Title: Outcomes of Adolescent Males with Extracranial Metastatic Germ Cell Tumors: A Report from the Malignant Germ Cell Tumor International Consortium.

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Furqan Shaikh, Daniel Stark, Adriana Fonseca, Ha Dang, Caihong Xia, Mark Krailo, Farzana Pashankar, Thomas Olson, James C. Nichols, Mathew J. Murray, James F. Amatruda, Deborah Billmire & Sara Stoneham: No Conflict to declare

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Author Contribution Statement:

Furqan Shaikh: Conceptualization, methodology, data curation, formal analysis, original draft, writing- review and editing.

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Lay Summary:

Adolescent males with metastatic germ cell tumors are frequently treated with regimens developed for children. In this study, we built a large dataset of male patients with metastatic germ cell tumors across different age groups to understand the outcomes of adolescent patients when compared with children and young adults. Our results suggest that adolescent males with metastatic germ cell tumors have worse results than children and are more similar to young adults with germ cell tumors. Therefore, the treatment of adolescents with germ cell tumors, should resemble young adult therapeutic approaches.

Précis for Table of Contents:

EFS for adolescent patients with metastatic germ cell tumors was similar to young adults but significantly worse than for children. This finding highlights the importance of coordinating initiatives across clinical trial organizations to improve outcomes for adolescents and young adults.

Abstract:

PURPOSE: Adolescents with extracranial metastatic germ cell tumors (GCTs) are often treated on regimens developed for children, but more closely resemble the clinical characteristics of young adult patients. We sought to determine event-free survival (EFS) for adolescents with GCTs and compared children and young adults.

PATIENTS AND METHODS: We assembled an individual patient database of eleven GCT trials: eight conducted by pediatric cooperative groups and three by an adult group. We included male patients aged 0-30 years with metastatic, non-seminomatous malignant GCTs of the testis, retroperitoneum, or mediastinum, treated with platinum-based chemotherapy. We categorized age-group as children (0 to <11 years), adolescents (11 to <18 years), or young adults (18 to <30 years old). We compared EFS and adjusted for risk-group using Cox proportional hazards analysis.

RESULTS: From a total of 2,024 individual records, 593 patients met inclusion criteria, of whom 90 were children, 109 were adolescents, and 394 were young adults. The 5-year EFS for adolescents [72 %; 95% confidence-interval (CI)=62-79%] was lower than for children (90%; CI=81-95%, p=0.003) or young adults (88%; CI=84-91%, p=0.0002). International Germ Cell Cancer Collaborative Group (IGCCCG) risk-group was associated with EFS in the adolescent age-group (p=0.0257). After adjusting for risk-group, the difference in EFS between adolescents and children remained significant (HR=0.30, p=0.001).

CONCLUSION: EFS for adolescent patients with metastatic GCTs was similar to young adults but significantly worse than for children. This finding highlights the importance of coordinating initiatives across clinical trial organizations to improve outcomes for adolescents and young adults.

Keywords: Germ cell tumors, adolescent males, outcomes, AYA, Testicular GCT.

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Background

Adolescents and young adults (AYAs) with cancer are a unique group of patients with special characteristics.[1-4] AYAs develop a specific spectrum of cancers,[5] require age-appropriate psychosocial support, and often inhabit a medical 'no man's land'[6] where they are neither the specific focus of pediatric or adult worlds of oncology.[7] This results in their care being under-researched, trials under-accrued, and optimal management disputed.[8] AYAs may sometimes be subject to professional competition for patient 'ownership' or an individual clinical conviction that the management used for one age-group is right for another.[9, 10] But specific attention to the needs of AYA cancer patients has yielded progress. In acute lymphoblastic leukemia, management has evolved based upon pooling of data from different treatment approaches, with greatly improved AYA outcomes in recent trials.[11] Similarly, Ewing sarcoma outcomes for AYAs were inferior to those seen in children, until collaborative protocols overcame this difference.[12, 13] In osteosarcoma, outcomes for AYAs are also inferior to those observed in children, and pooling of clinical trial data has hypothesised tractable reasons for these differences related to pharmacologic or clinical factors.[14] We believe similar advances can be made for AYA patients with GCTs through collaborative, investigative efforts.

Extracranial germ cell tumors (GCTs) account for approximately 3-4% of cancers in children, 14% of cancers in adolescents aged 15-19 years, and 18% of cancers in young adults aged 20-30 years.[15, 16] Thus, GCTs are among the few malignancies that are encountered relatively commonly by both pediatric and medical oncologists. However, treatment regimens have evolved separately within pediatric and adult oncology collaborative groups. The two groups use different

staging and risk stratification systems, different numbers of cycles, and different cumulative doses of chemotherapy.[17, 18]

Historically, patients under the age of 15-18 years in North America or under 16 years in the United Kingdom (UK) have been treated on pediatric regimens, and most adolescents within these ages have been treated with the approaches developed for young children. On the other hand, it can be argued that adolescents with GCTs seem to more closely resemble the characteristics of young adult patients with respect to clinical, biological and epidemiological characteristics.[19] Thus, there is a knowledge gap about the optimal approach to treating adolescents with GCTs. To date, it is not known whether adolescents with GCTs are more effectively treated with pediatric or adult approaches. Compounding this matter is the observation that adolescents with GCTs are under-represented in clinical trials, frequently too old to meet the age inclusion criteria of pediatric trials and too young to meet age eligibility for adult studies.[20]

We sought to determine whether adolescents with GCTs experience outcomes that are more alike to children or to young adults, and where the dividing line between pediatric and adult standards of care or clinical trial inclusion criteria should be drawn. There is only limited evidence to help guide such discussions. This limitation stems from the heterogeneous manifestations of GCTs across age-groups which precludes direct comparisons, as well as the relatively small sample size of individual trials which prevents adequately powered subgroup analyses. Previously, Cost et al. [21] reported on the outcomes among 20 children, 39 adolescents, and 354 adult patients with testicular GCTs treated at their institution. The EFS for adolescents was worse when compared with children and young adults, even after adjusting for stage, International Germ Cell

Cancer Collaborative Group (IGCCCG) risk-group, [17] and histology. However, this was a single centre analysis with a small sample size.

The Malignant Germ Cell Tumour International Consortium (MaGIC) assembled a large pooled dataset of extracranial GCT patients treated across multiple clinical trials and collaborative groups[20, 22], allowing for secondary analysis of prospective trial data. For this current study, we derived a relatively homogenous subgroup of male patients with GCT across three age-groups (children, adolescents, and young adults) in order to compare event-free survival (EFS). A secondary objective was to determine whether the IGCCCG risk stratification system used in adult studies[17] was predictive of outcome in pediatric or adolescent patients with GCTs.

Patients and Methods

At the time of this analysis, the MaGIC database included all patients enrolled in five trials conducted by the Children's Oncology Group (COG; INT-1016,[23] INT-0097,[18] AGCT0132,[24] AGCT01P1[25] and P9749[26]), three trials from the Children's Cancer and Leukemia Group (CCLG; GCI,[27] GCII[28] and GCIII[29]), and three trials from the Medical Research Council (MRC; TE09,[30] TE13[31] and TE20[32]). Each trial had received research ethics board approval from the relevant agencies. The project was reviewed and approved by the Institutional Review Board at the Dana-Farber Cancer Institute.

From the total dataset of 2,024 patients, we selected males age 0-30 years with newly diagnosed, metastatic, non-seminomatous malignant GCT of the testis, retroperitoneum or mediastinum. The resulting subgroup of 593 patients provided a population with relatively uniform

disease characteristics that was large enough to provide adequate numbers of patients within each of the three age-groups.

In order to maintain uniform treatment intensity, we only included patients treated with standard regimens with outcomes known to be similar to each other. The regimens included the adult standard-of-care BEP (weekly bleomycin, represented henceforth by the upper case letter 'B', and once per cycle etoposide and cisplatin), the pediatric standard-of-care PEb (cisplatin, etoposide and reduced bleomycin used once per cycle, represented henceforth by the lowercase letter 'b'), HD-PEb (high-dose cisplatin and Eb), C-PEb (cyclophosphamide and PEb), and pediatric JEb (carboplatin and Eb). We included pediatric JEb as it has similar outcomes to pediatric PEb [29, 33]. However, adult patients treated with carboplatin regimens were excluded as these regimens, which notably used lower doses of carboplatin than those used in paediatric regimens, have been shown to be inferior to BEP in randomized trials.[30, 34]

We categorized 'age-group' as children (age 0 to <11 years), adolescents (11 to <18 years), or young adults (18 to <30 years old). The selection of age 11 years as the cut-off between children and adolescents was based on our earlier analysis which showed this age to be the most significant and discriminant prognostic cut-off among pediatric GCTs.[22] We selected 18 years as the defining age between adolescents and young adults as it is the most frequent age of transition from pediatric to adult care in many centres and clinical trials. We defined 'metastatic' as lymph node metastasis or distant sites, classified in the MRC trials as stage II or III, in CCLG as stage II-IV, or in COG as stage III or IV.

Next, we retrospectively applied the IGCCCG risk stratification, assigning each patient to either the good-risk, intermediate-risk, or poor-risk group.[17] The IGCCCG criteria utilize histologic subtype, primary site, sites of metastases, and pre-chemotherapy serum levels of alpha fetoprotein (AFP), β subunit of human chorionic gonadotropin (βHCG), and lactate dehydrogenase (LDH) to determine risk-group, thus providing a composite variable of the most significant (adult) prognostic factors. Of note, tumor marker levels in pediatric trials measured at "diagnosis" may have been pre-surgical levels, rather than post-surgical levels as used by the IGCCCG. Furthermore, since some of the trial protocols of our pooled dataset were conducted prior to the IGCCCG classification, and because IGCCCG risk stratification has not traditionally been applied to pediatric GCT patients, we expected and encountered a high rate of missing values on the relevant data elements, especially LDH levels. If the particular value of a variable was not available to assign the IGCCCG risk group, we assumed (for the primary analysis) that the value would not have increased the assigned risk group (i.e., patients were assigned to the good-risk group by default and positive evidence was required to elevate a patient to the intermediate-risk or poor-risk groups) as this is analogous to what would be done in a clinical setting. A sensitivity analysis including only patients with complete stratifying data available was also performed.

The primary outcome was EFS, defined as the time interval from date of diagnosis to relapse or progression, second malignancy, death, or date last seen (whichever occurred first). The two potential predictor variables of main interest were age-group and IGCCCG risk-group. We constructed survival curves using the Kaplan-Meier method and used the log-rank test to compare EFS. We examined whether the IGCCCG risk-group within each age-group was significantly associated with EFS. We then conducted a multivariable Cox proportional hazards

regression analysis to determine whether age-group (with adolescent age as the reference level) remained independently significant when adjusting for IGCCCG risk group. Lastly, we conducted sensitivity analyses to determine whether the results remained the same if we excluded all patients a) who received carboplatin (given historic results of carboplatin studies in adult patients), and b) with mediastinal primary sites of disease (given that mediastinal primary non-seminomatous tumors are assigned to the IGCCCG poor-risk group regardless of any other risk factors). A P-value of ≤ 0.050 was considered as evidence of a significant difference. All analyses were conducted by the authors using Stata version 13.1 (College Station, TX).

Results

The Consort diagram (Fig.1) shows the flow of patients in this study. From a total of 2024 non-duplicated records in the pooled database, 593 patients met inclusion criteria, of which 191 were from pediatric studies and 402 from adult studies. Table 1 shows the characteristics of the source studies, including their patient populations, regimens used, and the number of patients from each trial who met eligibility criteria for this study.

The characteristics of all included patients are shown in Table 2. The mean ($\pm$standard deviation) age was 19.4 ($\pm$8.9) years. Five-hundred and thirty patients presented with testicular tumors (89.4%), 44 (7.4%) with mediastinal tumors, and 19 (3.3%) with retroperitoneal primary tumors. There were 90 children, 109 adolescents, and 394 young adults. Among the 90 children, 84 (93%) were less than 3 years old. Among the 109 adolescents, only four patients were between 11 and 13 years old. Tumour marker elevation was significantly different between age-groups: adolescents had the highest mean serum βHCG level (24,288 IU/L) and mean LDH level (934 U/L), while the pediatric group demonstrated the highest mean AFP elevation (29,717 ng/mL).

While there was a significant difference in the proportion of patients with poor-risk tumors in the pediatric and adolescent population (46% and 47% respectively) compared with the adult population (6%), this likely reflected the differences in the inclusion criteria of included studies rather than differences in natural distribution. In the adolescent group, 95/109 (87%) patients were treated with pediatric protocols, of whom 85 received cisplatin-based regimes (PEb) and 10 received carboplatin-based regimens (JEb). Fourteen of 109 (13%) adolescents were treated with adult-type regimens (BEP).

Among all 593 patients, there were 91 events and 35 deaths. The overall 5-year EFS was 85% [95% confidence intervals (CI) 82-88 %] and the overall 5-year overall survival (OS) was 94% (95%; CI 92-96%; Fig 2A). The median follow-up time for patients who survived without an event was 5.9 years (range 0.1 to 14.0 years). Age-group was strongly associated with EFS (p=0.0001) (Fig 2B). The 5-year EFS for adolescents (72%; CI = 62-79 %) was lower than for children (90%; CI=81-95 %, p=0.003) and for young adults (88%; CI=84-91%, p=0.0002). Risk-group was also strongly associated with EFS (p<0.0001) (Fig 2C). The 5-year EFS for the good-risk group (89%) was higher than for the intermediate-risk group (76%) (p=0.0003) and poor-risk group (76%) (p<0.0001).

Figure 3 shows the EFS curves for each age-group stratified by risk-group. Risk-group was not significantly associated with EFS among children (p=0.7162) or young adults in this cohort (p=0.2703) but was associated with EFS among adolescents (p=0.0020). Among the 51 adolescents with poor-risk disease, 5-year EFS was only 57% (95% CI=42-70%), the lowest value observed across all subgroup analyses. In an exploratory analysis, the poor outcome in these 51

patients was not driven by patients being treated on adult regimens (two patients, no events) or JEb regimens (four patients, no events). Adolescent patients treated with the pediatric regimen PEb had a 5- EFS of 64% (95% CI= 53-74%) compared to a 5-yr EFS of 92.9% (95%CI= 59-98%) in adolescent patients treated with the BEP regimen used in adult patients (log-rank p=0.0517).

The Cox regression model including both age-group and risk-group (Table 3) demonstrated that, after adjusting for risk-group, the effect of age-group remained statistically significant (likelihood-ratio test for significance of age-group adjusted for risk-group p=0.0025). The difference in EFS between adolescents and children remained significant (HR=0.30., p=0.001), but the difference between adolescents and young adults was no longer significant (HR 0.66, p=0.114). The results did not change if children treated on the carboplatin based JEb regimen were excluded (Table 3), or if patients with mediastinal primary tumors were excluded (Table 3).

In a sensitivity analysis, including only the 465 patients who had complete data for IGCCC risk stratification (78% of total sample size), the direction of results remained the same. In the proportional hazard analysis of these patients (Supplemental Table 1), the difference in EFS between adolescents and children remained significant (HR=0.21, p=0.001), and the difference between adolescents and adults was not significant (HR=0.59, p=0.081).

Discussion

Our study describes the outcomes of adolescent males with extracranial GCTs when compared against children and young adults within a large pooled dataset of collaborative phase III clinical trials. We showed that adolescent males had the lowest 5-year EFS (72%) compared with both children (90%) and young adults (88%) in unadjusted analysis. After adjusting for risk-

group, the difference between adolescents and children remained significant, but the difference between adolescents and young adults did not. Furthermore, we examined whether the IGCCCG risk-classification system could successfully discriminate outcome among children or adolescents. The risk-groups were associated with outcome among adolescents, but not among children. This showed that the IGCCCG can be usefully applied for adolescents. Children had excellent outcomes regardless of risk-group, further validating the results of the MaGIC risk stratification[22] where all patients <11y belong to the same risk group.

Our findings also pointed to the under-representation of adolescents in clinical trials. There were only 109 adolescent males with metastatic GCT in this entire dataset, pooled from every pediatric clinical trial across North America and the United Kingdom for the last thirty years. Considering that extracranial metastatic GCT is the most common cancer among adolescent males, and that 430 new testicular GCTs are diagnosed in boys aged 15-19 years in the United States each year,[15] this remarkably small number of patient provides a stark example of the adolescent and young adult (AYA) 'gap' in cancer care, research, and outcomes.[35]

A strength of our study was its pooling of multiple good quality clinical trials to assemble the largest sample size currently possible to conduct this comparison, which any individual trial would not have allowed. This analysis focused on the outcomes of non-germinomatous/non-seminomatous GCTs in males, therefore, the results cannot be extrapolated to female patients or patients with pure germinomas/seminomas. One of our major limitations was the inability to analyse the effect of different therapeutic modalities and their individual impact on outcomes. Surgery is a cornerstone in the management of GCTs and the role of retroperitoneal lymph node dissection (RPLND) for post-chemotherapy residual lesions has been well described in the adult

literature [36-39]; this analysis was unable to account for its contribution to outcome. A potential weakness of the study was its moderate rate of missing data on the variables needed to assign IGCCCG risk-group. However, the results remained unchanged in a sensitivity analysis in which patients with missing data were excluded, suggesting this factor did not affect conclusions. Lastly, since tumor marker levels in pediatric trials measured at diagnosis may have been pre-surgical levels rather than post-surgical levels, it is possible that some pediatric patients may have been miscategorized on their IGCCCG risk group, which would have biased our risk group analyses. However, the direction of this bias would not be expected to weaken the results.

Adolescents with metastatic GCT are biologically and clinically more similar to young adults than children[19], and this study demonstrates that they are also more alike in outcomes. While this study could not assess the superiority of any particular treatment approach or chemotherapy regimen, we believe it provides enough reason to consider treating adolescent males with GCTs differently than young children. We suggest that adolescent males with metastatic GCTs should be treated with approaches that have been developed with the wider evidence-base of adult testicular cancer, allowing them to receive the dose intensity of weekly bleomycin[40-44], the predictive stratification of the IGCCCG[17, 32, 45], and the surgical guidelines for procedures such as RPLND of post-chemotherapy residual tumors[36-39]. All of these are standards-of-care among medical oncologists and urologists treating adults with metastatic GCTs.

The results of this analysis, together with our earlier work on developing a revised GCT risk stratification[46], has already allowed us to incorporate these lessons into the current generation of GCT clinical trials in the United States and the United Kingdom. The current multi-group trial

AGCT1531 (NCT03067181) includes all standard-risk patients between age 11-25 years as a single study group and prescribes these standards to all Furthermore, the COG has petitioned and joined two clinical trials led by adult testicular cancer cooperative groups: the ANZUP P3BEP or COG-AGCT1532 trial of accelerated BEP for high-risk patients, and the Alliance-A031102 TIGER trial for patients with relapsed testicular GCTs. Both these studies were originally planned for adult patients alone, but on the evidence presented here, their eligibility criteria were modified to include adolescent patients. Taken together, these three trials cover the entire spectrum of adolescent GCTs. The availability of the data is due to the work of the Malignant Germ Cell international Consortium (MaGIC) which has galvanized a remarkable collaboration of multiple cooperative groups across the silos of age-groups and international borders[47]. Through MAGIC and other similar efforts, we hope to provide a path that will narrow the gap and improve outcomes for AYA patients with germ cell tumours.

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Table 1. Characteristics of Included Clinical Trials

Study	Patients in Source Studies	Regimens	Number in present study
TE09	598 adults with good-prognosis testicular NGGCTs (273 under 30Y)	4BEP	139
		4JEB (Carboplatin AUC 5)	0
TE13	380 adults with poor-prognosis NGGCTs (121 under 30Y)	BEP/EP	58
		BOP/VIP-B	0
TE20	812 adults with good-prognosis GCTs (230 NGGCTs under 30Y)	4BEP or 3BEP	205
GC2	137 children with MGCT	JEb (Carboplatin 600 mg/m^2)	39
GC3	138 children with MGCT	JEb (Carboplatin 600 mg/m^2)	9
POG 9048 (INT 1016)	74 children with intermediate-risk NGGCTs	4PEb	0
POG 9049 (INT 0097)	299 children with high-risk MGCTs	4PEb	43
		4HD-PEb	43
P9749	25 children with high-risk MGCT	4HD-PEb	4
AGCT01P1	19 children with high-risk NGGCT	4C-PEb	5
AGCT0132	218 children with intermediate-risk NGGCTs	3PEb	47

Abbreviations: AUC, area under the curve; b, bleomycin once per cycle; B, bleomycin once per week; C, cyclophosphamide; E, etoposide; HD-P, high dose cisplatin; I, ifosfamide; J, carboplatin; MGCT, malignant germ cell tumors; NGGCT, non-germinomatous germ cell tumors; O, vincristine; P, cisplatin; POG, Pediatric Oncology Group; V, etoposide. * includes 38 patients from GCT2 and 1 patient from GCT1

Table 2. Patient Characteristics

Variable	All Pts 0 to 30y N (%) N=593	0 to <11y N (%) N=90	11 to <18y N (%) N=109	18 to 30y N (%) N=394
Age mean (SD)	19.4 (8.9)	1.9 (1.9)	14.7 (1.5)	24.8 (3.6)
Testicular	530 (89%)	67 (74%)	82(75%)	381 (96.7%)
Mediastinal tumor	44 (7%)	16 (18%)	22 (20%)	6 (1.5%)
Retroperitoneal	19 (3%)	7(8%)	5(5%)	7 (1.7%)
AFP (ng/mL)				
Mean	6294	29717	6924	857
(range)	(0 -700000)	(8-700000)	(0-96000)	(0-63630)
<1000	449 (76%)	34 (38%)	57 (52%)	358 (91%)
1,000-10,000	68 (11%)	23 (26%)	25 (23%)	20 (5%)
>10,000	62 (10%)	30 (33%)	23 (21%)	9 (2%)
Missing	14 (2%)	3 (3%)	4 (4%)	7 (2%)
βHCG (IU/L)				
Mean	12358	5	24289	11592
(range)	(0-1057700)	(0-62)	(1-990000)	(0-1057700)
<5,000	435 (73%)	33 (37%)	44 (40%)	358 (91%)
5,000 – 50,000	30 (5%)	0 (0%)	12 (11%)	18 (5%)
>50,000	14 (2%)	0 (0%)	3 (3%)	11 (3%)
Missing	114 (19%)	57 (63%)	50 (46%)	7 (2%)
LDH (U/L)				
Mean	587	701	934	500
(range)	(77-5540)	(149-3631)	(77-5540)	(93-5186)
<930	318 (54%)	22 (24%)	40 (37%)	256 (65%)
930-6200	47 (8%)	7 (8%)	19 (17%)	21 (5%)
>6200	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	228 (38%)	61 (68%)	50 (46%)	117 (30%)
Non-pulmonary visceral metastases	34 (6%)	9 (10%)	16 (15 %)	9 (2%)
RiskGroup				
Good	267 (45 %)	4 (4%)	14 (13%)	249 (63%)
Intermediate	82 (14%)	21 (23%)	23 (21%)	38 (10%)
Poor	116 (20%)	41 (46%)	51 (47%)	24 (6%)
Missing	128 (21%)	24 (27%)	21 (19%)	83 (21%)

Abbreviations: AFP, a-fetoprotein; B-HCG, beta subunit of human chorionic gonadotropin; LDH, lactate dehydrogenase.

Table 3. Univariate Kaplan-Meier and Multivariable Cox Regression Analysis of Age-Group and Risk-Group.

	Univariate					Multivariate		
All Patients (N=593)								
Variable	**5y EFS (%)**	**Hazard Ratio**	**95% CI**	**P value**		**Hazard Ratio**	**95% CI**	**P value**
Age Group								
0 - <11	90	0.31	0.14-0.65	**0.002**		0.30	0.14 – 0.63	**0.001**
11 - <18	72	Reference				Reference		
18 - <30	88	0.43	0.27-0.68	**0.000**		0.66	0.40 – 1.11	0.114
Risk Group								
Good	89	0.42	0.26-0.67	**0.000**		0.42	0.24 – 0.72	**0.002**
Intermediate	76	0.87	0.48-1.56	0.634		0.88	0.48 – 1.60	0.663
Poor	76	Reference				Reference		
JEb patients excluded* (N=545)								
Age Group								
0 - <11	92	0.21	0.07-0.60	**0.004**		0.21	0.07 – 0.59	**0.003**
11 - <18	69	Reference				Reference		
18 - <30	88	0.38	0.24-0.60	**0.000**		0.62	0.36 – 1.03	0.066
Risk Group								
Good	89	0.36	0.22-0.58	**0.000**		0.39	0.22 – 0.68	**0.001**
Intermediate	75	0.77	0.42-1.42	0.401		0.81	0.44 – 1.50	0.489
Poor	73	Reference				Reference		
Mediastinal primary tumors excluded (N=549)**								
Age Group								
0 - <11	89	0.41	0.18-0.94	**0.035**		0.40	0.108– 0.91	**0.029**
11 - <18	77	Reference				Reference		
18 - <30	87	0.55	0.33-0.93	**0.024**		0.83	0.347– 1.47	0.506
Risk Group								
Good	89	0.43	0.25-0.75	**0.003**		0.40	0.22 – 0.74	**0.003**
Intermediate	76	0.89	0.46-1.72	0.737		0.88	0.45 – 1.71	0.693
Poor	77	Reference				Reference		

Abbreviations: CI, confidence interval; EFS, event-free survival; JEb, carboplatin/etoposide/reduced bleomycin; N, number; y, years. *48 Patients received JEb. **44 Patients with mediastinal tumours.

FIGURE LEGENDS

Figure 1. CONSORT diagram describing flow of patients through the study

Figure 2. A) Event-free survival (EFS) and overall survival (OS) for all patients (N=593) B) EFS by risk-group; C) EFS by age-group

Figure 3. A) EFS for children (age 0 to <11 years) by risk-group; B) EFS for adolescents (age 11 to <18 years) by risk-group; C) EFS for young adults (age 18 to <30 years) by risk-group.

Title: Outcomes of Adolescent Males with Extracranial Metastatic Germ Cell Tumors: A Report from the Malignant Germ Cell Tumor International Consortium.

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Lay Summary:

Adolescent males with metastatic germ cell tumors are frequently treated with regimens developed for children. In this study, we built a large dataset of male patients with metastatic germ cell tumors across different age groups to understand the outcomes of adolescent patients when compared with children and young adults. Our results suggest that adolescent males with metastatic germ cell tumors have worse results than children and are more similar to young adults with germ cell tumors. Therefore, the treatment of adolescents with germ cell tumors, should resemble young adult therapeutic approaches.

Précis for Table of Contents:

EFS for adolescent patients with metastatic germ cell tumors was similar to young adults but significantly worse than for children. This finding highlights the importance of coordinating initiatives across clinical trial organizations to improve outcomes for adolescents and young adults.

Abstract:

PURPOSE: Adolescents with extracranial metastatic germ cell tumors (GCTs) are often treated on regimens developed for children, but more closely resemble the clinical characteristics of young adult patients. We sought to determine event-free survival (EFS) for adolescents with GCTs and compared children and young adults.

PATIENTS AND METHODS: We assembled an individual patient database of eleven GCT trials: eight conducted by pediatric cooperative groups and three by an adult group. We included male patients aged 0-30 years with metastatic, non-seminomatous malignant GCTs of the testis, retroperitoneum, or mediastinum, treated with platinum-based chemotherapy. We categorized age-group as children (0 to <11 years), adolescents (11 to <18 years), or young adults (18 to <30 years old). We compared EFS and adjusted for risk-group using Cox proportional hazards analysis.

RESULTS: From a total of 2,024 individual records, 593 patients met inclusion criteria, of whom 90 were children, 109 were adolescents, and 394 were young adults. The 5-year EFS for adolescents [72 %; 95% confidence-interval (CI)=62-79%] was lower than for children (90%; CI=81-95%, p=0.003) or young adults (88%; CI=84-91%, p=0.0002). International Germ Cell Cancer Collaborative Group (IGCCCG) risk-group was associated with EFS in the adolescent age-group (p=0.0257). After adjusting for risk-group, the difference in EFS between adolescents and children remained significant (HR=0.30, p=0.001).

CONCLUSION: EFS for adolescent patients with metastatic GCTs was similar to young adults but significantly worse than for children. This finding highlights the importance of coordinating initiatives across clinical trial organizations to improve outcomes for adolescents and young adults.

Keywords: Germ cell tumors, adolescent males, outcomes, AYA, Testicular GCT.

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Background

Adolescents and young adults (AYAs) with cancer are a unique group of patients with special characteristics.[1-4] AYAs develop a specific spectrum of cancers,[5] require age-appropriate psychosocial support, and often inhabit a medical 'no man's land'[6] where they are neither the specific focus of pediatric or adult worlds of oncology.[7] This results in their care being under-researched, trials under-accrued, and optimal management disputed.[8] AYAs may sometimes be subject to professional competition for patient 'ownership' or an individual clinical conviction that the management used for one age-group is right for another.[9, 10] But specific attention to the needs of AYA cancer patients has yielded progress. In acute lymphoblastic leukemia, management has evolved based upon pooling of data from different treatment approaches, with greatly improved AYA outcomes in recent trials.[11] Similarly, Ewing sarcoma outcomes for AYAs were inferior to those seen in children, until collaborative protocols overcame this difference.[12, 13] In osteosarcoma, outcomes for AYAs are also inferior to those observed in children, and pooling of clinical trial data has hypothesised tractable reasons for these differences related to pharmacologic or clinical factors.[14] We believe similar advances can be made for AYA patients with GCTs through collaborative, investigative efforts.

Extracranial germ cell tumors (GCTs) account for approximately 3-4% of cancers in children, 14% of cancers in adolescents aged 15-19 years, and 18% of cancers in young adults aged 20-30 years.[15, 16] Thus, GCTs are among the few malignancies that are encountered relatively commonly by both pediatric and medical oncologists. However, treatment regimens have evolved separately within pediatric and adult oncology collaborative groups. The two groups use different

staging and risk stratification systems, different numbers of cycles, and different cumulative doses of chemotherapy.[17, 18]

Historically, patients under the age of 15-18 years in North America or under 16 years in the United Kingdom (UK) have been treated on pediatric regimens, and most adolescents within these ages have been treated with the approaches developed for young children. On the other hand, it can be argued that adolescents with GCTs seem to more closely resemble the characteristics of young adult patients with respect to clinical, biological and epidemiological characteristics.[19] Thus, there is a knowledge gap about the optimal approach to treating adolescents with GCTs. To date, it is not known whether adolescents with GCTs are more effectively treated with pediatric or adult approaches. Compounding this matter is the observation that adolescents with GCTs are under-represented in clinical trials, frequently too old to meet the age inclusion criteria of pediatric trials and too young to meet age eligibility for adult studies.[20]

We sought to determine whether adolescents with GCTs experience outcomes that are more alike to children or to young adults, and where the dividing line between pediatric and adult standards of care or clinical trial inclusion criteria should be drawn. There is only limited evidence to help guide such discussions. This limitation stems from the heterogeneous manifestations of GCTs across age-groups which precludes direct comparisons, as well as the relatively small sample size of individual trials which prevents adequately powered subgroup analyses. Previously, Cost et al. [21] reported on the outcomes among 20 children, 39 adolescents, and 354 adult patients with testicular GCTs treated at their institution. The EFS for adolescents was worse when compared with children and young adults, even after adjusting for stage, International Germ Cell

Cancer Collaborative Group (IGCCCG) risk-group, [17] and histology. However, this was a single centre analysis with a small sample size.

The Malignant Germ Cell Tumour International Consortium (MaGIC) assembled a large pooled dataset of extracranial GCT patients treated across multiple clinical trials and collaborative groups[20, 22], allowing for secondary analysis of prospective trial data. For this current study, we derived a relatively homogenous subgroup of male patients with GCT across three age-groups (children, adolescents, and young adults) in order to compare event-free survival (EFS). A secondary objective was to determine whether the IGCCCG risk stratification system used in adult studies[17] was predictive of outcome in pediatric or adolescent patients with GCTs.

Patients and Methods

At the time of this analysis, the MaGIC database included all patients enrolled in five trials conducted by the Children's Oncology Group (COG; INT-1016,[23] INT-0097,[18] AGCT0132,[24] AGCT01P1[25] and P9749[26]), three trials from the Children's Cancer and Leukemia Group (CCLG; GCI,[27] GCII[28] and GCIII[29]), and three trials from the Medical Research Council (MRC; TE09,[30] TE13[31] and TE20[32]). Each trial had received research ethics board approval from the relevant agencies. The project was reviewed and approved by the Institutional Review Board at the Dana-Farber Cancer Institute.

From the total dataset of 2,024 patients, we selected males age 0-30 years with newly diagnosed, metastatic, non-seminomatous malignant GCT of the testis, retroperitoneum or mediastinum. The resulting subgroup of 593 patients provided a population with relatively uniform

disease characteristics that was large enough to provide adequate numbers of patients within each of the three age-groups.

In order to maintain uniform treatment intensity, we only included patients treated with standard regimens with outcomes known to be similar to each other. The regimens included the adult standard-of-care BEP (weekly bleomycin, represented henceforth by the upper case letter 'B', and once per cycle etoposide and cisplatin), the pediatric standard-of-care PEb (cisplatin, etoposide and reduced bleomycin used once per cycle, represented henceforth by the lowercase letter 'b'), HD-PEb (high-dose cisplatin and Eb), C-PEb (cyclophosphamide and PEb), and pediatric JEb (carboplatin and Eb). We included pediatric JEb as it has similar outcomes to pediatric PEb [29, 33]. However, adult patients treated with carboplatin regimens were excluded as these regimens, which notably used lower doses of carboplatin than those used in paediatric regimens, have been shown to be inferior to BEP in randomized trials.[30, 34]

We categorized 'age-group' as children (age 0 to <11 years), adolescents (11 to <18 years), or young adults (18 to <30 years old). The selection of age 11 years as the cut-off between children and adolescents was based on our earlier analysis which showed this age to be the most significant and discriminant prognostic cut-off among pediatric GCTs.[22] We selected 18 years as the defining age between adolescents and young adults as it is the most frequent age of transition from pediatric to adult care in many centres and clinical trials. We defined 'metastatic' as lymph node metastasis or distant sites, classified in the MRC trials as stage II or III, in CCLG as stage II-IV, or in COG as stage III or IV.

Next, we retrospectively applied the IGCCCG risk stratification, assigning each patient to either the good-risk, intermediate-risk, or poor-risk group.[17] The IGCCCG criteria utilize histologic subtype, primary site, sites of metastases, and pre-chemotherapy serum levels of alpha fetoprotein (AFP), β subunit of human chorionic gonadotropin (βHCG), and lactate dehydrogenase (LDH) to determine risk-group, thus providing a composite variable of the most significant (adult) prognostic factors. Of note, tumor marker levels in pediatric trials measured at "diagnosis" may have been pre-surgical levels, rather than post-surgical levels as used by the IGCCCG. Furthermore, since some of the trial protocols of our pooled dataset were conducted prior to the IGCCCG classification, and because IGCCCG risk stratification has not traditionally been applied to pediatric GCT patients, we expected and encountered a high rate of missing values on the relevant data elements, especially LDH levels. If the particular value of a variable was not available to assign the IGCCCG risk group, we assumed (for the primary analysis) that the value would not have increased the assigned risk group (i.e., patients were assigned to the good-risk group by default and positive evidence was required to elevate a patient to the intermediate-risk or poor-risk groups) as this is analogous to what would be done in a clinical setting. A sensitivity analysis including only patients with complete stratifying data available was also performed.

The primary outcome was EFS, defined as the time interval from date of diagnosis to relapse or progression, second malignancy, death, or date last seen (whichever occurred first). The two potential predictor variables of main interest were age-group and IGCCCG risk-group. We constructed survival curves using the Kaplan-Meier method and used the log-rank test to compare EFS. We examined whether the IGCCCG risk-group within each age-group was significantly associated with EFS. We then conducted a multivariable Cox proportional hazards

regression analysis to determine whether age-group (with adolescent age as the reference level) remained independently significant when adjusting for IGCCCG risk group. Lastly, we conducted sensitivity analyses to determine whether the results remained the same if we excluded all patients a) who received carboplatin (given historic results of carboplatin studies in adult patients), and b) with mediastinal primary sites of disease (given that mediastinal primary non-seminomatous tumors are assigned to the IGCCCG poor-risk group regardless of any other risk factors). A P-value of ≤ 0.050 was considered as evidence of a significant difference. All analyses were conducted by the authors using Stata version 13.1 (College Station, TX).

Results

The Consort diagram (Fig.1) shows the flow of patients in this study. From a total of 2024 non-duplicated records in the pooled database, 593 patients met inclusion criteria, of which 191 were from pediatric studies and 402 from adult studies. Table 1 shows the characteristics of the source studies, including their patient populations, regimens used, and the number of patients from each trial who met eligibility criteria for this study.

The characteristics of all included patients are shown in Table 2. The mean (±standard deviation) age was 19.4 (±8.9) years. Five-hundred and thirty patients presented with testicular tumors (89.4%), 44 (7.4%) with mediastinal tumors, and 19 (3.3%) with retroperitoneal primary tumors. There were 90 children, 109 adolescents, and 394 young adults. Among the 90 children, 84 (93%) were less than 3 years old. Among the 109 adolescents, only four patients were between 11 and 13 years old. Tumour marker elevation was significantly different between age-groups: adolescents had the highest mean serum βHCG level (24,288 IU/L) and mean LDH level (934 U/L), while the pediatric group demonstrated the highest mean AFP elevation (29,717 ng/mL).

While there was a significant difference in the proportion of patients with poor-risk tumors in the pediatric and adolescent population (46% and 47% respectively) compared with the adult population (6%), this likely reflected the differences in the inclusion criteria of included studies rather than differences in natural distribution. In the adolescent group, 95/109 (87%) patients were treated with pediatric protocols, of wh om ich, 85 received cisplatin-based regimes (PEb) and 10 received carboplatin-based regimens (JEb). Fourteen of 109 (13%) adolescents were treated with adult-type regimens (BEP).

Among all 593 patients, there were 91 events and 35 deaths. The overall 5-year EFS was 85% [95% confidence intervals (CI) 82-88 %] and the overall 5-year overall survival (OS) was 94% (95%; CI 92-96%; Fig 2A). The median follow-up time for patients who survived without an event was 5.9 years (range 0.1 to 14.0 years). Age-group was strongly associated with EFS (p=0.0001) (Fig 2B). The 5-year EFS for adolescents (72%; CI = 62-79 %) was lower than for children (90%; CI=81-95 %, p=0.003) and for young adults (88%; CI=84-91%, p=0.0002). Risk-group was also strongly associated with EFS (p<0.0001) (Fig 2C). The 5-year EFS for the good-risk group (89%) was higher than for the intermediate-risk group (76%) (p=0.0003) and poor-risk group (76%) (p<0.0001).

Figure 3 shows the EFS curves for each age-group stratified by risk-group. Risk-group was not significantly associated with EFS among children (p=0.7162) or young adults in this cohort (p=0.2703) but was associated with EFS among adolescents (p=0.0020). Among the 51 adolescents with poor-risk disease, 5-year EFS was only 57% (95% CI=42-70%), the lowest value observed across all subgroup analyses. In an exploratory analysis, the poor outcome in these 51

patients was not driven by patients being treated on adult regimens (two patients, no events) or JEb regimens (four patients, no events). Adolescent patients treated with the pediatric regimen PEb had a 5- EFS of 64% (95% CI= 53-74%) compared to a 5-yr EFS of 92.9% (95%CI= 59-98%) in adolescent patients treated with the BEP regimen used in adult patients (log-rank p=0.0517).

The Cox regression model including both age-group and risk-group (Table 3) demonstrated that, after adjusting for risk-group, the effect of age-group remained statistically significant (likelihood-ratio test for significance of age-group adjusted for risk-group p=0.0025). The difference in EFS between adolescents and children remained significant (HR=0.30., p=0.001), but the difference between adolescents and young adults was no longer significant (HR 0.66, p=0.114). The results did not change if children treated on the carboplatin based JEb regimen were excluded (Table 3), or if patients with mediastinal primary tumors were excluded (Table 3).

In a sensitivity analysis, including only the 465 patients who had complete data for IGCCC risk stratification (78% of total sample size), the direction of results remained the same. In the proportional hazard analysis of these patients (Supplemental Table 1), the difference in EFS between adolescents and children remained significant (HR=0.21, p=0.001), and the difference between adolescents and adults was not significant (HR=0.59, p=0.081).

Discussion

Our study describes the outcomes of adolescent males with extracranial GCTs when compared against children and young adults within a large pooled dataset of collaborative phase III clinical trials. We showed that adolescent males had the lowest 5-year EFS (72%) compared with both children (90%) and young adults (88%) in unadjusted analysis. After adjusting for risk-

group, the difference between adolescents and children remained significant, but the difference between adolescents and young adults did not. Furthermore, we examined whether the IGCCCG risk-classification system could successfully discriminate outcome among children or adolescents. The risk-groups were associated with outcome among adolescents, but not among children. This showed that the IGCCCG can be usefully applied for adolescents. Children had excellent outcomes regardless of risk-group, further validating the results of the MaGIC risk stratification[22] where all patients <11y belong to the same risk group.

Our findings also pointed to the under-representation of adolescents in clinical trials. There were only 109 adolescent males with metastatic GCT in this entire dataset, pooled from every pediatric clinical trial across North America and the United Kingdom for the last thirty years. Considering that extracranial metastatic GCT is the most common cancer among adolescent males, and that 430 new testicular GCTs are diagnosed in boys aged 15-19 years in the United States each year,[15] this remarkably small number of patient provides a stark example of the adolescent and young adult (AYA) 'gap' in cancer care, research, and outcomes.[35]

A strength of our study was its pooling of multiple good quality clinical trials to assemble the largest sample size currently possible to conduct this comparison, which any individual trial would not have allowed. This analysis focused on the outcomes of non-germinomatous/non-seminomatous GCTs in males, therefore, the results cannot be extrapolated to female patients or patients with pure germinomas/seminomas. One of our major limitations was the inability to analyse the effect of different therapeutic modalities and their individual impact on outcomes. Surgery is a cornerstone in the management of GCTs and the role of retroperitoneal lymph node dissection (RPLND) for post-chemotherapy residual lesions has been well described in the adult

literature [36-39]; this analysis was unable to account for its contribution to outcome. A potential weakness of the study was its moderate rate of missing data on the variables needed to assign IGCCCG risk-group. However, the results remained unchanged in a sensitivity analysis in which patients with missing data were excluded, suggesting this factor did not affect conclusions. Lastly, since tumor marker levels in pediatric trials measured at diagnosis may have been pre-surgical levels rather than post-surgical levels, it is possible that some pediatric patients may have been miscategorized on their IGCCCG risk group, which would have biased our risk group analyses. However, the direction of this bias would not be expected to weaken the results.

Adolescents with metastatic GCT are biologically and clinically more similar to young adults than children[19], and this study demonstrates that they are also more alike in outcomes. While this study could not assess the superiority of any particular treatment approach or chemotherapy regimen, we believe it provides enough reason to consider treating adolescent males with GCTs differently than young children. We suggest that adolescent males with metastatic GCTs should be treated with approaches that have been developed with the wider evidence-base of adult testicular cancer, allowing them to receive the dose intensity of weekly bleomycin[40-44], the predictive stratification of the IGCCCG[17, 32, 45], and the surgical guidelines for procedures such as RPLND of post-chemotherapy residual tumors[36-39]. All of these are standards-of-care among medical oncologists and urologists treating adults with metastatic GCTs.

The results of this analysis, together with our earlier work on developing a revised GCT risk stratification[46], has already allowed us to incorporate these lessons into the current generation of GCT clinical trials in the United States and the United Kingdom. The current multi-group trial

AGCT1531 (NCT03067181) includes all standard-risk patients between age 11-25 years as a single study group and prescribes these standards to all Furthermore, the COG has petitioned and joined two clinical trials led by adult testicular cancer cooperative groups: the ANZUP P3BEP or COG-AGCT1532 trial of accelerated BEP for high-risk patients, and the Alliance-A031102 TIGER trial for patients with relapsed testicular GCTs. Both these studies were originally planned for adult patients alone, but on the evidence presented here, their eligibility criteria were modified to include adolescent patients. Taken together, these three trials cover the entire spectrum of adolescent GCTs. The availability of the data is due to the work of the Malignant Germ Cell international Consortium (MaGIC) which has galvanized a remarkable collaboration of multiple cooperative groups across the silos of age-groups and international borders[47]. Through MAGIC and other similar efforts, we hope to provide a path that will narrow the gap and improve outcomes for AYA patients with germ cell tumours.

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Table 1. Characteristics of Included Clinical Trials

Study	Patients in Source Studies	Regimens	Number in present study
TE09	598 adults with good-prognosis testicular NGGCTs (273 under 30Y)	4BEP	139
		4JEB (Carboplatin AUC 5)	0
TE13	380 adults with poor-prognosis NGGCTs (121 under 30Y)	BEP/EP	58
		BOP/VIP-B	0
TE20	812 adults with good-prognosis GCTs (230 NGGCTs under 30Y)	4BEP or 3BEP	205
GC2	137 children with MGCT	JEb (Carboplatin 600 mg/m^2)	39
GC3	138 children with MGCT	JEb (Carboplatin 600 mg/m^2)	9
POG 9048 (INT 1016)	74 children with intermediate-risk NGGCTs	4PEb	0
POG 9049 (INT 0097)	299 children with high-risk MGCTs	4PEb	43
		4HD-PEb	43
P9749	25 children with high-risk MGCT	4HD-PEb	4
AGCT01P1	19 children with high-risk NGGCT	4C-PEb	5
AGCT0132	218 children with intermediate-risk NGGCTs	3PEb	47

Abbreviations: AUC, area under the curve; b, bleomycin once per cycle; B, bleomycin once per week; C, cyclophosphamide; E, etoposide; HD-P, high dose cisplatin; I, ifosfamide; J, carboplatin; MGCT, malignant germ cell tumors; NGGCT, non-germinomatous germ cell tumors; O, vincristine; P, cisplatin; POG, Pediatric Oncology Group; V, etoposide. * includes 38 patients from GCT2 and 1 patient from GCT1

Table 2. Patient Characteristics

Variable	All Pts 0 to 30y N (%) N=593	0 to <11y N (%) N=90	11 to <18y N (%) N=109	18 to 30y N (%) N=394
Age mean (SD)	19.4 (8.9)	1.9 (1.9)	14.7 (1.5)	24.8 (3.6)
Testicular	530 (89%)	67 (74%)	82(75%)	381 (96.7%)
Mediastinal tumor	44 (7%)	16 (18%)	22 (20%)	6 (1.5%)
Retroperitoneal	19 (3%)	7(8%)	5(5%)	7 (1.7%)
AFP (ng/mL)				
Mean	6294	29717	6924	857
(range)	(0 -700000)	(8-700000)	(0-96000)	(0-63630)
<1000	449 (76%)	34 (38%)	57 (52%)	358 (91%)
1,000-10,000	68 (11%)	23 (26%)	25 (23%)	20 (5%)
>10,000	62 (10%)	30 (33%)	23 (21%)	9 (2%)
Missing	14 (2%)	3 (3%)	4 (4%)	7 (2%)
βHCG (IU/L)				
Mean	12358	5	24289	11592
(range)	(0-1057700)	(0-62)	(1-990000)	(0-1057700)
<5,000	435 (73%)	33 (37%)	44 (40%)	358 (91%)
5,000 – 50,000	30 (5%)	0 (0%)	12 (11%)	18 (5%)
>50,000	14 (2%)	0 (0%)	3 (3%)	11 (3%)
Missing	114 (19%)	57 (63%)	50 (46%)	7 (2%)
LDH (U/L)				
Mean	587	701	934	500
(range)	(77-5540)	(149-3631)	(77-5540)	(93-5186)
<930	318 (54%)	22 (24%)	40 (37%)	256 (65%)
930-6200	47 (8%)	7 (8%)	19 (17%)	21 (5%)
>6200	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	228 (38%)	61 (68%)	50 (46%)	117 (30%)
Non-pulmonary visceral metastases	34 (6%)	9 (10%)	16 (15 %)	9 (2%)
RiskGroup				
Good	267 (45 %)	4 (4%)	14 (13%)	249 (63%)
Intermediate	82 (14%)	21 (23%)	23 (21%)	38 (10%)
Poor	116 (20%)	41 (46%)	51 (47%)	24 (6%)
Missing	128 (21%)	24 (27%)	21 (19%)	83 (21%)

Abbreviations: AFP, a-fetoprotein; B-HCG, beta subunit of human chorionic gonadotropin; LDH, lactate dehydrogenase.

Table 3. Univariate Kaplan-Meier and Multivariable Cox Regression Analysis of Age-Group and Risk-Group.

	Univariate					Multivariate		
All Patients (N=593)								
Variable	**5y EFS (%)**	**Hazard Ratio**	**95% CI**	**P value**		**Hazard Ratio**	**95% CI**	**P value**
Age Group								
0 - <11	90	0.31	0.14-0.65	**0.002**		0.30	0.14 – 0.63	**0.001**
11 - <18	72	Reference				Reference		
18 - <30	88	0.43	0.27-0.68	**0.000**		0.66	0.40 – 1.11	0.114
Risk Group								
Good	89	0.42	0.26-0.67	**0.000**		0.42	0.24 – 0.72	**0.002**
Intermediate	76	0.87	0.48-1.56	0.634		0.88	0.48 – 1.60	0.663
Poor	76	Reference				Reference		
JEb patients excluded* (N=545)								
Age Group								
0 - <11	92	0.21	0.07-0.60	**0.004**		0.21	0.07 – 0.59	**0.003**
11 - <18	69	Reference				Reference		
18 - <30	88	0.38	0.24-0.60	**0.000**		0.62	0.36 – 1.03	0.066
Risk Group								
Good	89	0.36	0.22-0.58	**0.000**		0.39	0.22 – 0.68	**0.001**
Intermediate	75	0.77	0.42-1.42	0.401		0.81	0.44 – 1.50	0.489
Poor	73	Reference				Reference		
Mediastinal primary tumors excluded (N=549)**								
Age Group								
0 - <11	89	0.41	0.18-0.94	**0.035**		0.40	0.108– 0.91	**0.029**
11 - <18	77	Reference				Reference		
18 - <30	87	0.55	0.33-0.93	**0.024**		0.83	0.347– 1.47	0.506
Risk Group								
Good	89	0.43	0.25-0.75	**0.003**		0.40	0.22 – 0.74	**0.003**
Intermediate	76	0.89	0.46-1.72	0.737		0.88	0.45 – 1.71	0.693
Poor	77	Reference				Reference		

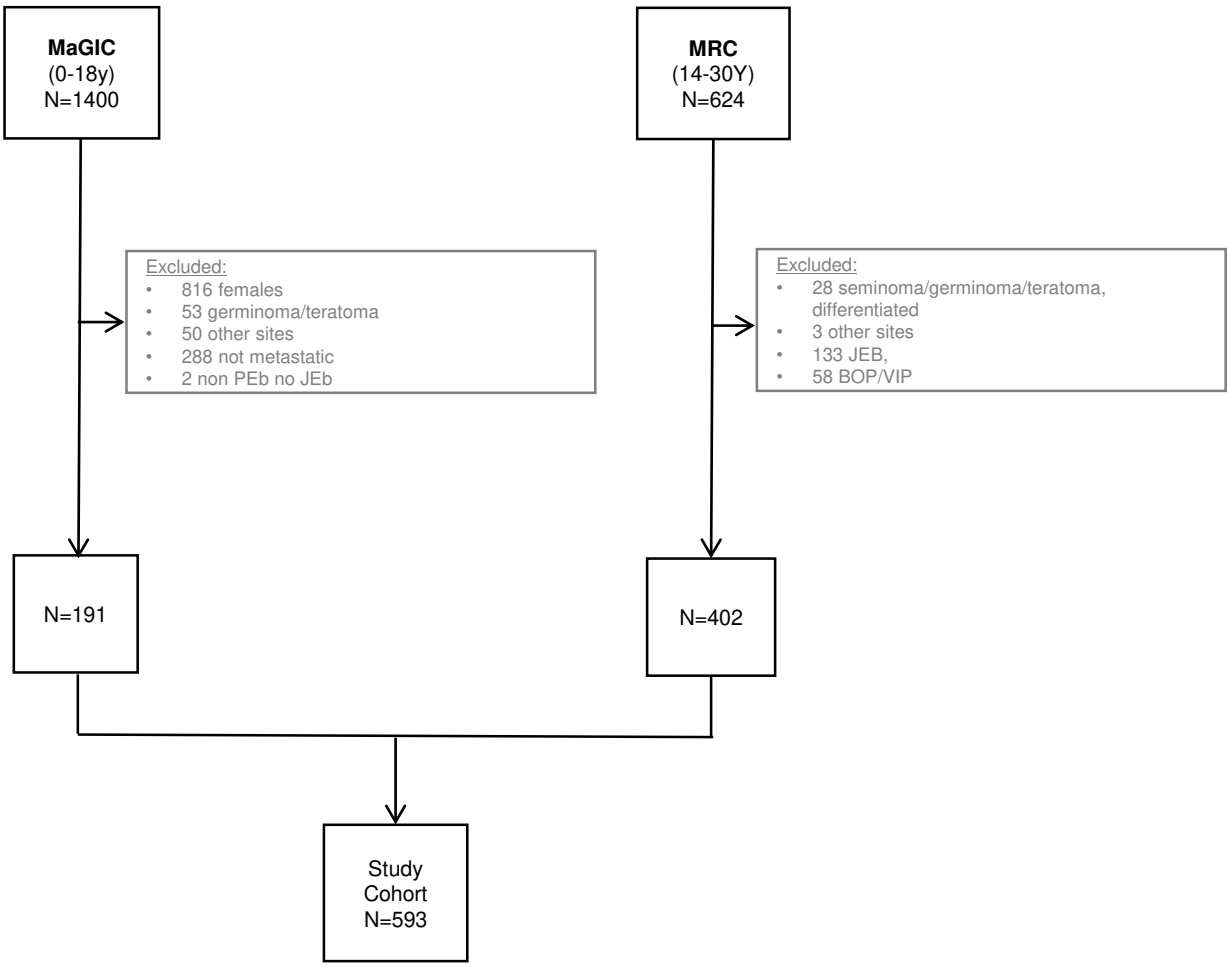
Abbreviations: CI, confidence interval; EFS, event-free survival; JEb, carboplatin/etoposide/reduced bleomycin; N, number; y, years. *48 Patients- received JEb. **44 Patients with mediastinal tumours.

FIGURE LEGENDS

Figure 1. CONSORT diagram describing flow of patients through the study

Figure 2. A) Event-free survival (EFS) and overall survival (OS) for all patients (N=593) B) EFS by risk-group; C) EFS by age-group

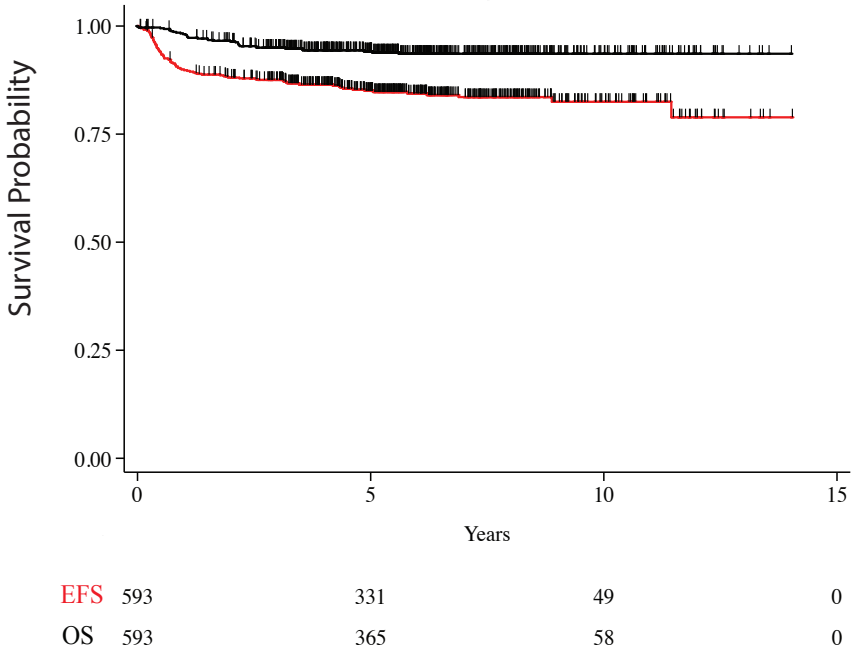
Figure 3. A) EFS for children (age 0 to <11 years) by risk-group; B) EFS for adolescents (age 11 to <18 years) by risk-group; C) EFS for young adults (age 18 to <30 years) by risk-group.



MRC: Medical Research Council

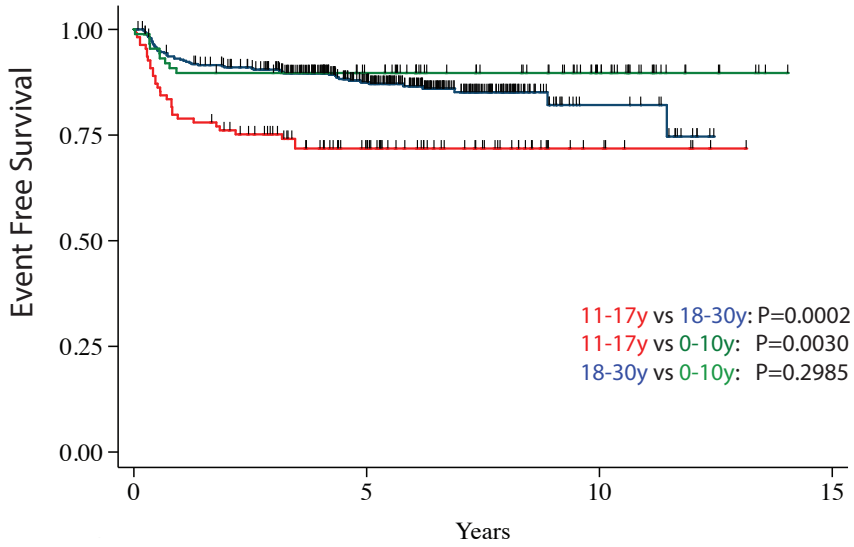
Figure 2.

A.



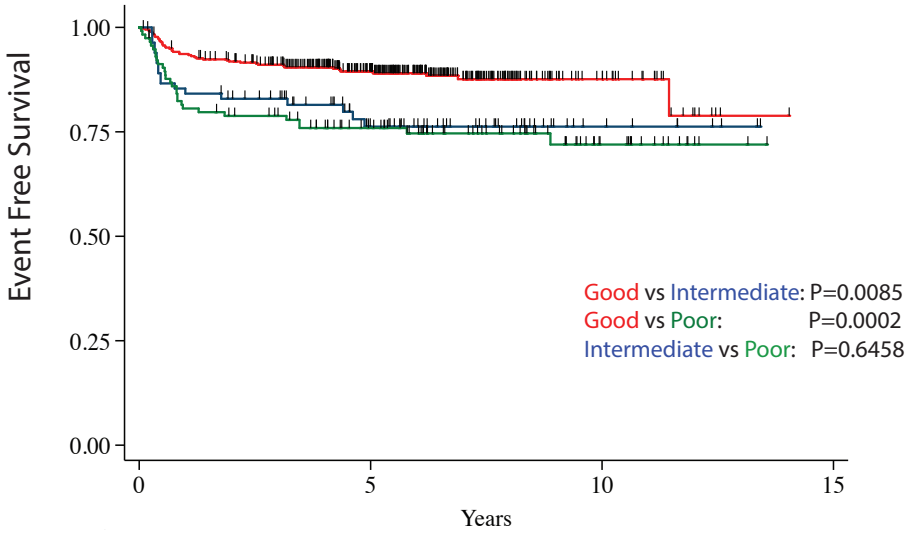
EFS	593	331	49	0
OS	593	365	58	0

B.



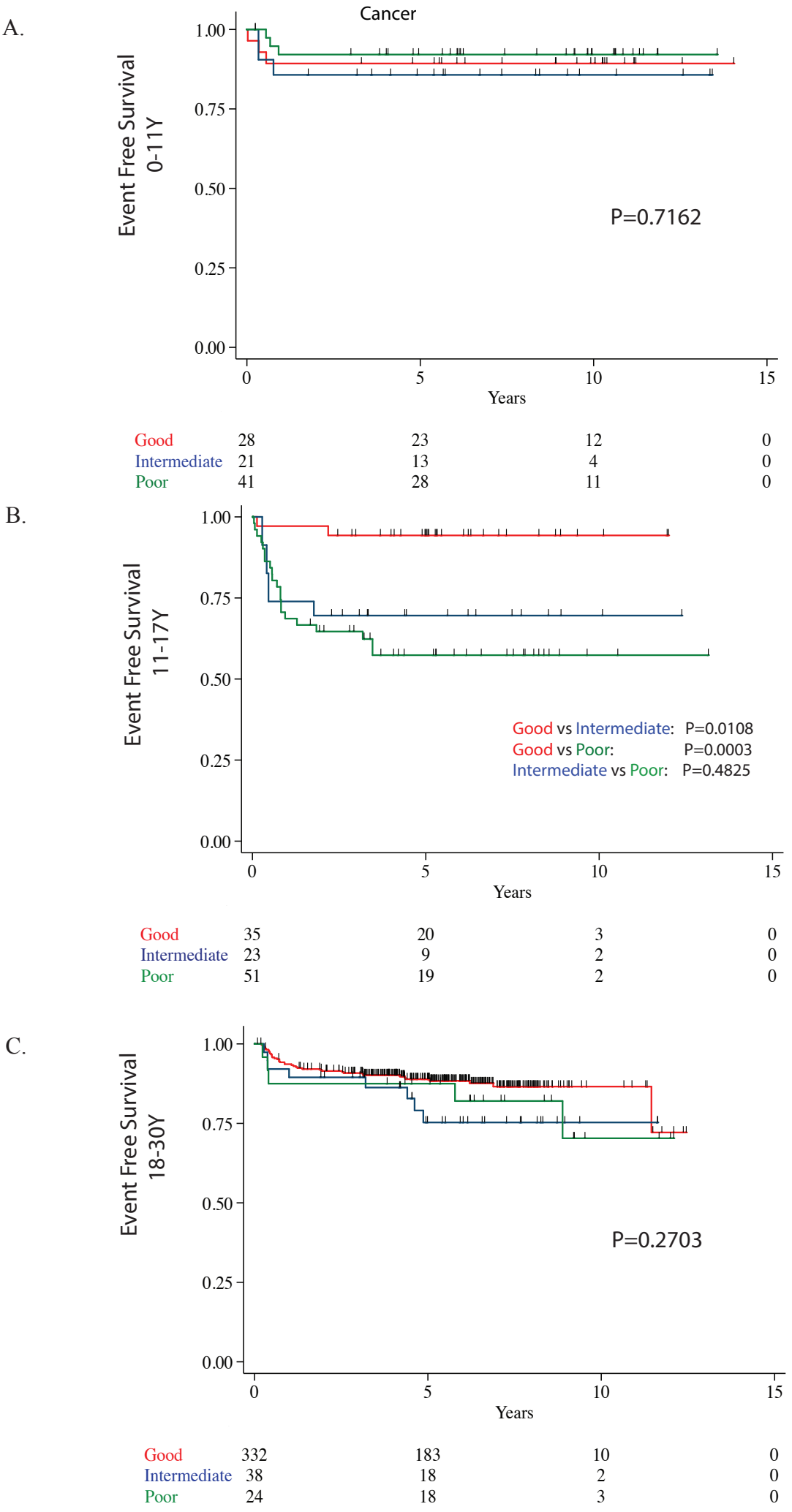
11-17Y	109	48	7	0
18-30Y	394	219	15	0
0-10Y	90	64	27	0

C.



Good	395	226	25	0
Intermediate	82	40	8	0
Poor	116	65	16	0

Figure 3.


A.
Cancer
Event Free Survival
0-11Y
1.00
0.75
0.50
0.25
0.00
P=0.7162
0
5
10
15
Years
Good 28 23 12 0
Intermediate 21 13 4 0
Poor 41 28 11 0
B.
Event Free Survival
11-17Y
1.00
0.75
0.50
0.25
0.00
Good vs Intermediate: P=0.0108
Good vs Poor: P=0.0003
Intermediate vs Poor: P=0.4825
0
5
10
15
Years
Good 35 20 3 0
Intermediate 23 9 2 0
Poor 51 19 2 0
C.
Event Free Survival
18-30Y
1.00
0.75
0.50
0.25
0.00
P=0.2703
0
5
10
15
Years
Good 332 183 10 0
Intermediate 38 18 2 0
Poor 24 18 3 0

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		4HD-PEb	43
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Age mean (SD)	19.4 (8.9)	1.9 (1.9)	14.7 (1.5)	24.8 (3.6)
Testicular	530 (89%)	67 (74%)	82(75%)	381 (96.7%)
Mediastinal tumor	44 (7%)	16 (18%)	22 (20%)	6 (1.5%)
Retroperitoneal	19 (3%)	7(8%)	5(5%)	7 (1.7%)
AFP (ng/mL)				
Mean	6294	29717	6924	857
(range)	(0 -700000)	(8-700000)	(0-96000)	(0-63630)
<1000	449 (76%)	34 (38%)	57 (52%)	358 (91%)
1,000-10,000	68 (11%)	23 (26%)	25 (23%)	20 (5%)
>10,000	62 (10%)	30 (33%)	23 (21%)	9 (2%)
Missing	14 (2%)	3 (3%)	4 (4%)	7 (2%)
βHCG (IU/L)				
Mean	12358	5	24289	11592
(range)	(0-1057700)	(0-62)	(1-990000)	(0-1057700)
<5,000	435 (73%)	33 (37%)	44 (40%)	358 (91%)
5,000 – 50,000	30 (5%)	0 (0%)	12 (11%)	18 (5%)
>50,000	14 (2%)	0 (0%)	3 (3%)	11 (3%)
Missing	114 (19%)	57 (63%)	50 (46%)	7 (2%)
LDH (U/L)				
Mean	587	701	934	500
(range)	(77-5540)	(149-3631)	(77-5540)	(93-5186)
<930	318 (54%)	22 (24%)	40 (37%)	256 (65%)
930-6200	47 (8%)	7 (8%)	19 (17%)	21 (5%)
>6200	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	228 (38%)	61 (68%)	50 (46%)	117 (30%)
Non-pulmonary visceral metastases	34 (6%)	9 (10%)	16 (15 %)	9 (2%)
RiskGroup				
Good	267 (45 %)	4 (4%)	14 (13%)	249 (63%)
Intermediate	82 (14%)	21 (23%)	23 (21%)	38 (10%)
Poor	116 (20%)	41 (46%)	51 (47%)	24 (6%)
Missing	128 (21%)	24 (27%)	21 (19%)	83 (21%)

Abbreviations: AFP, a-fetoprotein; B-HCG, beta subunit of human chorionic gonadotropin; LDH, lactate dehydrogenase.

	Univariate				Multivariate		
All Patient (N=593)							
Variable	**5y EFS (%)**	**Hazard Ratio**	**95% CI**	**P value**	**Hazard Ratio**	**95% CI**	**P value**
Age Group							
0 - <11	90	0.31	0.14-0.65	**0.002**	0.30	0.14 – 0.63	**0.001**
11 - <18	72	Reference			Reference		
18 - <30	88	0.43	0.27-0.68	**0.000**	0.66	0.40 – 1.11	0.114
Risk Group							
Good	89	0.42	0.26-0.67	**0.000**	0.42	0.24 – 0.72	**0.002**
Intermediate	76	0.87	0.48-1.56	0.634	0.88	0.48 – 1.60	0.663
Poor	76	Reference			Reference		
JEb patients excluded* (N=545)							
Age Group							
0 - <11	92	0.21	0.07-0.60	**0.004**	0.21	0.07 – 0.59	**0.003**
11 - <18	69	Reference			Reference		
18 - <30	88	0.38	0.24-0.60	**0.000**	0.62	0.36 – 1.03	0.066
Risk Group							
Good	89	0.36	0.22-0.58	**0.000**	0.39	0.22 – 0.68	**0.001**
Intermediate	75	0.77	0.42-1.42	0.401	0.81	0.44 – 1.50	0.489
Poor	73	Reference			Reference		
Mediastinal primary tumors excluded (N=549)**							
Age Group							
0 - <11	89	0.41	0.18-0.94	**0.035**	0.40	0.108– 0.91	**0.029**
11 - <18	77	Reference			Reference		
18 - <30	87	0.55	0.33-0.93	**0.024**	0.83	0.347– 1.47	0.506
Risk Group							
Good	89	0.43	0.25-0.75	**0.003**	0.40	0.22 – 0.74	**0.003**
Intermediate	76	0.89	0.46-1.72	0.737	0.88	0.45 – 1.71	0.693
Poor	77	Reference			Reference		

Abbreviations: CI, confidence interval; EFS, event-free survival; JEb, carboplatin/etoposide/reduced bleomycin; N, number; y, years. *48 Patients received JEb. **44 Patients with mediastinal tumours.

	Univariate			Multivariate		
All Patient with non-missing IGCCCG (N=465)						
Variable	**Hazard Ratio**	**95% CI**	**P value**	**Hazard Ratio**	**95% CI**	**P value**
Age Group						
0 - <11	0.31	0.14-0.65	**0.000**	0.21	0.09 – 0.52	**0.001**
11 - <18	Reference			Reference		
18 - <30	0.43	0.14-0.65	**0.002**	0.59	0.32 – 1.07	0.081
Risk Group						
Good	0.29	0.17-0.51	**0.000**	0.29	0.15 – 0.58	**<0.001**
Intermediate	0.87	0.48-1.57	0.646	0.89	0.49 – 1.63	0.706
Poor	Reference			Reference		