

Original Article

Running Title: Long-term Outcomes of NHL Post Autologous Stem Cell Transplantation

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Outcomes of Autologous Stem Cell Transplantation for Non-Hodgkin Lymphoma Patients at a Tertiary Referral Centre

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Abstract

Background: We performed a retrospective analysis of non-Hodgkin's lymphoma (NHL) patients who received autologous stem cell transplant (ASCT) (n = 140) in our centre from 1992-2015. The study aimed to evaluate the patient outcomes based on age, NHL subtypes, and conditioning regimen.

Method: Data were gathered for this retrospective investigation using electronic records and case notes. Refractory illness, relapse, progressive disease, or death were all considered progression events. Time from ASCT to the last follow-up or progression event was used to define progression-free survival (PFS), and time from ASCT to death or the final follow-up was used to define overall survival (OS).

Results: Median age at ASCT was 55 years (16-68). Amongst patients ≤ 60 years (n = 109) and > 60 years (n = 31), there was no significant difference in PFS ($P = 0.756$), OS ($P = 0.711$), neutrophil (12.5 vs 11 days) and platelet (12 vs 14 days) engraftment times. Amongst follicular lymphoma (FL) patients (n = 54) who received BEAM (carmustine, etoposide, cytarabine, melphalan) (n = 30) or Cy/TBI (cyclophosphamide/total body irradiation) (n=24) conditioning, there was no significant difference between PFS ($P = 0.111$) and OS ($P = 0.667$). There was no significant difference ($P = 0.46$) in the incidence of second malignancies in the patient receiving BEAM or TBI-based conditioning.

Conclusion: ASCT can be safely performed for NHL in patients > 60 years with outcomes similar to those ≤ 60 years. TBI based conditioning appear safe with similar outcomes to BEAM in FL patients. Prospective studies are needed to confirm these findings.

Keywords: Non-Hodgkin lymphoma, Stem cell transplant, Autologous, Total body irradiation, Transplantation conditioning

Introduction

Autologous haematopoietic stem cell transplantation (ASCT) was successfully used as a consolidative treatment modality in non-Hodgkin's lymphomas (NHL) for many years, but its role to manage NHLs continues to evolve.

Results of therapies for many indolent lymphoma subtypes have improved dramatically over the last several years using the monoclonal antibodies like rituximab^{1,2} and radio-immunoconjugates³ and in turn resulted in re-defining the use of ASCT in first complete remission for these subtypes. However, recent studies have further verified the effectiveness of ASCT in primary central nervous system (CNS) lymphoma and further supported that ASCT continues to be a significant consolidative therapeutic strategy for many forms of NHL in relapse/refractory context.⁴

Data from different centres differ in terms of the outcomes, toxicity and overall survival (OS) with various conditioning regimens and disease subtypes.⁵ It is reflected, for example, in the differences in conditioning regimens. There are conflicting reports about negative outcomes in patients over the age of 60 years undergoing ASCT.^{6,7} The increased incidence of secondary myelodysplastic syndrome/acute myeloid leukaemia (sMDS/sAML) following ASCT is well documented.^{8,9} Factors reported to be associated with an increased risk of sMDS/sAML after ASCT include older patient age,^{7,8} multiple lines of chemotherapy particularly with alkylating agents,¹⁰ etoposide¹¹ or fludarabine,⁸ and using TBI with transplant conditioning¹² and so on.

We report retrospective data of 140 NHL patients who received ASCT at Waikato Hospital, Hamilton, New Zealand over a period of 23 years with the purpose of adding to the data on these difficulties (1992-2015). Based on age, NHL subtypes, and exercise routine, we assess patient outcomes and sequelae as well as potential confounding variables.

Patients and Methods

All patients (n = 140) who underwent their first ASCT for NHL between 1992 and 2015 at Waikato Hospital, Hamilton, New Zealand were included in this retrospective study. Patients were found using a prospective ASCT database, and information was gathered from both digital and analog clinical records. The study was approved by the department of haematology of Waikato hospital, New Zealand, and by Health and Disability Ethics Committees of New Zealand under the study project to evaluate outcomes of patients managed in New Zealand blood and cancer centers (ethics code: 16/STH/251).

Age alone was not employed as a decisive criterion to determine ASCT eligibility as a departmental policy, and the entire clinical state, together with additional comorbidities, was used to assess transplant eligibility in an individual patient. The transplant physician made the decision on the regimen, namely between Cy/TBI and BEAM. However, in recent years, there has been a broad tendency among clinicians to use BEAM as a conditioning program. Transplant outcome parameters included neutrophil engraftment (defined as first day of recovery to $>0.5 \times 10^9/L$), platelet engraftment (first day of spontaneous recovery to $>20 \times 10^9/L$) and admission duration. Transplant related mortality (TRM) was defined as death during the hospital admission for ASCT or any time within 100 days of ASCT unless due to progressive disease.

Disease response, relapse and progression were assessed by the International Working Group response criteria.¹³ In brief, these are:

- a) Relapse was defined as disease recurrence after remaining in complete remission for at least 90 days from end of treatment.
- b) Refractory disease was defined as response $<PR$, or disease recurrence within 90 days of ASCT.
- c) Disease progression was defined as new site/s of disease or $> 50\%$ increase in previously involved sites as measured clinically or by radiological scans after achieving

partial remission and stable disease for at least 90 days.

Relapse, refractory disease, progressive disease, or death were all considered progression events. PFS was defined as the time from transplant to a progression event, or if no progression event occurred, the time from transplant to the date of final follow-up. OS was defined as time from transplant till death, or if no death then time from transplant till date of last follow-up.

XLSTAT v2016.03 (Addinsoft) was used for statistical analysis. Kaplan Meier method was used to calculate PFS and OS and differences were assessed by log-rank technique.

Results

140 patients were identified, 89 (64%) male / 51 (36%) female with a median age of 53 years (16-68).

The transplanted diseases are listed in table 1. The vast majority of patients (100, 71%) had conditioning with BEAM (BCNU/carmustine, etoposide, ara-C/cytarabine, melphalan), 29 had Cy/TBI (cyclophosphamide/total body irradiation), 7 had thiotepa/BCNU and 4 had etoposide/TBI as conditioning regimen (Table 1).

The median period of follow-up was 29.1 months (0.2-282.6). The median PFS and OS for the whole cohort were 20.9 months (0.2-273.7) and 48.8 months (0.2-281.5), respectively (Figure1).

The median age at transplant was 53 years (16-68). 109 patients were ≤ 60 years with a median age at transplant of 50 years; and total 31 patients were >60 years with a median age at transplant of 64 years (Table 1). Age did not affect transplant outcome. Median time to neutrophil recovery, platelet recovery and inpatient days were 12.5, 12, 21 days for age ≤ 60 years and 11, 14, 20 days for age >60 years, respectively. By a median follow-up of 30.6 months (0.2-282.7) and 21.4 months (0.4-84) for patients aged ≤ 60 years and >60 years, respectively, there was no difference in PFS ($P = 0.756$) or OS ($P = 0.711$) (Figure 2).

54 patients with follicular lymphoma underwent conditioning treatments: 30 got BEAM (FL-BEAM) and 24 received Cy/TBI (FL-Cy/TBI) (Table 3). The median time to neutrophil recovery, platelet recovery, and inpatient days were 11, 12, and 10, 11, 19 days, respectively, and were quite close to one another. There was no TRM in either of the group. By a median follow-up of 44.5 months (0.5- 139.1) and 44.1 months (0.4-128.6) for patients in FL-BEAM and FL-Cy/TBI groups respectively, the differences in PFS ($P = 0.111$) and OS ($P = 0.667$) were not statistically significant (Figure 3). Long-term adverse effects were also similar. Secondary MDS/AML developed in 2 patients in each group. Cataract as side-effect was exclusively seen in Cy/TBI group. Persistent cytopenias were more common in FL-cy/TBI group than FL-BEAM group (4 vs. 1 respectively).

There were 36 DLBCL patients (excluding primary mediastinal B-cell [PMBC], CNS lymphoma and double hit lymphoma) who had an ASCT during this period with a median age of 55 years (28-68) (Table 2). The majority of patients were treated during their second remission. The BEAM conditioning protocol was administered to all DLBCL patients. The median time to recover neutrophils, platelets, and hospital days was 11, 14, and 22 days, respectively. There was one transplant related death (TRM), with the patient dying of *Staphylococcus aureus* sepsis on Day +7. By a median follow-up of 17.81 months (0.2- 282.7), the median PFS was 13.6 months and median OS was 17.8 months. Two year PFS and OS were 36.1% and 44.4%, respectively.

Cy/TBI conditioning was used in 29 patients, the majority (24) for FL (Lymphoblastic lymphoma-2, Burkitt's-like-2 and marginal zone lymphoma-1).

100 patients received BEAM conditioning. The majority (36) had DLBCL or FL (30). The median age at transplantation was 52 (23-68). The median time to recover neutrophils, platelets, and hospital days was 11, 13, and 21 days, respectively. There were 2 TRM, both due to sepsis. By a median follow-up of 25.8 months (0.2-282.7), the

median PFS and OS were 18.20 months (range 0.2-273.7) and 21.57 months (range 0.2-282.7), respectively. The 2-year PFS and OS was 40% and 49%, respectively. The most common complication was prolonged cytopenia (10 patients), followed by *Clostridium difficile* infection, Paroxysmal Atrial Fibrillation and cardiomyopathy developing in 3 patients each.

The total numbers of other NHL subtypes were low. The combined data to remain B-cell NHL (including Mantle cell, Marginal zone, Primary CNS, Secondary CNS, Double Hit, Burkitt's, Burkitt's like, Primary mediastinal B cell, Plasmablastic) and T cell NHL (including Peripheral T cell lymphoma, NK/T Cell, T Lymphoblastic lymphoma) are presented in table 2. The outcomes for these individual NHL subtypes were difficult to interpret due to low numbers.

The adverse impacts were looked at. Only 2/140 early non-disease related fatalities, both from sepsis, indicated low TRM. Two patients had secondary MDS after BEAM, while four patients experienced sAML after BEAM and two after Cy/TBI. The median time from ASCT to sAML was 65.5 months (48-83). Non-haematological second malignancies developed in five patients with a mix of NHL types and conditioning regimens. Amongst these five patients, two developed bowel carcinoma and one developed both right renal transitional cell carcinoma and metastatic squamous cell Lung carcinoma. Out of remaining two, one developed lung carcinoma and other had right medial canthus basal cell carcinoma.

In total, 5/100 (5%) patients receiving BEAM conditioning developed secondary malignancy (haematological and non-haematological) in comparison to 3 out of 33 (9%) patients who received TBI-based conditioning regimen. This difference was not statistically significant ($P = 0.46$).

Discussion

ASCT is still a very important consolidative treatment for many types of NHL. The goal of this retrospective study of ASCT-treated NHL patients at our facility was to assess

patient outcomes depending on age, NHL subtypes, and conditioning regimens. Based on these criteria, we also tried to assess the side effect profiles. The typical limitations of a retrospective research were present in our analysis. However, it offered some distinct results that were in line with certain other research that had already been published.

Older NHL patients have been historically considered to be having increased risk of therapy-related toxicity, including TRM and sMDS/AML.⁸ It is believed to be because of age-related physiological changes and frequent co-morbidities. Age is one of the factors included in Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI).^{14,15} Other publications, however, suggest that the patient's overall clinical condition rather than age alone should guide eligibility for ASCT in elderly patients. This conclusion is supported by our investigation, which identified no differences in second malignancies, TRM, neutrophil or platelet engraftment times, or survival outcomes between individuals older or younger than 60.

Nevertheless, the oldest patient in our series was 68, reflecting persisting caution amongst clinicians. French Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC)¹⁶ recently reported a retrospective analysis of 81 NHL patients over 70 years (median 72.3) who received ASCT. Engraftment and toxicity were satisfactory, and the main cause of death was relapse rather than adverse effects. This study concluded that ASCT appears acceptable in NHL patients over 70 years if clinical condition is adequate. Similar conclusions were drawn by Dahi et al in a retrospective analysis of 202 NHL patients aged ≥ 60 years that had ASCT.¹⁷ With a median age of 65 years (60-74), the OS, PFS and TRM were similar to historic controls of younger patients. There are some data to the contrary, with Jantunen et al reporting a high TRM of 11% for ASCT in NHL patients >60 years⁶ and another group reporting age at ASCT as a principal factor for developing second malignancy ($P = 0.0002$).⁷

Internationally and across centers, several conditioning programs are used for ASCT. Our facility has performed several FL ASCTs with Cy/TBI due to FL's radiosensitivity. After TBI-based conditioning, there is considerable worry regarding the potential of hematologic and other subsequent cancers.^{7,12,18}

Our data did not show any significant difference among the outcomes of FL patients treated with BEAM or Cy/TBI based regimen in terms of PFS, OS, TRM, secondary malignancies or neutrophil/platelet engraftment times. Results from earlier investigations have shown contradictory results. Data from 605 individuals who had ASCT for B-cell NHL and received Cy/TBI conditioning before receiving purged autologous stem cells were published by Brown et al. This study reported a 10-year incidence of second malignancy as 21%. A 2007 EBMT registry study¹⁸ reported ASCT outcomes of 693 FL patients; the 58% who received TBI-based conditioning had a shorter OS ($P = 0.004$), higher NRM ($P = 0.04$) and a higher incidence of sMDS/AML. In total, 39 patients developed sMDS/AML, out of which 34 cases received TBI as conditioning regimen. This study concluded that TBI-containing regimens are associated with a negative impact on survival. The same study showed that older age was associated with shorter OS ($P < 0.001$) and higher NRM ($P < 0.001$).

On the contrary, El-Najjar et al. for the EBMT Lymphoma Working Party¹⁹ reported in 2014 that in the patients with FL who received TBI-based ASCT after 1995, there was no statistically significant difference in the incidence of non-relapse mortality (NRM) and sMDS/AML, when compared with BEAM, while disease control was at least equivalent.

Furthermore, a 2003 retrospective case-control study showed no significant increase in incidence of sMDS/AML in the patient receiving TBI dose of 12 Gy or less in conditioning regimen.¹⁰

We are aware that many patients who had transplants in the early stages of the cohort in our analysis did not have access to

information on the histologic grade of FL. Further subgroup analysis to compare ASCT results between low-grade and high-grade FL patient groups would have benefited from this information. It would have been fascinating to see how the different conditioning regimens (BEAM vs. Cy/TBI) affected these subgroups.

We acknowledge that the lack of difference in PFS and OS between younger and older groups, as well as FL patients receiving BEAM vs. Cy/TBI could be in terms of small numbers, and the heterogeneity of diseases included.

DLBCL continues to be a significant indication for ASCT in many relapsed/refractory patients as consolidative therapy and in certain chosen individuals as upfront therapy. There are many factors which were shown to affect ASCT outcomes in DLBCL, including disease status at ASCT, age and international prognostic index (IPI) risk category.²⁰

In total, there were 36 DLBCL patients who had ASCT during this period in our centre. Unfortunately, further subgrouping of DLBCL patients based on IPI score could not be done in terms of the non-availability of this information in many patients transplanted in 1990s. Most of our patients 29/36 (80.6%) did not have upfront ASCT in line with the mostly negative data for upfront ASCT.²¹

The relatively poor PFS and OS outcomes in our DLBCL patients²² could be multifactorial and be because of a significant percentage 12/36 (33.3%) of them being in PR at time of ASCT. Non-availability of follow-up data for some patients transplanted in 90s could affect survival outcomes.

It was clearly unable to do the molecular categorization of DLBCL (GCB (germinal center B cell) vs. non-GCB), which is known to affect treatment results in DLBCL patients,²³ since these entities were essentially non-existent for a significant beginning portion of our research period.

Various factors were implicated in development of secondary malignancies in the setting of ASCT, including conditioning regimen, age, previous chemotherapy

regimens and time from diagnosis to transplant/number of relapses.^{7,11,12,24} Besides, one report found an increased risk of sMDS/AML in patients who required more than 5 days of apheresis, suggesting that a difficult stem cell harvest is a marker of genotoxic damage.²⁵

A shorter period of follow-up for some patients in our study could have contributed to relatively low incidence of sAML (4/140), as many studies have reported a higher incidence of sMDS/AML with 5 plus years of follow-up post-transplant.²⁶

We believe the study has following strengths and weaknesses:

1. The retrospective nature, single institution data and heterogeneity of the cases presented.
2. Our study did not evaluate the effect of stage/grade of FL or the subtype of DLBCL on the side effect profile, PFS and OS in patient receiving BEAM and Cy/TBI regimen.
3. Our study has relatively reasonable number of studied patients compared to other published studies.
4. There was a long period of follow up which could highlight the long-term complications of ASCT, in particular secondary malignancies.

Conclusion

This study of 140 lymphoma ASCT recipients allowed us to examine several factors that remain uncertain in the literature. Firstly, there was no discernible difference between patients under and over 60 in terms of PFS and OS. This implies that older individuals may undergo ASCT safely with results that are comparable to those of comparatively younger patients, and that age alone should not be a factor used to disqualify people from ASCT. Secondly, there was no significant difference between BEAM and Cy/TBI conditioning in FL patients in terms of toxicity, PFS and OS. Hence, we cannot recommend one over other in Follicular Lymphoma patients. We recommend that prospective studies are required to further corroborate this as there are no prospective trials contrasting these two conditioning regimens side by side. Our study, however,

did not evaluate the effect of grade of Follicular Lymphoma on the side effect profile, PFS and OS in patient receiving BEAM and Cy/TBI regimen.

We did not find any significant increase in the incidence of sMDS/sAML in patients who had Cy/TBI conditioning compared to BEAM conditioning. Considering small number of patients developing sMDS / sAML, no particular chemotherapy or conditioning regimen could be implicated in developing sMDS / sAML. Moreover, there was no suggestion towards age being a factor for developing sAML, as 3 out of 4 patients with sAML were less than 60 years.

Our study did not suggest any significant increase in incidence of secondary malignancy (haematological and non-haematological) in any particular conditioning, NHL subtype or age group (greater or less than 60 years).

Only 2 patients out of 140 had transplant related mortality (TRM) suggesting ASCT can be performed safely in most patients regardless of age, NHL subtype or conditioning regimen.

However, all these results need to be confirmed with focused randomised prospective studies.

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Conflict of Interest

None declared.

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	Age ≤60 years	Age > 60 years
Total	109	31
Sex distribution	Female= 39, Male= 70	Female= 9, Male= 22
Conditioning	BEAM=78, Cy/TBI= 22, Etoposide/TBI=4, Thiotepa/BCNU= 5	BEAM= 22, Cy/TBI= 7, Thiotepa/BCNU= 2
Diagnosis	DLBCL-28, FL-41, Burkitt's -3, Burkitt's Like-3 Lymphoblastic - 6, Mantle-6, Marginal Zone-1, NHL NOS- 2, NK/T Cell-2, PTCL-9, PMBC-2, Primary CNS-4, Secondary CNS-1 Plasmablastic -1	DLBCL-8, FL- 13, Double HIT-3 Burkitt's Like-1, Mantle-2, Marginal- 1, PTCL- 1, Primary CNS-1 Secondary CNS-1
Median Age at transplant, Years (range)	50 (16-60)	64 (61-68)
Median Neutrophil recovery Days (range)	12.5 (8-20)	11 (9-41)
Median Platelet recovery Days (range)	12 (8-50)	14 (8-78)
Median Days In hospital (range)	21 (16-47)	20 (16-35)
TRM	2	0
Relapse/Refractory	57	13
Death	46	9
Follow-up, Months (range)	30.6 (0.2-282.7)	21.4 (0.4-84)
Median PFS, Months (range)	23.8 (0.2-273.7)	13.7 (0.6-87.4)
Median OS, Months (range)	31.1 (0.2-282.7)	28.3 (0.6-141.2)
2 year PFS (%)	49.5	45.2
2 year OS (%)	57.8	51.6

FL: Follicular lymphoma; DLBCL: Diffuse large B cell lymphoma; CNS: Central nervous system; PMBC: Primary mediastinal B cell lymphoma; PTCL: Peripheral T cell Lymphoma; NK: Natural Killer cell; NOS: Not otherwise specified; TBI: Total body irradiation; Cy: Cyclophosphamide; BEAM: Carmustine, etoposide, cytarabine, melphalan, TRM: Transplant related mortality; BCNU= Carmustine; PFS: Progression-free survival, OS: Overall survival

Table 2. Data as per NHL subtype

NHL Type	FL	DLBCL	Other B cell †	T, Nk cell ‡
Number	54	36	32	18
Follow-up Months (range)	45.1(0.4-140.9)	17.8 (0.2- 282.7)	16.4(0.4-143.1)	39.6(5.3-185.8)
Median Age , years (Range)	54(34-67)	55 (28-68)	53(31-65)	37 (16-64)
Remission status	CR1=2, CR2=31, CR3=6, CR4=2, PR1=3, PR2=8, PR3=2	CR1=2, CR2=22, PR1- 5, PR2- 6, PR3- 1	CR1=20, CR2=4, CR3=1CR4=1, PR1=1, PR2=5	CR1=9, CR2=6, PR1=1, PR2=2
Conditioning	BEAM30, CyTBI-24	BEAM (All)	BEAM-22, Thiotepa/BCNU-7, CyTBI-3	BEAM-12, Etoposide/TBI-4, CyTBI-2
Median PFS Months (Range)	26.3(0.4-128.6)	13.6(0.2-273.7)	12.5(0.4-87.4)	38.5(1.2-183.3)
Median OS Months (Range)	44.5(0.4-139.1)	17.8(0.2-282.7)	19.5(0.4-259)	46(5.2-264.6)

† Burkitt's-3, Burkitt's Like-4, PMBC-2, Plasmablastic-1, Mantle cell-8, Marginal zone-2, Primary CNS-5, Secondary CNS-2, Double Hit-3, NOS-2

‡ PTCL-10, NK/T Cell-2, T Lymphoblastic-6

FL: Follicular lymphoma, DLBCL: Diffuse large B cell lymphoma, CNS: Central nervous system, PMBC: Primary mediastinal B cell lymphoma, PTCL: Peripheral T cell Lymphoma; NK: Natural killer cell, NOS: Not otherwise specified, TBI: Total body irradiation, Cy: Cyclophosphamide, BEAM: Carmustine, etoposide, cytarabine, melphalan, BCNU: Carmustine, CR: Complete remission, PR: Partial remission, PFS= Progression-free survival, OS: Overall survival

Table 3. Follicular lymphoma data as per conditioning

(Cy/TBI)	FL (BEAM)	FL
Total	30	24
Median Age at Transplant, (34-67) Years (Range)	51 (35-67)	57
TRM	0	0
Median Neutrophil Recovery (18) (days)	11 (8-19)	10 (9-18)
Median Platelet Recovery (20) (days)	12 (8-29)	11 (8-20)
Median Days In hospital (16-23)	21 (17-38)	19
Relapse/refractory	16	9
Death (Total/ Relapse related)	12/8	8/6
Median Follow-up, (0.4- 129) Months (range)	44.5 (0.5- 139.1)	44.1
Median PFS, Months (range) (0.4-129)	24.2 (0.5-119.4)	37.8
Median OS, Months (range) (0.4-129)	44.5 (0.5-139.1)	44.1
2 year OS (%)	63.3	66.8
2 year PFS (%)	50	54.2

FL: Follicular lymphoma; TBI: Total body irradiation; Cy: cyclophosphamide; BEAM: Carmustine, etoposide, cytarabine, melphalan; TRM: Transplant related mortality, PFS: Progression-free survival, OS: Overall survival

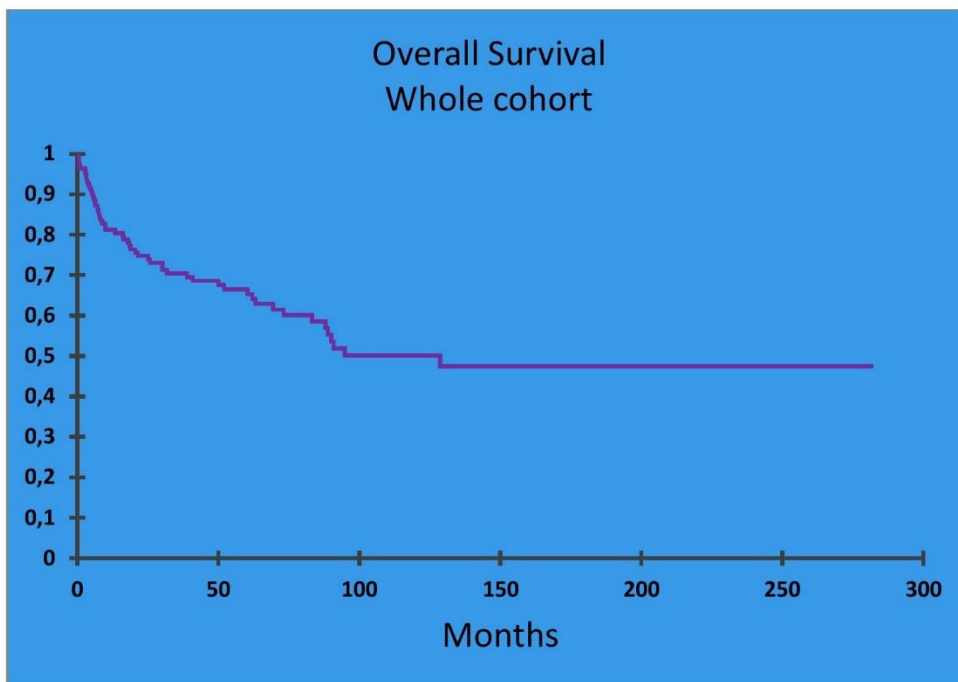
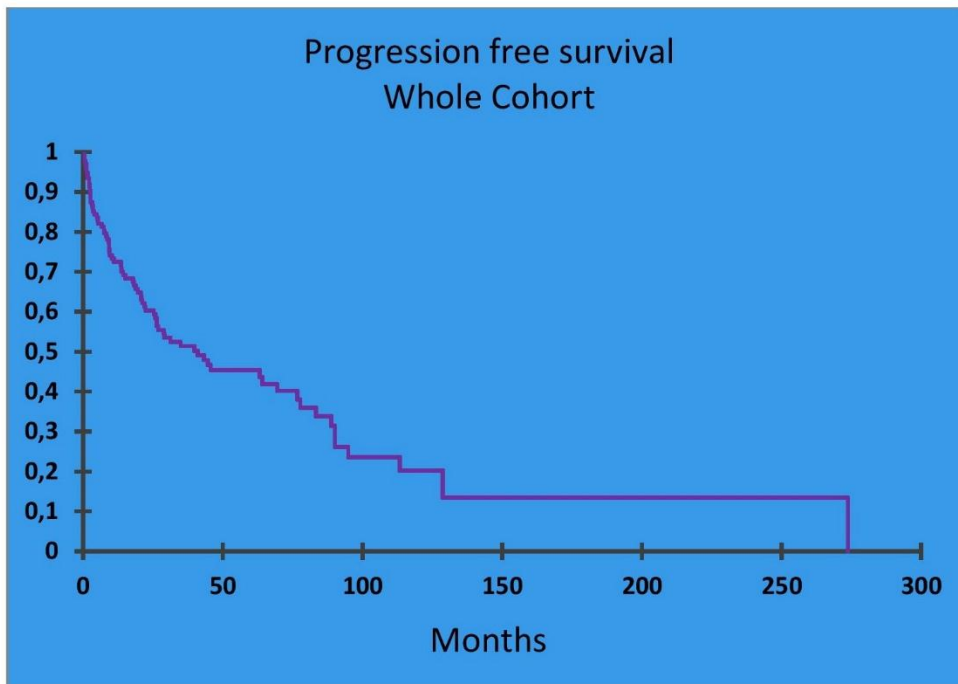


Figure 1. This figure shows the progression-free survival and the overall survival for whole cohort.

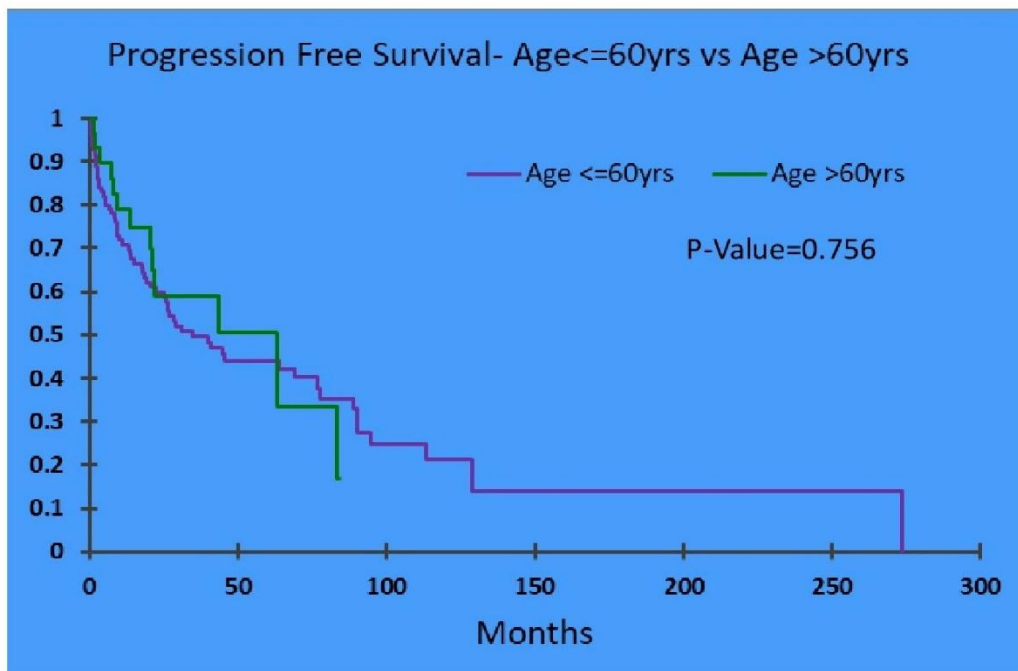
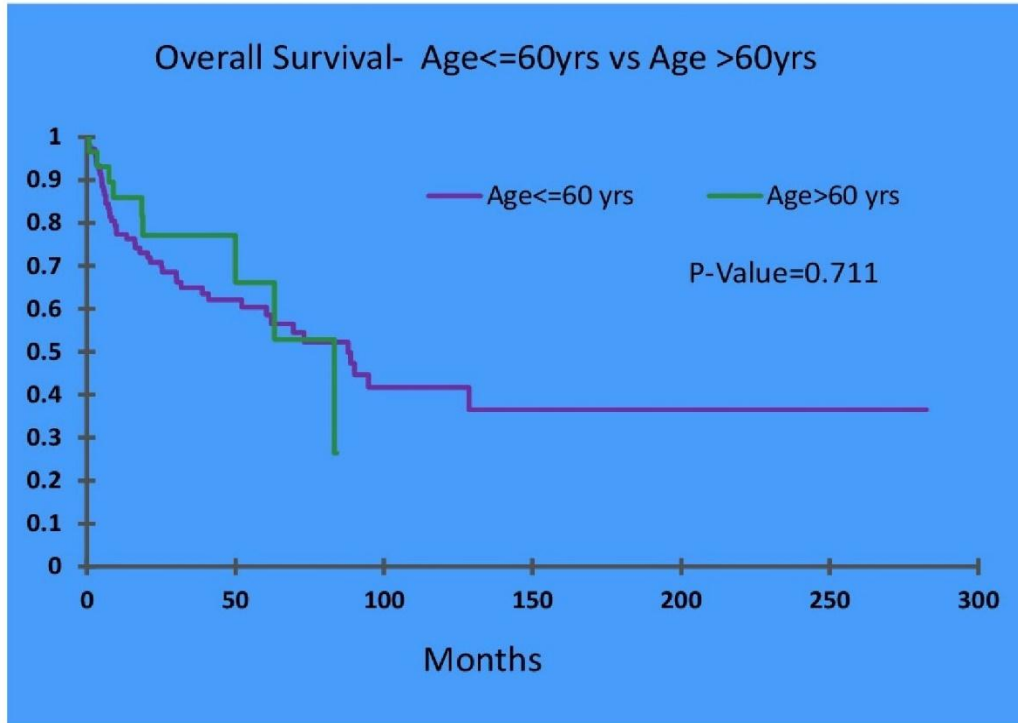


Figure 2. This figure shows the progression-free survival and the overall survival for the patients aged \leq 60 and $>$ 60 years.

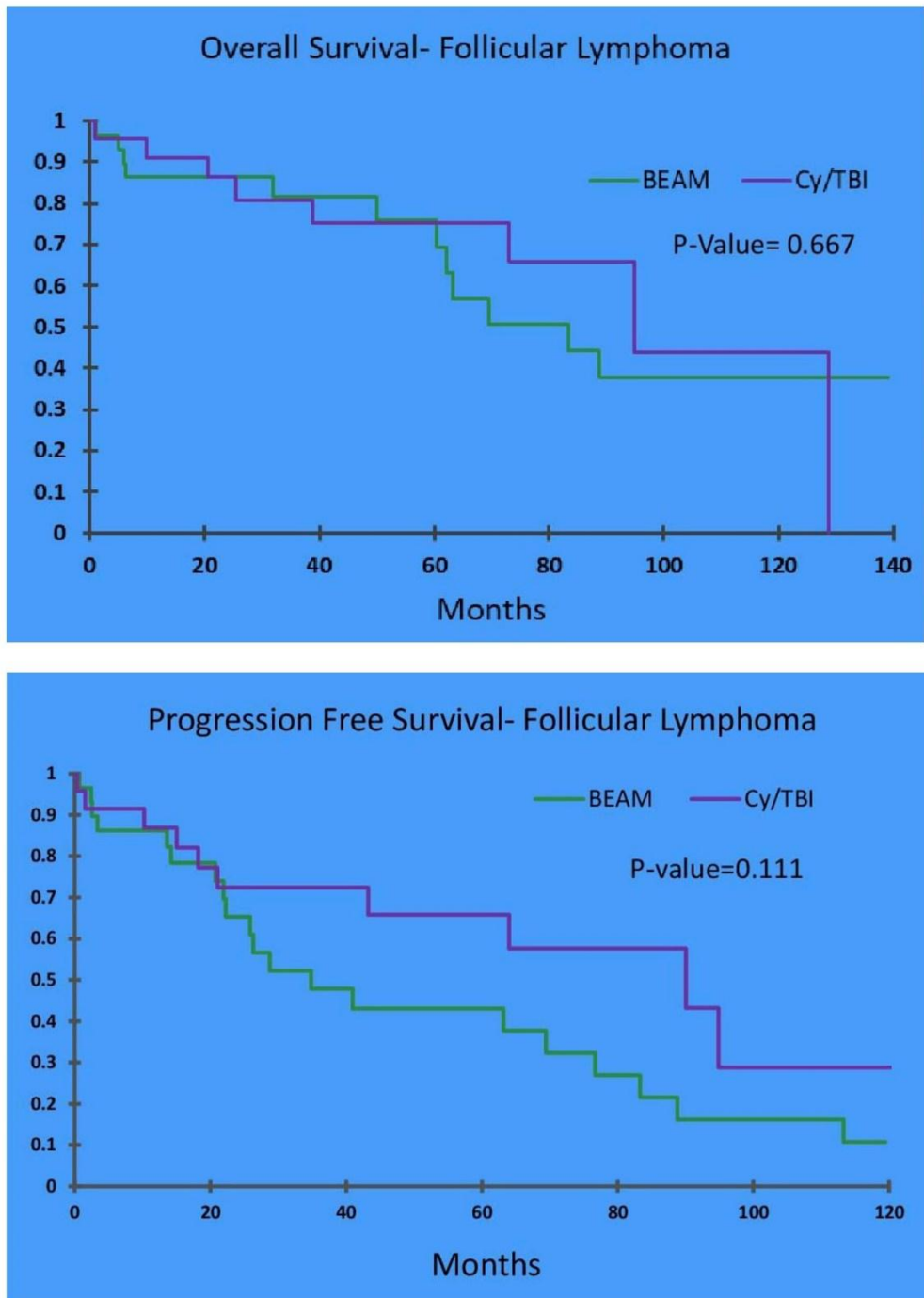


Figure 3. This figure shows the progression-free survival and the overall survival for follicular lymphoma patients as per conditioning.

TBI: Total body irradiation; Cy: Cyclophosphamide; BEAM: carmustine, etoposide, cytarabine, melphalan