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ORIGINAL REPORT

Revised Risk Classification for Pediatric Extracranial Germ Cell Tumors Based on 25 Years of Clinical Trial Data From the United Kingdom and United States

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ABSTRACT

Purpose
To risk stratify malignant extracranial pediatric germ cell tumors (GCTs).

Patients and Methods
Data from seven GCT trials conducted by the Children's Oncology Group (United States) or the Children's Cancer and Leukemia Group (United Kingdom) between 1985 and 2009 were merged to create a data set of patients with stage II to IV disease treated with platinum-based therapy. A parametric cure model was used to evaluate the prognostic importance of age, tumor site, stage, histology, tumor markers, and treatment regimen and estimate the percentage of patients who achieved long-term disease-free (LTDF) survival in each subgroup of the final model. Validation of the model was conducted using the bootstrap method.

Results
In multivariable analysis of 519 patients with GCTs, stage IV disease ($P = .001$), age $\geq$ 11 years ($P < .001$), and tumor site ($P < .001$) were significant predictors of worse LTDF survival. Elevated alpha-fetoprotein (AFP) $\geq$ 10,000 ng/mL was associated with worse outcome, whereas pure yolk sac tumor (YST) was associated with better outcome, although neither met criteria for statistical significance. The analysis identified a group of patients age > 11 years with either stage III to IV extragonadal tumors or stage IV ovarian tumors with predicted LTDF survival < 70%. A bootstrap procedure showed retention of age, tumor site, and stage in > 94%, AFP in 12%, and YST in 27% of the replications.

Conclusion
Clinical trial data from two large national pediatric clinical trial organizations have produced a new evidence-based risk stratification of malignant pediatric GCTs that identifies a poor-risk group warranting intensified therapy.

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INTRODUCTION

Although clinical trials in many countries have shown that outcomes for pediatric germ cell tumors (GCTs) are generally excellent,[1-4] 15% to 20% of patients with metastatic tumors still succumb to the disease.[5] Moreover, cure is not synonymous with normal life expectancy. Significant late effects of treatment in men treated with BEP (cisplatin, etoposide, and bleomycin) for testicular GCTs (TGCTs) include a two-fold increase in the rate of second malignant neoplasms (SMNs) and cardiovascular disease.[6] Furthermore, the risk of SMNs does not plateau but instead continues to grow with age[7]; consequently, a patient treated for a TGCT at age 20 years has nearly a 50% chance of developing an SMN by age 75 years.[8] Similar data are not available for children treated for GCTs, in part because GCTs were not included in the Childhood Cancer Survivor Study.[9] However, because the treatment regimens delivered are nearly identical, it is reasonable to extrapolate from men with testicular cancer to children with GCTs. Therefore, despite the encouraging 5-year overall survival rates, therapies for pediatric GCTs still need to evolve.

A major advance in therapy for men with testicular cancer was the International Germ Cell Consensus Classification (IGCCC), derived from an analysis of > 5,000 patients treated in clinical trials, which stratified patients into good-, intermediate-, and poor-risk groups.[10] IGCCC became the common language internationally, allowing for joint

Table 1. Clinical Trials Included in MaGIC Study

Trial	National Group	Trial Eligibility Criteria	Treatment Regimen	Cycles		No. of Patients
				Length (days)	No.	
GC1[15]	UK	All patients with MGCTs	Etoposide 120 mg/m^2 on days 1 to 3, bleomycin 15 IU/m^2 on day 2, cisplatin 100 mg/m^2 on day 1	21	n + 2*	14
GC2[2]	UK	All patients with MGCTs	JEB	21	n + 2*	135
INT-0106/POG9048/CCG-8891[10]	US	Stage II testicular and stage I to II ovarian tumors	PEB	21	4 (+ 2 if PR)	33
INT-0097/POG9049/CCG-8882[3]	US	Stage III to IV gonadal and extragonadal tumors	PEB *v* HDPEB	21	4 (+ 2 if PR)	250
P9749[12]	US	Stage III to IV extragonadal tumors	Amifostine 825 mg/m2 on days 1 to 5 plus HDPEB	21	4 (+ 2 if PR)	26
AGCT01P1[16]	US	Stage III to IV extragonadal tumors	C-PEB	21	4 (+ 2 if PR)	14
AGCT0132[17]	US	Stage I to III ovarian, stage I to IV testicular, and stage I to II extragonadal tumors	Compressed PEB	21	3 (+ 3 if PR)	47

Abbreviations: C-PEB, cyclophosphamide, cisplatin, etoposide, and bleomycin; CCG, Children's Cancer Group; HDPEB, cisplatin, etoposide, and bleomycin; JEB, carboplatin, etoposide, and bleomycin; MaGIC, Malignant Germ Cell International Collaborative; MGCT, malignant germ cell tumor; PEB, cisplatin, etoposide, and bleomycin; POG, Pediatric Oncology Group; PR, partial response.
*No. of courses to marker normalization.

clinical trial design and comparison of results. The rarity of pediatric GCTs has historically impeded the development of refined risk-stratification models comparable to IGCCC. Previous analyses have generally identified extragonadal tumor site as an adverse prognostic factor,[2,11-13] but the importance of age and level of serum alpha-fetoprotein (AFP) at diagnosis has varied among studies. Furthermore, direct comparisons of pediatric GCT trials have been confounded by differences in both inclusion criteria for enrollment and treatment regimens. To overcome these limitations, the Children's Oncology Group (COG; United States) and the Children's Cancer and Leukemia Group (CCLG; United Kingdom) agreed to merge 25 years of clinical trial data on pediatric GCTs. Although COG used a cisplatin-based regimen (PEB [ie, pediatric BEP]), and CCLG used a carboplatin-based regimen (JEB [carboplatin, etoposide, and bleomycin]), the pooling of the clinical trial data was justified by a comparison of published results[2,3,10] that indicated similar outcomes.

The objective of the Malignant Germ Cell Tumor International Collaborative (MaGIC) was to produce a robust system for stratification of pediatric and adolescent patients that could serve as the basis for future international collaborative clinical trials. In particular, we were interested in developing consensus on which patients had a sufficiently poor projected outcome to warrant more intensive first-line therapy. The parametric cure model[14] was used to identify risk groups based on the principle that in a highly curable group of tumors such as GCTs, the total fraction continuously disease free is a more relevant outcome measure than the analysis of how risk of event varies with time under observation, which serves as the basis of inference in proportional hazards models, such as Kaplan Meier.

PATIENTS AND METHODS

Patient Population

After signing a memorandum of understanding, which specified the variables to be included in the database and how information was to be deidentified, patient data from seven clinical trials conducted by either CCLG or COG between 1983 and 2009 were included in the MaGIC data set (Table 1[2,3,10,12,15-17]). The project was reviewed and exempted by the institutional review board at the Dana-Farber Cancer Institute.

Chemotherapeutic Regimens

In the United Kingdom, the JEB regimen consisted of carboplatin 600 mg/m^2 (area under the curve [AUC], 7.9 mg/mL per minute), etoposide 360 mg/m^2, and bleomycin 15 mg/m^2, administered every 21 days for four to six cycles. In the United States, the PEB regimen comprised cisplatin 100 mg/m^2, etoposide 500 mg/m^2, and bleomycin 15 mg/m^2, administered every 21 days for three to six cycles. One COG trial (AGCT01P1) used an additional agent (cyclophosphamide), and two COG trials (INT-0106 and P9747) tested high-dose cisplatin (200 mg/m^2 per cycle). Inclusion in this analysis required that patients had been treated with a platinum-based regimen and that primary tumors contained malignant germ cell histology (ie, yolk sac tumor [YST], choriocarcinoma, or embryonal carcinoma). Patients with pure immature teratoma (n = 191), pure seminoma or dysgerminoma (n = 77), treatment with surgery only (n = 128), stage I disease (n = 139), treatment with non–platinum-based chemotherapy (n = 5), and missing data on stage (n = 4) or event-free survival (EFS) time (n = 2) and patients initially treated with surgery only who subsequently received chemotherapy because of residual or recurrent disease (n = 42) were excluded. After exclusions, the data set included 519 patients.

Patient characteristics included in the data set were age, date of initial surgery, disease stage (II to IV), disease site, tumor marker levels (AFP and, when available, beta-human chorionic gonadotropin), treatment regimen, and histology. YST was defined as any tumor that contained either pure YST or YST combined with immature or mature teratoma. Mixed malignant GCTs were defined as containing at least two of the following components: YST, embryonal carcinoma, or choriocarcinoma. Patient cases coded as embryonal carcinoma or choriocarcinoma only contained the single histology. COG staging of extracranial GCTs has been reported elsewhere.[10]

Statistical Analysis

Outcome measure. EFS was calculated as time from start of chemotherapy to disease progression, diagnosis of a second malignancy, death, or date of last follow-up, whichever came first.

Covariates. Age at start of follow-up was calculated in whole years and dichotomized as ≤ the target age or > the target age. The target age was varied between 8 and 14 years in single years. The cut point that maximized the log-rank test was used for additional analyses.[18]

Preoperative serum AFP was used in the analysis. AFP results reported as IU/mL were converted to ng/mL using the conversion factor of 1 IU/mL = 1.21 ng/mL.[19] Other included variables were: site of primary tumor (testicular *v* ovarian *v* extragonadal), treatment regimen (JEB *v* PEB), and histology (YST *v* other).

Statistical model. A nonmixture cure model was used to characterize the relationship between covariates and EFS. This methodology has been shown to provide excellent fit to childhood cancer outcome data.[14] The model provides a coherent methodology to investigate the effects of covariates on rate of failure separately from their effect on ultimate cure. Backward selection was used to select a parsimonious survivor function model. For the initial part of the fitting procedure, a Weibull kernel with no covariates was used. The cure function was modeled as a logistic function. The likelihood ratio test with a P value $> .050$ was used to eliminate terms from the cure fraction model. Interactions were tested first, and if an interaction term was included, the associated main effects were included. Main effects not associated with a significant interaction were then tested. The parameters from the final fitted model were used to estimate the proportion of patients remaining long-term disease free (LTDF; ie, cure) for each of subgroups defined by the combinations of the significant predictors.

Even in this aggregated clinical data set, the sample size within the strata of certain risk factors was small. Posthoc, within certain subgroups, we estimated EFS in selected risk factor subgroups, such as stage II versus III disease, using Kaplan-Meier methodology.[20] To compare MaGIC risk stratification with that of IGCCC, we reclassified patients according to their IGCCC risk group. The log-rank test was used to compare equality of risk across selected patient groups.[21]

The robustness of the final cure model was assessed using the bootstrap procedure[22]; 1,000 bootstrap samples were drawn randomly with replacement and the model fitting repeated for each sample with all predictor variables. The number of times each of the terms, including the interaction terms, were identified for inclusion in the final model was tabulated to identify factors that were not selected in the entire data set but may hold information regarding prognosis for cure.

RESULTS

The characteristics of the cohort are summarized in Table 2. More female (66%) than male patients were included in the clinical trials. A majority of the patients were age < 4 years (53%); the second-largest age group was 10 to 14 years (21%). The most common histology was YST (55%), followed by mixed malignant GCTs (40%). Serum AFP was ≥ 10,000 ng/mL in 49% of patients. Stage III or IV disease

Table 2. Characteristics of MaGIC Cohort Patients

Characteristic	No. With Testicular Tumors (n = 92)	No. With Ovarian Tumors (n = 141)	No. With Extragonadal Tumors (n = 283)	Total (N = 519)	
				No.	%
Sex					
Male	92	0	84	176	34
Female	0	141	202	343	66
Age, years					
0 to 4	43	8	244	295	53
5 to 9	2	39	8	49	10
10 to 14	15	72	14	101	21
≥ 15	32	22	20	74	15
Histology					
Embryonal carcinoma	3	2	2	7	1
YST*	44	47	196	287	55
Choriocarcinoma	1	2	6	9	2
Mixed germ cell tumor†	44	88	76	208	40
Missing	0	2	6	8	2
AFP, ng/mL					
0 to 9,999	67	78	94	239	46
≥ 10,000	19	56	178	253	49
Missing	6	7	14	27	5
Stage					
II	24	38	47	109	21
III	26	86	103	215	41
IV	42	17	136	195	38
Years of treatment					
1984 to 1989	1	6	14	21	4
1990 to 1994	66	65	142	273	53
1995 to 1999	12	33	64	109	21
≥ 2000	13	37	66	116	22
Treatment regimen					
HDPEB	28	26	95	149	29
PEB	51	72	98	221	43
C-PEB	0	0	14	14	3
JEB	13	43	79	135	26

Abbreviations: AFP, alpha-fetoprotein; C-PEB, cyclophosphamide, cisplatin, etoposide, and bleomycin; HDPEB, cisplatin, etoposide, and bleomycin; JEB, carboplatin, etoposide, and bleomycin; MaGIC, Malignant Germ Cell International Collaborative; PEB, cisplatin, etoposide, and bleomycin; YST, yolk sac tumor.
*Includes patients with pure YST or YST combined with either mature or immature teratoma.
†Includes patients who had ≥ two of following histologies: YST, embryonal carcinoma, or choriocarcinoma.

Table 3. Cure Model of Prognostic Factors for Pediatric Germ Cell Tumors (N = 519)

Characteristic	Estimated Log-Odds Ratio*	*P*
Tumor site		
Testicular	—	
Ovarian	−0.83	< .001†
Extragonadal	−1.97	
Extent of disease, stage		
II to III	—	
IV	−1.02	.001‡
Age at enrollment, years		
< 11	—	
≥ 11	−1.72	< .001‡

*Log-odds ratios < 0 indicate characteristics associated with decreased probability of cure; log-odds ratios > 0 indicate characteristics associated with increased probability of cure.
†*P* value associated with the statistical test that the log-odds of cure is 0 for both ovarian and extragonadal sites.
‡*P* value associated with the statistical test that the log-odds of cure associated with the particular value of the characteristic is 0.

accounted for 79% of patients; 26% of children were treated with a carboplatin-based regimen (JEB).

In univariable analysis (data not shown), the optimal cut point for age, based on the maximum value of the log-rank test, was determined to be < 11 versus ≥ 11 years. This was significant at the < .01 level based on the approximate permutation distribution of the maximal log-rank test. The importance of stage was compared for each stage separately, and then combinations of stage were considered. Stage III was not significantly different from stage II ($P = .34$) in the overall model; therefore, stage was coded as II to III versus IV for the purposes of model fitting.

In multivariable analyses using backward selection, age ≥ 11 years, tumor site (categorized as testicular *v* ovarian *v* extragonadal), and stage IV were significant predictors of poor outcome (Table 3). No interactions were statistically significant. Serum AFP ≥ 10,000 ng/mL was not significant in the overall model ($P = .45$). Too few patients had elevated beta-human chorionic gonadotropin at diagnosis to assess its significance. YST predicted a better outcome than other histologies ($P = .06$) but did not meet the *P* value criterion for inclusion in the final model. Treatment regimen was not significant (JEB *v* PEB; $P = .25$). None of the factors associated with cure significantly influenced the rate of failure.

The parameters associated with cure (age, site, and stage) were then used to calculate point estimates of LTDF survival and approximate CIs for the subgroups identified by the model (Table 4). LTDF survival ranged from 99% (95% CI, 96% to 100%) for boys age < 11 years with stage II to III testicular GCTs to 40% (95% CI, 24% to 56%) for patients age ≥ 11 years with stage IV extragonadal GCTs. We identified a poor-risk group of patients who had LTDF survival < 70%. The group included patients age ≥ 11 years with stage IV ovarian GCTs (LTDF survival, 67%; 95% CI, 49% to 80%), stage II to III extragonadal GCTs (LTDF survival, 65%; 95% CI, 48% to 78%), or stage IV extragonadal disease (LTDF survival, 40%; 95% CI, 24% to 56%).

We noted that 19 (90%) of the 21 patients in the stage II to III extragonadal group had stage III disease. We further explored EFS for those with stage III versus II extragonadal disease using nonparametric methods. Estimated 4-year EFS for stage II extragonadal disease was 100% (n = 2), compared with 61% for stage III (95% CI, 34% to 79%; $P = .33$).

EFS for patients age ≥ 11 years with advanced-stage testicular disease (estimated 4-year EFS: stage III, 94%; 95% CI, 67% to 99%; stage IV, 83%; 95% CI, 67% to 91%) was more favorable than for

Table 4. Predicted Fraction of Pediatric Germ Cell Tumors Cured by Site, Age, and Stage Using Parameter Estimates From Cure Model

	Cure Model		
Group	No. of Patients	Predicted LTDF Survival (%)	95% CI (%)
Patients age < 11 years with stage II to III testicular tumors	28	99	96 to 100
Patients age < 11 years with stage II to III ovarian tumors	49	97	93 to 99
Patients age < 11 years with stage IV testicular tumors	17	96	91 to 99
Patients age ≥ 11 years with stage II to III testicular tumors	22	93	84 to 97
Patients age < 11 years with stage IV ovarian tumors	8	92	83 to 96
Patients age < 11 years with stage II to III extragonadal tumors	129	91	86 to 94
Patients age ≥ 11 years with stage II to III ovarian tumors	75	85	77 to 91
Patients age ≥ 11 years with stage IV testicular tumors	25	83	67 to 91
Patients age < 11 years with stage IV extragonadal tumors	124	79	71 to 84
Patients age ≥ 11 years with stage IV ovarian tumors	9	67	49 to 80
Patients age ≥ 11 years with stage II to III extragonadal tumors	21	65	48 to 78
Patients age ≥ 11 years with stage IV extragonadal tumors	12	40	24 to 56

	IGCCC		
Poor-Risk Group	No. of Patients	4-Year Kaplan-Meier EFS (%)	95% CI (%)
Both sexes age > 11 years (all sites)	65	74	61 to 83
Boys age > 11 years (all sites)	27	57	36 to 74
Boys age > 11 years (testicular site)	15	80	50 to 93
Boys age > 11 years (extragonadal site)	12	50*	21 to 74

Abbreviations: EFS, event-free survival; IGCCC, International Germ Cell Consensus Classification; LTDF, long-term disease free.
*3-year EFS is used here because longest follow-up in this category was 3.5 years.

Table 5. Bootstrap Results Based on 1,000 Random Samples of Size for Patients With Stage II to IV Disease (n = 492)*

Patient Characteristic	Proportion of Replications in Which Final Model Included Particular Models That Included That Patient Characteristic (%)†
Age ≥ 11 years	99.8
Stage IV disease	94.1
Tumor site	98.0
YST	27.6
AFP ≥ 10,000 ng/mL at enrollment	12.1

Abbreviations: AFP, alpha-fetoprotein; YST, yolk sac tumor.
*With available stage, age, site, and AFP information. Before performing bootstrap, 27 patients with missing AFP data were removed.
†Bootstrap method used backward selection procedure with $P < .05$ as criterion to select final model. Percentages show proportion of final models that contain particular term.

those with ovarian or extragonadal disease. We examined whether application of the IGCCC criteria would identify a subgroup with a worse prognosis among patients with metastatic disease, compared with MaGIC. Unfortunately, 60% of patients age ≥ 11 years lacked detail on site of metastasis, which prevented us from differentiating between pulmonary versus nonpulmonary visceral metastases and thus assigning an IGCCC risk group. Hence, our ability to examine the performance of IGCCC was limited. As can be seen from Table 4, estimated 4-year EFS of IGCCC poor-risk patients of either sex was 74% (95% CI, 61% to 83%). When the analysis was limited to boys, those deemed poor risk by IGCCC had a worse outcome (4-year EFS, 57%; 95% CI, 36% to 74%). However, this poor outcome was the result of including boys with extragonadal disease (4-year EFS for IGCCC poor-risk patients with extragonadal disease, 50%; 95% CI, 21% to 74%); IGCCC poor-risk patients with testicular disease had a 4-year EFS of 80% (95% CI, 50% to 93%). Therefore, application of the IGCCC criteria did not result in any refinement of risk beyond that already noted in the MaGIC analysis.

Robustness of the model was assessed using the bootstrap method[22] (Table 5). Stage IV disease was identified as an adverse prognostic factor in 94.1% of the replications. Age ≥ 11 years and tumor site were identified in 99.8% and 98% of the replications, respectively. AFP entered the model as a poor prognostic factor in only 12% of the replications, whereas YST predicted a better outcome in approximately 28% of the replications.

DISCUSSION

In this analysis, which represents the largest assembled database of pediatric extracranial GCTs to our knowledge, we identify that age ≥ 11 years, ovarian stage IV disease, and extragonadal stage III to IV disease confer a significantly worse prognosis. Patients with pure YST histology seemed to have a better outcome, although this latter finding was of borderline significance ($P = .06$). Diagnostic levels of serum AFP ≥ 10,000 ng/mL were not significant in this data set ($P = .45$). Bootstrap results confirmed the validity of the model; the primary effects were all retained in the model in > 94% of the 1,000 replications, whereas AFP was retained in the model in just 12% and YST in 28% of the replications.

The risk groups determined by the MaGIC analysis are different than those previously used in clinical trials in the United States and United Kingdom. Although previous studies had recognized that older patients,[12,13] extragonadal site,[3] higher disease stage,[2,11] and elevated AFP[2,11,13] were adverse prognostic factors, the results were not consistent across studies. Our study, because of sufficient sample size, has allowed for careful consideration of each of these factors and whether there is significant interaction between these factors in multivariable analyses. Given that factors such as site, age, and histology are highly correlated, a data set this size is necessary to begin to understand which factors are the principal drivers of outcome. As an illustration of the more nuanced insights permitted by this analysis, the conclusion from the last published COG trial, INT-0097 (POG9049/CCSG8882), was that patients with stage III to IV extragonadal disease had a poor prognosis, with an EFS of 72.5% ± standard deviation of 7.4%[3]; however, patient age was not taken into account. Conversely, in our analysis, we show that poor prognosis was restricted to patients with stage III to IV extragonadal tumors age ≥ 11 years; patients with stage III to IV extragonadal tumors age < 11 years are likely to be cured with standard therapy (4-year Kaplan-Meier EFS, 83%; 95% CI, 77% to 88%), and less toxic but equally efficacious therapy should be considered. The MaGIC risk stratification also highlights the poor outcome of female patients age ≥ 11 years with stage IV ovarian GCTs, which had not been previously noted in other clinical trials (LTDF survival, 67%; 95% CI, 49% to 80%). These insights will be the basis of a joint US-UK clinical trial currently under development that will include both pediatric and adult gynecologic oncology patients.

We did attempt to evaluate whether the adult IGCCC criteria would identify a poor-risk group among postpubertal male patients with greater specificity than the MaGIC classification. Although we were limited by the number of patients who had complete data on site of metastasis, adolescent boys with IGCCC poor-risk disease and a testicular primary tumor had a significantly better outcome than that reported in the literature, including a modern series of poor-risk patients from Indiana University (MaGIC, 80% *v* Indiana University, 56%).[23] However, even in our data set, the population of those age 15 to 19 years was small, and it remains unknown whether adolescents would fare better or worse than young adults. A cautionary report from a single-institution study of outcome for pediatric and adult patients with testicular cancer over a 20-year period did show that adolescent boys age 13 to 19 years were 2.2× more likely to experience an adverse event than younger or older patients, despite controlling for risk group, histology, and stage at diagnosis.[24]

Several groups, including the Children's Cancer and Leukaemia Group, the French Society of Paediatric Oncology, and COG, have previously identified serum AFP as a prognostic factor.[2,11,13] The entrance of AFP into the model in 12% of the bootstrapping replications indicates that it is of marginal significance and merits further exploration. AFP levels are elevated for at least the first 6 months of life and in some children until age 2 years.[25] Further analysis of AFP should adjust for age-standardized values, which may improve its predictive power. It should also be noted that in men with TGCTs, postoperative AFP levels have been shown to be prognostic, rather than the preoperative levels used in pediatric analyses. The significance of pre- versus postoperative levels should also be explored in future clinical trials. In this analysis, we did not have serial data on AFP levels and therefore could not assess the potential importance of tumor

marker decline, which has been shown to be prognostic among men with TGCTs.[26]

To date, no molecular markers of outcome have been identified for pediatric GCTs. In contrast, among men with nonseminomatous testicular GCTs, gene expression profiling has identified a gene classifier predictive of poor 5-year overall survival in a training set, which was subsequently confirmed in a validation cohort, but these observations are not currently incorporated into routine clinical practice. With the densely clinically annotated data set described herein, the biobanks of COG and CCLG can now be fully interrogated, studying both protein-coding and non–protein-coding gene expression, with the goal of identifying molecular markers of outcome that would further refine our understanding of prognosis.

In conclusion, application of the cure model to the MaGIC data set has led to a comprehensive clinical risk group stratification of pediatric malignant extracranial GCTs that will inform future study design, allowing for intensification of first-line therapy for patients with the worst prognosis and deintensification of therapy among those with a potentially excellent outcome.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

AFP (alpha fetoprotein): a protein normally produced by the liver of a fetus. The amount of AFP in the blood of a pregnant woman may serve as an indicator for disorders that a growing fetus may have, such as spina bifida, anencephaly, or Down syndrome. Normal values for men and nonpregnant women vary between laboratories and range between 0 and 6.4 IU/mL or 0 and 20 ng/mL (the same as 0-20 μg/L). In a woman who is 15 to 22 weeks pregnant, the normal values range from 19 to 75 IU/mL or 7 to 124 ng/mL. High values in a pregnant woman may be indicative of an inaccurate gestational age, multiple pregnancies, a fetus with a neural tube or abdominal wall defect, or a dead fetus. In nonpregnant adults, a high value of AFP may indicate cancer of the liver, testicles, or ovaries.

area under the curve (AUC): a measure of the amount of drug in the blood over a set period of time (eg, 24 hours) that can be used to determine drug exposure.

bootstrap procedure: a nonparametric statistical method to estimate sampling distributions of an estimator by resampling with a replacement from the original sample. In prognostic research, the bootstrap helps to obtain an impression of the validity of predictions in new but similar patients.

event-free survival: calculated from the date of diagnosis to the date of the first event, which is resistance, relapse, death, or second malignant neoplasm.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Revised Risk Classification for Pediatric Extracranial Germ Cell Tumors Based on 25 Years of Clinical Trial Data From the United Kingdom and United States

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