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Clinicopathologic predictors of outcomes in children with stage I testicular germ cell tumors: A pooled *post hoc* analysis of trials from the Children's Oncology Group

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SUMMARY

Background: Patients with clinical stage I (CS I: cN0M0) testicular germ cell tumors (TGCT) exhibit favorable oncologic outcomes. While prognostic features can help inform treatment in adults with CS I TGCT, we lack reliable means to predict relapse among pediatric and adolescent patients.

Objective: We sought to identify predictors of relapse in children with CS I TGCT.

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CONFLICT OF INTEREST STATEMENT

The authors do not have any conflicts of interest to declare.

Study Design: We performed a pooled *post hoc* analysis on pediatric and adolescent AJCC CS I TGCT patients enrolled in 3 prospective trials: INT-0097 (phase II), INT-0106 (phase III), and AGCT0132 (phase III). Pathology was centrally reviewed. Patient demographics, pT stage, serum tumor markers, margin status, histology, relapse, and survival were compiled. Cox regression analyses were used to identify predictors of events, defined as relapse, secondary malignant neoplasm, or death.

Results: 106 patients were identified with outcomes data available. Most patients were pT1-2 stage. Among patients with evaluable histopathology, yolk sac tumor elements were present in all patients and lymphovascular invasion in 51% of patients. Over a median follow-up of 56 months, no patients died, and 25 patients (24%) experienced an event (median event-free survival not reached). Independent predictors of events on multivariable analysis included age ≥12 years at diagnosis (HR 8.87, p<0.001) and higher pT stage (pT2 HR 7.31, p=0.0017; pT3 HR 13.5, p=0.0043).

Discussion: Although our study population reflects the largest pooled prospective cohort of CS I pediatric and adolescent TGCT to our knowledge, the relatively low event rate limits our multivariable analysis, and longer follow-up duration would help further characterize the natural history of these patients. Centralized pathologic review was also unable to be performed for several patients.

Conclusion: Pediatric and adolescent CS I TGCT patients exhibit remarkable 5-year survival. Using combined data from multiple prospective trials, our study identifies clinicopathologic features that predict relapse and inform personalized treatment for these patients by potentially guiding surveillance versus adjuvant treatment strategies.

Keywords

testis cancer; germ cell tumor; children; clinical stage I; predictors; relapse

INTRODUCTION

While testicular germ cell tumors (TGCT) represent the most common solid tumor in young men between the ages of 15 and 35,[1] malignant TGCT comprise only 0.5–3.5% of cancers in children less than 15 years of age.[2,3] Given their relatively uncommon incidence in children, cooperative trials have been essential to guide management for pediatric and adolescent patients with TGCT. Fortunately, the majority of pediatric TGCT are low risk and exhibit excellent clinical outcomes.

Surveillance is the recommended approach to manage patients with low risk TGCT while minimizing overtreatment, with approximately 20% of patients experiencing relapse.[4] In adults, multiple pathologic features predicting relapse have been identified, including lymphovascular invasion (LVI) and embryonal carcinoma-predominant histology.[5] Such knowledge, gleaned from the primary orchiectomy specimen alone, is particularly useful to personalize upfront, risk-adapted, active treatment strategies for low-stage TGCT patients with a higher likelihood of harboring occult metastases or more aggressive tumor biology.

Unlike in adults, however, there are currently no reliable prognostic features to individualize risk among children with low stage TGCT. In adults, “low risk” classically refers to clinical stage I (CS I: pTany cN0M0) per the American Joint Committee on Cancer (AJCC) TNM staging classification for TGCT.[6] Notably, AJCC TNM stage is not included in the Children’s Oncology Group (COG) staging criteria, which is commonly the referent in pediatric TGCT studies.[7] In a recent analysis of pediatric and adolescent patients with low risk (defined as COG stage I) TGCT, age ≥11 years, mixed histology, and the presence of LVI were significantly associated with relapse.[8] In the present study, we sought to identify clinicopathologic predictors of relapse in children with AJCC CS I TGCT using data from three COG studies, INT-0097, INT-0106, and AGCT0132.

METHODS

Following institutional review board approval at all participating institutions, prospective clinical trial data were pooled and analyzed *post hoc* from patients who were enrolled in one of three trials: INT-0097 (An intergroup study of the treatment of children with localized malignant germ cell tumors; phase II),[9] INT-0106 (An intergroup study of high-risk malignant germ cell tumors in children; phase III),[10] and AGCT0132 (A phase III study of reduced therapy in the treatment of children with low and intermediate risk extracranial germ cell tumors; ClinicalTrials.gov identifier: NCT00053352).[11] Tumor stage was classified according to AJCC TNM staging criteria for TGCT. [6] Pediatric and adolescent males 15 years of age or less with AJCC clinical stage I (pTany cN0M0) TGCT were included for analysis. For reference, the AJCC TNM and COG clinical staging criteria for TGCT are provided in Supplementary Tables 1 and 2. Histopathology from the primary orchiectomy specimen was centrally reviewed by a dedicated genitourinary pathologist at the time of trial completion and reporting. Patients without the full complement of pathologic variables available per the contemporary College of American Pathologists (CAP) reporting protocol/template were coded as having “Unknown” pathologic parameters to maintain consistency.

Clinicopathologic data were then extracted, including patient demographics, pT stage, serum tumor markers at enrollment, surgical margin status, histologic composition, dominant tumor size, and LVI. Our primary outcome was event-free survival (EFS), defined by time from enrollment to relapse, subsequent malignant neoplasm, or death. EFS was assessed using Kaplan-Meier methods and multivariable proportional hazards regression modeling with models selected using backwards stepwise regression (variables conditionally removed for $p>0.05$) to identify independent predictors of outcomes. After the independent predictors were identified, the final multivariable model was fitted using data from all patients who had defined values for those variables. Statistical analyses were conducted using SAS 9.4 (Cary, NC). Reported p-values are 2-sided, with statistical significance defined as $p<0.05$.

RESULTS

Among 119 patients who met the inclusion criteria in the pooled cohort, 106 patients had outcomes data recorded and were included in our final analytic cohort. This final cohort included 80 patients from AGCT0132, 22 patients from INT-0106, and four patients from

INT-0097, who were all managed with observation initially. Treatment after progression while on observation was at the discretion of the treating physician. For four INT-0106 patients, this included treatment using the INT-0097 treatment plan.

The majority of patients (84.9%) were age 3 or less at diagnosis, though 13.2% were adolescents (13–15 years of age), as displayed in Figure 1. Pathologic data from the primary orchiectomy specimen following central review and stratified by age < or ≥ 12 years is summarized in Table 1, including pT stage, surgical margin status, histologic composition, serum tumor markers at enrollment, and presence of LVI. In particular, among patients with evaluable pathology, most harbored pT1 or pT2 disease, approximately half harbored LVI, and only 1 patient was noted to have a positive spermatic cord margin. Notably, older patients were more likely to harbor mixed GCT elements, including choriocarcinoma, embryonal carcinoma, or teratoma. Older patients were also more likely to harbor LVI and exhibit elevated β-HCG at diagnosis. Yolk sac tumor elements were present in all patients with assessable histology in the resection specimen.

Across a median follow-up of 55.9 (IQR 36.5–73.9) months from enrollment, there were no deaths among any of the 106 patients included (100% overall survival). Median EFS was not reached, and overall EFS was 75.0% at 150 months (12.5 years) following enrollment (Figure 2). Significant predictors of events on univariable analysis included higher pT stage, older age at diagnosis (≥12 years), positive surgical margin status, LVI, the presence of choriocarcinoma elements, the presence of embryonal carcinoma elements, and the presence of teratoma elements (Table 2). Variables included in the initial multivariable model included age, pT stage, LVI, presence of choriocarcinoma, presence of embryonal carcinoma, and presence of teratoma; positive surgical margin was omitted since it applied to only one patient with extremely wide confidence intervals. Following backward stepwise selection, the final model included age ≥ 12 years and higher pT stage, both of which were independent predictors for events (Table 2, Figure 3).

DISCUSSION

Using a pooled cohort derived from three prospective cooperative trials, we report 100% 5-year survival among children with CS I TGCT and identified clinicopathologic predictors of relapse in these patients. In particular, we note that older age and higher primary tumor stage were the strongest independent predictors of relapse. As pediatric and adolescent patients with TGCT remain poorly studied, management of these patients is frequently extrapolated from data in adult populations. Identifying features predictive for relapse in children with low-risk TGCT is important to inform personalized treatment strategies for these patients while minimizing the risks and long-term toxicities associated with overtreatment.

Accepted management options for older patients (>18 years of age) with CS I non-seminomas (NSGCT) include surveillance, primary retroperitoneal lymph node dissection (RPLND), and adjuvant chemotherapy (typically one cycle of bleomycin, etoposide, and cisplatin).[12] In adults, surveillance is the preferred management strategy for patients with CS IA NSGCT, given cure rates of 85–90% with orchiectomy alone.[13] RPLND and adjuvant chemotherapy do not improve survival in patients with CS IA NSGCT and would thus

overtreat the majority of patients with CS IA NSGCT while exposing them to both short- and long-term toxicities. In contrast, adults with CS IB NSGCT, which by definition entails a higher primary tumor stage, experience recurrence rates as high as 45–50%, largely felt to be driven by LVI.[14] Thus, active adjuvant treatment strategies are more commonly used in this setting. LVI and embryonal carcinoma-predominant NSGCT, in particular, are associated with high rates of occult metastatic disease in adults, and may be helpful to guide the use of adjuvant treatment strategies among low-risk patients.[5]

Compared to adults, prognostic factors specific to children with low stage TGCT have not been elucidated, largely due to inherent challenges in studying this population of patients. Balancing a sufficiently aggressive treatment strategy while minimizing long-term toxicities from overtreatment is paramount for these highly curable patients. In earlier work assessing the low-risk stratum of the AGCT0132 cohort (defined as COG stage I), Rescorla et al. reported that age ≥11 years, mixed histology, and the presence of LVI were associated with relapse,[8] similar to our results reported herein from three pooled trials. In the present study, we uniquely classified patients according to the AJCC TNM staging criteria, which is used to guide management in adults with TGCT.[12,15] The TNM classification scheme is not directly included in the COG staging criteria, however, which is contingent on surgical control at orchiectomy and serves as the common referent in pediatric TGCT studies.[7] As the presence of LVI inherently defines primary tumors >pT1 stage, our findings suggest similarities in the biological factors driving aggressiveness in low-stage pediatric and adult TGCTs. Thus, our work highlights the important value of a combined approach that integrates expertise from adult urologic oncologists and pediatric oncologists who treat testicular cancer.

Curiously, while age is a less prominent prognostic feature in adults, our results reveal that older children with TGCT are more likely to experience relapse. Pediatric TGCTs demonstrate a bimodal age distribution, and histologic composition, particularly the extent of pure yolk sac elements, which tend to predominate in the younger age groups, may explain the differences in EFS. Aside from a greater propensity to harbor mixed histologic elements, including choriocarcinoma, embryonal carcinoma, or teratoma, older patients were also noted more likely to harbor LVI. Notably, in a recent analysis of patients with extracranial metastatic GCTs derived from 11 pooled trials, Shaikh et al. trichotomized patients by age, to include children (0 to <11 years), adolescents (11 to <18 years), and young adults (18 to ≤30 years).[16] They found adolescents to have worse 5-year event-free survival—defined as relapse or progression, second malignancy, or death—compared to children or young adults (72% for adolescents; 90% for children (p=0.003 vs. adolescents); 88% for young adults (p=0.0002 vs. adolescents)). Their findings highlight the recommendation to treat adolescents with advanced TGCT using regimens developed for adults rather than those developed for children. Evaluation of biological differences in TGCTs by age may help further elucidate these clinical observations, particularly in the low risk setting, which demonstrates the natural history of disease on surveillance.

Serum microRNAs (miRNAs) have recently emerged as encouraging candidate biomarkers for both diagnosing and monitoring TGCT in adults.[17–27] Specifically, we have observed that circulating miR-371a-3p levels have the ability to predict occult viable GCT in low-risk

patients undergoing primary RPLND with greater sensitivity than conventional serum tumor markers or contemporary cross-sectional radiographic imaging techniques.[26] The role of miRNAs in children with TGCT has yet to be evaluated systematically, but we speculate that, taken together with the clinicopathologic features identified herein, miRNA may similarly inform personalized management strategies for children with CS I disease and warrants attention in future efforts.

Although our study population reflects the largest pooled prospective cohort of CS I pediatric and adolescent TGCT to our knowledge, the relatively low event rate limits our multivariable analysis, and longer follow-up duration would help further characterize the natural history of these patients. Furthermore, our pooled cohort was highly skewed towards patients enrolled in AGCT0132, with relatively fewer patients from INT-0106 and INT-0097, introducing potential selection bias, and observation protocols were not standardized across the three trials. Centralized pathologic review using the contemporary CAP reporting template for TGCT was also unable to be performed for several patients. The reason for this stems from the long time span across which patients had been enrolled in the 3 trials (1990–2010), including INT-0097 (1990–1995), INT-0106 (1990–1996), and AGCT-0132 (2003–2010). Centralized pathologic review for each of these trials had been conducted at the time of trial completion/reporting, while the CAP reporting template has evolved substantially over this time period as more evidence has emerged regarding relevant pathologic variables to report from radical orchiectomy specimens. In the interest of maintaining statistical integrity and rigor, if patients were missing any of the relevant elements in the contemporary CAP template, then the rest of the variables were coded as “Unknown.” Nevertheless, by shedding light on clinicopathologic features predictive for relapse among children with low-risk TGCT, our work represents an important step in informing personalized treatment strategies for these patients.

CONCLUSION

In a pooled cohort derived from three prospective cooperative trials, we found that children with CS I TGCT exhibit 100% 5-year survival. We also identified older age at presentation and higher primary tumor stage as independent predictors of relapse among this cohort. Identifying features predictive for relapse in children with low-risk TGCT can help inform personalized treatment strategies (surveillance versus adjuvant treatment approaches) for these highly curable patients while minimizing the risks and long-term toxicities associated with overtreatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30. [PubMed: 31912902]
2. Walsh TJ, Grady RW, Porter MP, Lin DW, Weiss NS. Incidence of testicular germ cell cancers in U.S. children: SEER program experience 1973 to 2000. Urology. 2006;68(2):402–405; discussion 405. [PubMed: 16904461]
3. Gobel U, Schneider DT, Calaminus G, Haas RJ, Schmidt P, Harms D. Germ-cell tumors in childhood and adolescence. GPOH MAKEI and the MAHO study groups. Ann Oncol. 2000;11(3):263–271. [PubMed: 10811491]
4. Bagrodia A, Pierorazio P, Singla N, Albers P. The Complex and Nuanced Care for Early-stage Testicular Cancer: Lessons from the European Association of Urology and American Urological Association Testis Cancer Guidelines. Eur Urol. 2020;77(2):139–141. [PubMed: 31672465]
5. Blok JM, Pluim I, Daugaard G, et al. Lymphovascular invasion and presence of embryonal carcinoma as risk factors for occult metastatic disease in clinical stage I nonseminomatous germ cell tumour: a systematic review and meta-analysis. BJU Int. 2020;125(3):355–368. [PubMed: 31797520]
6. Brimo F, Srigley J, Ryan C: Testis. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 727–35.
7. Schlatter M, Rescorla F, Giller R, et al. Excellent outcome in patients with stage I germ cell tumors of the testes: a study of the Children's Cancer Group/Pediatric Oncology Group. J Pediatr Surg. 2003;38(3):319–324; discussion 319–324. [PubMed: 12632342]
8. Rescorla FJ, Ross JH, Billmire DF, et al. Surveillance after initial surgery for Stage I pediatric and adolescent boys with malignant testicular germ cell tumors: Report from the Children's Oncology Group. J Pediatr Surg. 2015;50(6):1000–1003. [PubMed: 25812445]
9. Cushing B, Giller R, Cullen JW, et al. Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study--Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol. 2004;22(13):2691–2700. [PubMed: 15226336]
10. Rogers PC, Olson TA, Cullen JW, et al. Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: A Pediatric Intergroup Study--Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol. 2004;22(17):3563–3569. [PubMed: 15337806]
11. Billmire DF, Cullen JW, Rescorla FJ, et al. Surveillance after initial surgery for pediatric and adolescent girls with stage I ovarian germ cell tumors: report from the Children's Oncology Group. J Clin Oncol. 2014;32(5):465–470. [PubMed: 24395845]
12. Stephenson A, Eggener SE, Bass EB, et al. Diagnosis and Treatment of Early Stage Testicular Cancer: AUA Guideline. J Urol. 2019;202(2):272–281. [PubMed: 31059667]
13. Nayan M, Jewett MA, Hosni A, et al. Conditional Risk of Relapse in Surveillance for Clinical Stage I Testicular Cancer. Eur Urol. 2017;71(1):120–127. [PubMed: 27527805]
14. Huddart RA, Reid AM. Adjuvant Therapy for Stage IB Germ Cell Tumors: One versus Two Cycles of BEP. Adv Urol. 2018;2018:8781698. [PubMed: 29808086]
15. Gilligan T, Lin DW, Aggarwal R, et al. Testicular Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(12):1529–1554. [PubMed: 31805523]
16. Shaikh F, Stark D, Fonseca A, et al. Outcomes of adolescent males with extracranial metastatic germ cell tumors: A report from the Malignant Germ Cell Tumor International Consortium. Cancer. 2020.
17. Murray MJ, Halsall DJ, Hook CE, Williams DM, Nicholson JC, Coleman N. Identification of microRNAs From the miR-371~373 and miR-302 clusters as potential serum biomarkers of malignant germ cell tumors. Am J Clin Pathol. 2011;135(1):119–125. [PubMed: 21173133]
18. Belge G, Dieckmann KP, Spiekermann M, Balks T, Bullerdiek J. Serum levels of microRNAs miR-371–3: a novel class of serum biomarkers for testicular germ cell tumors? Eur Urol. 2012;61(5):1068–1069. [PubMed: 22386195]

19. Syring I, Bartels J, Holdenrieder S, Kristiansen G, Muller SC, Ellinger J. Circulating serum miRNA (miR-367-3p, miR-371a-3p, miR-372-3p and miR-373-3p) as biomarkers in patients with testicular germ cell cancer. J Urol. 2015;193(1):331–337. [PubMed: 25046619]

20. van Agthoven T, Looijenga LHJ. Accurate primary germ cell cancer diagnosis using serum based microRNA detection (ampTSmiR test). Oncotarget. 2017;8(35):58037–58049. [PubMed: 28938535]

21. Bezan A, Gerger A, Pichler M. MicroRNAs in testicular cancer: implications for pathogenesis, diagnosis, prognosis and therapy. Anticancer Res. 2014;34(6):2709–2713. [PubMed: 24922631]

22. van Agthoven T, Eijkenboom WMH, Looijenga LHJ. microRNA-371a-3p as informative biomarker for the follow-up of testicular germ cell cancer patients. Cell Oncol (Dordr). 2017;40(4):379–388. [PubMed: 28612337]

23. Radtke A, Hennig F, Ikogho R, et al. The Novel Biomarker of Germ Cell Tumours, Micro-RNA-371a-3p, Has a Very Rapid Decay in Patients with Clinical Stage 1. Urol Int. 2018;100(4):470–475. [PubMed: 29698973]

24. Dieckmann KP, Radtke A, Geczi L, et al. Serum Levels of MicroRNA-371a-3p (M371 Test) as a New Biomarker of Testicular Germ Cell Tumors: Results of a Prospective Multicentric Study. J Clin Oncol. 2019:JCO1801480.

25. Singla N, Lafin JT, Bagrodia A. MicroRNAs: Turning the Tide in Testicular Cancer. Eur Urol. 2019;76(5):541–542. [PubMed: 31230742]

26. Lafin JT, Singla N, Woldu SL, et al. Serum MicroRNA-371a-3p Levels Predict Viable Germ Cell Tumor in Chemotherapy-naive Patients Undergoing Retroperitoneal Lymph Node Dissection. Eur Urol. 2020;77(2):290–292. [PubMed: 31699528]

27. Badia RR, Abe D, Wong D, et al. Real-World Application of Pre-orchiectomy miR-371a-3p Test in Testicular Germ Cell Tumor Management. J Urol. 2020:101097JU0000000000001337.

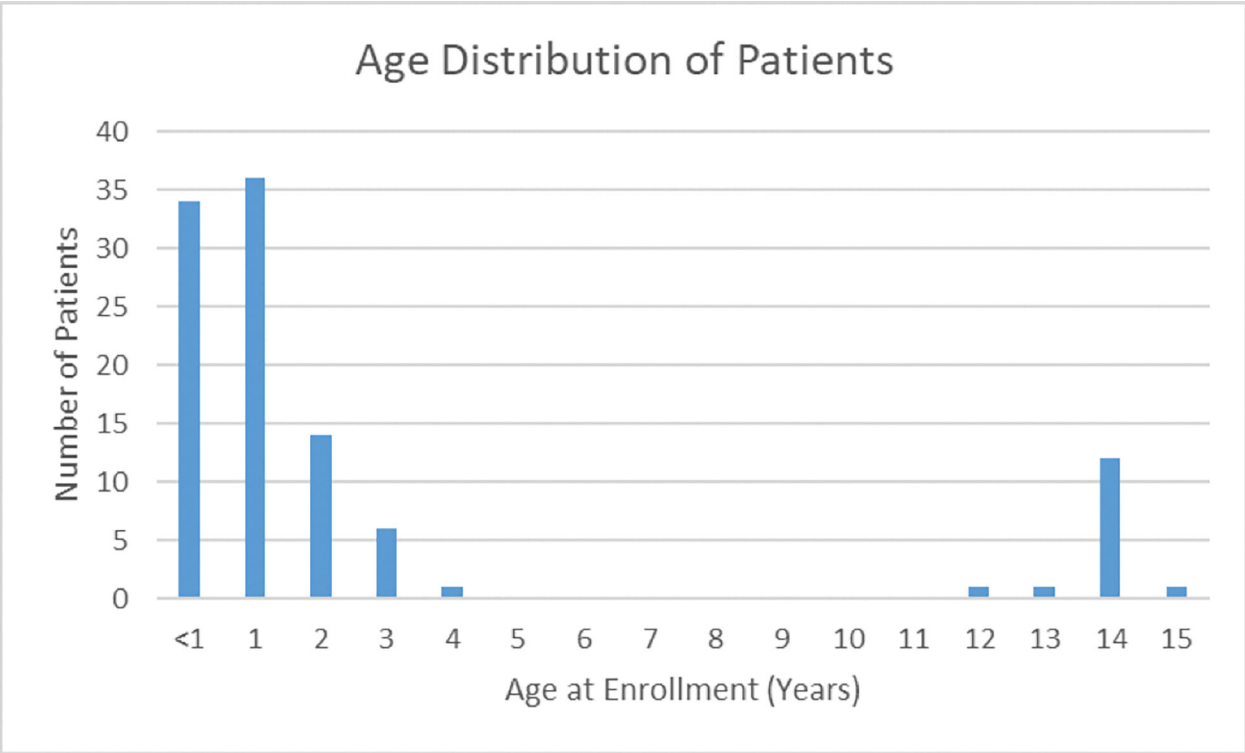

Figure 1.
Age distribution of the analytic cohort.

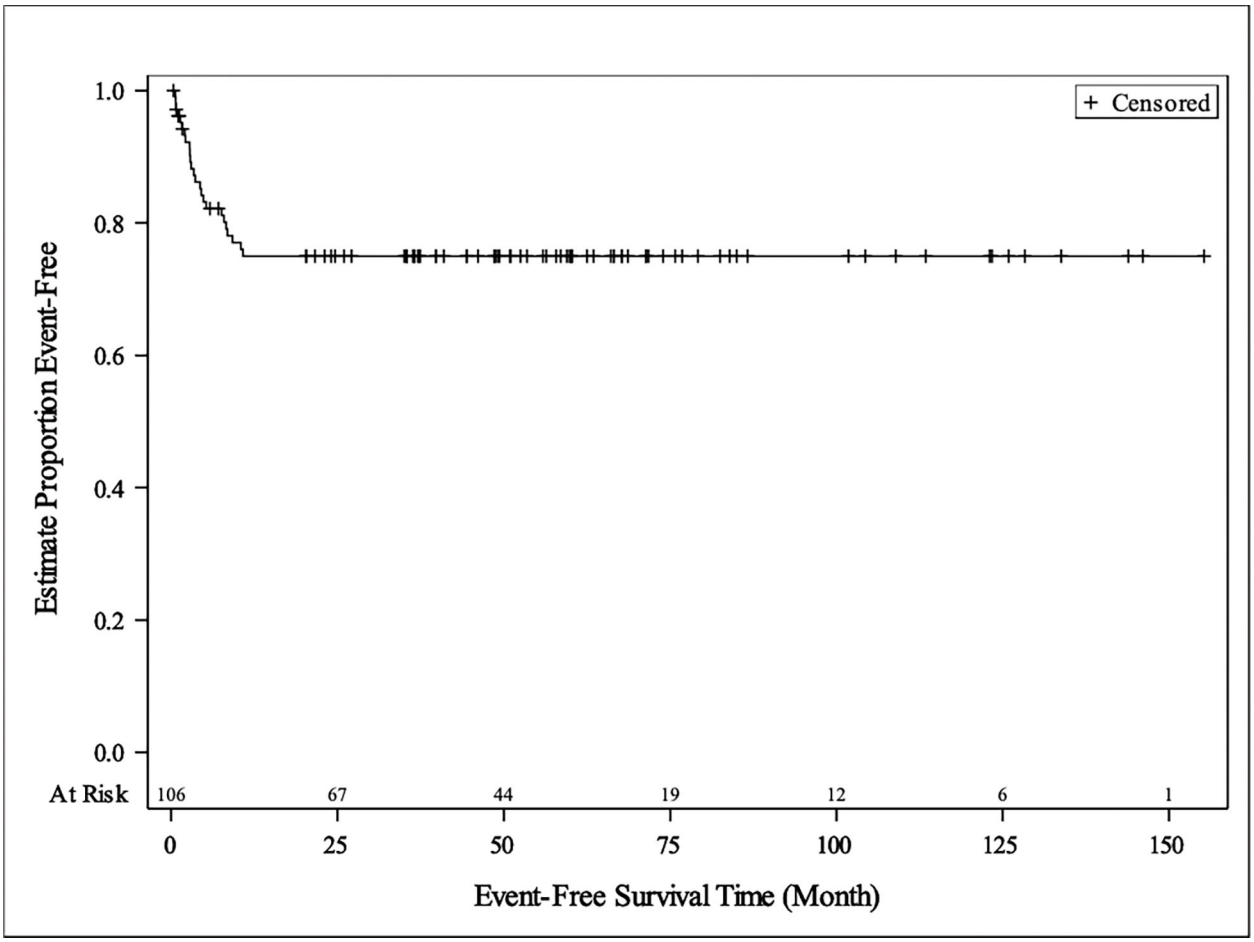

Figure 2.
Event-free survival from enrollment for the analytic cohort.

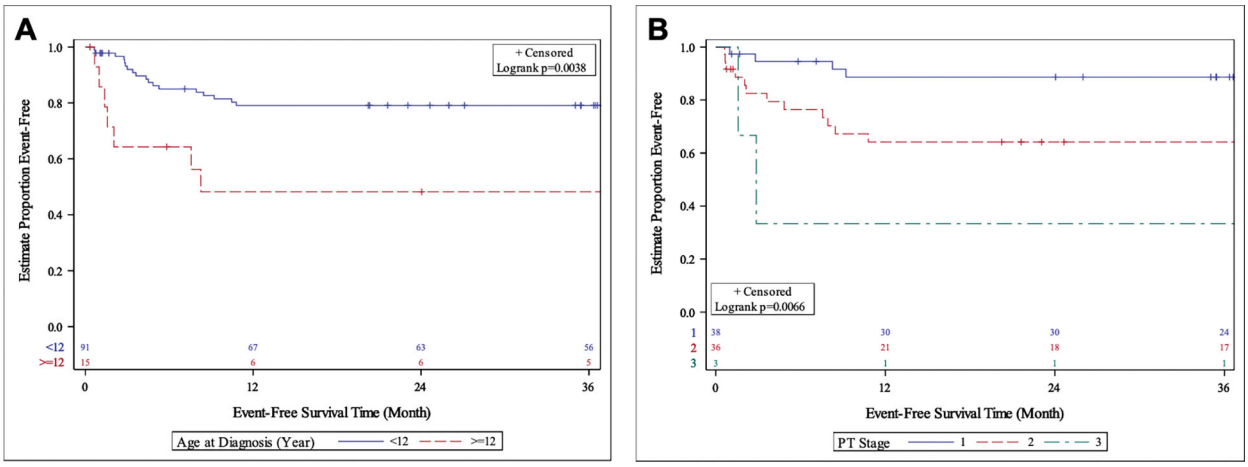

Figure 3.
Event-free survival stratified by (A) age at diagnosis and (B) pT stage.

Table 1.

Pathologic characteristics of primary radical orchiectomy tumor specimen stratified by age.

Characteristic	Total patients, n (%)	Patients <12 years old, n (%)	Patients ≥12 years old, n (%)
Number of patients	106	91	15
pT stage:			
-pT1	38 (35.8%)	30 (33.0%)	8 (53.3%)
-pT2	36 (34.0%)	32 (35.2%)	4 (26.7%)
-pT3	3 (2.8%)	2 (2.2%)	1 (6.7%)
-Unknown	29 (27.4%)	27 (29.7%)	2 (13.3%)
Surgical margin status:			
-Positive	1 (0.9%)	0 (0%)	1 (6.7%)
-Negative	72 (67.9%)	62 (68.1%)	10 (66.7%)
-Unknown	33 (31.1%)	29 (31.9%)	4 (26.7%)
Lymphovascular invasion:			
-Present	39 (36.8%)	31 (34.1%)	8 (53.3%)
-Absent	38 (35.8%)	31 (34.1%)	7 (46.7%)
-Unknown	29 (27.4%)	29 (31.9%)	0 (0%)
Choriocarcinoma elements:			
-Present	9 (8.5%)	1 (1.1%)	8 (53.3%)
-Absent	70 (66.0%)	64 (70.3%)	6 (40.0%)
-Unknown	27 (25.5%)	26 (28.6%)	1 (6.7%)
Embryonal carcinoma elements:			
-Present	15 (14.2%)	1 (1.1%)	14 (93.3%)
-Absent	64 (60.4%)	64 (70.3%)	0 (0%)
-Unknown	27 (25.5%)	26 (28.6%)	1 (6.7%)
Yolk sac tumor elements:			
-Present	79 (74.5%)	65 (71.4%)	14 (93.3%)
-Absent	0 (0%)	0 (0%)	0 (0%)
-Unknown	27 (25.5%)	26 (28.6%)	1 (6.7%)
Teratoma elements:			
-Present	15 (14.2%)	4 (4.4%)	11 (73.3%)
-Absent	64 (60.4%)	61 (67.0%)	3 (20.0%)
-Unknown	27 (25.5%)	26 (28.6%)	1 (6.7%)
Seminoma elements:			
-Present	5 (4.7%)	0 (0%)	5 (33.3%)
-Absent	74 (69.8%)	65 (71.4%)	9 (60.0%)
-Unknown	27 (25.5%)	26 (28.6%)	1 (6.7%)

Characteristic	Total patients, n (%)	Patients <12 years old, n (%)	Patients ≥12 years old, n (%)
AFP level at enrollment (ng/ml):			
-Normal	8 (7.5%)	5 (5.5%)	3 (20.0%)
-Elevated, <9,999 ng/ml	83 (78.3%)	71 (78.0%)	12 (80.0%)
-Elevated, ≥10,000 ng/ml	15 (14.2%)	15 (16.5%)	0 (0%)
P-HCG level at enrollment (IU/ml):			
-<11	54 (50.9%)	51 (56.0%)	3 (20.0%)
->11	6 (5.7%)	0 (0%)	6 (40.0%)
-Unknown	46 (43.4%)	40 (44.0%)	6 (40.0%)

Table 2.

Univariable and multivariable predictors of events.

Predictor	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age ≥12 years	3.38 (1.41–8.12)	0.0064	8.87 (2.97–26.5)	<0.0001
pT stage:				
-pT1	Ref.	Ref.	Ref.	Ref.
-pT2	3.77 (1.22–11.69)	0.0216	7.31 (2.11–25.3)	0.0017
-pT3	9.69 (1.76–53.45)	0.0092	13.5 (2.27–80.8)	0.0043
Lymphovascular invasion	2.80 (1.06–7.38)	0.0371	*	
Positive surgical margin	71.50 (4.47–1143.10)	0.0025		
Presence of choriocarcinoma	4.18 (1.49–11.69)	0.0064	*	
Presence of embryonal carcinoma	4.38 (1.76–10.94)	0.0015	*	
Presence of teratoma	4.63 (1.85–11.60)	0.0011	*	
Presence of seminoma	2.51 (0.58–10.88)	0.2198		
AFP at enrollment:				
-Normal	Ref.	Ref.		
-<9,999 ng/ml	1.32 (0.39–4.43)	0.6575		
-≥10,000 ng/ml	1.47 (0.25–8.80)	0.6729		
β-HCG at enrollment ≥11 IU/ml	3.39 (0.93–12.35)	0.0643		
Dominant tumor size less than median	0.28 (0.08–1.01)	0.0515		

* Variables removed from multivariable model following backwards stepwise selection.