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Association between Lung Dose and Incidence of Pulmonary Toxicity after Total Body Irradiation

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Master of Science in Public Health

Biostatistics and Bioinformatics

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2018

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Abstract

Association between Lung Dose and Incidence of Pulmonary Toxicity after Total Body Irradiation

By Mengda Yu

Background: Previous studies regarding the effect of total body irradiation (TBI) on pulmonary injury is continuously disputed. Our study was designed to examine factors related to exaggerated risk of pulmonary toxicity (PT) among pediatric patients when myeloablative conditioning is performed by TBI followed with allogeneic hematopoietic stem cell transplantation (HSCT). We tried to find an undeniable association between incidence of PT and higher total body irradiation dose rate within the setting of comparatively homogenized TBI techniques.

Methods and Materials: Medical data of 148 pediatric patients that received TBI-based myeloablative conditioning in a single institution from 2003 to 2018 have been reviewed. Pulmonary toxicity was identified by development of clinical symptoms, radiographic evidence, or ventilatory defects on pulmonary function tests. We used univariate association analysis to compare incidence of infectious pneumonitis and non-infectious. Multivariable analysis of pulmonary toxicity was done by involving covariates in the logistic regression model. Differences in relapse-free survival and overall survival were examined by Kaplan-Meier method and log-rank test.

Results: Patients were divided into two groups: >8Gy lung dose group and 8Gy lung dose group. 111 patients out of 119 (93.28%) developed pneumonitis in the >8Gy lung dose group, and 11 patients out of 29 (37.93%) developed pneumonitis in the 8Gy group. We found that pneumonitis toxicity is strongly related to lung dose limit (infectious pneumonitis: $p<0.001$ and non-infectious pneumonitis: $p=0.046$). The odds ratio for relapse rate with a lung dose limit of 8Gy compared to >8Gy is 0.426 ($p<0.029$). Pulmonary toxicity developed in 85.0% of patients with higher GVHD grade ($p=0.001$). TBI dose rate is a significant factor associated with PT ($p=0.002$). PT is 5.33 times more likely to occur in pediatric patients undergoing higher than 15Gy/min than patients treated with dose rates of 5-10Gy/min ($p=0.018$).

Conclusions: Within this cohort of homogeneously treated pediatric patients receiving TBI for allogeneic HSCT, we found a large incidence of pulmonic toxicity. The existence of high grade (III and IV) GVHD and infection were the foremost important factor tributary to pulmonic toxicity. To reduce the danger of pulmonic toxicity, TBI rate ought to be controlled below 15cGy/min. Reducing lung dose constraint has a positive impact on decreasing incidence of pneumonitis. And this procedure is not a risk towards overall survival.

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Contents

Introduction

Pulmonary injury is a common complication of stem cell transplantation (1,2). Clinically, patients present with cough, the constellation of fever, dyspnea, and hypoxia. Besides, bilateral diffuse shadowing is often showed under chest x-rays. Pulmonary function tests will indicate defects like restrictive ventilatory defect and low diffusing capacity (3,4). According to the time and speed of progression after transplantation, pulmonary complications after hematopoietic stem cell transplantation are divided into early pulmonary complications and advanced pulmonary complications. The definition of the first stages is approximately 3 to 4 months after transplantation. The incidence of pulmonary complications after transplantation is about 25% to 55%, accounting for about half of the causes of transplantation death (1,2,3). Thirty years ago, the purpose of pulmonary complications after transplantation was mainly infectious diseases. With the update and widespread use of many types of broad-spectrum antibiotics, researchers have been able to detect common bacterial or fungal pathogens in various clinical specimens. Therefore, since 2002, non-infectious factors in the etiology of pulmonary complications after transplantation have been frequently mentioned in the reports (12,13). The incidence of non-infectious pulmonary complications after transplantation is related to factors such as the intensity of pretreatment, the age of the patient, and whether the patient has pulmonary comorbidity before transplantation. Two of the most common types of stem cell transplants are autologous and allogeneic transplants. During autologous transplantation, one's stem cells are collected and used. Allogeneic transplantation uses donor-derived stem cells whose human leukocyte antigen (HLA) matches the patient. Although non-infectious pulmonary complications

can also occur after autologous transplantation, the incidence is higher after allogeneic transplantation. The mortality rate is high, and the conventional treatment is ineffective (11,12).

Pulmonary toxicity (PT) is the clinical name of side effects on the lungs. Although side effects of medicinal drugs lead to most cases of PT, many cases are due to side effects of radiation and radiotherapy. PT has acute to the late-onset and includes various syndromes principally divided into infectious and non-infectious categories (2,3,6,7). The exact pathophysiology behind these conditions remains unclear and is likely to be multifactorial. Various syndromes and commonly heterogeneous study populations, combining adult and pediatric patients, disease and treatment factors are included in previous study data according to literature from 2009 to 2012 (2,12).

Total body irradiation (TBI) is a type of radiation therapy that is mainly used as part of a preparation procedure for hematopoietic stem cell transplantation. Pulmonary toxicity is a prevalent complication of patients undergoing TBI for bone marrow ablation in preparation for hematopoietic stem cell transplantation (HSCT) (5,8). Relationship between PT and pre-transplant TBI conditioning has been suggested but remains somewhat controversial (2,4,5,8,9,10). The critical point is there is a lack of consensus on the optimal radiation dose regimen, TBI technology, and lung dose limits. To clarify this contentious subject, we want to find which factors affect the development of Pulmonary toxicity according to a large institutional coterie of pediatric patients undergoing homogenous TBI-based myeloablative conditioning before allogeneic HSCT.

Historically, we tend to use a respiratory lung dose constraint of 10Gy once designing TBI. Recently, we tend to employ a stricter lung dose constraint of 8Gy. We reviewed medical and

radiation treatment records for pediatric patients treated with TBI in preparation for HSCT from 2003 to 2019 at one establishment. We hypothesized that the more stringent for lung dose constraint, the lower incidence of pulmonary toxicity (PT) in pediatric patients receiving TBI. PT is outlined by the event of clinical symptoms (cough, dyspnea, hypoxia, cyanosis), radiographic evidence, or ventilatory defects on pulmonary function tests (1,3). The association between pulmonary toxicity (PT) with other variables is examined by ANOVA. We use multivariable regression analysis to check for a distinction within the incidence of PT by lung constraint group. Kaplan-Meier method and Cox model are employed to estimate overall survival (OS). In the remainder of this thesis, we will describe details of statistical methods and tools we use in Section 2. In section 3, the modelling study and survival analysis outcomes will be presented to examine the incidence of pulmonary toxicity. In Section 4, we will discuss the results and limitations. Applications of this study will also be involved.

Methods and Materials

Study Population We performed a retrospective analysis on consecutive pediatric patients with hematologic malignancies that were treated between 2003 and 2019 with myeloablative TBI as part of a conditioning regimen for HSCT. Myeloablation means the administration of TBI, at doses which won't allow autologous hematologic recovery (13). We didn’t count multiple bone marrow transplant (BMT) patients.

Bone marrow transplant procedure Based on current best practice guidelines and contemporary clinical trials, all the patients took standard pre-HSCT assessment and adjustment process. Most patients received treatment with cyclophosphamide. Doctors derive stem cells

from bone marrow, or umbilical cord blood from donors included allogeneic matched unrelated parent donors, matched sibling donors, partially matched parent donors, and partially matched unrelated donors. According to the treatment regimen, patients receive different combinations of methotrexate, sirolimus, cyclosporine, and steroids to prevent graft-versus-host disease (GVHD) after transplantation.

All patients undergoing TBI were treated with unified TBI technology and treated with Anterior Posterior/Posteroanterior Position (AP/PA) Technology with 6MV beams twice daily for 6-8 fractions. From 2003 to 2009, the dose rate ranges from 5.57cGy/min to 20.85cGy/min. However, since 2009, the dose rate has been restricted to between 7 and 10cGy/min. Patients were positioned in the lateral decubitus position on a stretcher against the far wall of the linear accelerator room to maximize the SSD and field size to encompass the entire patient. The AP treatment area is used when the patient is in the left lying position and the PA area is used when the patient is in the right lying position. A spoiler made of 3/8-inch plexiglass is held in front of the patient to increase the surface dose and fix the lung block. Heterogeneity of lung tissue was accounted by age-prorated formula and a sufficient chest thickness was calculated using the measured patient separation and lung thickness as determined by CT at the level of the carina. Partial transmission lung blocks were then manufactured and placed to attenuate the beam so that lung tissue received the desired dose of 8 to 10Gy.

Evaluation of PT and Other Clinical Outcomes During the follow-up period based on previously recognized criteria, patients were noted as having PT if they met any one of the three following definitions (4,13,14). (Table 1) These values were recorded when available.

Table 1: Three symptoms indicating pulmonary toxicity

Two of three of the following clinical symptoms	Dyspnea/Cough or any reference to respiratory symptoms Pyrexia Hypoxia/cyanosis	
Radiographic evidence	Chest x-ray with bilateral diffuse shadowing Increased density Increased interstitial markings Opacities, or chest CT with diffuse ground-glass opacities	
Ventilatory defects as noted on pulmonary function tests (PFTs)	Restrictive patterns	Decreased total lung capacity (TLC) Vital capacity (VC) with a low diffusing capacity (DLCO)
	Destructive patterns Increased TLC with a low DLCO and the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) less than 0.70	

Descriptive analysis Descriptive table for pulmonary toxicity and possible causative variables was firstly constructed. We hold the following criteria that, since there are no continuous variables, for binary and categorical variables, the frequencies and percentage was presented. For each variable, we examined whether there exists interaction among different levels.

Statistical Analysis First, we hypothesized a lung dose limit of 8Gy is associated with reduced incidence of pulmonary toxicity compared to a higher lung dose constraint (>8Gy). We used univariate association analysis to compare rate of pneumonitis and non-infectious pneumonitis between those who had a lung dose limit of 8Gy and >8Gy. And differences in Overall survival (OS), relapse-free survival and time to relapse was also conducted using Kaplan-Meier method. All related variables were compared between the two groups (8Gy and >8Gy) to determine whether there is any difference between them.

And we examined factors related to accumulated risk of pulmonary toxicity in pediatric patients once myeloablative acquisition using TBI followed by allogeneic HSCT. Univariate association of the pulmonary toxicity with other variables (age, gender, engraftment status, donor type, TBI total dose, TBI fraction dose, TBI dose rate, grade of GVHD (Graft Versus Host Disease), lung thickness, lung dose limit, multi-system organ failure) was examined with ANOVA. When appropriate, Fisher's exact test or Chi-square test was used for categorical covariates. Survival analysis was conducted to determine whether patients with GVHD more or less likely to relapse or die. For GVHD grade, we defined another level by combining grade 1 and grade 2. Analysis for separate grades and combination was both conducted to examine the association between GVHD and pulmonary toxicity. Multivariable analysis of pulmonary toxicity was done by involving covariates in a logistic regression model and backward selection method was used. Survival analysis were conducted by Kaplan-Meier method and we used a log-rank test to identify the difference in overall survival (OS) and relapse-free survival (RFS) between patients with and without pulmonary toxicity. For complete remission (CR) and minimal residual disease (MRD) status, whether CR status and MRD status at time of transplant are associated with overall survival and incidence of relapse was analyzed by log rank test. All analysis was done with a significance level of 0.05.

Results

A total of 148 pediatric patients were analyzed with a median age of 11 years (range, 0.67-22 years). 118 patients were treated with a lung dose constraint of >8Gy, and 30 were treated with a lung dose constraint of 8Gy. Patient demographics and treatment details are listed in Table 4 and Table 6. Median follow-up time is 1.30 years (range, 1 month -11.5 years). Pulmonary toxicity,

represented with both infectious and non-infectious types, developed in 92 patients (64.3%) and contributed to death in 35 (38.0%). Incidence of non-infectious pulmonary toxicity is 20.9%. Median time to onset of pulmonary toxicity after TBI is 39 days (range, 3-1,116 days).

Differences between lung dose limit of 8Gy and >8Gy According to univariate analysis to all related variables, we find that TBI dose per fraction ($p<0.001$), TBI dose rate ($p<0.001$) , TBI total dose ($p<0.001$) and relapse-free mortality ($p=0.015$) have significant difference between two groups. Comparison between incidence of pneumonitis ($p<0.001$) and non-infectious pneumonitis ($p=0.046$) of those who had a lung dose limit of 8Gy and >8Gy are shown in table 4. Regardless of infection, pneumonitis toxicity is highly related to lung dose limit. According to log-rank test, there is no statistically significant difference in survival rates between two groups ($p=0.930$). In Cox regression analysis, we find with higher dose levels, there will be higher mortality rates and lower survival rates. This is a positive correlation so that higher doses present risk factors for survival. (Table 5, Figure 1) For incidence of relapse, there is a significant statistical difference between two groups, and the relapse rate was higher at >8Gy ($p=0.029$). (Table 5) As the dose level is higher, the non-relapse rate is lower, which is negatively correlated. (Table 5, Figure 2)

Effects of CR status and MRD status According to log rank test results, complete remission status (CR) at time of HSCT preparation is associated with worse OS ($p<0.001$) and relapse free mortality ($p=0.006$). (Figure 3 and Figure 4). Minimal residual disease status (MRD) at time of HSCT preparation is associated with worse OS ($p=0.038$). (Figure 5 and Figure 6) Hazard ratio and 95% confidence interval are shown in Table 2.

Table 2: Hazard ratio and 95% confidence interval for CR and MRD

		OS	Relapse Free Mortality
Parameter			**HR (95% CI)**
CR	1	1.00 (ref.)	1.00 (ref.)
	2	1.178 (0.544, 2.549)	1.247 (0.429, 3.627)
	3	1.761 (0.392, 7.906)	8.219 (1.489, 45.353)
	4	21.557 (4.32, 107.556)	6.616 (1.192, 36.712)
MRD	1	1.00 (ref.)	1.00 (ref.)
	2	1.178 (0.544, 2.549)	0.629 (0.139, 2.849)

Effects of GVHD Acute GVHD developed in 93 patients (65.0%), with grade I-II developing in 52 patients (36.4%) and grade III-IV in 41 patients (28.7%). Based on univariate analysis, the presence of grade I-II of GVHD is not associated with an increased incidence of pulmonary toxicity (p=0.061) but pulmonary toxicity developed in 85.0% of patients with grade III-IV GVHD (p=0.001). However, this association in grade III-IV does not reach statistical significance on multivariate analysis (P=0.393). There is no significant difference in time to onset of GVHD in patients with and without pulmonary toxicity. For the association between GVHD and OS and relapse free mortality, hazard ratio and 95% confidence interval are shown in Table 3. According to log rank test results, it is associated with relapse free mortality (p<0.001). (Figure 8) There is no significant correlation between GVHD and OS (p=0.777). (Figure 7) The result remains same when we combine GVHD 1 and GVHD 2 as one group. (Relapse free mortality: p=0.003, OS: p=0.660) (Figure 9, Figure 10)

Table 3 Hazard ratio and 95% confidence interval for GVHD

		OS	Relapse Free Mortality
Parameter			**HR (95% CI)**
GVHD	0	1.00 (ref.)	1.00 (ref.)

	1	1.062 (0.49, 2.302)	3.499 (0.946, 12.944)
	2	1.313 (0.589, 2.928)	14.841 (3.526, 62.472)
GVHD	0	1.00 (ref.)	1.00 (ref.)
	1 & 2	1.165 (0.586, 2.314)	5.201 (1.611, 16.793)

Effects of TBI total dose, TBI dose per fraction, TBI dose rate, lung thickness Total radiation dose delivered, consistently between 10-15Gy, does not affect the incidence of pulmonary toxicity regardless of infection (p=0.802 in IP, p= 0.238 in Non-infection IP). Similarly, as the dose limit to the lungs is consistently kept between 8-10Gy, lung dose is not associated with pulmonary outcome. In multivariate analysis, after adjusting for other variables such as Donor type, TBI dose rate is significantly related to the development of pulmonary toxicity (p=0.002). Pulmonary toxicity is 5.33 times more likely to develop in patients receiving higher than 15Gy/min than patients treated with dose rates of 5-10Gy/min (p=0.018). There is no significant association with pulmonary toxicity since TBI dose per fraction is relatively consistent and ranged between 1.5 and 2Gy.The lung thickness in patients does not affect incidence of pulmonary toxicity (p=0.345).

Effects of age, gender, donor type and engraftment We found that neither age (p=0.596) nor gender (p=0.214) significantly impacted the incidence of pulmonary toxicity. There was no statistical significance between those patients who had received related versus unrelated grafts (p=0.309), regardless of whether the donor is matched or partially matched (p=0.147). (Table 6)

Discussion

After allogeneic HSCT, PT is a significant complication, occurring in 25% -80% of patients and accounting for approximately 50% of transplant-related deaths (4,14-25). Idiopathic, non-infectious pneumonia syndrome (IPS) usually occurs within the following four months after HSCT,

and the typical outbreak process develops rapidly with significant mortality (25). For these reasons, it is challenging to compare lung toxicity in different studies (27,28). Most studies used the results of a combination of pediatric and adult cohort studies in their studies (10,16,17). In addition, there exist differences in pre-transplant conditioning protocols (like TBI) and post-transplant patient management (like GVHD), that would lead to the development of lung toxicity (20).

During this research, we included all sorts of PT since TBI may cause acute and delayed infectious and non-infectious lung injury (16,17,29,30). We found that the incidence of pulmonary toxicity reached 64.3% and the mortality rate was 38%, indicating that this toxicity is still a dangerous risk in all the patients undergoing more contemporary HSCT. Nonetheless, we believe incidence of pulmonary toxicity is relatively high in our series, in part because it includes patients with a wide range of clinical manifestations: infectious and non-infectious pneumonia, mild to severe toxicity, including early and late stages attack.

When compared two groups with lung dose limit of 8Gy and a higher lung dose constraint (>8Gy), we found that reducing lung dose limit in pediatric patients receiving TBI is associated with lower incidence of pneumonitis and seems not appear to compromise OS. Higher lung dose level is associated with lower non-relapse rate. Severe CR and MRD status at time of HSCT lead to worse overall survival and higher relapse-free mortality.

We observed that the median time to pulmonary toxicity in TBI recipients was 39 days, which is relatively consistent with the previous researches, stating that the most common seizures occurred within 22 to 60 days of TBI (10, 16, 17, 18) and BMT For 4 months (27). OS in patients

with pneumonia was significantly reduced, a finding previously seen in the literature (10,16). In our cohort, non-infectious lung toxicity accounted for only 20.9% of the total incidence of lung toxicity. Even if the morbidity is comparable to others, its importance cannot be ignored, since non-infectious pulmonary toxicity remains the reason of death of these patients (14, 23). Furthermore, radiation therapy may contribute to both infectious and non-infectious pulmonary toxicity. Therefore, we chose not to exclude patients who were not toxic to infection.

The relationship between TBI and the development of PT has been vigorously debated. It is hard to draw conclusions from existing researches due to differences in radiotherapy techniques, lung shielding, lung dose limit, total dose, dose rate and classification, and other potential factors. Although some reports have found that dose grading helps reduce acute lung toxicity (15,20), others have opposite view (17,31). In this study, a significant correlation between TBI dose rate and pulmonary toxicity was found. The effect of dose rate on PT has been previously proposed in previous studies (4,11,14,15,16). Does rate differences provided in our study reflect two different treatment eras. Nevertheless, the effect of the dose rate becomes more reasonable when given a relatively homogenous total dose to each group. Thus, the relationship between TBI dose rate and PT is worthy of our attention, and lower dose rates should be chosen to avoid high risk of lung injury. Even after reducing the incidence of lung toxicity to a dose rate of 8Gy, high levels of lung toxicity were noticed. This indicates that other TBI factors must be explored, such as lung dose and non-radiation risk factors.

GVHD and drugs used for treatment have been proposed as interaction factors with radiation-induced lung injury (10,14,15,18,20,21), while other studies contradict this view (17,32). In this

study, we found an association between GVHD and pulmonary toxicity, especially for high-grade GVHD, although it has no meaning in multivariate analysis. However, better GVHD management and prevention are still essential to reduce pneumonia incidence due to the potential impact of GVHD and its treatment on pulmonary toxicity.

Our work shows the importance of pulmonary confinement as a predictor of PT and provides support to the development of highly conformal TBI technology. Due to its retrospective, our study has inherent limitations: we lack complete information about pre-transplant disease states and treatment states that may affect patient prognosis. The homogeneity of lung dose limit and TBI dose rate could be seen as both an strength and a disadvantage for our study: though it gives us with the chance to control TBI variables better, it limits our ability to identify association between TBI total dose, lung dose, fraction dose and pulmonary toxicity. Present research provides new idea for the factors which affect the development of lung toxicity in pediatric patients treated with contemporary homogeneous TBI and we still need to work on the existing questions in the further.

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Appendix

Table 4: Analysis of variables (lung dose limit of 8Gy and >8Gy)

	8	>8	P-value*	Method	Time Unit
Development of GVHD					
None	6 (20.7%)	40 (33.6%)			
Grade 1-2	14 (48.3%)	38 (31.9%)	0.306	Pearson chi square	
Grade 3-4	8 (27.6%)	32 (26.9%)			
Unknown	1 (3.5%)	9 (7.6%)			
Time to GVHD	1.2 ± 0.9	1.4 ± 1.9	0.483		Month
TBI dose per fraction	2 ± 0.1	1.8 ± 0.2	**<0.001**		
TBI dose rate	9.1 ± 3.4	12.2 ± 4.8	**<0.001**	T test	
TBI total dose	12.1 ± 0.6	13.1 ± 0.8	**<0.001**		
Lung thickness	10.5 ± 2.3	11 ± 2.1	0.314		
Age at time of BMT	9.7 ± 5.6	11.4 ± 4.7	0.099		Year
CR status					
CRs=1	9 (31%)	44 (37%)			
CR2=2	16 (55.2%)	42 (35.3%)			
CR3=3	0 (0%)	8 (6.7%)	0.204	Pearson chi square	
CR4=4	0 (0%)	2 (1.7%)			
Unknown=5	3 (10.3%)	8 (6.7%)			
Does not apply=6	1 (3.5%)	15 (12.6%)			
MRD status					
No=0	19 (65.5%)	88 (74%)			
Yes=1	7 (24.1%)	9 (7.6%)	0.052	Pearson chi square	
Unknown=3	2 (6.9%)	8 (6.7%)			
Does not apply=4	1 (3.5%)	14 (11.8%)			
Type of BMT					
Allogenic matched sibling donor=1	7 (24.1%)	36 (30.3%)			
Allogenic matched unrelated donor=2	11 (37.9%)	32 (26.9%)	0.659	Pearson chi square	
Allogenic partially matched related donor=3	4 (13.8%)	15 (12.6%)			
Allogenic partially matched unrelated donor=4	7 (24.1%)	36 (30.3%)			
Engraftment by day 100					
Yes=1	26 (89.7%)	98 (82.4%)	0.050	Pearson chi square	
No=2	2 (6.9%)	21 (17.7%)			
Unknown=3	1 (3.5%)	0 (0%)			
Time to IP	3.6 ± 5.9	4.0 ± 7.2	0.843	T test	Month

Transplant-related mortality			0.494	Yates's correction for continuity
No=0	12 (85.7%)	93 (78.2%)		
Yes=1	2 (14.3%)	26 (21.9%)		
Relapse-free mortality			**0.015**	Yates's correction for continuity
Yes=1	2 (25%)	25 (71.4%)		
No=2	6 (75%)	10 (28.6%)		
Male and female				
Male=1	15 (51.7%)	82 (68.9%)	0.081	Pearson chi square
Female=2	14 (48.3%)	37 (31.1%)		

Table 5: Difference in incidence of Pneumonitis and non-infectious pneumonitis (lung dose limit of 8Gy and >8Gy)

	8	>8	P-value*	Method
Pneumonitis incidence				
Yes	9 (31.0%)	83 (69.7%)	<0.001	Pearson chi square
No	19(65.5%)	32 (26.9%)		
Unknow	1 (3.5%)	4 (3.4%)		
Non-infectious pneumonitis incidence				
Yes	2 (6.9%)	28 (23.5%)	0.046	Pearson chi square
No	27 (93.1%)	91 (76.5%)		
Differences in OS and Relapse free survival (lung dose limit of 8Gy and >8Gy)				
Overall survival				
Alive	21 (72.4%)	84 (70.6%)	0.846	Pearson chi square
Dead	8 (27.6%)	35 (29.4%)		
Relapse Free Mortality				
Yes	2 (25.0%)	25 (71.4%)	0.041	Yates's correction for continuity
No	6 (75.0%)	10 (28.6%)		

Cox regression analysis in OS and Relapse free survival (lung dose limit of 8Gy and >8Gy)

	Hazard Ratio	**95% Hazard Ratio Confidence Limits**		**Pr > ChiSq**
Overall survival (month)	1.035	0.478	2.242	0.930
Relapse (month)	0.436	0.207	0.918	0.029

Table 6: Descriptive and Univariate analysis for related variables

			Pulmonary Toxicity (Unknown=5)		
Covariate	**Level**	**All patients (N=148)**	**Yes (N=92/143)**	**No (N=51/143)**	**P-value***
Gender	Female	97 (65.54)	28 (60.87)	18 (39.13)	0.214
	Male	51 (34.46)	64 (65.98)	33 (34.02)	
Donor type	Allogenic matched sibling	43 (29.05)	25 (60.98)	16 (39.02)	0.147
	Allogenic matched unrelated	43 (29.05)	24 (57.14)	18 (42.86)	
	Allogenic partially matched	19 (12.85)	12 (66.67)	6 (33.33)	
	Allogenic partially matched unrelated	43 (29.05)	31 (73.81)	11 (26.19)	
Engraftment by day 100	No	23 (15.54)	16 (76.19)	5 (23.81)	0.309
	Yes	124 (83.78)	76 (62.30)	46 (37.70)	
	Unknown	1 (0.68)			
GVHD grade	Grade 1-2	52 (35.14)	26 (50)	26 (50)	0.442
	Grade 3-4	40 (27.03)	34 (85)	6 (15)	
	None	46 (31.08)	26 (57.78)	19 (42.22)	
	Unknown	10 (6.75)	6 (100)	0 (0)	
MRD status	No=0	107 (72.30)	64 (62.14)	39 (37.86)	**0.021**
	Yes=1	16 (10.8)	7 (46.67)	8 (53.33)	
	Unknown=3	10 (6.75)	7 (70)	3 (30)	
	Does not apply=4	15 (10.14)	14 (93.33)	1 (6.67)	
CR status	CRs=1	53 (35.81)	31 (62.00)	19 (38.00)	**0.003**
	CR2=2	58 (39.19)	31 (55.36)	25 (44.64)	
	CR3=3	8 (5.41)	5 (62.5)	3 (37.5)	
	CR4=4	2 (1.35)	2 (100)	0 (0)	
	Unknown=5	11 (7.43)	8 (72.73)	3 (27.27)	
	Does not apply=6	16 (10.81)	15 (93.75)	1 (6.25)	
Multi-system organ failure as cause of death	No	16 (37.21)	13 (81.25)	3 (18.75)	0.662
	Yes	27 (62.79)	22 (88)	3 (12)	
Age	Median (Range)	11 (0.67 - 22)	12 (1 - 20)	12 (2 - 22)	0.596
TBI total dose (Gy)	Median (Range)	13.2 (10.5 - 14)	13.2 (10.5 - 14)	13.2 (12 - 14)	0.532
TBI dose/fx (Gy)	Median (Range)	1.75 (1.5 - 2)	1.75 (1.5 - 2)	1.75 (1.5 - 2)	0.676
TBI dose rate (cGy/min)	Median (Range)	9.66 (5.57 - 20.85)	13.69 (5.57 - 20.07)	8.02 (6.04 - 20.85)	0.444
Lung thickness (cm)	Mean (± SD)	10.80 (± 2.18)	10.91 (± 2.31)	10.81 (± 2.05)	0.345

* Data are presented as number of patients (%), mean (± SD) or median (range).

Table 7: Univariate logistic regression on IP (Total dose rate as category variable)

			Pulmonary Toxicity		
Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
TBI dose rate	>15	44	4.59 (1.80, 11.71)	0.026	0.003
	10-15	27	2.43 (0.91, 6.53)	0.802	
	5-<10	72	-	-	

* N=143

Univariate logistic regression on Non-infection IP (Total dose rate as category variable)

			Non-infection IP		
Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
TBI dose rate	>15	44	0.16 (0.06, 0.42)	<0.001	<0.001
	10-15	27	0.86 (0.21, 3.61)	0.238	
	5-<10	72	-	-	

* N=143

Multivariate logistic regression on Pulmonary Toxicity

		Pulmonary Toxicity		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
TBI dose rate	>15	5.33 (1.99, 14.32)	0.018	0.002
	10-15	2.53 (0.91, 6.99)	0.864	
	5-<10	-	-	
Donor type	Matched sibling	0.36 (0.13, 1.03)	0.277	0.188
	Matched unrelated	0.38 (0.14, 1.02)	0.310	
	Partially matched	0.54 (0.15, 1.97)	0.939	
	Partially matched unrelated	-	-	

* Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Engraftment by day 100, GVHD, age and gender.

Multivariate logistic regression on Non-infection IP

		Non-infection IP		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
TBI dose rate	>15	0.18 (0.07, 0.5)	0.001	0.002
	10-15	0.83 (0.2, 3.53)	0.327	
	5-<10	-	-	
Donor type	Matched sibling	0.61 (0.2, 1.87)	0.107	0.359
	Matched unrelated	1.87 (0.48, 7.31)	0.251	
	Partially matched	1.26 (0.26, 6.07)	0.792	
	Partially matched unrelated	-	-	

* Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Engraftment by day 100, GVHD, age and gender.

Figure 1: Kaplan-Meier analysis of overall survival between two groups (lung dose limit of 8Gy and >8Gy)

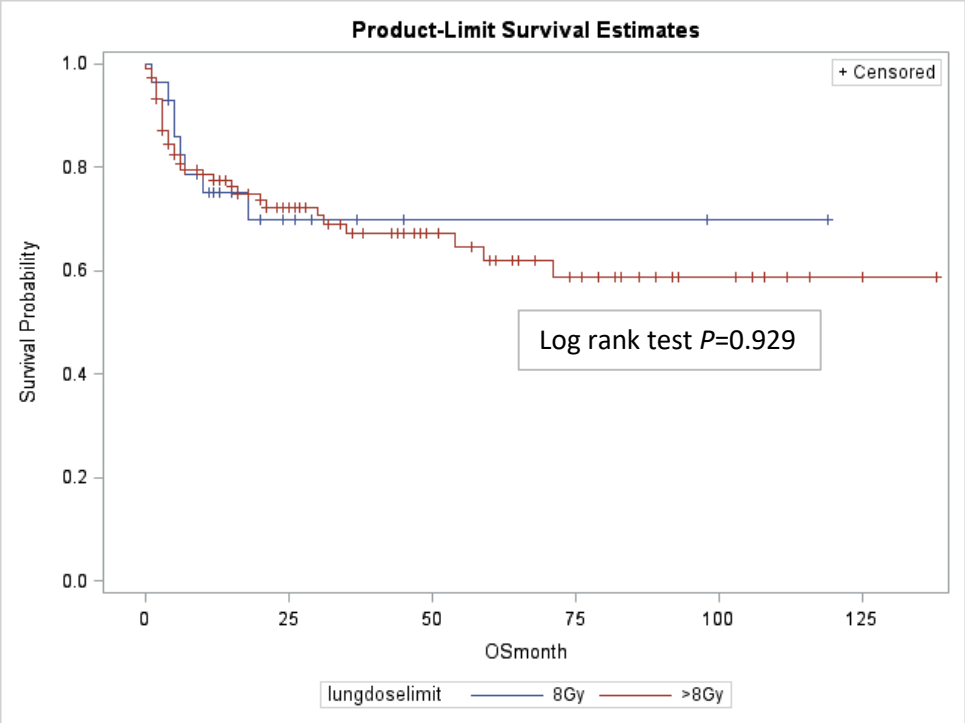

Figure 2: Kaplan-Meier analysis of relapse free mortality between two groups (lung dose limit of 8Gy and >8Gy)

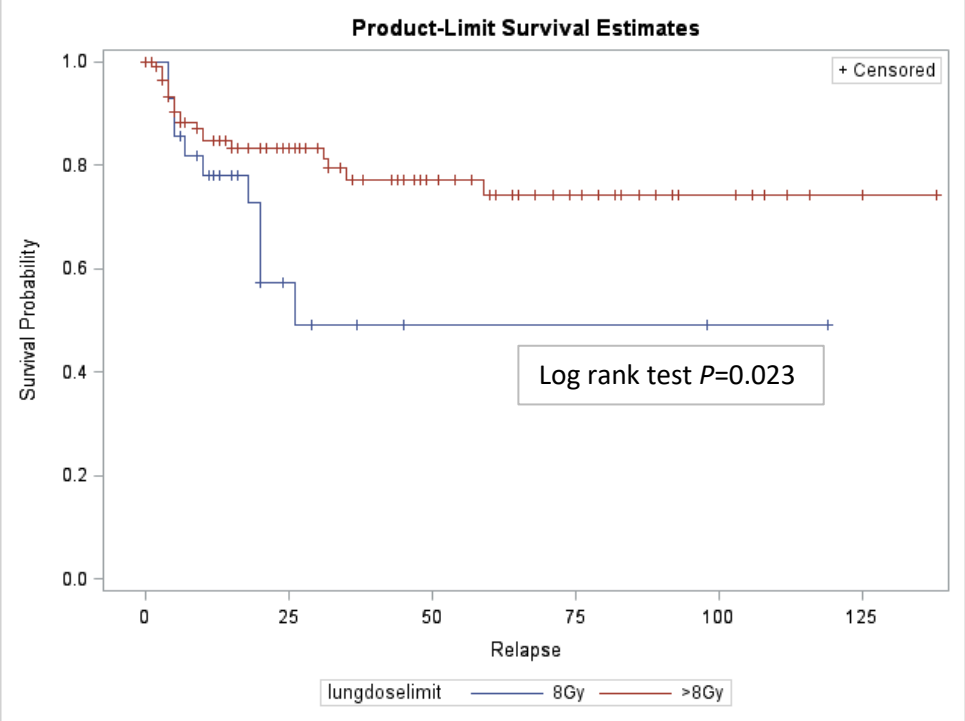

Figure 3: Kaplan-Meier analysis of overall survival for CR Status

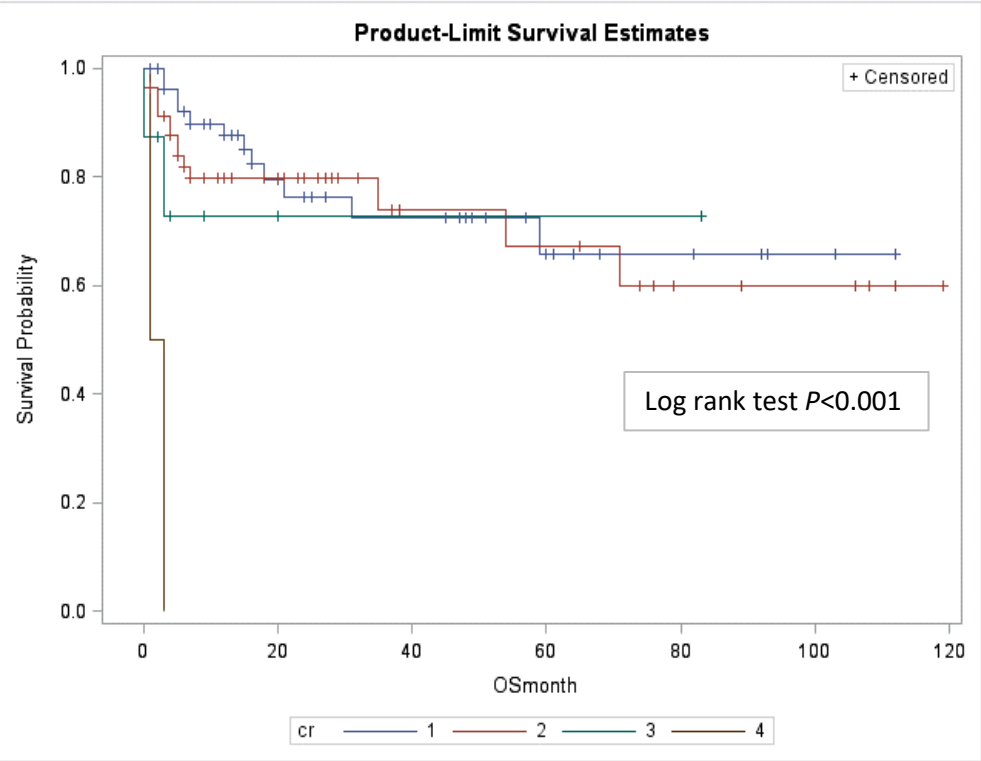

Figure 4: Kaplan-Meier analysis of relapse free mortality for CR Status

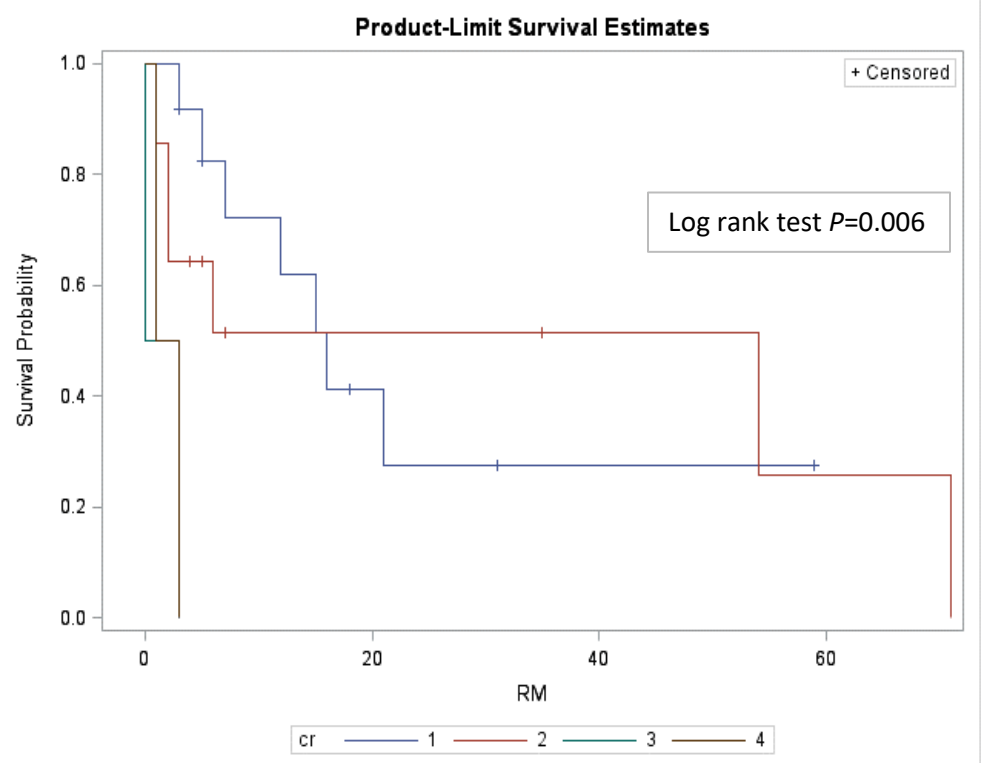

Figure 5: Kaplan-Meier analysis of overall survival for MRD Status

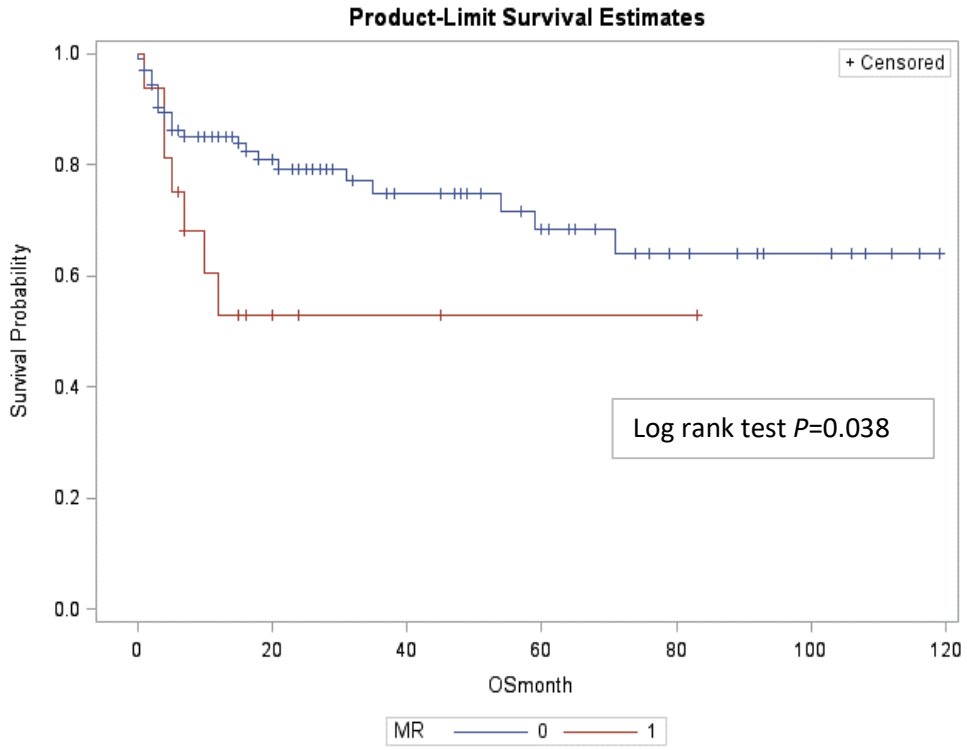

Figure 6: Kaplan-Meier analysis of relapse free mortality for MRD Status

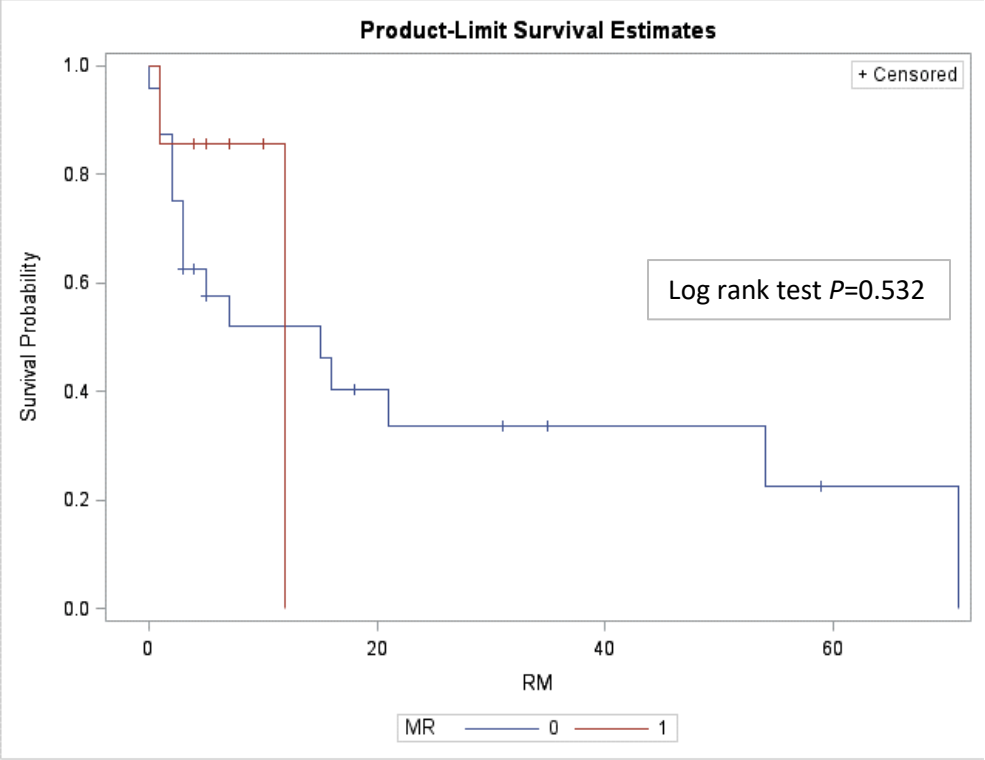

Figure 7: Kaplan-Meier analysis of overall survival for GVHD

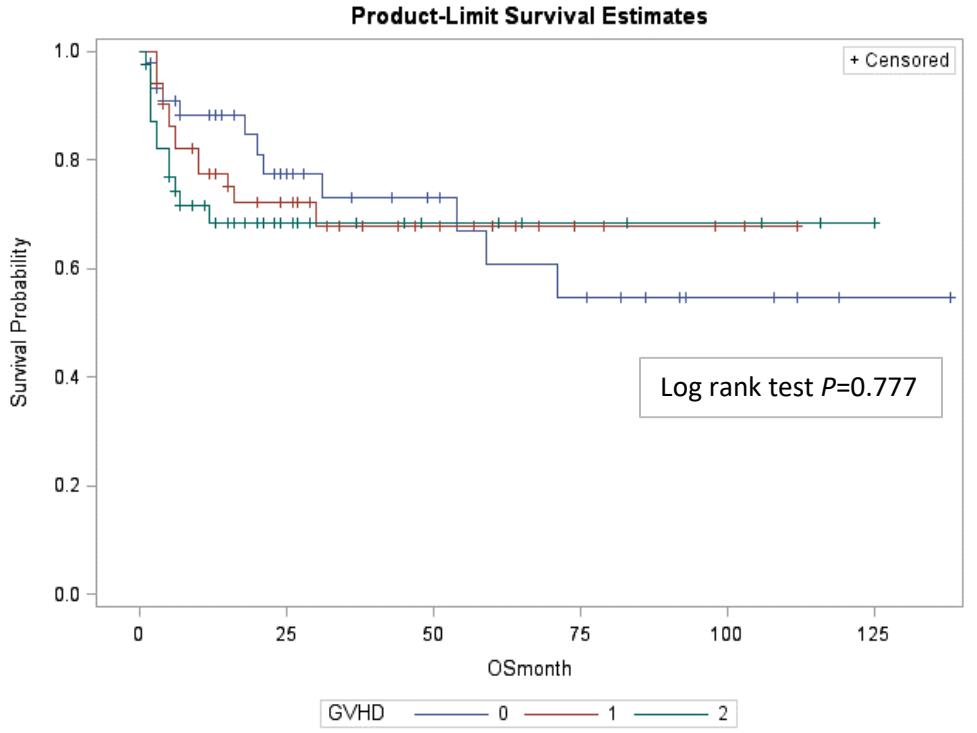

Figure 8: Kaplan-Meier analysis of relapse free mortality for GVHD

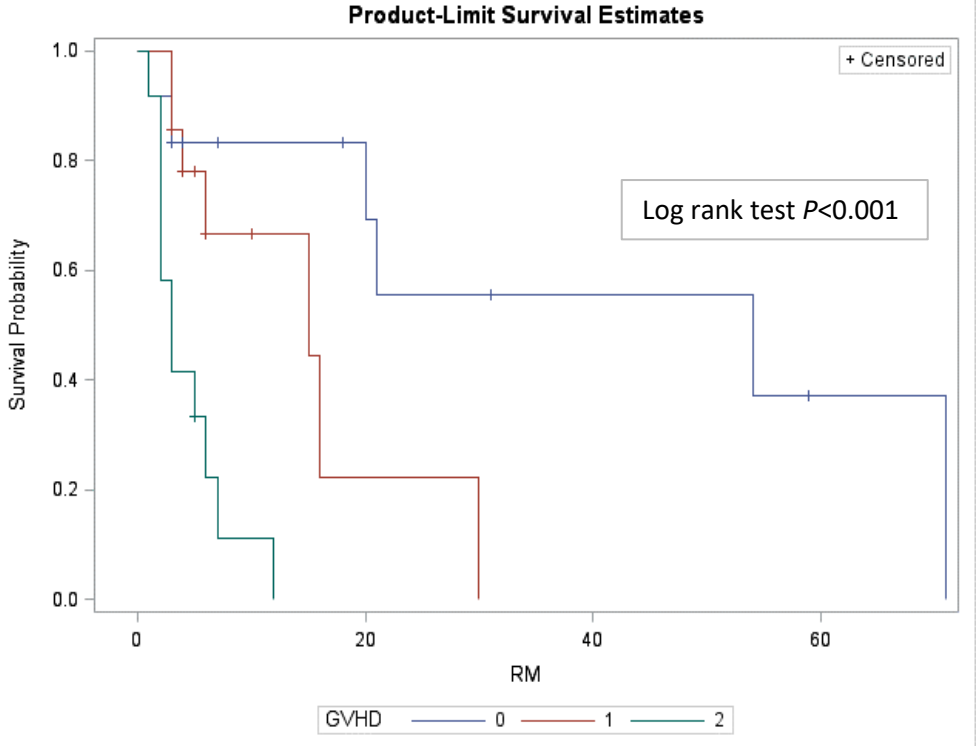

Figure 9: Kaplan-Meier analysis of overall survival for GVHD (Combine GVHD 1 and GVHD 2)

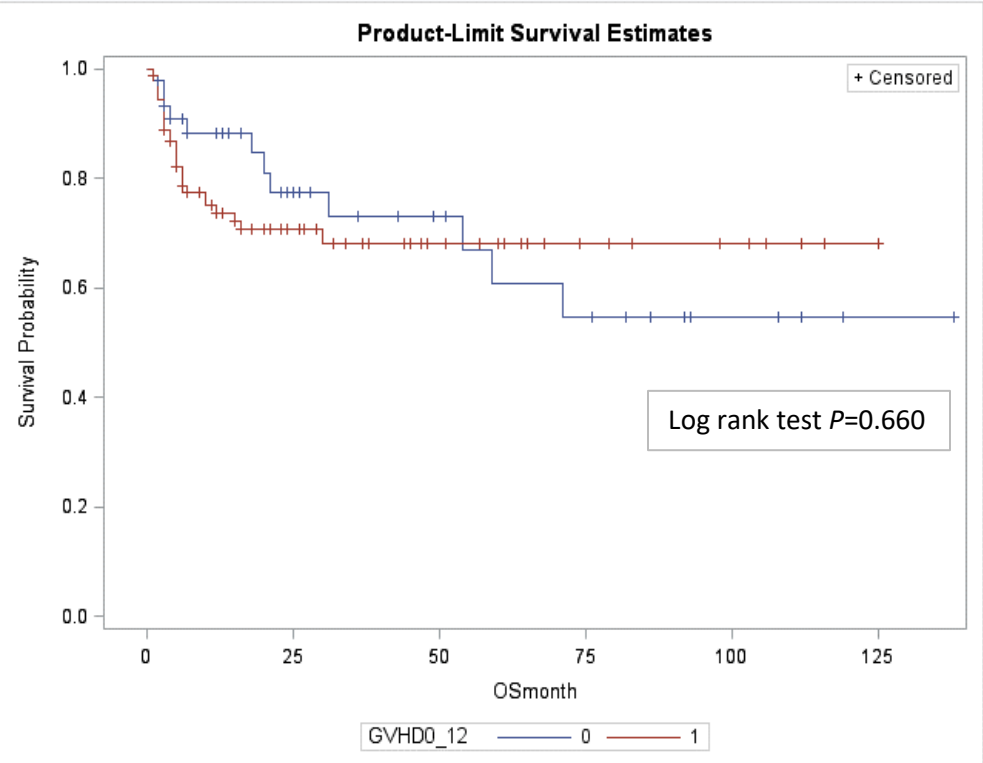

Figure 10: Kaplan-Meier analysis of relapse free mortality for GVHD (Combine GVHD 1 and GVHD 2)