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Malignant transformation and tumour recurrence in sacrococcygeal teratoma: a global, retrospective cohort study.

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Highlights

- This global retrospective cohort study includes 3612 sacrococcygeal teratoma patients from 62 countries worldwide
- The risk of malignant transformation increases with age
- The risk of recurrent sacrococcygeal teratoma after initial resection is 10%.
- If possible, complete resection of sacrococcygeal teratoma is recommended before age 1 month
- Postoperatively, six years of follow-up is advised to detect possible recurrence.

Abbreviations

AFP = Alpha-fetoprotein
CS = Currarino Syndrome
CT= Computed tomography
HIC= High-income country
HMIC= Higher-middle income country
LIC = Low-income country
LMIC = Lower-middle income country
MRI= Magnetic resonance imaging
UMIC= Upper-middle income country
SCT= Sacrococcygeal teratoma
YST= Yolk sac tumour

Abstract

Introduction

Sacrococcygeal teratoma (SCT) is a rare congenital tumour. The risk of malignancy and recurrence are not well defined. Previous studies are small and report differing conclusions

about the timing of surgery and the duration of follow-up. We studied the risk of malignant transformation and SCT recurrence after surgery to address these gaps.

Methods

This was a global retrospective cohort study. Data of consecutive SCT patients was obtained from 145 institutes in 62 countries.

Malignant transformation, defined as malignancy at initial resection, malignant recurrence or death due to malignancy, and its risk factors were analysed.

Results

Of the 3612 included patients, 3407 entered analysis. Risk of malignant transformation of the initial tumour, was 3.3%, 5.1%, 10.1%, and 32.9% at age three months, six months, one year, and two years, respectively. After six years, the censored risk of malignancy (64%) did not further increase. Recurrent SCT was diagnosed in 349 (10·2%) children with 126 (36·1%) malignant recurrences. Risk factors for recurrence were Altman type II (odds ratio (OR): 1·6, 95% confidence interval (CI): 1·2-2·3), Altman type III (OR: 1·6, 95% CI: 1·2-2·3), initial immature histology (OR: 1·9, 95% CI: 1·4-2·6), and initial malignant histology (OR: 4·0, 95% CI: 2·9-5·4).

Conclusion

The risk of malignancy at initial resection in SCT increases with age reaching a plateau at six years of age. Recurrence after resection occurred in 10% of patients and 36% of these were malignant at that time. Altman type II or type III, and immature or malignant histology were associated with recurrence.

Keywords: sacrococcygeal teratoma, recurrence, malignant transformation

1. Introduction

Sacrococcygeal teratoma (SCT) is the most common neonatal tumour with a reported incidence of one per 14,000 to 35,000 live births.[1] The preferred treatment for SCT is complete resection at young age. However, there is no generally accepted age at which resection should be done. Some clinicians advocate early surgery to minimize the risk of malignant tumour transformation as malignancy rates up to 70% have been reported if SCT is resected at age one year or older.[2] Others claim that surgery at young age may lead to more operative and postoperative complications.[3]

Tumour recurrence after surgery occurs in two to 33% of patients and decreases the overall 10-year survival ranging from 60% to 92%.[2, 4, 5] Recurrent SCT is much more often malignant than SCT at initial resection with yolk sac tumour (YST) found in 22-56% of recurrences.[1, 6-8] Definitive risk factors for tumour recurrence are relatively unknown, although tumour histology and completeness of resection including coccygectomy are reported as potential risk factors for recurrence.[2, 5] However, most studied series are relatively small due to the rarity of the disease and the results are often contradictory. Furthermore, the duration of follow-up varies in the existing literature, which likely impacts the reported recurrence rate; although most recurrences present within three years after initial SCT resection, late recurrences up to 15 years have been described.[1, 5] From a clinical perspective, there is no consensus regarding the appropriate duration of oncological follow-up of SCT patients.

The vast majority of the reported series of patients with SCT are from high income countries (HICs) in which SCT patients are operated on within a few weeks after birth. The number of publications about SCT from low income countries (LICs) and lower-middle income countries (LMICs) is very limited.[9, 10] Recently, unacceptable differences in mortality for congenital gastrointestinal anomalies have been shown in LICs, compared to middle-income countries (MICs), and HICs.[11] It is unknown if these differences are also present for SCT.

Given these uncertainties, we aimed to estimate the risk of malignant transformation of untreated SCT at different ages and hence the optimal time for resection. Furthermore, we aimed to identify factors associated with recurrent SCT and finally compare treatment and outcome of SCT patients from different income countries.

2. Methods

2.1 Study design and participants

We did a global retrospective cohort study of SCT patients: 'The SCT-study'. STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology) and STROCSS, Supplemental Digital Content 1, http://links.lww.com/JS9/D406 (Strengthening the reporting of cohort, cross-sectional and case-control studies in surgery) 2021 guidelines were followed.[12, 13]

We recruited as many patients from participating hospitals as possible regardless of geography. Paediatric surgeons and paediatric oncologists were invited to participate in the study through personal communication, the European Paediatric Surgeons' Association (EUPSA) Network Office, Pubmed publications, and a network of national and international study leads. Study information was provided in English, Spanish, French, and Russian. Participation was voluntary; no payment was made for data collection. Centres, which could include ten or more patients were invited to participate. An exception was made for centres from LICs and LMICs. For these centres, the minimum number of inclusions was set at five. The supplementary appendix, Supplemental Digital Content 2, http://links.lww.com/JS9/D407 provides an overview of the participating countries.

Due to the rarity of the condition, no sample size calculation was done and all eligible patients were included. Consecutive patients treated for SCT between 1982 and 2020 or a shorter time period in this era could be included into the study. Exclusion criteria were (a) born before 1982, (b) born after 2020, or (c) SCT as part of Currarino Syndrome (CS) as the risk of malignant transformation in (CS) may be reduced compared to 'ordinary' SCT.[14, 15] The exact period of time for inclusions was determined by each individual participating centre as long as all consecutive patients in the chosen period were included.

All participating centres obtained local approval to participate in the study following their own legal and ethical regulations. Data transfer agreements were used to guarantee safe data use and storage.

Charts were reviewed by the individual local investigator. Data were validated with warning messages about possible errors when entered in Castor Electronic Data Capture (EDC). Furthermore, Castor files were structured so that out-of-range values could not be entered. Dependency fields were used for data and included initial resection, recurrence, death and follow-up. Furthermore, overall data distribution and frequencies in SPSS were checked to detect invalid entered data.

2.2 Procedures

Data was anonymized by the local investigator to transform individual patient data into general anonymous information. Transformed patient data were uploaded with a personal link in Castor EDC and encrypted.[16] Every participating centre had only access to its own transformed patient data.

Included data was carefully selected by a group of experienced paediatric surgeons with interest in SCT treatment and was chosen based on main outcome variables used in previously published studies.

Collected data included generic and condition-specific variables. Generic variables included: country, gender (male/female/unknown), age at diagnosis (days), pre-operative imaging modalities (none/ultrasound/computed tomography/magnetic resonance imaging/unknown), initial tumour resection at the participating centre (yes/no/unknown), age at initial resection (days), outcome (survival/deceased/unknown), age at follow-up (days), age at death (days), and cause of death. Condition-specific variables were Altman classification (I/II/III/IV/unknown)[17], CS (yes/no/unknown), initial SCT treatment (chemotherapy/surgery/no treatment/unknown), pathology (mature/immature/malignant/unknown), recurrence (yes/no/unknown), period between birth and recurrence (days), detection of recurrence (clinical examination/imaging/AFP/unknown), serum AFP-level at recurrence (µg/L), recurrent SCT pathology (mature/immature/malignant/unknown) and treatment of recurrent SCT (chemotherapy/surgery/no treatment/unknown).

Cause of death was collected as a free-text category. Participating country was used to categorize the country's income status into LICs, LMICs, HMICs and HICs according to the World Bank criteria.[18]

2.3 Statistical analysis

Data are presented as mean with standard deviation (SD) if normally distributed and median with interquartile range (IQRs) if skewed; count data are presented as numbers and percentages. To assess malignant transformation of initial SCT and risk of recurrence over time an risk of , Kaplan-Meier curves were used.

Identification of factors associated with recurrent SCT was done by univariable and multivariable logistic regression analysis. All variables included in multivariable logistic regression analysis had maximum of 6·8% missing data. Sensitivity analysis was performed to analyse the effect of data imputation on the results of the multivariable logistic regression analysis.

Forward Wald selection was used to select variables significantly related to recurrent SCT. We report variables with the odds ratio (OR) and accompanying 95% confidence interval (95% CI)

Differences in patient demographics between country income were analysed with Fisher exact test for categorical variables, one-way ANOVA for normally distributed continuous variables and Kruskal Wallis test for non- normal continuous variables.

Statistical analyses were performed using SPSS for Windows version 25.0 software (SPSS) and Graph Pad Prism 8 (Graph Pad Software, Incl.). $P < 0{\cdot}05$ was considered statistically significant.

2.4 Definitions

SCTs were classified according to the criteria proposed by the Surgical Section of the American Academy of Paediatrics.[17] Recurrence was defined as relapse of SCT at least three months after initial resection.[15] Recurrent SCT before three months is unlikely and is probably due to incomplete resection, therefore, these recurrences were excluded from data analysis. Malignancy free survival was defined as time from birth to malignancy or death due to malignancy. Patients were censored at the number of days from birth to resection. In case of malignant recurrence or death due to malignancy, the number of days from birth to recurrence detection or death was used.

Variables investigated for recurrent SCT, with their respective categories, were Altman classification (I, II, III, IV), histology (mature, immature, malignant), age at diagnosis (days), income of the country (LIC, LMIC, HMIC, HIC), and age at initial resection (days).

3. Results

3.1 Patient characteristics

In total, 145 centres from 62 countries treated 3612 patients for SCT. In 205 patients, SCT was associated with CS. These patients were excluded from analysis. In total, 3407 patients were included in the study. Patient characteristics for the total population are described in Table 1.

Pre-operative imaging was done with ultrasound in 595 (17·5%), CT in 280 (8·2%), and MRI in 526 (15·4%) patients, respectively. A combination of imaging modalities was performed in 1400 (41·1%) patients. In 606 children (17·8%), no imaging was performed or was unknown.

Surgery was the initial treatment in 2947 (86·5%) children. Surgery and chemotherapy were applied in 388 (11.4%) patients. Sixteen (0·4%) children received only chemotherapy. Furthermore, 13 (0·4%) children received no treatment and died immediately after birth due to bleeding or respiratory distress. In 43 (1·3%) children, treatment was unknown.

Overall for the entire cohort, the median follow-up was 5.1 years (IQR 2·3-9·2 years) after resection. In total, 140 (4·1%) patients died at a median age of 10.2 months (IQR 3 days-3·2 years). Ten years after initial resection, 505 patients remained in follow-up. The five-year survival was 95·4% and ten-year survival was 94·8%.

3.2 Malignant Transformation

Histological diagnosis after initial resection was mature teratoma in 2168 patients (63·7%), immature teratoma in 625 (18·3%) and malignant teratoma in 366 (10·7%). In 248 patients (7·3%) the histological diagnosis was unknown. The proportion of patients with malignant SCT increased with age. Probability of malignant transformation diagnosed at initial resection starts to increase directly after birth and increases further with age. The risk was 3·3%, 5·1%, 10·3%, and 32·9% at three months, six months, one year, and two years, respectively (Figure 1). After six years of age, the probability of initial malignant SCT did not further increase (64·2%). After six years, only one patient presented with an initial malignant SCT at the age of eight years.

Malignancy-free survival including initial malignancies, malignant recurrences and deaths due to malignant disease, was 94·7% at age one year and 88·2% at two years (Figure 2). Probability of overall malignancy-free survival remained relatively stable after the age of six years at 80·2%. After this period, four late malignancies were found; one initial malignancy, one malignant recurrence and two deaths due to malignancy. Late malignancies up to 15 years of age were found with an overall malignancy-free survival of 79·1%.

3.3 Recurrent sacrococcygeal teratoma

349 children (10·2%) developed recurrences at a median period of 11·4 months (IQR 6·4 months to 1·8 years) after surgery. Ninety-six percent of recurrences presented within the first five years after initial resection with a probability of recurrence-free survival after five years of 85·9% (Figure 3). Late recurrences occurred up to 22·1 year after initial resection. Forty children died after recurrence at a median age of 15·6 months (IQR 6·2 months – 2·3 years) after recurrence detection. Thirty died due to tumour progression or complications of

chemotherapy. In ten patients cause of death was unknown. The other 284 survived; in 25 patients the outcome after recurrence was unknown.

Recurrent SCT was resected in 131 children, in 157 resections was combined with chemotherapy, and 33 children were treated with chemotherapy only. Four children received no treatment and treatment was unknown in 24 children.

Histology of recurrent SCT was mature teratoma in 117, immature teratoma in 34 and malignant teratoma in 126 children. Histology of recurrent SCT was unknown in 72 children. In 65 tumours (18.6%) there was a shift towards immaturity or malignancy.

3.4 Income Country

In this global study, 62 countries participated. Table 1 shows the main patient characteristics per income group. SCT diagnosis and resection were later in LICs compared to LMICs, HMICs and HICs. Median age at diagnosis was 30 days (IQR 2·5-556·5) in LICs, 8 (0-150) in LMICs, 1 (0-108·5) UMICs and 0 (0-17·5) in HICs (p<0·001). The median age at resection was older: 52 days (IQR 14·0-570) in LICs compared to 40 (14-271·5), 17 (6-187·3) and 9 (3-99) days in LMICs, UMICs and HICs, respectively (p<0·001). Despite the earlier diagnosis and resection, a higher proportion of malignant SCTs at initial treatment was found in HICs (n=245, 10·7%) and UMICs (n=91, 13·4%) compared to LMICs (n=27, 7·2%) and LICs (n=3, 5·3%) (p=0·004). The recurrence rates in all income groups were equivalent (p=0·604). Recurrence histology differed between groups with a malignancy percentage of 100% in LIC compared to 21.2%, 39.3% and 35.8% in LMICs, UMICs and HICs, respectively (p=0·001). However, only six (12·2%) patients in LICs presented with recurrent SCT.

3.5 *Factors associated with recurrent SCT*

Logistic regression analysis with forward selection using the Wald statistics was used to determine factors associated with recurrent SCT. Sensitivity analysis with multiple imputation showed no effect of the imputed data on the multivariable outcomes. Therefore, missing data imputation was not done. The final models showed a good fit according to the Hosmer and Lemeshow test with a value of 0·993 and a Concordance Index of 0·655 with the following variables being associated with recurrent SCT: Altman type II (OR 1·62, 95% CI 1·18-2·23), Altman type III (OR 1·63, CI 1·23-2·35), immature pathology of the initial tumour (OR 1·91, CI 1·43-2·56), and malignant pathology of the initial tumour (OR 4·0, CI 2·91-5·41). Income of countries (p=0·760), age at diagnosis (p=0·254), and age at resection (p=0·073) were not associated with recurrence (Table 3).

4. Discussion

This global, retrospective study provides information about the treatment and outcome of 3407 patients with SCT in 62 countries. We found that risk of initial malignant transformation increases with age with a malignancy rate of approximately 30% after 2 years. After six years, the risk of initial malignant transformation stabilized at 64%. Furthermore, due to the increasing risk of malignant transformation, initial resection is preferably done at young age. However, young neonates and infants are at higher risk of operative and postoperative complications.[3] In the current study, information about gestational age at birth or operative and postoperative complications has not been collected which could influence the optimal time for resection.

Overall malignancy-free survival was 94·7% at age one year and 88·2% at two years. This was higher than reported by others with 80% and 58% of malignancy-free survival at age one and two years, respectively.[15] However, the latter study defined malignancy-free survival as time from birth to malignancy or death. In the present study, only deaths due to malignant disease were included in the survival analysis. Malignancy-free survival stabilized after the age of six years at 80%.

In this study, 349 (10·2%) children developed recurrence after a median period of 11·4 months after initial resection with late recurrences up to 22 years after initial resection. Others have also described occasional late recurrences up to 15 years after surgery.[1] There is no consensus about the duration of follow-up after SCT resection and recommendation varies from three to six years after resection.[5, 19] In the current study, 96% of the recurrences were found within five years after initial resection including all malignant recurrences.

Factors associated with SCT recurrence were Altman type II or type III and initial immature or malignant histology, which has been previously documented.[5] Other risk factors for recurrence described by others included incomplete resection, no coccyx removal and tumour spillage.[5, 20] In the current study, data of these risk factors was not collected.

4.1 Income countries

Age at diagnosis and initial SCT resection were older in patients from LICs and LMICs compared to HMICs and HICs. This was also found in a recent study in children with retinoblastoma. This is probably due to late recognition and limited access to care.[21] In LIC Uganda only, it is estimated that only 15·2% of the Ugandan children with SCT presents in the hospital.[22] Moreover, the lack of paediatric intensive care facilities may force surgeons to postpone the SCT operation to an age with more physiological reserve.

In our study, the overall patient survival of children for all income countries was equivalent, which shows that SCT surgery can be done well and safely in LICs and LMICs. This is in contrast with others who found far better surgical outcomes for infants with other congenital disorders in HICs than in LICs or LMICs and found the income of the country as the greatest risk of mortality.[11]

The difference with our study results may be explained by the very small and selected proportion of SCT patients who present for surgery in LICs and LMICs.[22] In many LICs and LMICs, patients with large tumours might have died without reaching the hospital due to cultural believes or inability to access paediatric surgical care. Evidence for this presumption comes from the fact that many centres invited to participate in the study declined because they never resected an SCT. Furthermore, the proportion of LICs and LMICs with a traditionally good healthcare system such as Syria, was relatively high in our study.

Many SCT patients who present in hospitals in LICs and LMICs do not receive components of neonatal surgical care that are considered essential in HICs. It is estimated that only half of the hospitals, with paediatric surgery in West African countries have neonatal intensive care units and many countries have fewer than one paediatric surgeon per million children.[9, 11, 23-25]

4.2 Limitations

This study has several limitations such as its retrospective study design and long inclusion period. The incidence of SCT is very low, therefore, it would take a very long time before a similar prospective dataset could be obtained. Secondly, the number of collected variables was limited. This may have facilitated participation. Most or all variables could be obtained from electronic data files or patient letters. The percentage of missing data used in the analyses was therefore small, with a maximum percentage of 6·8%. Thirdly, the use of anonymized data made data validation not possible. On the other hand, this also may have reduced the risk of selection bias by not sharing data with an unfavourable outcome. Finally, there is bias because an unknown proportion of patients has not been included in the study. In an unknown, but probably relatively small number of patients in western countries the pregnancy of SCT patients is discontinued. Many SCT patients in LICs and LMICs do not receive any treatment.

4.3 Recommendations

We recommend complete resection of SCT before 1 month of age to minimize the risk of malignant transformation as long as it is safe and feasible. Furthermore, we advise to follow-up to six years of age since the vast majority of recurrences present within this timeframe. After this period, the chance of malignant transformation is probably small.

4.4 Conclusion

The United Nations encourages nations to create networks of experts for rare diseases and to increase support for research, by strengthening international collaboration and coordination of research efforts and the sharing of data, while respecting its protection and privacy.[26] We have shown that it is feasible to set up a large global study for a rare disease. The comprehensive study design herein and the large patient cohort enabled the identification of risk factors for recurrent SCT and essential information regarding malignant SCT transformation. With large, shared patient data-sets is possible to answer important clinical questions that cannot be answered otherwise in order to, improve the quality of care in every part of the world.

Contributors

The EUPSA Network office conceived the idea for the study. LWEH gained study funding and wrote the study protocol and established the SCT-study consortium. LJH designed the data collection forms, coordinated the data collection and validation, undertook the data analysis, and wrote and revised the manuscript. The writing committee (JHA, MMB, LBC, JPMD, SF, NJH, AH, LJH, LWEH, TS, SSP, JT and TY) contributed to the data interpretation, manuscript content, and revisions. Statistical analysis was done by LJH and JT. LWEH, LJH, JPMD and statistician (JT) had full access to all the study data. LJH and statistician (JT) validated the data. All authors approved the manuscript and had final responsibility for the decision to submit for publication. All authors were local investigators. Local investigators gained local study approval, used the protocol to identify eligible patients, collected data, entered data in Castor EDC, and checked the data to prevent duplicate entries and ensure accuracy. All authors have read and approved the final manuscript.

Declaration of interest

All authors declare no conflicts of interest

Data sharing

Following publication of the study results, the full, anonymous de-identified patient dataset will be made available. Data requestors will need to sign a data access agreement.

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Following publication of the study results, the full, anonymous de-identified patient dataset will be made available. Proposals should be directed to sct-study@amsterdamumc.nl to gain access. Data requestors will need to sign a data access agreement.

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Table 1 Patient characteristics for the total population and stratified per income countries

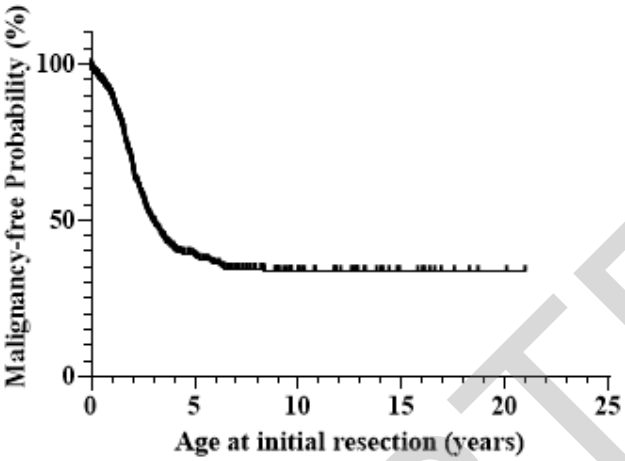
	Total (n=3407)	**High-income countries (n=2296)**	**Higher-middle income countries (n=677)**	**Lower-middle income countries (n=377)**	**Low-income countries (n=57)**	**p-value**
Sex						
Male	844 (24·8%)	571 (24·9%)	161 (23·8%)	103 (27·3%)	9 (15·8%)	0·067
Female	2500 (73·4%)	1722 (75·0%)	491 (72·5%)	239 (63·4%)	48 (84·2%)	
Missing	63 (1·8%)	3 (0·1%)	25 (3·7%)	35 (9·3%)		
Median age at diagnosis, days	0 (0-54)	0 (0-17·5)	1 (0-108·5)	8 (0-150)	30 (2·5-556·5)	<0·001
Altman classification						
I	1036 (30·4%)	669 (29·1%)	227 (33·5%)	125 (33·2%)	15 (26·3%)	<0·001
II	1118 (32·8%)	753 (32·8%)	201 (29·7%)	137 (36·3%)	27 (47·4%)	
III	609 (17·9%)	407 (17·7%)	130 (19·2%)	63 (16·7%)	9 (15·8%)	
IV	548 (16·1%)	432 (18·8%)	851 (12·6%)	25 (6·6%)	6 (10·5%)	
Missing	96 (2·8%)	35 (1·5%)	34 (5·0%)	27 (7·2%)	..	
Median age at resection, days	13 (4-134·3)	9 (3-99)	17 (6-187·3)	40 (14-271·5)	52 (14·0-570)	<0·001
Pathology						
Mature	2168 (63·7%)	1504 (65·5%)	442 (65·3%)	184 (48·8%)	38 (66·7%)	0·004
Immature	625 (18·3%)	469 (20·4%)	91 (13·4%)	54 (14·3%)	11 (19·3%)	
Malignant	366 (10·7%)	245 (10·7%)	91 (13·4%)	27 (7·2%)	3 (5·3%)	
Missing	248 (7·3%)	78 (3·4%)	53 (7·8%)	112 (29·7%)	5 (8·8%)	
Recurrence						
Yes	349 (10·2%)	254 (11·1%)	56 (8·3%)	33 (8·8%)	6 (12·3%)	0·604
No			536 (79·2%)	276 (73·2%)		

Missing	2829 (83·0%) 229 (6·8%)	1967 (85·7%) 75 (3·3%)	85 (12·6%)	68 (18·0%)	50 (87·7%) 1 (1·8%)	
Median time between primary resection and recurrence, days	348 (196-666)	348 (200.5-679)	358 (182.5-673·8)	357 (195·5-668)	311·5 (131·5-654·5)	0·948
Recurrence pathology Mature Immature Malignant Missing	117 (33·5%) 34 (9·7%) 126 (36·1%) 72 (20·6%)	96 (37·8%) 23 (9·1%) 91 (35·8%) 44 (17·3%)	14 (25·0%) 4 (7·1%) 22 (39·3%) 16 (28·6%)	7 (21·2%) 7 (21·2%) 7 (21·2%) 12 (36·4%)	.. .. 6 (100%) ..	0·001
Outcome Alive Death Missing	2876 (84·4%) 140 (4·1%) 391 (11·5%)	2073 (90·3%) 93 (4·1%) 130 (5·7%)	534 (78·9%) 25 (3·7%) 118 (17·4%)	219 (58·1%) 20 (5·3%) 138 (36·6%)	50 (87·7%) 2 (3·5%) 5 (8·8%)	0·059
Data are n(%) or median (IQR). *p values represent univariable testing between country income strata.						

Table 2 Risk factors for recurrent SCT

	Recurrence rate	**Univariable**		**Multivariable**	
		Odds ratio	p-value	Odds ratio	p-value
Altman classification					
I	73 of 1036	1			
II	122 of 1118	1·631 (1·203-2·211)	0·002*	1·624 (1·180-2·234)	0·003*
III	76 of 609	1·900 (1·353-2·668)	<0·001*	1·627 (1·227-2·348)	0·009
IV	63 of 548	1·696 (1·189-2·419)	0·004	1·423 (0·967-2·093)	0·073
Income country					
Low	6 of 57	1			
Lower-middle	33 of 377	0·996 (0·397-2·502)	0·994		
Higher-middle	56 of 677	0·871 (0·357-2·121)	0·760		
High	254 of 2296	1·076 (0·457-2·535)	0·867		
Primary histology					
Mature	155 of 2168	1			
Immature	80 of 625	1·863 (1·3980-2·481)	<0·001*	1·911 (1·427-2.558)	<0·001*
Malignant	91 of 366	4·337 (3·245-5·795)	<0·001*	3·965 (2·906-5·411)	<0·001*
Median age at diagnosis (days)					
Yes	1 (0-248·3)		0·254		
No	0 (0-40)				
Median age at resection (days)					
Yes	17 (4-318)		0·073		
No	13 (4-120)				

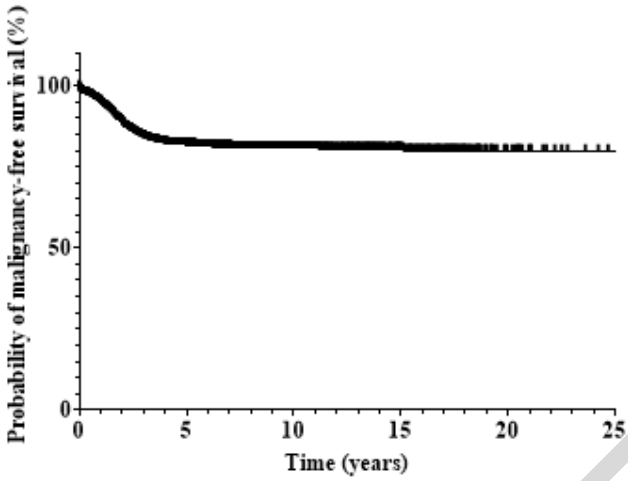
Figure 1 Malignancy-free probability at initial SCT resection



Numbers at risk

3050	102	36	13	2

Figure 2 Probability of malignancy free survival



Numbers at risk

2688	1196	453	149	33	16

Figure 3 Probability of recurrence free survival