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Application of the Adult International Germ Cell Classification System to Pediatric Malignant Non-Seminomatous Germ Cell Tumors: A Report From the Children's Oncology Group

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Abstract

Background—The purpose of this analysis is to explore whether the International Germ Cell Classification Consensus (IGCCC) tumor marker criteria, developed for adult males with metastatic malignant germ cell tumors (MGCT), are prognostic among pediatric patients and whether tumor marker data may be relevant in pediatric risk stratification.

Procedure—The IGCCC was applied to 436 pediatric germ cell patients treated on Pediatric Intergroup Studies from 1990 to 1996. Multivariable Cox proportional hazards model identified prognostic variables; survival rates among IGCCC risk groups were compared using the log-rank test. Concordance and relative performance of IGCCC versus COG risk stratification was evaluated.

Results—Applying the IGCCC, 21% of pediatric patients were good risk (GR), 35% intermediate risk (IR), and 44% poor risk (PR). Only modest concordance between IGCCC and COG stratification systems was noted (49%). Nonetheless, the IGCCC identified a group of PR patients who had significantly worse event-free survival (EFS) versus GR/IR patients (6-year EFS 80% vs. 91%), which was similar to the difference observed using the COG system (6-year EFS 77% vs. 90%). The IGCCC performed well within subgroups for which the IGCCC is not intended (prepubertal, female, and non-metastatic patients).

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Conclusions—Applying the IGCCC system to pediatric patients produces a different stratification than does the application of the COG system, although both are prognostic. Development of a de novo pediatric prognostic classification is warranted.

Keywords

germ cell tumors; International Germ Cell Classification; pediatric germ cell tumors; risk stratification; tumor markers

INTRODUCTION

The development of an international classification system for adult males with metastatic malignant germ cell tumors (MGCT) was an important advance for several reasons [1]. Identification of risk groups allowed for tailoring of treatment as well as comparison of results across populations of similarly defined individuals, and a common classification system has formed the basis for collaboration for international clinical trials. The International Germ Cell Classification Consensus (IGCCC) divides patients into three groups: good, intermediate, and poor prognosis groups based on the presence of primary mediastinal tumor, non-pulmonary metastases, and level of tumors markers [1] (Appendix I, Table I).

Pediatric germ cell tumors are much less common than their adult counterparts; only 350 pediatric germ cell tumors are diagnosed each year, compared to 6,000 adult males with metastatic germ cell tumors. In the United States, pediatric germ cell tumors have typically been divided into risk groups according to stage; grade III and IV tumors, regardless of site, have been considered as higher risk. Analysis of the last intergroup pediatric study, however, showed that site was an important discriminator in outcome [2,3]. Stage III and IV tumors that originated in the gonad had excellent overall survival (OS) (ovarian $97.3 \pm 2.6\%$; testicular $93.3 \pm 4.4\%$) whereas extragonadal (EG) stage III–IV tumors had a significantly worse OS (EG stage III $81\% \pm 8\%$; EG stage IV $82\% \pm 7\%$) [2,3]. Therefore, a new classification system was devised for pediatric germ cell tumors. Low risk was defined as stage I gonadal tumors, intermediate risk (IR) as stage I/II EG and stage II–IV gonadal tumors, and high risk as stage III/IV EG tumors. The purpose of this analysis is to see if the additional factors used in the adult classification system, specifically elevation of tumor markers and/or presence of a mediastinal primary, might be useful in the stratification of pediatric patients. This analysis will (1) retrospectively compare the performance and concordance of the IGCCC system to the newly revised COG classification of pediatric germ cell tumors; and (2) explore whether the risk stratification of the IGCCC, when applied to pediatrics, varies by gender, stage (non-metastatic vs. metastatic), and age.

Several important caveats about this analysis warrant mention. Genetic and histologic differences do exist between adult and pediatric tumors. Among children <4 years with endodermal sinus tumors, gains of 1q and chromosome 3 are the most common abnormalities, whereas malignant ovarian tumors from older girls have a broader spectrum of abnormalities: loss of 1p/gain of 1q, +3, +8, +14, and +21. Adolescent boys, however, have chromosomal abnormalities that most resemble adult testicular GCT, most notably isochromosome 12p. Type of germ cell tumor histology differs between adult and pediatric patients. Yolk sac or endodermal sinus tumor is the most common histology among pediatric patients, often presenting as the sole histology, especially in prepubertal germ cell patients, whereas among adults, endodermal sinus tumor is much less common and usually is present in the setting of other malignant histologies. A final caveat is that the IGCCC was developed for men with metastatic MGCT and not for women or children with germ cell tumors. Nonetheless, investigators from other countries have noted that elevation of tumor markers

at diagnosis are significant predictors of outcome among pediatric patients of both genders, in all sites and stages making examination of the US data warranted [4,5].

METHODS

Patient Population

The population consisted of all patients ≥ 21 years of age from intergroup studies POG 9048/CCG 8891 and POG 9049/CCG 8882 with MGCT resulting in an analytic population of 436 patients [2,3]. The specific aims and therapies used in these two studies are detailed in Appendix II. The pediatric patients were retrospectively stratified into the three IGCCC risk groups. Because location of metastasis was not required as part of the data collection for the intergroup studies, no pediatric patient could qualify as “high risk” on the basis of extra-pulmonary metastases. As a result, the only IGCCC criteria applied were the level of tumor markers AFP, HCG, and LDH at diagnosis and/or mediastinal primary site.

Several secondary analyses were conducted. First, because the IGCCC was developed specifically for male germ cell tumors, the population was stratified by gender to check performance of the IGCCC within females. Secondly, the IGCCC was developed for testicular patients with metastatic disease. In a secondary analysis, stage I/II patients were excluded and the analytic cohort restricted to patients with stage III/IV disease. Third, one of the criterion of the IGCCC is the level of AFP. The fetal liver synthesizes AFP, with synthesis continuing normally for several months after birth. Therefore, an AFP of up to 10,000 ng/ml can be normal in infants up to 6 months of age [6,7]. For this reason, a secondary analysis was performed, excluding patients <6 months of age.

Statistical Considerations

Survival rates were calculated using the method of Kaplan and Meier [8] with standard errors according to Peto and Peto [9]. Comparisons of the survival curves were performed with a two-sided log-rank test. The time to event for EFS was calculated as the time from study enrollment to first occurrence of relapse, progressive disease, secondary malignancy or death, or the time to last contact with the patient, if no event occurred. The time to event for OS was the time from study enrollment until the time of death or the time of last contact if the patient was alive. Prognostic significance of the risk group factors was analyzed using a Cox proportional hazards regression model constructed with a stepwise backwards model-building technique [10]. For univariate and multivariable analyses, factors were dichotomized as follows: AFP ($\leq 10,000$ ng/ml vs. $>10,000$ ng/ml), HCG ($\leq 5,000$ IU/L vs. $>5,000$ IU/L), LDH ($\leq 1.5 \times N$ vs. $>1.5 \times N$). In search of an age cut-off that was optimal for maximizing the difference in the outcome between the two age groups in terms of EFS and OS, log-rank tests for age cut-offs for each year from 10 to 20 years of age were performed. The age cut-off that gave the lowest *P*-value for the difference in outcome between two age groups was selected. Kendall's tau-*b* was used to test for association of the ordinal risk groups of the IGCCC and the COG systems. A sensitivity analysis was performed to determine the implications of potentially under-classifying patients who had missing data for one or more factors. The EFS and OS rates were calculated by risk group for: (a) all patients and (b) excluding patients who were missing data which could potentially classify them in a higher risk group.

RESULTS

Characteristics of the analytic cohort that included 194 males and 242 females are summarized in Table II. There were 63 stage I testicular germ cell tumors who received surgery only. Distribution by stage was: stage I/II (38.3%); stage III (31.2%); and stage IV

(30.5%). Median follow-up of the 436 patients was 6.3 years. For both EFS and OS, the optimal age cut-off that maximized the survival rate difference between age groups was 15 years ($P = 0.02$ and $P = 0.0001$, respectively). The majority of patients were <15 years of age ($n = 370$). The most common primary tumor site was ovary in females ($n = 126$) and testis in males ($n = 137$). Only 39 patients had mediastinal primaries; 13 of the 39 patients were >15 years of age. AFP was 10,000 ng/ml in 265 patients and >10,000 in 161 patients (only 5 patients had AFP >100,000 ng/ml). HCG was 5,000 IU/L in 335 patients and >5,000 IU/L in 19 patients. No patients had HCG >50,000 IU/L. LDH was $1.5 \times$ normal in 191 cases and $>1.5 \times$ normal in 148 cases; only 10 of the pediatric patients had LDH $>10 \times$ normal.

We investigated the prognostic significance of these factors in pediatric germ cell tumors (Table III). For EFS, univariate analyses identified the following prognostic variables: AFP >10,000 ng/ml ($P = 0.006$), mediastinal primary ($P = 0.0013$), and age >15 years ($P = 0.02$); and for OS, AFP 10,000 ng/ml ($P = 0.008$), LDH $1.5 \times$ normal ($P = 0.03$), mediastinal primary ($P < 0.0001$), and age 15 years ($P = 0.0002$). A multivariable Cox proportional hazards model using patients with complete data on the factors found to be significant in the univariate model was used to determine which variables were independently prognostic (Table III). For EFS, mediastinal primary and AFP >10,000 ng/ml were found to be predictive of poor outcome. For OS, mediastinal primary, age 15 years, and AFP >10,000 ng/ml were predictive of poor outcome.

We evaluated the performance of the IGCCC when applied to pediatric patients. Overall, 21% of pediatric patients were good risk (GR) by IGCCC criteria, 35% were intermediate risk (IR), and 44% were poor risk (PR) (Table V). Only modest concordance was observed in the assignment of patients to COG versus IGCCC risk groups, and there was not a statistically significant association of the two systems ($P = 0.3859$, Table V). Out of 435 patients, only 212 (49%) are assigned to the same risk level (good = low, intermediate = intermediate, poor = high) in both stratification systems. Only 6 patients (1%) were GR by adult IGCCC but high risk by COG pediatric stratification, but 20 patients (5%, none of whom were infants <6 months of age with AFP >10,000) were PR by adult IGCCC but low risk by COG pediatric stratification. Sixty-six patients were PR by adult IGCCC but were IR by COG criteria.

We examined the ability of the two systems to discriminate patients with lower versus higher survival rates (Table VI). The EFS and OS rates for high-risk patients per the COG system are slightly lower than those of the PR group per the adult IGCCC (EFS: COG $77\% \pm 5\%$ vs. IGCCC $80\% \pm 3\%$; OS: COG $81\% \pm 4\%$ vs. IGCCC $86\% \pm 3\%$). The intermediate/low-risk patients per the COG system had similar EFS and OS rates as the intermediate/good cohort per the adult IGCCC.

Due to missing data, some patients may have been under-classified. However, the results of the sensitivity analysis showed that there was no statistically significant difference between the EFS or OS rates within a given risk group for: (a) all patients versus (b) the cohort excluding patients with missing data that could potentially upgrade them to higher risk. In fact, the rates were virtually identical (data not shown). Therefore, without data evidence to upgrade a patient to a higher risk group, it was reasonable to include patients with missing data in the lower risk group.

The performance of the IGCCC was examined within several subsets of patients. Although the IGCCC was not developed for these particular cohorts, it performed equally well (a) within females; (b) within non-metastatic disease (stage I/II); and (c) within patients >6 months of age (i.e., excluding 10 patients who were less than 6 months of age for whom an

elevated AFP might have been normal for age) (data not shown). In each case, results were similar to those obtained in the overall cohort.

DISCUSSION

Several of the factors used to stratify adult patients (AFP, LDH, and mediastinal primary) were found to be prognostic of outcome in pediatric patients, and therefore potentially useful in pediatric-risk stratification. HCG level, however, was not found to be prognostic of outcome. In this pediatric population, 95% of the patients had HCG $\leq 5,000$ IU/L, none of the patients had a level $>50,000$ IU/L, so the adult cutpoint is not informative for pediatric patients. No data were available in this cohort on the presence of non-pulmonary visceral metastases. Because non-pulmonary visceral metastases are very rare in pediatrics, it is doubtful that this additional factor would be helpful for pediatric-risk group assignment. In addition, among pediatric patients, age was predictive of outcome; patients ≥ 15 -years-old had worse outcome than younger children.

At least four other studies of pediatric germ cell tumors have been conducted to identify prognostic factors. It is important to note that prognosis is largely dependent on the patient having received the most appropriate treatment and so any analysis of risk factors is confounded by differences in treatment. French investigators found that elevations of AFP $>10,000$ ng/ml predicted worse outcome [4]. In univariate analysis, site and stage were also predictive of poor outcome, but only AFP was significant in multivariable analysis. Combining the three factors, however, the French investigators were able to identify three risk groups with significantly different outcomes (100% vs. 81% vs. 43%).

The United Kingdom Children's Cancer Study Group reported on the treatment of 137 patients aged 0–16 years of age with malignant extracranial germ cell tumors treated with JEB-carboplatin, etoposide, and bleomycin. [11]. In univariate analyses, the most significant prognostic factor in their set of patients was an AFP $>10,000$ ng/ml (EFS $>10,000$ ng/ml: 76.5% vs. EFS $\leq 10,000$ ng/ml: 95.3%; $P = 0.01$). Neither site nor stages were significantly related to survival in their data. Two studies have focused on prognostic factors among patients with EG germ cell tumors. In a German study of 76 patients with sacrococcygeal germ cell tumors, investigators examined the prognostic significance of metastatic disease, extension into bone, and AFP elevations $>10,000$ ng/ml [5]. Although none of these factors were found to predict outcome, sample size, and restriction of the analysis to those with single site of disease, may have limited their ability to detect a difference between groups. Marina et al. [12] examined prognostic factors among the subset of patients with EG germ cell tumors who were treated on the same protocols that constitute the basis for this analysis. The results reported in their analyses differed somewhat from our analysis on the total cohort of patients, which is not unexpected in subset analyses. In the analysis restricted only to patients with EG tumors, age >12 was associated with a worse prognosis, whereas in the full cohort analysis, age >15 was associated with a worse prognosis. Among EG tumors only, AFP was not prognostic, whereas, among the entire cohort, AFP was prognostic. The differences between these two analyses highlight the importance of large sample size. This strategy was used to develop the IGCCC criteria-pooled data from multiple centers to increase the size of the analytic cohort. Large sample size reduces the variability and chance observation that could occur when only a subset of the overall cohort is examined. A global cooperative effort, using an analytic cohort as close as possible to population-based, would be preferable for identification and agreement on prognostic factors for pediatric germ cell tumors.

The adult International Germ Cell Classification System and the pediatric COG system are both able to stratify pediatric patients into two distinct risk groups although the two systems

are not highly concordant and one is not clearly superior to the other. Development of a de novo pediatric risk stratification system, using pooled data from multiple studies, that incorporates site, stage, as well as tumor markers, molecular studies, and age, to create a more refined stratification to assign patients to the appropriate level of therapy, is warranted and would clearly advance the field by allowing for more direct comparisons between different clinical trials.

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TABLE I**Adult International Germ Cell Consensus Classification System**

Good risk	Intermediate risk	Poor risk
Testis/retroperitoneal primary and no non-pulmonary visceral metastases	Testis/retroperitoneal primary and no non-pulmonary visceral metastases	Mediastinal primary or non-pulmonary visceral metastases
Good markers—all of:	Intermediate markers—any of:	Poor markers—any of:
AFP $\leq 1,000$ ng/ml	AFP $>1,000$ ng/ml to $\leq 10,000$ ng/ml	AFP $>10,000$ ng/ml
Beta-hCG $\leq 5,000$ IU/L	Beta-hCG $>5,000$ IU/L and $\leq 50,000$ IU/L	Beta-hCG $>50,000$ IU/L
LDH $\leq 1.59 \times N$	LDH $>1.5 \times N$ and $\leq 10 \times N$	LDH $>10 \times N$

(Reference: [1]) AFP, alphafetoprotein; HCG, β subunit of human chorionic gonadotropin; LDH, lactate dehydrogenase; N, normal.

TABLE II

Characteristics of Analytic Cohort: Patients on POG 9048/CCG 8891 or POG 9049/CCG 8882

Variable	n	%	5-year EFS rate $\pm$ std error	P-value *	5-Year OS rate $\pm$ std error	P-value *
Overall	436	100	86 $\pm$ 2	NA	92 $\pm$ 2	NA
Sex						
Males	194	44.5	82 $\pm$ 3	0.0405	90 $\pm$ 3	0.3601
Females	242	55.5	89 $\pm$ 3		93 $\pm$ 2	
Age group						
<15 years	370	84.9	87 $\pm$ 2	0.0207	94 $\pm$ 2	<0.0001
15 years	66	15.1	76 $\pm$ 6		80 $\pm$ 6	
Primary site						
Ovary	126	29.3	94 $\pm$ 3	0.0008 **	96 $\pm$ 2	<0.0001 **
Testes	137	31.8	86 $\pm$ 3		97 $\pm$ 2	
Retroperitoneal	36	8.4	79 $\pm$ 9		88 $\pm$ 7	
Mediastinal	39	9.1	69 $\pm$ 10		71 $\pm$ 10	
Sacrococcygeal	89	20.7	83 $\pm$ 5		88 $\pm$ 4	
Other site	3	0.7				
Unknown	6		67 $\pm$ 27		67 $\pm$ 27	
FP						
10,000	265	62.2	90 $\pm$ 2	0.0046 ***	95 $\pm$ 2	0.0062 ***
>10,000	161	37.8	80 $\pm$ 4		87 $\pm$ 3	
Unknown	10					
-HCG						
5,000	335	94.6	88 $\pm$ 2	0.2609 ***	93 $\pm$ 2	0.4724 ***
>5,000	19	5.4	78 $\pm$ 11		90 $\pm$ 8	
Unknown	82		80 $\pm$ 6		85 $\pm$ 5	
LDH						
1.5 times N	158	45.3	88 $\pm$ 3	0.2578 ***	95 $\pm$ 2	0.0212 ***
>1.5 times N	191	54.7	83 $\pm$ 4		87 $\pm$ 3	
Unknown	87		86 $\pm$ 5		93 $\pm$ 3	

Variable	n	%	5-year EFS rate $\pm$ std error	P-value [*]	5-Year OS rate $\pm$ std error	P-value [*]
Treatment						
Surgery only	63	14.4	79 $\pm$ 6	0.0704	100	0.0421
BEP	224	51.4	85 $\pm$ 3		89 $\pm$ 3	
High-dose BEP	149	34.2	90 $\pm$ 3		92 $\pm$ 3	
COG risk group						
Low	192	44.1	80 $\pm$ 4	0.0050	86 $\pm$ 3	0.0036
Intermediate	150	34.5	89 $\pm$ 3		96 $\pm$ 2	
High	93	21.4	93 $\pm$ 3		96 $\pm$ 3	
Unable to assign	1					
Stage						
I ^a	134	30.7	86 $\pm$ 4	0.4191	97 $\pm$ 2	0.0120
II	33	7.6	94 $\pm$ 5		97 $\pm$ 3	
III	136	31.2	87 $\pm$ 4		91 $\pm$ 3	
IV	133	30.5	82 $\pm$ 4		86 $\pm$ 4	

^{*} P-value is for two-sided log-rank test;

^{**} comparison of mediastinal (thoracic/head/neck) primary versus all other sites;

^{***} test excludes "Unknown" cohort from comparison;

^a includes extragonadal stage II patients;

NA, not applicable.

TABLE III

Multivariable Predictors of EFS and OS (n = 421 with complete data)

Covariate ^a	EFS		OS	
	Hazard ratio	P-value*	Hazard ratio	P-value*
Cox Model #1				
Mediastinal primary	2.5	0.0079	4.3	0.0002
AFP >10,000 ng/ml	2.2	0.0040	2.8	0.0042
Age 15 years (OS only)	NA	0.0614**	3.0	0.0038
Cox Model #2 (same as Model #1, plus adjustment for treatment effect)				
Mediastinal Primary	2.9	0.0029	3.9	0.0004
AFP >10,000 ng/ml	2.7	0.0004	2.6	0.0096
Age 15 years	2.2	0.0166	2.7	0.0097
Treatment with PEB	0.4	0.0087	NA	0.9891**
Treatment with HD/PEB	0.2	0.0002	NA	0.9895**

^aOther covariates tested in the models and found to be not significant were HCG & LDH;

*P-value from Cox proportional hazards model;

** this covariate was excluded from the final model;

NA-not applicable.

TABLE IV
Distribution of Pediatric Germ Cell Tumor Marker Levels According to Adult IGCCC Criteria

Risk group factor	Marker level per IGCCC criteria				Total
	Good n (%)	Intermediate n (%)	Poor n (%)	Unknown n	
AFP ^a	146 (34)	119 (28)	161 (38)	10	436
HCG ^b	335 (95)	19 (5)	0 (0)	82	436
LDH ^c	191 (55)	148 (42)	10 (3)	87	436

^aAFP (alpha fetoprotein): good risk 1,000 ng/ml; intermediate risk >1,000 ng/ml to 10,000 ng/ml; poor risk >10,000 ng/ml;
^bHCG (human chorionic gonadotropin): good risk 5,000 IU/L; intermediate risk >5,000 IU/L to 50,000 IU/L; poor risk >50,000 IU/L;
^cLDH (lactate dehydrogenase): good risk 1.5× normal; intermediate risk >1.5× normal to 10× normal; poor risk >10× normal.

TABLE VFrequency Tabulation of COG Pediatric Risk Stratification by IGCCC Risk Group Category ($P = 0.3859$)

COG pediatric risk stratification	IGCCC risk group category			
	Good risk n (%)	Intermediate risk n (%)	Poor risk n (%)	Unknown n
Low risk	31 (33)	52 (35)	20 (10)	1
Intermediate risk	56 (60)	75 (50)	66 (35)	0
High risk	6 (7)	23 (15)	106 (55)	0
Total IGCCC risk group	93 (21)	150 (35)	192 (44)	1

TABLE VI
All Pediatric Patients (n = 435): Pairwise Comparisons of EFS and OS Rates by IGCCC Risk Group Category

Cohort	n	5-year EFS rate $\pm$ std error (%)	P-value [*]	5-Year OS rate $\pm$ std error (%)	P-value [*]
By adult IGCCC risk group category					
Overall					
Poor	192	80 $\pm$ 4	0.0017	86 $\pm$ 3	0.0008
Intermediate/good	243	91 $\pm$ 2		96 $\pm$ 2	
By pediatric COG risk stratification					
Overall					
High	135	77 $\pm$ 5	0.0004	81 $\pm$ 4	<0.0001
Intermediate/low	301	90 $\pm$ 2		96 $\pm$ 1	

^{*}Two-sided log-rank test.