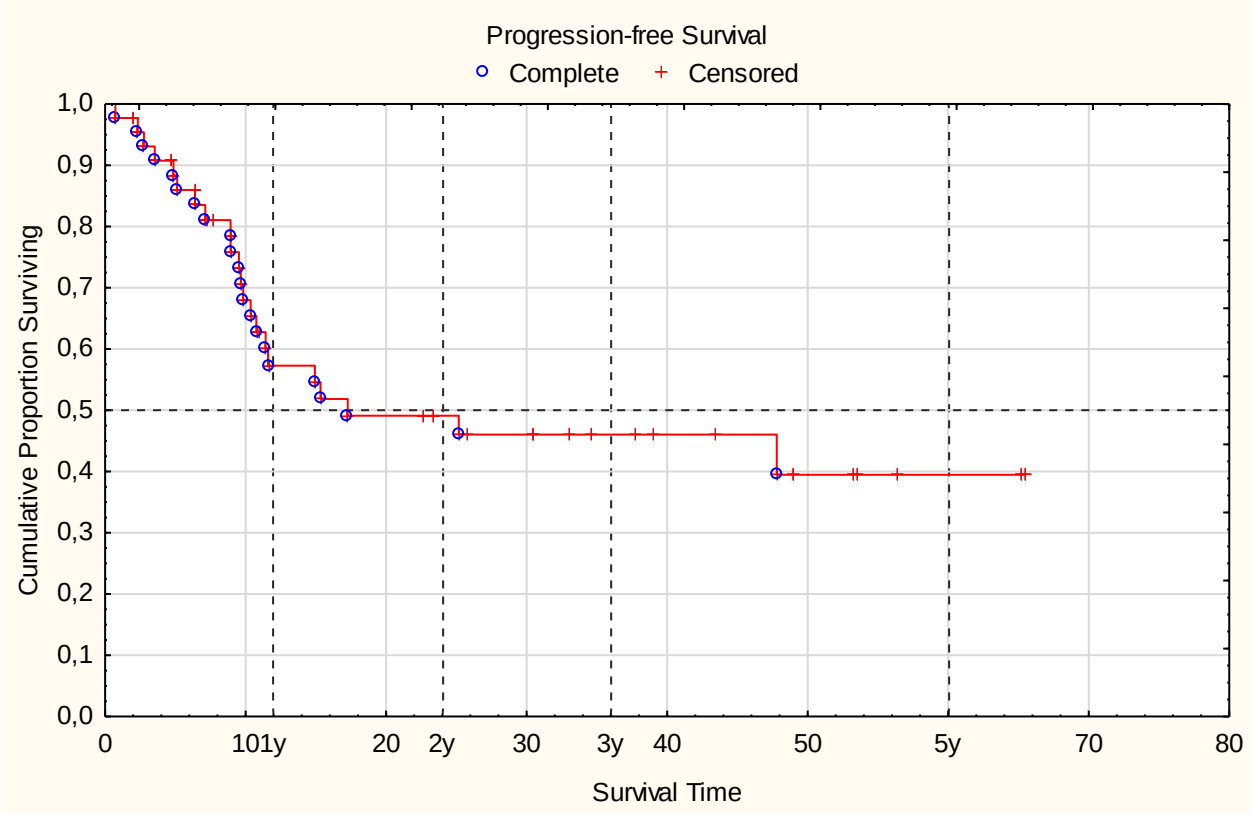

Figure 3: Progression-free survival

Table 9: Median survival and log-rank results for overall survival in relation to tested variables

Variable	**50th percentile (median)** *months*	**Log-rank test p-value** *α = 0.05*
Sex *(Figure 4)*	Male = 27.1 Female = N/A	*p = 0.70942*
Age *(Figure 5)*	≤70 = 53.1 >70 = 16.4	***p = 0.04726***
Stage *(Figure 6)*	I or II = 9.7 III or IV = 28.6	*p = 0.65654*
ECOG *(Figure 7)*	1 or 2 =41.9 3 or 4 =12.2	*p = 0.06376*
B symptoms *(Figure 8)*	Present =15.7 Absent = 28.1	*p = 0.69666*
Extranodal localization *(Figure 9)*	Present = N/A Absent = 20.4	*p = 0.51793*
LDH *(Figure 10)*	Normal = 37.6 Elevated =12.5	***p = 0.02706***
Beta-2 microglobulins *(Figure 11)*	Normal = 40.6 Elevated = 11.8	*p = 0.07871*
IPI *(Figure 12)*	1 or 2 = 29.4 3, 4 or 5 = 19.0	*p = 0.60954*
GCB vs. non-GCB *(Figure 13)*	GCB = N/A non-GCB = 28.6	*p = 0.21112*
B cell vs. T cell *(Figure 14)*	B cell = 46.0 T cell = 16.3	*p = 0.12388s*

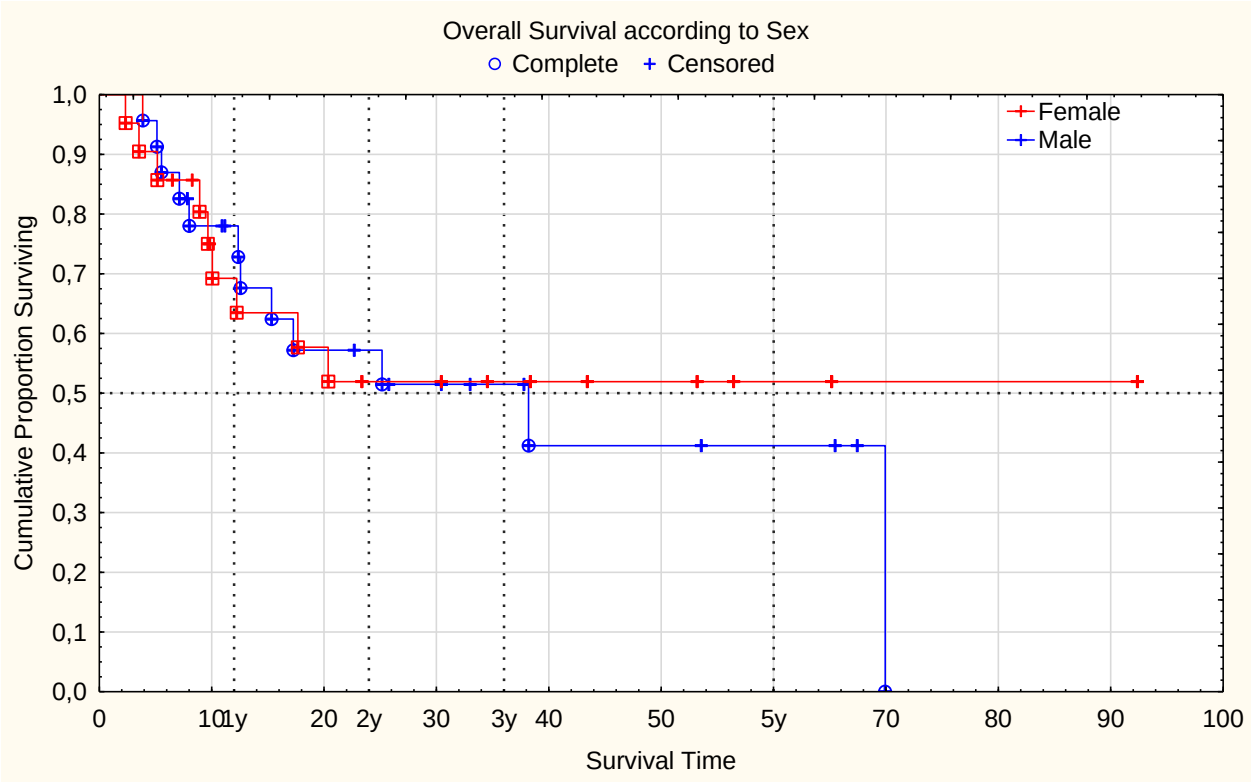

Figure 4: Overall survival according to sex

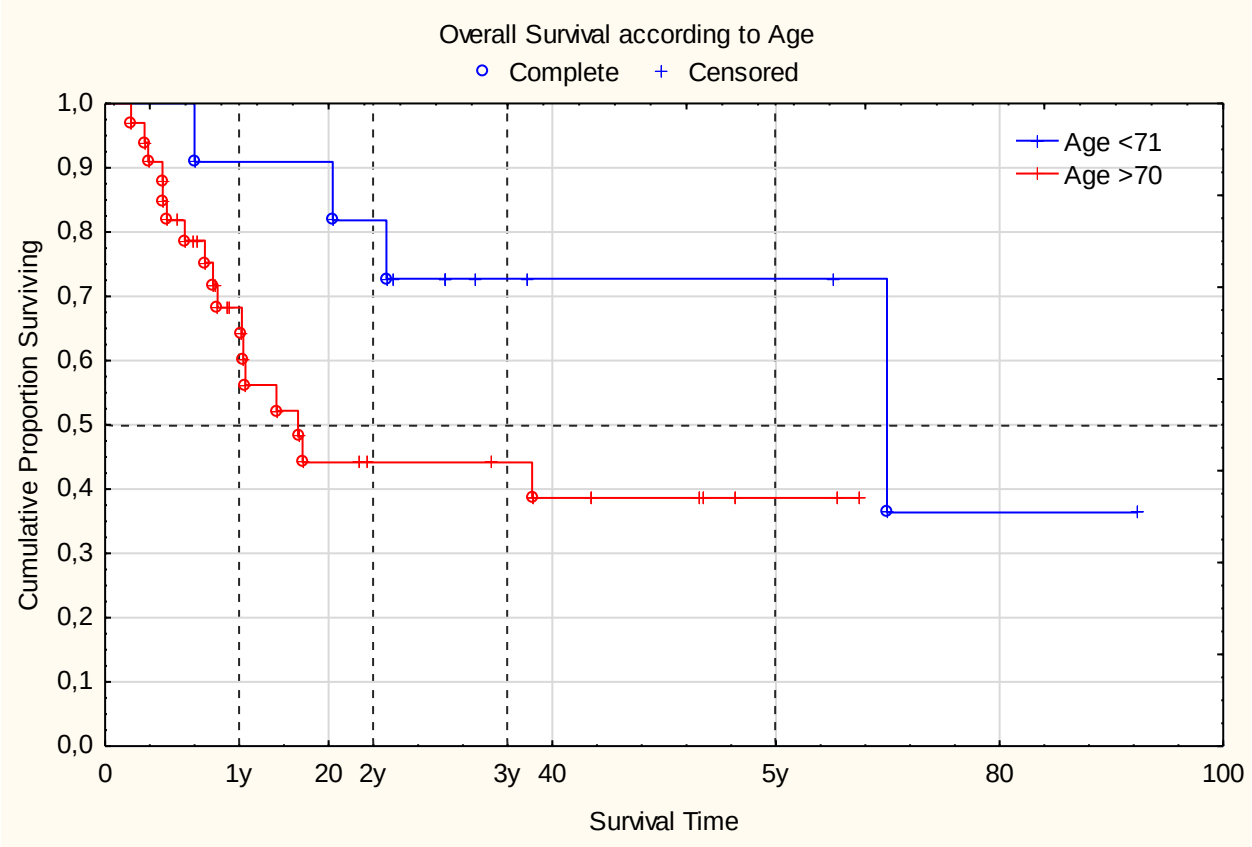

Figure 5: Overall survival according to age

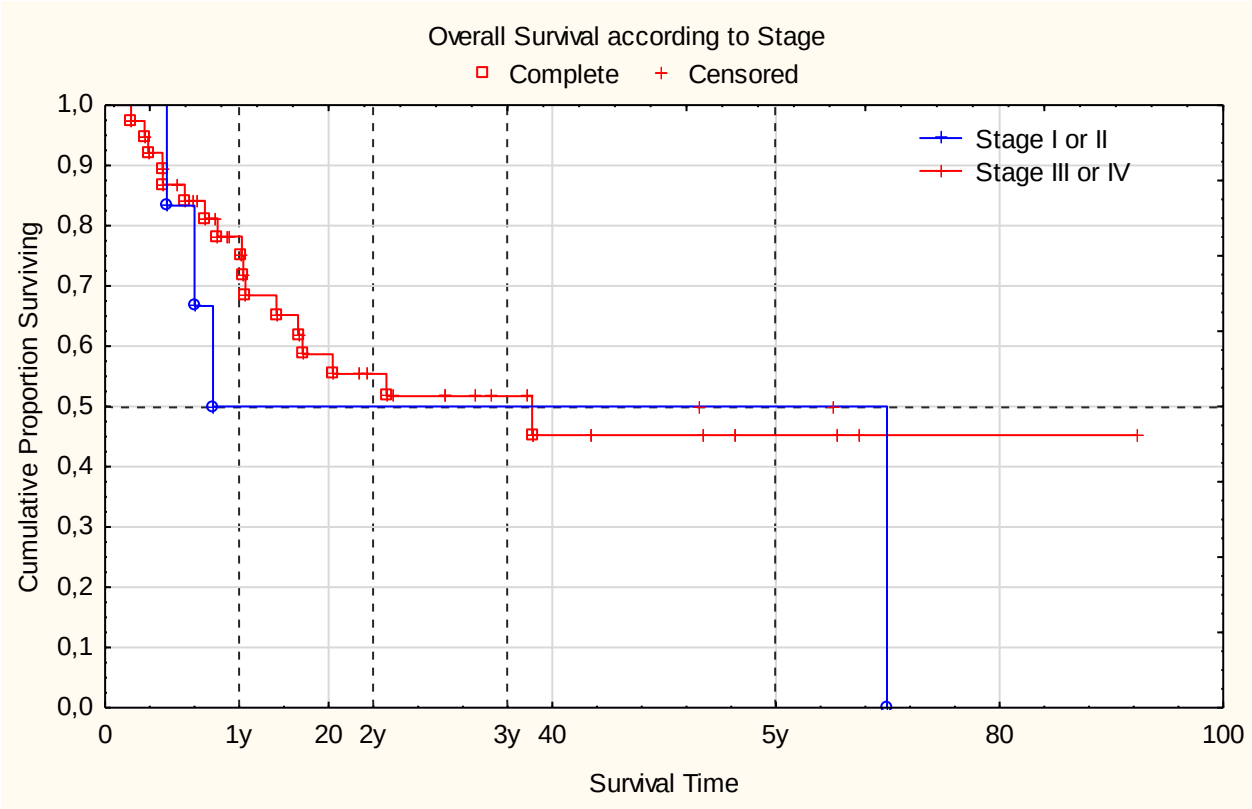

Figure 6: Overall survival according to stage

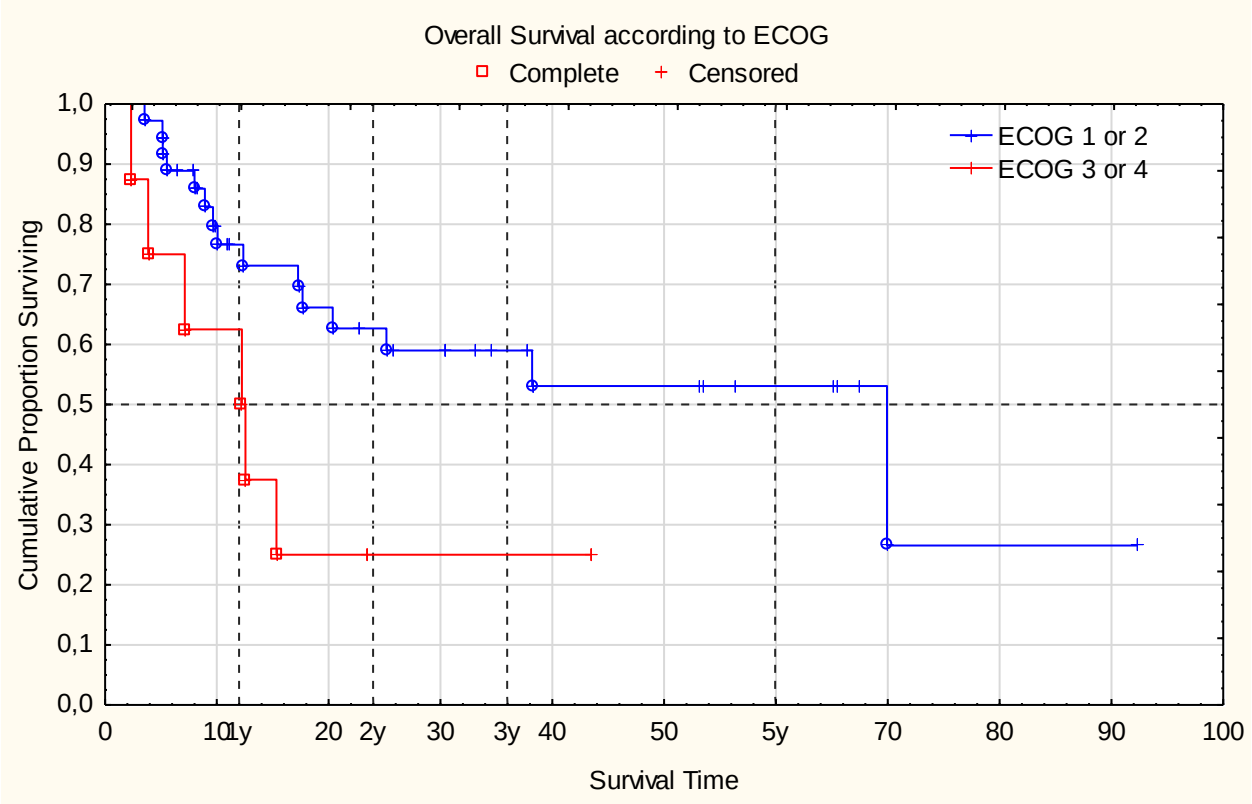

Figure 7: Overall survival according to ECOG

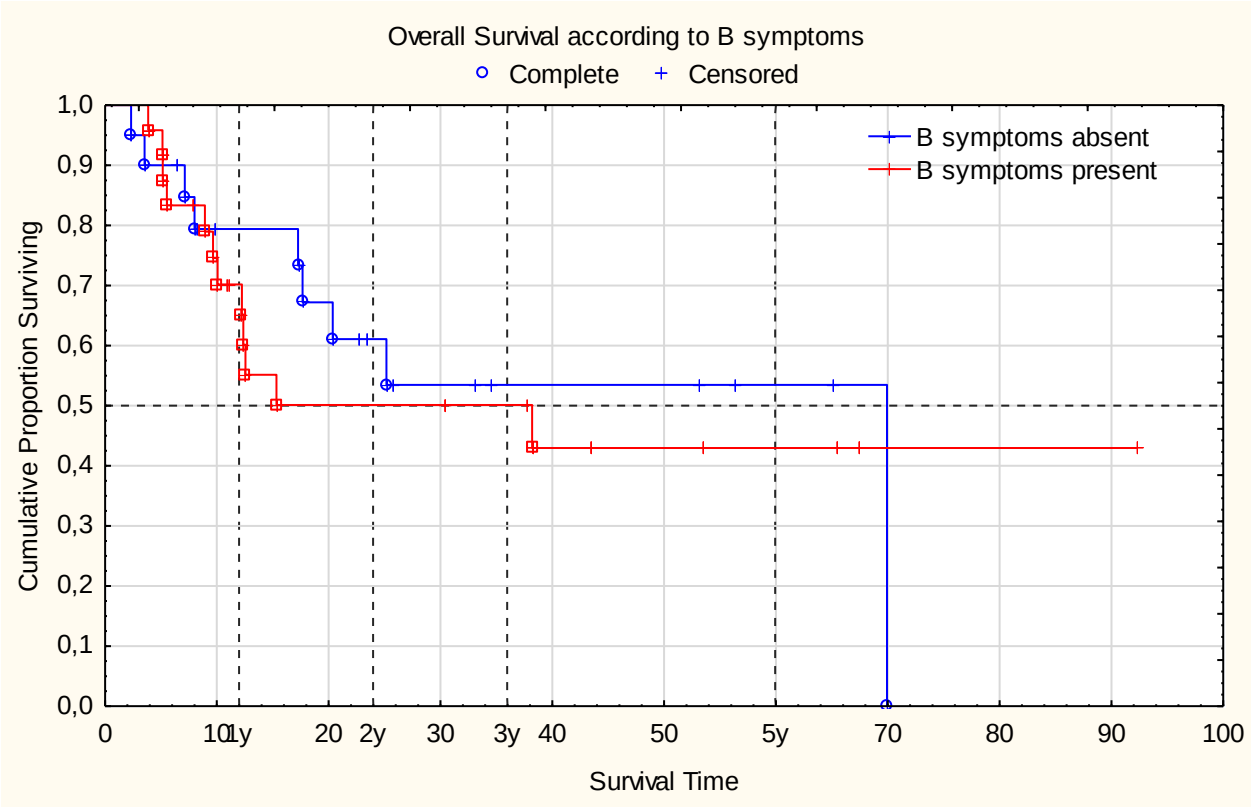

Figure 8: Overall survival according to presence of B symptoms

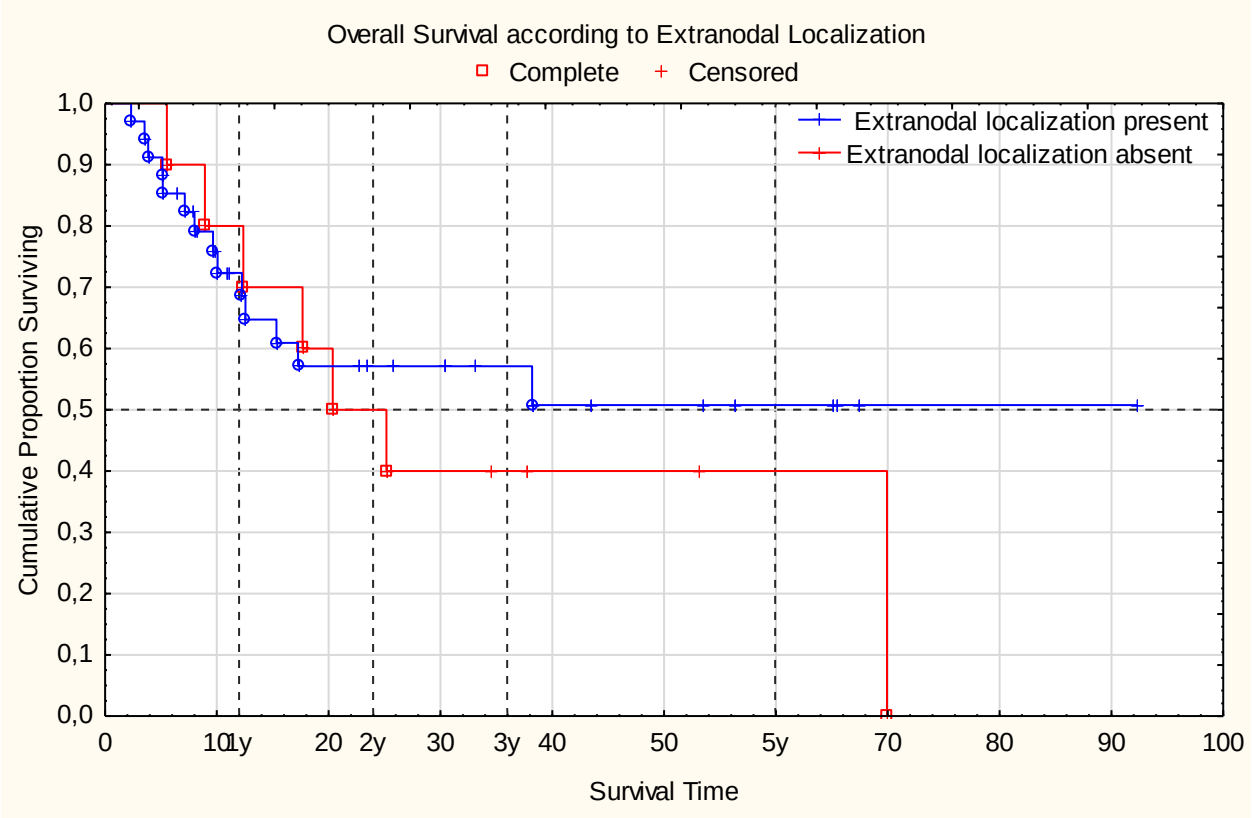

Figure 9: Overall survival according to extent of extranodal localization

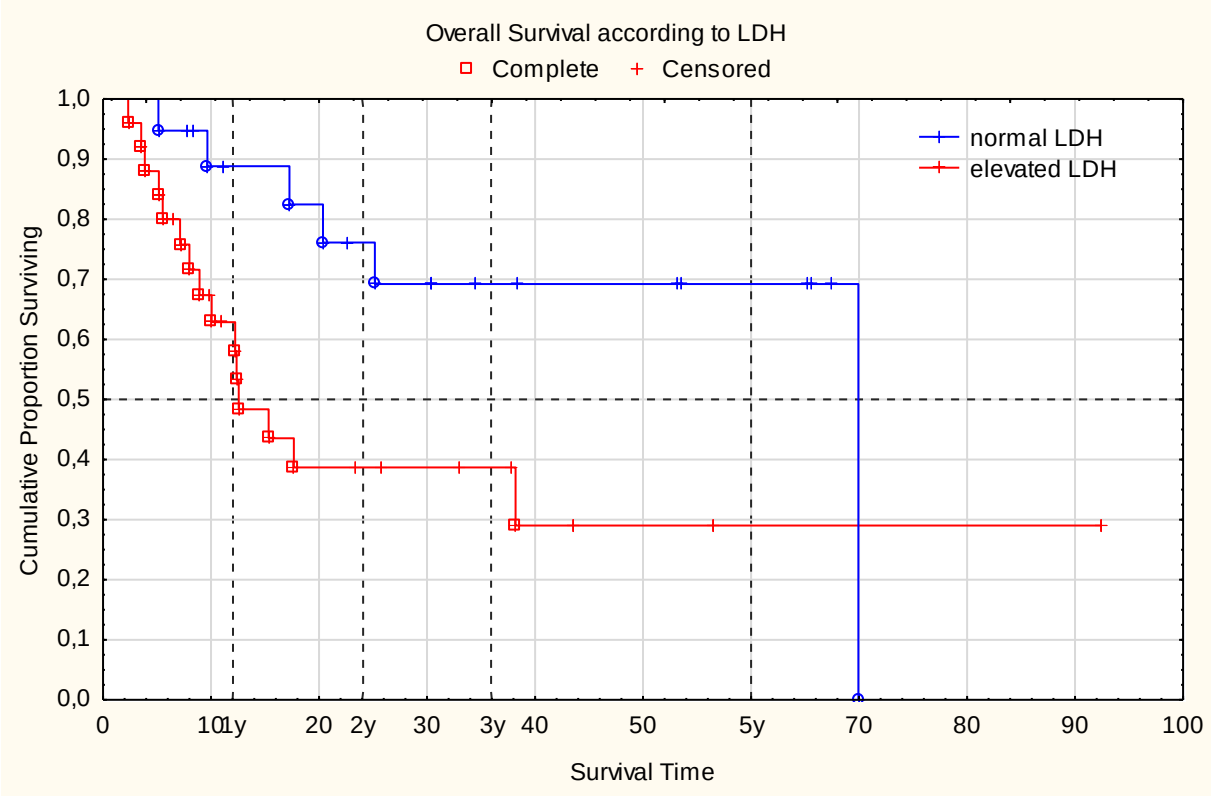

Figure 10: Overall survival according to LDH

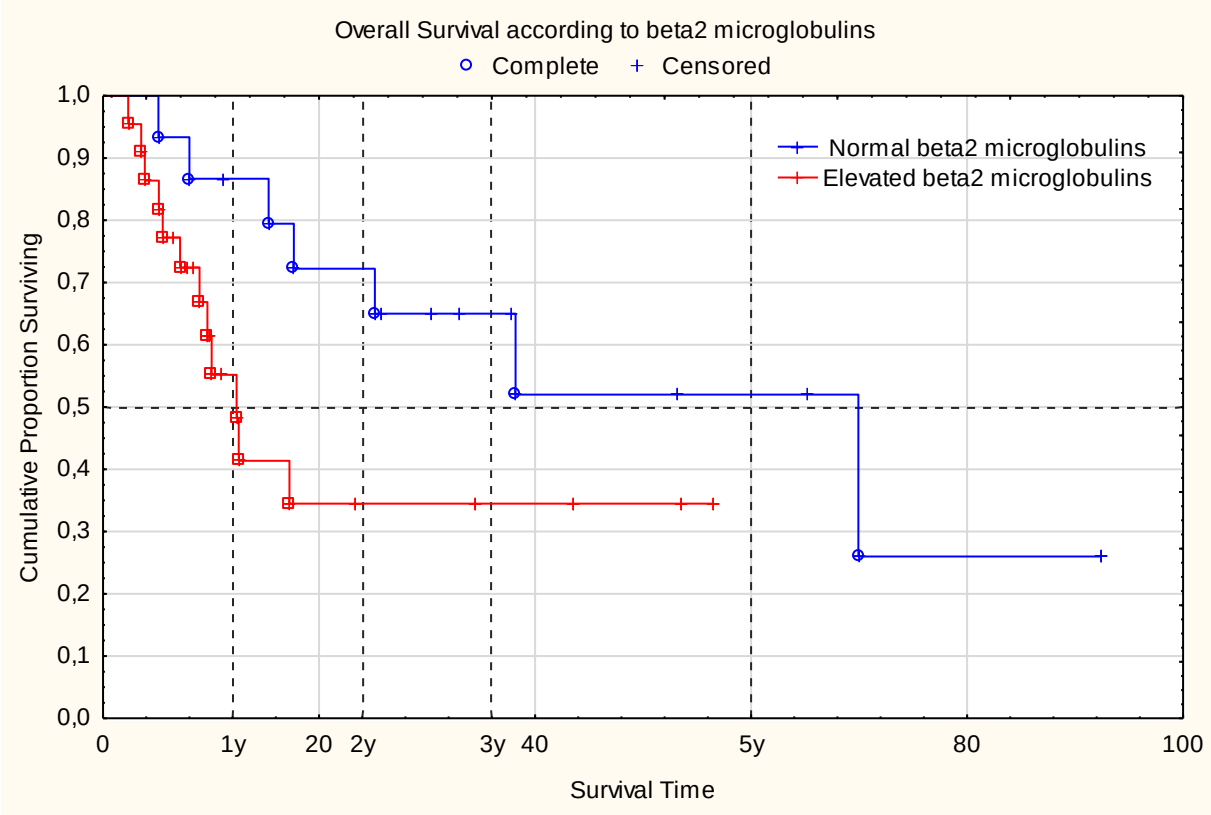

Figure 11: Overall survival according to beta-2 microglobulins

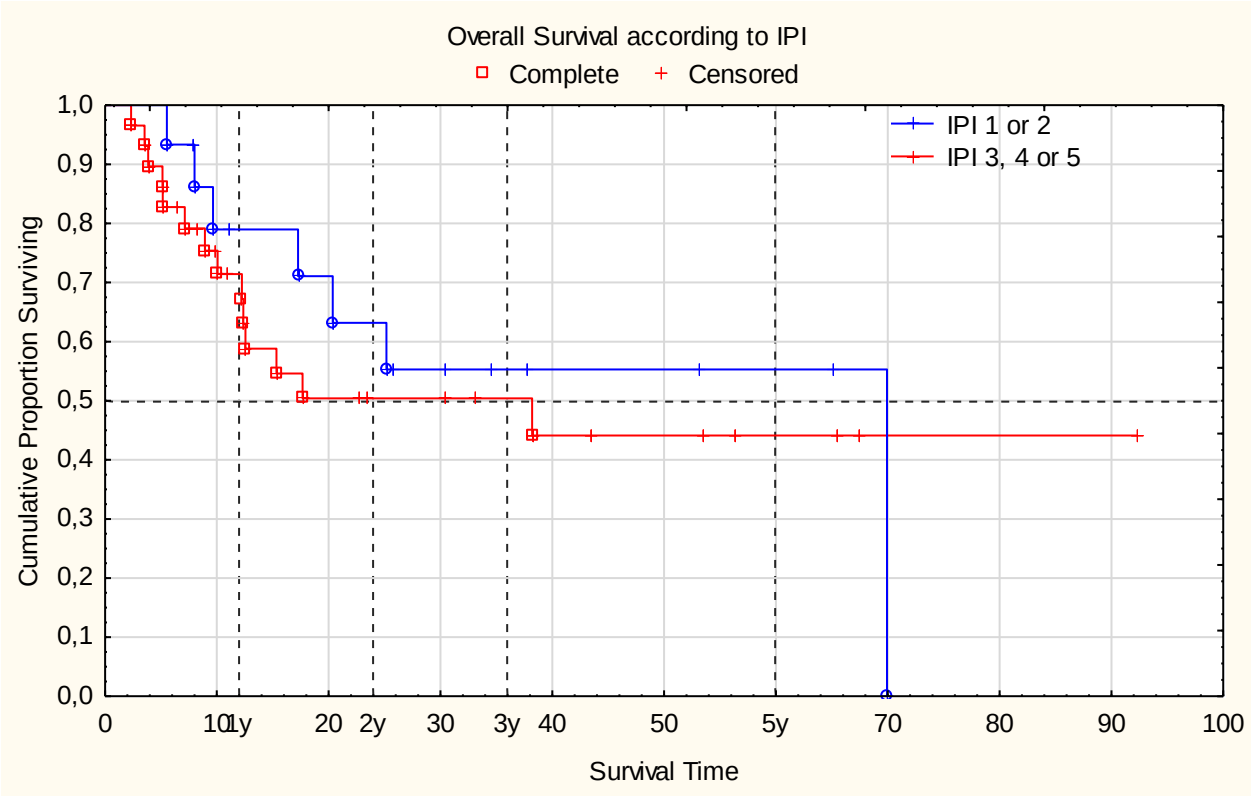

Figure 12: Overall survival according to IPI score

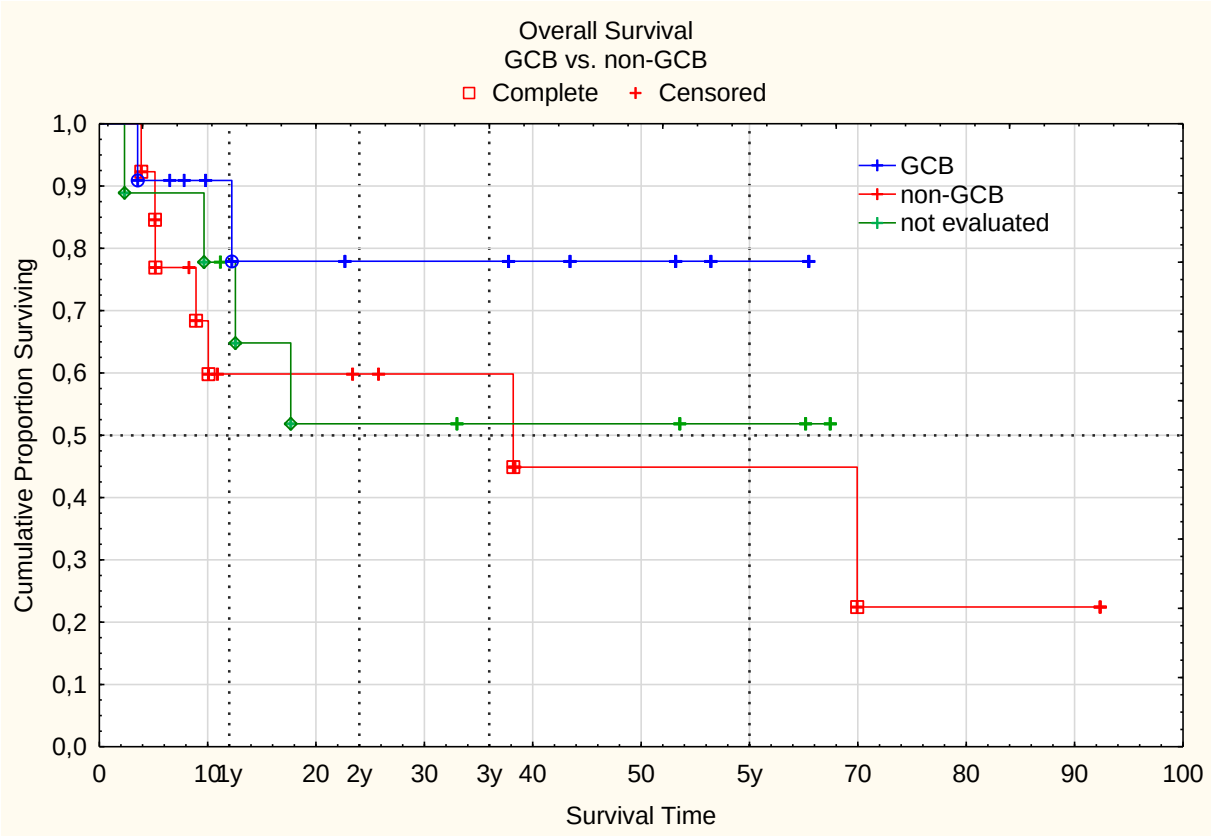

Figure 13: Overall survival in DLBCL patients according to cell of origin

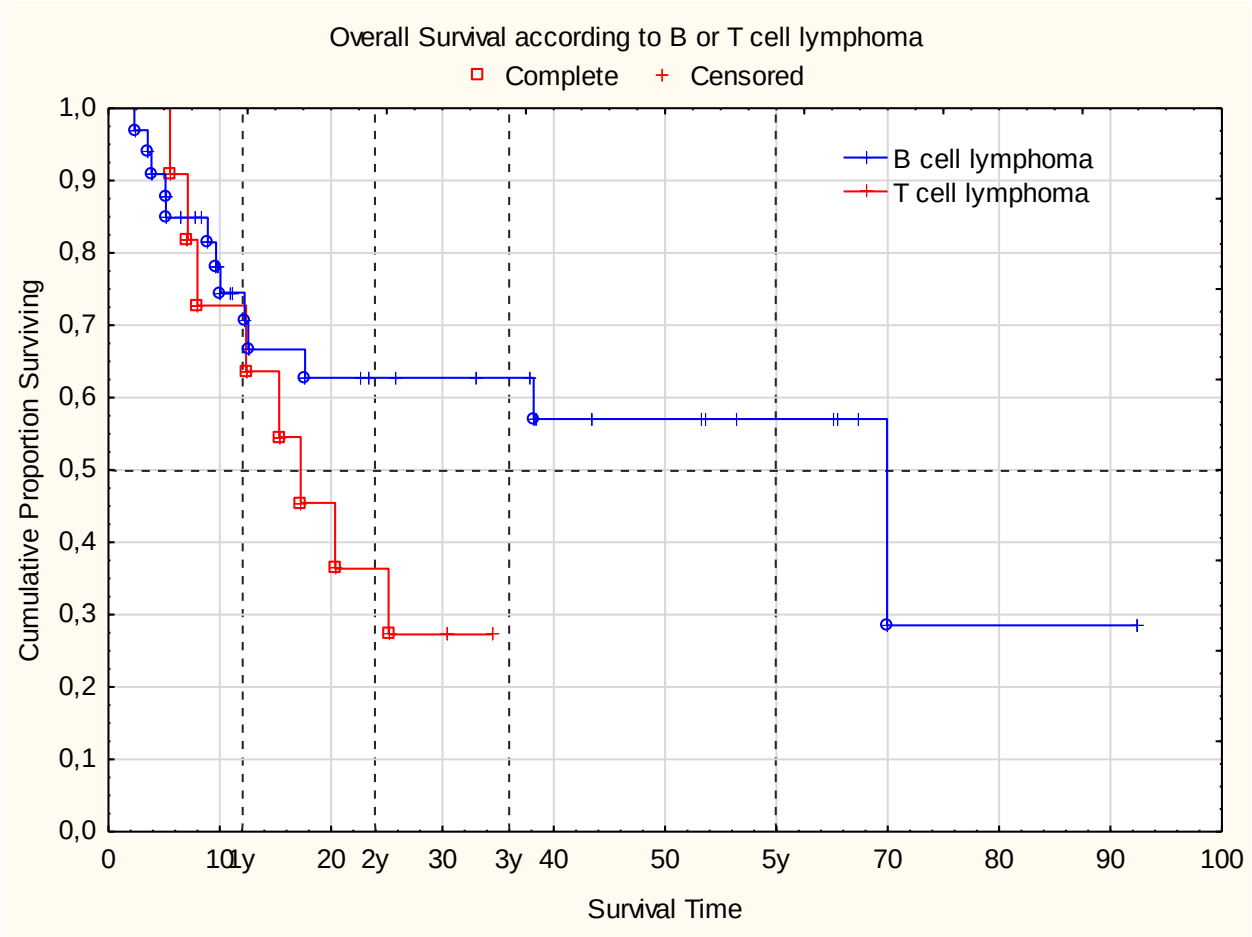

Figure 14: Overall survival according to B or T cell lymphoma

Toxicities

The most common toxicities were cytopenia and febrile neutropenia. Twenty-one patients were hospitalized due to unwanted toxicity, 8 patients developed some type of cardiovascular toxicity that was primarily thromboembolic in nature, and 15 patients developed infectious complications. Overall, 8 patients died from treatment-related causes, giving a treatment-related mortality of 18%. Other toxicities experienced by patients include nausea, constipation, neuropathy, hyponatremia, fatigue, hypogammaglobulinemia, edema, dysphagia, and pleural effusion.

Table 10: Toxicities

Toxicity	Number of Patients *N = 44 (%)*
Hematologic toxicity grade 3 or 4	15 *(34%)*
Infectious complications grade 3 or 4	15 *(34%)*
Cardiovascular toxicity grade 3 or 4 (including thromboembolic events)	8 *(18%)*
Hospitalization	21 *(48%)*
Treatment-related mortality	8 *(18%)*

8. Discussion

This study set out to examine the outcomes of patients receiving (R)CEOP treatment, looking at various prognostic factors to determine effect on overall survival, and to report toxicities that developed in this group. Of the prognostic factors considered, only elevated LDH at time of diagnosis and age >70 were found to have a statistically significant impact on survival outcomes. Of note, there was no statistically significant difference when considering cell of origin (GCB vs. non-GCB) in DLBCL patients. This is different than most other published study findings. It is possible that the number of patients included in cell of origin analysis was not large enough. Of the 33 patients with DLBCL, only 24 had cell of origin data available. If more patients were included, or a larger number of patients had cell of origin data available, this may change the results. Regardless, this study indicates that the R-CEOP treatment outcomes in patients with non-GCB DLBCL are not statistically significantly worse than those of GCB patients.

Patients who receive (R)CEOP rather than (R)CHOP generally do so because of pre-existing cardiac co-morbidities, which is also often associated with advanced age. For this reason, it is typically expected that these patients have worse overall outcomes in comparison to patients without these co-morbidities. When comparing the results of this study to that of other published findings, such as those published by Rashidi et. al. (19), the 2 year overall survival (54% vs. 59%) and progression-free survival (49% vs. 49%) are similar. However, the study conducted by Rashidi et. al. only included DLBCL patients, while this research also included T cell lymphoma patients. Thirty patients (68%) achieved response to therapy, with 22 (50%) achieving complete remission.

Several toxicities developed in the patients included in the study. Hematologic and infectious complications are frequent in this treatment regimen, as described in the preface. As this treatment protocol is intended to reduce cardiac toxicity, it is important to note that only one patient developed a myocardial infarction, which appeared almost two years after treatment was completed. Other cardiovascular toxicities were thromboembolic in nature, including deep venous thrombosis and pulmonary emboli. As the primary

indication for CEOP over CHOP is cardiac co-morbidity and concern over anthracycline impact, this is a positive result.

To obtain a better perspective on how effective (R)CEOP is in treating aggressive lymphoma patients, it would be appropriate to create a control group of comparable (R)CHOP patients and evaluate the differences in outcome when controlling for age, sex, and socioeconomic status. A sufficiently large sample size may be difficult to achieve if only including patients from one hospital center, and data from several centers could be combined to achieve a more robust result. Toxicities that develop during and after treatment could also be considered, and this would provide further information on the appropriateness of administering (R)CEOP rather than (R)CHOP in specific patient subgroups. Comparing (R)CEOP to other alternative regimens for aggressive lymphoma patients with anthracycline contraindications, such as bendamustine, replacing doxorubicin with procarbazine, continuously infusing doxorubicin, or using liposome-enacpsulated doxorubicin, would allow further conclusions to be drawn about what is the most appropriate treatment to use in this patient subgroup.

9. Conclusions

Patients who received (R)CEOP at KCB Zagreb due to anthracycline contraindication developed minimal cardiac toxicity during treatment and 68% achieved some level of response to therapy. In this patient population, elevated LDH at diagnosis and advanced age were negatively associated with survival outcomes. Based on these results, (R)CEOP is an appropriate chemotherapeutic regimen in aggressive NHL, including both B and T cell lymphomas. Additional studies may be performed to compare the patient population examined to those who received first line (R)CHOP therapy to draw further conclusions regarding this chemotherapeutic protocol.

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12. Biography

Meredith Olivia Terry was born on February 9th, 1993, in Washington in the United States of America. She completed secondary education at Liberty High School in Issaquah, Washington, after which she enrolled in the Medical Studies in English Program at the University of Zagreb.

During her studies, she was a student demonstrator in several subjects, including Clinical Anatomy, Medical Biology, Fundamentals of Neuroscience, Medical Biochemistry, Pathophysiology, and History Taking & Physical Examination. She attended the Croatian Student Summit from 2013-2017. Additionally, she was awarded for being in the top 10% of students at the University of Zagreb according to overall grade point average from the 2013/2014 academic year to the 2016/2017 academic year.

Meredith's interests lie in Family Medicine and Internal Medicine, particularly in Hematology-Oncology, and she hopes to pursue a career in these fields in the future.