Original Article

Outcomes of Adolescent Males With Extracranial Metastatic Germ Cell Tumors: A Report From the Malignant Germ Cell Tumor International Consortium

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BACKGROUND: Adolescents with extracranial metastatic germ cell tumors (GCTs) are often treated with regimens developed for children, but their clinical characteristics more closely resemble those of young adult patients. This study was designed to determine event-free survival (EFS) for adolescents with GCTs and compared them with children and young adults. **METHODS:** An individual patient database of 11 GCT trials was assembled: 8 conducted by pediatric cooperative groups and 3 conducted by an adult group. Male patients aged 0 to 30 years with metastatic, nonseminomatous, malignant GCTs of the testis, retroperitoneum, or mediastinum who were treated with platinum-based chemotherapy were included. The age groups were categorized as children (0 to <11 years), adolescents (11 to <18 years), and young adults (18 to ≤30 years). The study compared EFS and adjusted for risk group by using Cox proportional hazards analysis. **RESULTS:** From a total of 2024 individual records, 593 patients met the inclusion criteria: 90 were children, 109 were adolescents, and 394 were young adults. The 5-year EFS rate was lower for adolescents (72%; 95% confidence interval [CI], 62%-79%) than children (90%; 95% CI, 81%-95%; $P = .003$) or young adults (88%; 95% CI, 84%-91%; $P = .0002$). The International Germ Cell Cancer Collaborative Group risk group was associated with EFS in the adolescent age group ($P = .0020$). After adjustments for risk group, the difference in EFS between adolescents and children remained significant (hazard ratio, 0.30; $P = .001$). **CONCLUSIONS:** EFS for adolescent patients with metastatic GCTs was similar to that for young adults but significantly worse than for that children. This finding highlights the importance of coordinating initiatives across clinical trial organizations to improve outcomes for adolescents and young adults. ***Cancer* 2021;127:193-202**. © *2020 American Cancer Society*.

LAY SUMMARY:

- Adolescent males with metastatic germ cell tumors (GCTs) are frequently treated with regimens developed for children.
- In this study, a large data set of male patients with metastatic GCTs across different age groups has been built to understand the outcomes of adolescent patients in comparison with children and young adults.
- The results suggest that adolescent males with metastatic GCTs have worse results than children and are more similar to young adults with GCTs. Therefore, the treatment of adolescents with GCTs should resemble therapeutic approaches for young adults.

KEYWORDS: adolescent males, adolescents and young adults (AYAs), germ cell tumors, outcomes, testicular germ cell tumor (GCT).

INTRODUCTION

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 the specific focus of neither the pediatric nor adult world of oncology.[7] This results in their care being underresearched, trials being underaccrued, and optimal management being 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] However, specific attention to the needs of AYA patients

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with cancer has yielded progress. In acute lymphoblastic leukemia, management has evolved on the basis of 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 been used to hypothesize tractable reasons for these differences related to pharmacologic or clinical factors.[14] We believe that similar advances can be made for AYA patients with germ cell tumors (GCTs) through collaborative, investigative efforts.

Extracranial GCTs account for approximately 3% to 4% of cancers in children, 14% of cancers in adolescents aged 15 to 19 years, and 18% of cancers in young adults aged 20 to 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 2 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 to 18 years in North America or under the age of 16 years in the United Kingdom 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 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 underrepresented in clinical trials, frequently being 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 like those of children or 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 to guide such discussions. This limitation stems from the heterogeneous manifestations of GCTs across age groups, which preclude 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 of 20 children, 39 adolescents, and 354 adult patients with testicular GCTs treated at their institution. The event-free survival (EFS) was worse for adolescents in comparison with children and young adults, even after adjustments for stage, International Germ Cell Cancer Collaborative Group (IGCCCG) risk group,[17] and histology. However, this was a single-center analysis with a small sample size.

The Malignant Germ Cell International Consortium (MaGIC) assembled a large pooled data set of patients with extracranial GCTs treated across multiple clinical trials and collaborative groups,[20,22] and this allowed for a secondary analysis of prospective trial data. For the current study, we derived a relatively homogeneous subgroup of male patients with GCTs across 3 age groups (children, adolescents, and young adults) in order to compare EFS. A secondary objective was to determine whether the IGCCCG risk stratification system used in adult studies[17] would be predictive of outcomes for pediatric or adolescent patients with GCTs.

MATERIALS AND METHODS

At the time of this analysis, the MaGIC database included all patients enrolled in 5 trials conducted by the Children's Oncology Group (COG; INT-1016,[23] INT-0097,[18] AGCT0132,[24] AGCT01P1,[25] and P9749[26]), in 3 trials from the Children's Cancer and Leukemia Group (GCI,[27] GCII,[28] and GCIII[29]), and in 3 trials from the Medical Research Council (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 data set of 2024 patients, we selected males aged 0 to 30 years with newly diagnosed, metastatic, nonseminomatous, malignant GCTs 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 3 age groups.

To maintain uniform treatment intensity, we included only patients treated with standard regimens with outcomes known to be similar to one another. The regimens included the adult standard of care of weekly bleomycin and once per cycle etoposide and cisplatin (BEP); the pediatric standard of care of cisplatin,

etoposide, and reduced bleomycin used once per cycle (PEb); high-dose cisplatin, etoposide, and reduced bleomycin used once per cycle (HD-PEb); cyclophosphamide, cisplatin, etoposide, and reduced bleomycin used once per cycle (C-PEb); and pediatric carboplatin, etoposide, and reduced bleomycin used once per cycle (JEb). We included pediatric JEb because it has outcomes similar to those of pediatric PEb.[29,33] However, adult patients treated with carboplatin regimens were excluded because these regimens, which notably use lower doses of carboplatin than those used in pediatric regimens, have been shown to be inferior to BEP in randomized trials.[30,34]

We categorized the age groups as children (0 to <11 years old), adolescents (11 to <18 years old), and young adults (18 to <30 years old). The selection of 11 years as the cutoff between children and adolescents was based on our earlier analysis, which showed this age to be the most significant and discriminant prognostic cutoff among pediatric GCTs.[22] We selected 18 years as the defining age between adolescents and young adults because it is the most frequent age of transition from pediatric care to adult care in many centers and clinical trials. We defined *metastatic* as a lymph node metastasis or distant sites (classified in the Medical Research Council trials as stage II or III, by the Children's Cancer and Leukemia Group as stages II to IV, and by the COG as stage III or IV).

Next, we retrospectively applied the IGCCCG risk stratification and assigned each patient to either the good-, intermediate-, or poor-risk group.[17] The IGCCCG criteria use the histologic subtype, primary site, sites of metastases, and prechemotherapy serum levels of α-fetoprotein, β subunit of human chorionic gonadotropin, and lactate dehydrogenase (LDH) to determine risk group and thus provide a composite variable of the most significant (adult) prognostic factors. Notably, tumor marker levels in pediatric trials measured at diagnosis may have been presurgical levels rather than postsurgical levels as used by the IGCCCG. Furthermore, because some of the trial protocols of our pooled data set were conducted before the IGCCCG classification and because IGCCCG risk stratification has not traditionally been applied to pediatric patients with GCTs, we expected and encountered a high rate of missing values for 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 (ie, patients were assigned to the good-risk group by default, and positive evidence was required to elevate a patient to the intermediate- or poor-risk group) because 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, which was defined as the time interval from the date of diagnosis to relapse or progression, second malignancy, death, or the date last seen (whichever occurred first). The 2 potential predictor variables of main interest were age group and IGCCCG risk group. We constructed survival curves with 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 adjustments were made for IGCCCG risk group. Lastly, we conducted sensitivity analyses to determine whether the results remained the same if we excluded all patients 1) who received carboplatin (given historical results of carboplatin studies in adult patients) and 2) who had mediastinal primary disease sites (given that mediastinal primary nonseminomatous tumors are assigned to the IGCCCG poor-risk group, regardless of any other risk factors). A P value $\leq$.050 was considered to be evidence of a significant difference. All analyses were conducted by the authors with Stata (version 13.1; StataCorp, College Station, Texas).

RESULTS

A Consolidated Standards of Reporting Trials diagram (Fig. 1) shows the flow of patients in this study. From a total of 2024 nonduplicated records in the pooled database, 593 patients met the inclusion criteria: 191 were from pediatric studies, and 402 were from adult studies. Table 1 shows the characteristics of the source studies, including the patient populations, the regimens used, and the number of patients from each trial who met the eligibility criteria for this study.

The characteristics of all included patients are shown in Table 2. The mean age was 19.4 years (SD, ±8.9 years). Five hundred thirty patients presented with testicular tumors (89.4%), 44 (7.4%) presented with mediastinal tumors, and 19 (3.2%) presented with retroperitoneal primary tumors. There were 90 children, 109 adolescents, and 394 young adults. Among

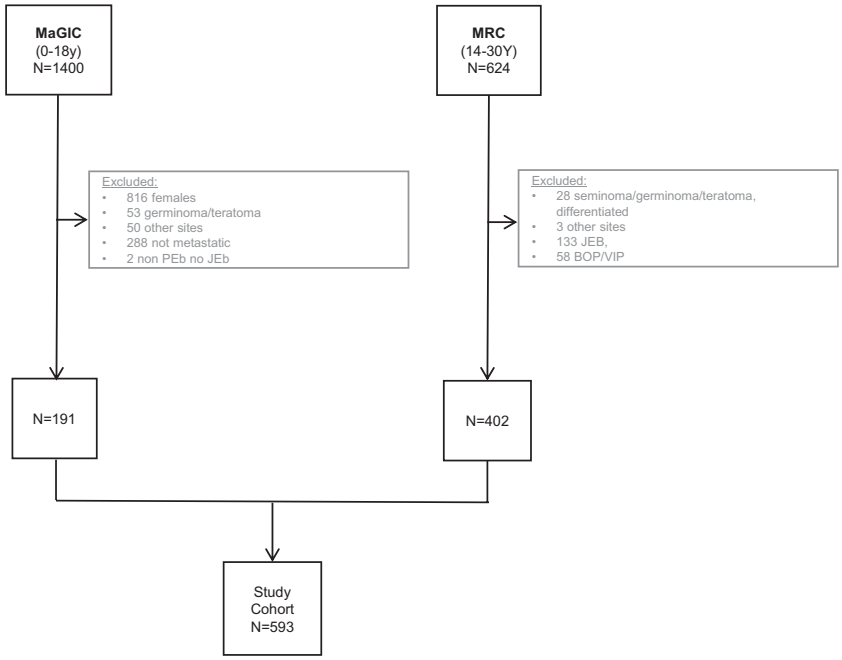

Figure 1. Consolidated Standards of Reporting Trials diagram describing the flow of patients through the study. BOP indicates bleomycin once per week, vincristine, and cisplatin; JEb, carboplatin, etoposide, and bleomycin once per cycle; JEB, carboplatin, etoposide, and bleomycin once per week; MaGIC, Malignant Germ Cell International Consortium; MRC, Medical Research Council; PEb, cisplatin, etoposide, and bleomycin once per cycle; VIP, etoposide, ifosfamide, and cisplatin.

TABLE 1. Characteristics of the Included Clinical Trials

Study	Patients in Source Studies	Regimen	No. in This Study
TE09	598 adults with good-prognosis testicular NGGCTs (273 under 30 y)	4BEP	139
		4JEB (carboplatin at AUC 5)	0
TE13	380 adults with poor-prognosis NGGCTs (121 under 30 y)	BEP/EP	58
		BOP/VIP-B	0
TE20	812 adults with good-prognosis GCTs (230 NGGCTs under 30 y)	4BEP or 3BEP	205
GCII	137 children with MGCTs	JEb (carboplatin at 600 mg/m^2)	39[a]
GCIII	138 children with MGCTs	JEb (carboplatin at 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 MGCTs	4HD-PEb	4
AGCT01P1	19 children with high-risk NGGCTs	4C-PEb	5
AGCT0132	218 children with intermediate-risk NGGCTs	3PEb	47

Abbreviations: AUC, area under the curve; BEP, bleomycin once per week, etoposide, and cisplatin; BOP, bleomycin once per week, vincristine, and cisplatin; C-PEb, cyclophosphamide, cisplatin, etoposide, and bleomycin once per cycle; EP, etoposide and cisplatin; GCT, germ cell tumor; HD-PEb, high-dose cisplatin, etoposide, and bleomycin once per cycle; JEb, carboplatin, etoposide, and bleomycin once per cycle; JEB, carboplatin, etoposide, and bleomycin once per week; MGCT, malignant germ cell tumor; NGGCT, nongerminomatous germ cell tumor; PEb, cisplatin, etoposide, and bleomycin once per cycle; POG, Pediatric Oncology Group; VIP-B, etoposide, ifosfamide, cisplatin, and bleomycin once per week; GCII: germ cell Study II; CGIII: Germ Cell study III.
[a]Includes 38 patients from GCTII and 1 patient from GCTI.

the 90 children, 84 (93%) were younger than 3 years. Among the 109 adolescents, only 4 patients were between the ages of 11 and 13 years. Tumor marker elevation was significantly different among the age groups: adolescents had the highest mean serum level of β subunit of human chorionic gonadotropin (24,289 IU/L) and highest mean LDH level (934 U/L), whereas the pediatric group demonstrated the highest mean α-fetoprotein elevation (29,717 ng/mL). Although there was a significant difference in the proportion of patients with poor-risk tumors in the pediatric and adolescent population (46% and 47%, respectively) in comparison with the adult population (6%), this likely reflected the differences in the inclusion criteria of the included

TABLE 2. Patient Characteristics

Variable	All Patients, 0 to 30 y (n = 593)	0 to <11 y (n = 90)	11 to <18 y (n = 109)	18 to 30 y (n = 394)
Age, mean (SD), y	19.4 (8.9)	1.9 (1.9)	14.7 (1.5)	24.8 (3.6)
Testicular tumor, No. (%)	530 (89)	67 (74)	82 (75)	381 (96.7)
Mediastinal tumor, No. (%)	44 (7)	16 (18)	22 (20)	6 (1.5)
Retroperitoneal tumor, No. (%)	19 (3)	7 (8)	5 (5)	7 (1.7)
AFP, mean (range), ng/mL	6294 (0-700,000)	29,717 (8-700,000)	6924 (0-96,000)	857 (0-63,630)
AFP, No. (%)				
<1000 ng/mL	449 (76)	34 (38)	57 (52)	358 (91)
1000-10,000 ng/mL	68 (11)	23 (26)	25 (23)	20 (5)
>10,000 ng/mL	62 (10)	30 (33)	23 (21)	9 (2)
Missing	14 (2)	3 (3)	4 (4)	7 (2)
βHCG, mean (range), IU/L	12,358 (0-1,057,700)	5 (0-62)	24,289 (1-990,000)	11,592 (0-1,057,700)
βHCG, No. (%)				
<5000 IU/L	435 (73)	33 (37)	44 (40)	358 (91)
5000-50,000 IU/L	30 (5)	0 (0)	12 (11)	18 (5)
>50,000 IU/L	14 (2)	0 (0)	3 (3)	11 (3)
Missing	114 (19)	57 (63)	50 (46)	7 (2)
LDH, mean (range), U/L	587 (77-5540)	701 (149-3631)	934 (77-5540)	500 (93-5186)
LDH, No. (%)				
<930 U/L	318 (54)	22 (24)	40 (37)	256 (65)
930-6200 U/L	47 (8)	7 (8)	19 (17)	21 (5)
>6200 U/L	0 (0)	0 (0)	0 (0)	0 (0)
Missing	228 (38)	61 (68)	50 (46)	117 (30)
Nonpulmonary visceral metastases, No. (%)	34 (6)	9 (10)	16 (15)	9 (2)
Risk group, No. (%)				
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, α-fetoprotein; βHCG, β subunit of human chorionic gonadotropin; LDH, lactate dehydrogenase.

studies rather than differences in natural distribution. In the adolescent group, 95 of 109 patients (87%) were treated with pediatric protocols; 85 of these patients received cisplatin-based regimens (PEb), and 10 received carboplatin-based regimens (JEb). Fourteen of the 109 adolescents (13%) were treated with adult-type regimens (BEP).

Among all 593 patients, there were 91 events and 35 deaths. The overall 5-year EFS rate was 85% (95% confidence interval [CI], 82%-88%), and the overall 5-year overall survival rate was 94% (95%; 95% CI, 92%-96%; Fig. 2A). The median follow-up time for patients who survived without an event was 5.9 years (range, 0.1-14.0 years). Age group was strongly associated with EFS ($P = .0001$; Fig. 2B). The 5-year EFS rate was lower for adolescents (72%; 95% CI, 62%-79%) than children (90%; 95% CI, 81%-95%; $P = .003$) and young adults (88%; 95% CI, 84%-91%; $P = .0002$). Risk group was also strongly associated with EFS ($P < .0001$; Fig. 2C). The 5-year EFS rate was higher for the good-risk group (89%) than the intermediate-risk group (76%; $P = .0085$) and the poor-risk group (76%; $P < .0002$).

Figure 3 shows the EFS curves for each age group stratified by risk group. Risk group was not significantly associated with EFS among children ($P = .7162$) or young adults in this cohort ($P = .2703$) but was associated with EFS among adolescents ($P = .0020$). Among the 51 adolescents with poor-risk disease, the 5-year EFS rate was only 57% (95% CI, 42%-70%), the lowest value observed across all subgroup analyses. In an exploratory analysis, the poor outcome of these 51 patients was not driven by patients being treated on adult regimens (2 patients, no events) or JEb regimens (4 patients, no events). Adolescent patients treated with the pediatric regimen PEb had a 5-year EFS rate of 64% (95% CI, 53%-74%), whereas a 5-year EFS rate of 92.9% (95% CI, 59%-98%) was found for adolescent patients treated with the BEP regimen used in adult patients (log-rank $P = .0517$).

A Cox regression model including both age group and risk group (Table 3) demonstrated that, after adjustments for risk group, the effect of age group remained statistically significant ($P = .0025$ [likelihood ratio test for the significance of age group adjusted for risk group]). The difference in EFS between adolescents and children remained significant (hazard ratio [HR], 0.30; $P = .001$), but the difference between adolescents and young adults was no longer significant (HR, 0.66;

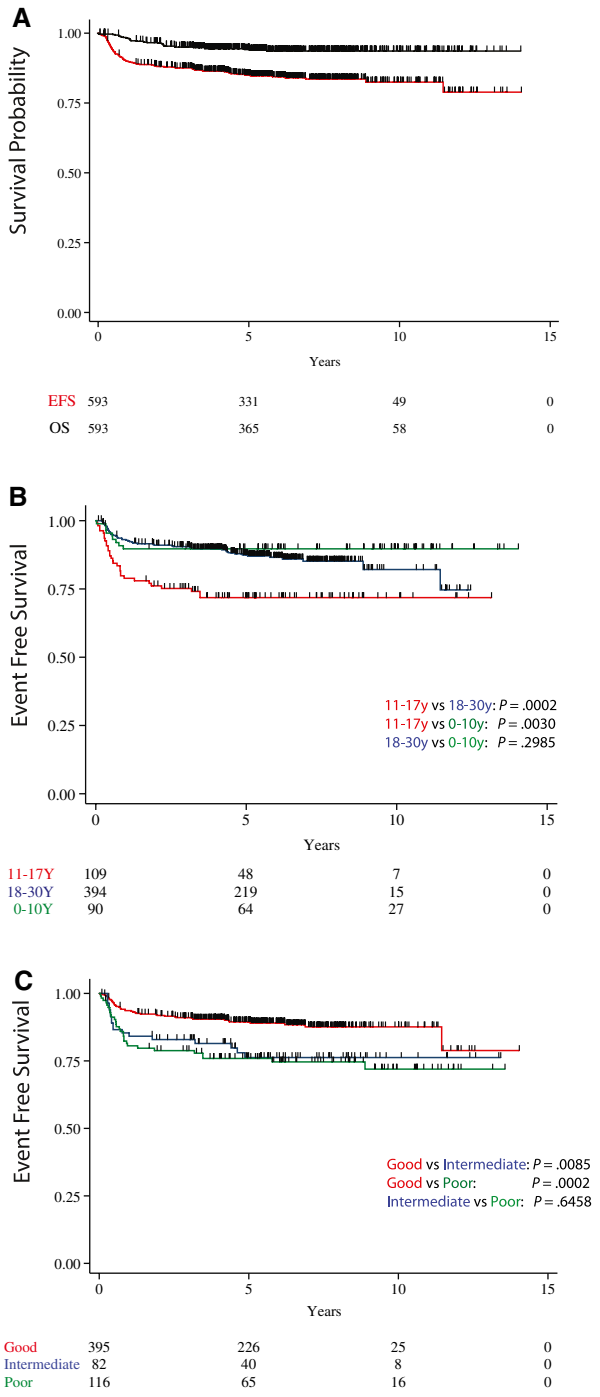

Figure 2. (A) EFS and OS for all patients (n = 593), (B) EFS by age group, and (C) EFS by risk group. EFS indicates event-free survival; OS, overall survival.

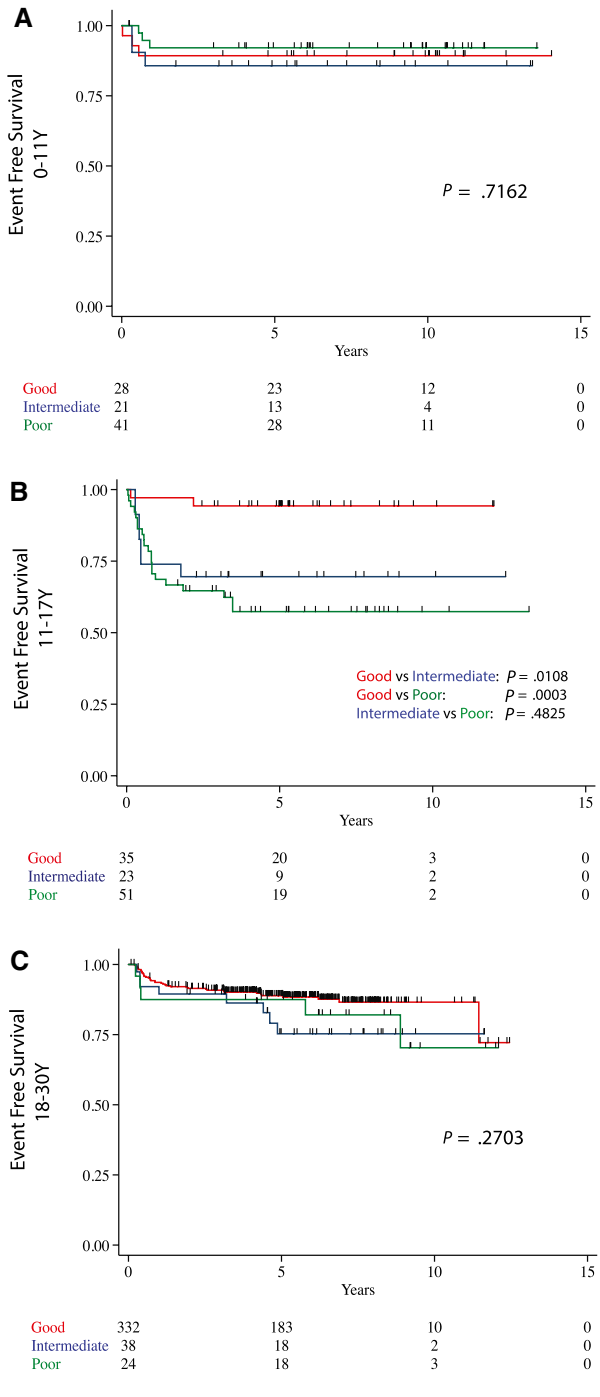

Figure 3. (A) EFS for children (0 to <11 years old) by risk group, (B) EFS for adolescents (11 to <18 years old) by risk group, and (C) EFS for young adults (18 to <30 years old) by risk group. EFS indicates event-free survival.

$P = .114$). The results did not change if children treated on the carboplatin-based JEb regimen were excluded 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 IGCCCG risk stratification (78% of the total sample size), the direction of results remained the same. In the proportional hazards analysis

TABLE 3. Univariate Kaplan-Meier and Multivariable Cox Regression Analyses of Age and Risk Groups

		Univariate			Multivariate		
Variable	5-y EFS, %	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
All patients (n = 593)							
Age group							
0 to <11 y	90	0.31	0.14-0.65	**.002**	0.30	0.14-0.63	**.001**
11 to <18 y	72	Reference			Reference		
18 to <30 y	88	0.43	0.27-0.68	**.000**	0.66	0.40-1.11	.114
Risk group							
Good	89	0.42	0.26-0.67	**.000**	0.42	0.24-0.72	**.002**
Intermediate	76	0.87	0.48-1.56	.634	0.88	0.48-1.60	.663
Poor	76	Reference			Reference		
JEb patients excluded (n = 545)[a]							
Age group							
0 to <11 y	92	0.21	0.07-0.60	**.004**	0.21	0.07-0.59	**.003**
11 to <18 y	69	Reference			Reference		
18 to <30 y	88	0.38	0.24-0.60	**.000**	0.62	0.36-1.03	.066
Risk group							
Good	89	0.36	0.22-0.58	**.000**	0.39	0.22-0.68	**.001**
Intermediate	75	0.77	0.42-1.42	.401	0.81	0.44-1.50	.489
Poor	73	Reference			Reference		
Mediastinal primary tumors excluded (n = 549)[b]							
Age group							
0 to <11 y	89	0.41	0.18-0.94	**.035**	0.40	0.108-0.91	**.029**
11 to <18 y	77	Reference			Reference		
18 to <30 y	87	0.55	0.33-0.93	**.024**	0.83	0.347-1.47	.506
Risk group							
Good	89	0.43	0.25-0.75	**.003**	0.40	0.22-0.74	**.003**
Intermediate	76	0.89	0.46-1.72	.737	0.88	0.45-1.71	.693
Poor	77	Reference			Reference		

Abbreviations: CI, confidence interval; EFS, event-free survival; JEb, carboplatin, etoposide, and reduced bleomycin.
Bold values indicate significance.
[a]Forty-eight patients received JEb.
[b]Forty-four patients had mediastinal tumors.

of these patients (Supporting Table 1), the difference in EFS between adolescents and children remained significant (HR, 0.21; $P = .001$), and the difference between adolescents and adults was not significant (HR, 0.59; $P = .081$).

DISCUSSION

Our study describes the outcomes of adolescent males with extracranial GCTs in comparison with children and young adults within a large pooled data set of collaborative, phase 3 clinical trials. We showed that adolescent males had the lowest 5-year EFS (72%) in comparison with both children (90%) and young adults (88%) in an unadjusted analysis. After adjustments 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 outcomes among children or adolescents. The risk groups were associated with outcomes among adolescents but not among children. This showed that the IGCCCG system can be usefully applied to adolescents. Children had excellent outcomes, regardless of risk group, and this further validated the results of the MaGIC risk stratification,[22] in which all patients younger than 11 years belong to the same risk group.

Our findings also pointed to the underrepresentation of adolescents in clinical trials. There were only 109 adolescent males with metastatic GCTs in this entire data set, which was pooled from every pediatric clinical trial across North America and the United Kingdom for the last 30 years. Because extracranial metastatic GCTs are the most common cancer among adolescent males and 430 new testicular GCTs are diagnosed in boys aged 15 to 19 years in the United States each year,[15] this remarkably small number of patients provides a stark example of the 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 nongerminomatous/nonseminomatous 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 analyze the effects 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 for postchemotherapy 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 for the variables needed to assign the IGCCCG risk group. However, the results remained unchanged in a sensitivity analysis in which patients with missing data were excluded, and this suggested that this factor did not affect conclusions. Lastly, because tumor marker levels in pediatric trials measured at diagnosis may have been presurgical levels rather than postsurgical levels, it is possible that some pediatric patients may have been miscategorized for their IGCCCG risk group, and this would have biased our risk group analyses. However, the direction of this bias would not be expected to weaken the results.

Adolescents with metastatic GCTs are biologically and clinically more similar to young adults than children,[19] and this study demonstrates that they are also more alike in outcomes. Although this study could not assess the superiority of any particular treatment approach or chemotherapy regimen, we believe that 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 adult-like approaches; thus prescribing the dose intensity of weekly bleomycin[40-44] and following the predictive stratification of the IGCCCG[17,32,45] and surgical guidelines for procedures such as retroperitoneal lymph node dissection of postchemotherapy 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,[22] have 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 multigroup trial AGCT1531 (NCT03067181) includes all standard-risk patients between the ages of 11 and 25 years as a single study group and prescribes these standards to all. Furthermore, the COG has petitioned and joined 2 clinical trials led by adult testicular cancer cooperative groups: the Australian and New Zealand Urogenital and Prostate Cancer Trials Group 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 3 trials cover the entire spectrum of adolescent GCTs. The availability of the data is due to the work of MaGIC, which has galvanized a remarkable collaboration of multiple cooperative groups across the silos of age groups and international borders.[46] Through MAGIC and other similar efforts, we hope to provide a path that will narrow the gap and improve outcomes for AYA patients with GCTs.

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CONFLICT OF INTEREST DISCLOSURES

Carlos Rodriguez-Galindo reports belonging to an advisory board for NovImmune. A. Lindsay Frazier reports belonging to a clinical advisory board for Decibel Therapeutics. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Furqan Shaikh: Conceptualization, methodology, data curation, formal analysis, writing–original draft, writing–review and editing, meaningful contributions, approval of the final version of the manuscript, and accountability for all aspects of the work. **Daniel Stark:** Conceptualization, methodology, data acquisition, writing–review and editing, meaningful contributions, approval of the final version of the manuscript, and accountability for all aspects of the work. **Adriana Fonseca:** Data curation, formal analysis, writing–original draft, writing–review and editing, meaningful contributions, approval of the final version of the manuscript, and accountability for all aspects of the work. **Ha Dang:** Data curation, methodology, formal analysis, writing–review and editing, meaningful contributions, approval of the final version of the manuscript, and accountability for all aspects of the work. **Caihong Xia:** Data curation, methodology, formal analysis, writing–review and editing, meaningful contributions, approval of the final version of the manuscript, and accountability for all aspects of the work. **Mark Krailo:** Conceptualization, methodology, data curation, formal analysis, writing–review and editing, meaningful contributions, approval of the final version of the manuscript, and accountability for all aspects of the work. **Farzana Pashankar:** Conceptualization, methodology, data acquisition, writing–review and editing, meaningful contributions, approval of the final version of the manuscript, and accountability for all aspects of the work. **Carlos Rodriguez-Galindo:** Conceptualization, funding acquisition, methodology, writing–review and editing, meaningful contributions, approval of the final version of the manuscript, and accountability for all aspects of the work. **Thomas Olson:** Conceptualization, methodology, data acquisition, writing–review and editing, meaningful contributions,

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