

Phase II Trial Assessing the Ability of Neoadjuvant Chemotherapy With or Without Second-Look Surgery to Eliminate Measurable Disease for Nongerminomatous Germ Cell Tumors: A Children's Oncology Group Study

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A B S T R A C T

Purpose

This phase II trial evaluated the effect of neoadjuvant chemotherapy with or without second-look surgery before craniospinal irradiation on response rates and survival outcomes in children with newly diagnosed nongerminomatous germ cell tumors.

Patients and Methods

Induction chemotherapy consisted of six cycles of carboplatin/etoposide alternating with ifosfamide/etoposide. Patients demonstrating less than complete response after induction chemotherapy were encouraged to undergo second-look surgery. Patients who did not achieve complete response or partial response after chemotherapy with or without second-look surgery proceeded to high-dose chemotherapy with thiotepa and etoposide and autologous peripheral blood stem-cell rescue before craniospinal irradiation.

Results

The study included 102 patients treated between January 2004 and July 2008. Median age was 12 years, and 76% were male; 53.9% had pineal region masses, and 23.5% had suprasellar lesions. Sixty-nine percent of patients achieved complete response or partial response with neoadjuvant chemotherapy. At 5 years, event-free survival was $84\% \pm 4\%$ (SE) and overall survival was $93\% \pm 3\%$. During the median follow-up of 5.1 years, 16 patients recurred or progressed, with seven deaths after relapse. No deaths were attributed to therapy-related toxicity. Relapse occurred at the site of primary disease in 10 patients, at a distant site in three patients, or both in one patient. In two patients, progression was detected by marker increase alone. Increased serum α -fetoprotein was a negative prognostic variable. Histologic subtype and increase of beta-human chorionic gonadotropin were not significantly correlated with worse outcomes.

Conclusion

Neoadjuvant chemotherapy with or without second-look surgery achieved high response rates contributing to excellent survival outcomes in children with newly diagnosed nongerminomatous germ cell tumors. This regimen should be included as a backbone for further studies.

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INTRODUCTION

Primary germ cell tumors (GCTs) are relatively uncommon CNS malignancies, comprising less than 4% of brain tumors in children in Western countries.^{1,2} In Japan and continental Asia, CNS GCTs account for approximately 11% of pediatric brain tumors.³⁻⁶ These tumors arise predominantly in pineal and suprasellar locations, and approximately 90% of these tumors occur before age 20 years with peak incidence at age 10 to 12 years.³ Overall, CNS GCTs predominate in males at a ratio of 3:1.^{7,8}

CNS GCTs include a heterogeneous group of histologic subtypes linked to prognosis and treatment success and divided into germinoma and nongerminomatous germ cell tumors (NGGCTs). The NGGCT group comprises several histologies, including embryonal carcinoma, endodermal sinus tumor (yolk sac tumors), choriocarcinoma, immature teratoma, teratoma with malignant transformation, and mixed tumors. Mixed tumors may include any of these components as well as germinomatous elements.⁷ Compared with pure germinomas, NGGCTs are less radiosensitive, and their

prognosis with radiotherapy alone has been poor (5-year survival of 20% to 45%).⁹

The Children’s Oncology Group (COG) developed a phase II study (ACNS0122; Phase II Study to Assess the Ability of Neoadjuvant Chemotherapy With or Without Second Look Surgery to Eliminate All Measurable Disease Prior to Radiotherapy for NGGCT) to assess the ability of neoadjuvant chemotherapy, with or without second-look surgery before radiotherapy, to eliminate measurable disease in children with newly diagnosed NGGCTs. The trial measured response rates after six cycles of neoadjuvant chemotherapy, evaluated event-free survival (EFS) and overall survival (OS), and correlated serum and CSF tumor markers (α -fetoprotein [AFP] and beta-human chorionic gonadotropin [β -hCG]) with radiographic response. This trial also attempted to determine whether high-dose chemotherapy (HDCT) and autologous peripheral blood stem-cell rescue (PBSCR) could improve response before craniospinal irradiation (CSI) for patients with poor response to neoadjuvant chemotherapy.

PATIENTS AND METHODS

Patients

Between January 26, 2004, and July 18, 2008, patients 3 to 24 years of age with newly diagnosed NGGCTs or high-risk germinoma were eligible for study inclusion (Fig 1). Histologic diagnoses of NGGCTs included endoder-

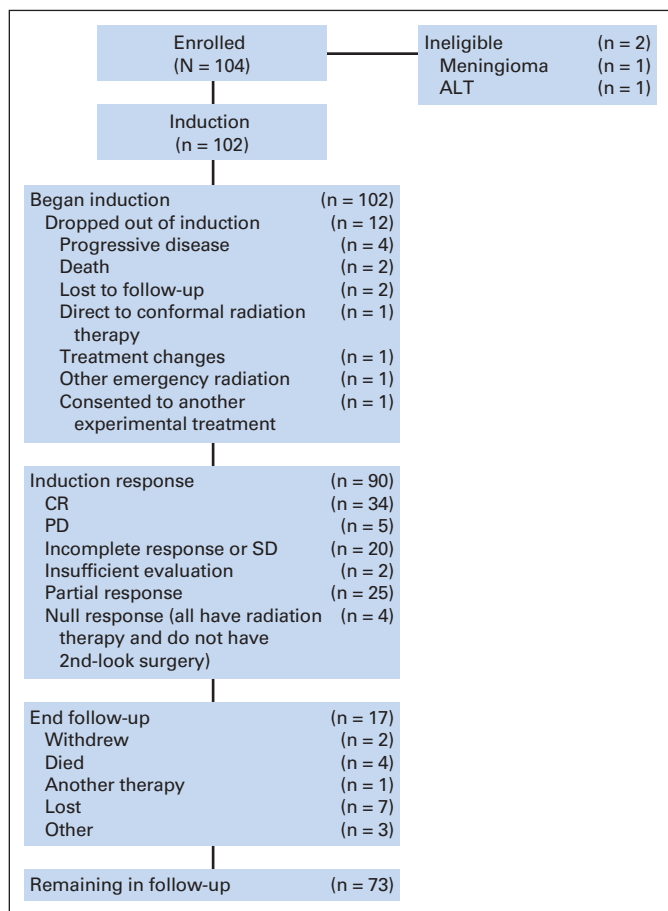


Fig 1. CONSORT diagram. CR, complete response; PD, progressive disease; SD, stable disease.

mal sinus tumor (yolk sac tumor), embryonal carcinoma, choriocarcinoma, immature teratoma, teratoma with malignant transformation, and mixed germ cell tumors. Patients were eligible for study without histologic confirmation if serum and/or CSF β -hCG was more than 50 IU/L, or if AFP was more than 10 IU/L or above the institutional normal range. Any germinoma with serum or CSF β -hCG of more than 50 IU/L was defined as high risk and was eligible for study. No previous therapy was allowed other than surgical intervention and corticosteroids.

Tests and Examinations

Baseline magnetic resonance imaging (MRI) scans of the brain and spine with and without gadolinium were required. For patients who underwent initial surgical resection, postoperative MRI scans were required within 72 hours of surgery or after a minimum of 21 days after resection. Serum and CSF β -hCG and AFP were measured at the time of enrollment; CSF was obtained unless clinically contraindicated. Serum tumor markers were determined before each chemotherapy cycle, and CSF markers and cytology were repeated every other cycle (Appendix Table A1, online only).

Study Treatments

The treatment schema and dosing regimens are outlined in Figure 2. All patients began therapy within 31 days of diagnosis. Patients received six cycles of intravenous neoadjuvant chemotherapy on a 21-day cycle consisting of carboplatin 600 mg/m² on day 1 plus etoposide 90 mg/m² on days 1 through 3 (cycles 1, 3, and 5) alternating with ifosfamide 1,800 mg/m² on days 1 through 5 and etoposide 90 mg/m² on days 1 through 5 (cycles 2, 4, and 6). Granulocyte colony-stimulating factor (5 μ g/kg per day) was given after each cycle. After completion of induction therapy, patients with residual tumor and/or persistently elevated tumor markers were strongly encouraged to undergo second-look surgery. Patients whose tumor met the criteria for complete response (CR) or partial response (PR), with or without second-look surgery, proceeded to CSI. For those who did not meet the criteria for CR or PR, it was recommended that they undergo consolidation therapy with thiotepa 300 mg/m² and etoposide 500 mg/m² on days -5 to -3, followed by PBSCR and CSI.

Radiation was administered to the craniospinal axis to 36 Gy with a boost to tumor bed sites totaling 54 Gy. For patients with disseminated disease at diagnosis, sites of bulky metastasis received a boost to 45 Gy regardless of response to induction chemotherapy.

Study End Points

The primary end point was response to induction chemotherapy, determined on the basis of MRI response, second-look surgery, and serum and CSF tumor markers. Centralized review of induction response occurred at the Quality Assurance Review Center (QARC). Tumor response was measured in three dimensions by using either T1- or T2-weighted MRI images. CR was defined as disappearance of all radiographic disease or evidence of only fibrosis or mature teratomatous elements on second-look surgery, as well as normalization of serum and CSF tumor markers. PR was defined as a more than 65% decrease in the sum of the products of the three perpendicular diameters of all target lesions on MRI scan and normalization of serum and CSF tumor markers. Stable disease (SD) was defined as neither sufficient decrease nor increase in the product of the three-dimensional (3D) measurements of a lesion to meet response or progression criteria without increase of tumor markers from baseline. Progressive disease (PD) was defined as a more than 40% increase in the products of a lesion, taking as a reference the smallest product observed since the start of treatment, the appearance of any new lesion, or an increase in tumor markers. If 3D measurements could not be obtained, then standard 2D definitions of imaging response were applied.

Secondary end points of treatment efficacy were EFS and OS. EFS was defined as the time to first disease progression, disease recurrence, death as a result of any cause, or occurrence of a second malignant neoplasm. OS was defined as the time to death as a result of any cause.

Statistical Analysis

The primary statistical analysis estimated response rate of NGGCTs to induction chemotherapy. Secondary analyses included estimating long-term

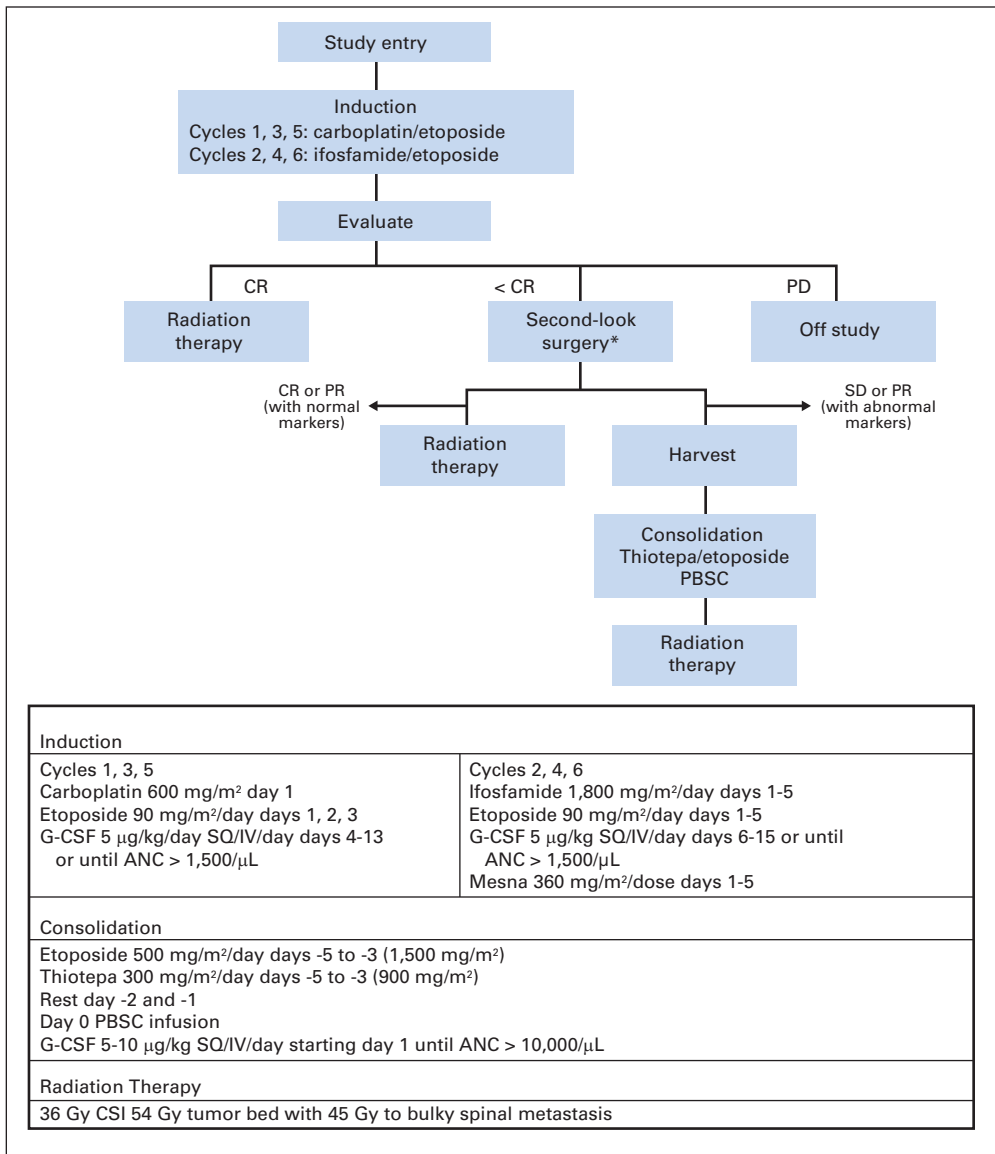


Fig 2. Treatment schema and dosing. ANC, absolute neutrophil count; CSI, cranio-spinal irradiation; CR, complete response; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; PBSC, peripheral blood stem cell; PD, progressive disease; PR, partial response; SD, stable disease; SQ, subcutaneous. (*) Strongly recommended but not required.

EFS and OS rates and the rates of key toxicities. Nonparametric EFS and OS curves were computed by using product-limit (Kaplan-Meier) estimates, with standard errors calculated by using the Greenwood formula.

RESULTS

Patient Characteristics

One hundred four patients were enrolled onto the study, of whom 102 were eligible. Age ranged from 3 to 23 years (median 12 years). Seventy-nine patients (76%) were male. Other patient and tumor characteristics are presented in Table 1. Primary tumor sites were pineal (53.9%) and suprasellar (23.5%). Pineal involvement was present in five (21%) of 24 females and 50 (64%) of 78 males, whereas tumor was located in the suprasellar region in 14 (58%) of 24 females and only 10 (13%) of 78 males. Eight patients presented with bifocal (pineal and suprasellar) disease, of whom six were male.

Thirty-two patients (31.4%) underwent resection or biopsy at the time of diagnosis: 14 patients underwent gross total resection; one

patient had a near total resection, eight had a subtotal resection, six had a partial resection, and three patients underwent biopsy only. The other 70 patients (68.6%) were enrolled based solely on the presence of increased serum and/or CSF β -hCG or AFP.

Tumor marker data are presented in Table 2. At study entry, both serum and CSF β -hCG and AFP were measured for 70.6% of patients (72). Thirty patients were missing data for at least one marker. Overall, 89% of patients (91 of 102) had at least one marker increased at baseline.

Response to Induction Chemotherapy

End-of-induction response was reviewed for 89 patients: 34 (38%) achieved CR, 25 (28%) PR, and 20 (22%) SD, whereas five patients had PD and five had insufficient (2) or missing (3) data for evaluation of response. Overall, induction produced a 69% objective response rate (CR or PR) in the evaluable patients. Of the 89 patients reviewed centrally by the QARC, four were not reviewed secondary to missing data. For the evaluable patients, QARC reported 51% (43 of

Table 1. Patient Demographic Characteristics and Primary Disease Sites

Characteristic	No.	%
Eligible patients	102	
Sex		
Male	78	76
Female	24	24
Race/ethnicity		
White	71	78.9
Black	9	10.0
Other	10	11.1
Missing	12	11.8
Ethnicity		
Non-Hispanic	83	83
Hispanic	17	17
Missing	2	2
Primary disease site		
Pineal	55	53.9
Suprasellar	24	23.5
Third ventricle	8	7.8
Basal ganglia-thalamus	6	5.9
Hypothalamus-optic chiasm	3	2.9
Frontal lobe	2	2.0
Lateral ventricle	1	1.0
Midbrain	1	1.0
Optic nerve	1	1.0
Other supratentorial	1	1.0

85) CR, 36% (31 of 85) PR, 5% (four of 85) SD, and 8% (seven of 85) PD rates. Overall, QARC reported an 87% response rate (CR plus PR) to induction chemotherapy (Table 3).

Second-Look Surgery

Fifteen patients underwent second-look surgery after induction chemotherapy. Only two of these patients (13%) had residual NGGCTs (one embryonal carcinoma and one mixed germ cell tumor). Nine had teratomas (six mature teratomas and three malignant teratomas) and four had fibrosis/no evidence of tumor. Four of five patients who underwent second-look surgery at progression were also found to have teratoma with no other GCT elements. Subsequently, one of these four had further progression, and one was found to have increased AFP without any identifiable CNS or systemic lesion.

Response to Consolidation Therapy and PBSCR

Two patients with residual disease underwent consolidation therapy with PBSCR while on study. Both patients achieved a CR 39 to 53 months after therapy.

Table 2. Tumor Markers at Study Entry

Tumor Marker/Source	No. Evaluated/ No. Evaluable	%	Median (IU/L)	Range (IU/L)
β -hCG \geq 50 IU/L				
Serum	36/98	37	212	50-6,900
CSF	39/84	46	220	51.8-26,610
AFP \geq 10 IU/L				
Serum	59/94	63	171	12.2-106,000
CSF	37/84	44	110	10.6-18,000

Abbreviations: AFP, α -fetoprotein; β -hCG, beta-human chorionic gonadotropin.

Table 3. Institutional and Central Review Results

Results	Institutional Review No. (%)	QARC Review No. (%)
Institutional and central review		
Complete response	34 (40)	43 (51)
Partial response	25 (30)	31 (36)
Incomplete response/stable disease	20 (24)	4 (5)
Progressive disease	5 (6)	7 (8)
Insufficient evaluation	2 (2)	0 (0)
Missing	3 (3)	4 (4)
Institutional and central review, non-GTR		
Complete response	24 (33)	33 (45)
Partial response	25 (34)	31 (42)
Incomplete response/stable disease	19 (26)	3 (4)
Progressive disease	5 (7)	6 (8)
Insufficient evaluation	2 (3)	0 (0)
Missing	2 (3)	4 (5)
Institutional and central review, GTR		
Complete response	10 (91)	10 (83)
Partial response	0 (0)	0 (0)
Incomplete response/stable disease	1 (9)	1 (8)
Progressive disease	0 (0)	1 (8)
Insufficient evaluation	0 (0)	0 (0)
Missing	1 (8)	0 (0)

Abbreviations: GTR, gross total resection; QARC, Quality Assurance Review Center.

Survival Outcomes

For the 102 eligible patients in the study, the median follow-up without an event was 5.1 years (range, 0.06 to 8.0 years). Five-year EFS and OS were 84% \pm 4% and 93% \pm 3%, respectively (Fig 3A). For the 14 patients without radiographic disease at diagnosis, 5-year EFS and OS were both 100%. The 88 patients with measurable/evaluable disease at diagnosis had 5-year EFS of 81% \pm 4% and OS of 92% \pm 3% (Fig 3B). Histologic stratification did not reveal any significant differences in OS rate (Fig 3C).

Patients with serum or CSF β -hCG \geq 100 IU/L had a 5-year EFS rate of 84% and OS rate of 92% (Fig 4A). There was no significant difference in survival of patients stratified by serum or CSF β -hCG \geq 1,000 IU/L (EFS: 86%, $P = .960$; OS: 91%, $P = .378$; Fig 4B). Increased serum or CSF AFP (\geq 10 IU/L or within institutional normal rates) was associated with EFS of 78% and OS of 91%. Increased AFP approached a statistically significant negative association with EFS ($P = .063$; Fig 4C). Of note, patients who met eligibility for the study based solely on marker increases in serum and/or CSF were coded as mixed germ cell tumors independent of any histologic findings determined by second-look surgery.

The EFS was 92% and the OS was 98% at 3 years for all patients who achieved CR or PR either after induction chemotherapy or with documentation of absence of malignant elements at second-look surgery (Fig 5).

Treatment Failures

At a median follow-up of 5.1 years, 16 of the 102 patients had recurred or progressed, of whom seven died. One patient died without relapse, for a total of 17 treatment failure events. There were 10 local failures, one combined local and distant, three distant, and two by

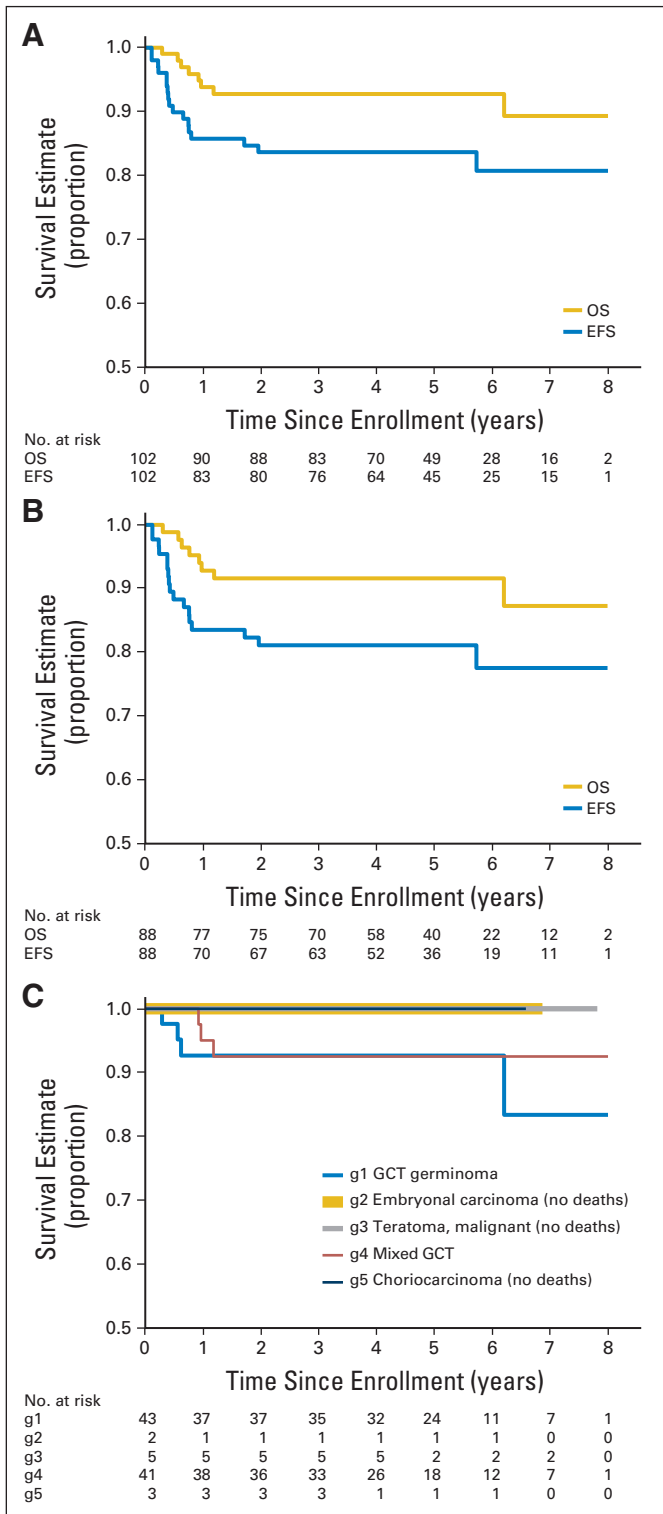


Fig 3. Overall survival (OS) and event-free survival (EFS). (A) OS and EFS for all eligible patients. (B) OS and EFS for eligible patients excluding those with gross total resection. (C) OS by histology (blue line, germinoma with > 50 IU/L hCG; gold, embryonal carcinoma; gray, teratoma malignant; red, mixed germ cell tumor [GCT]; black, choriocarcinoma). Of note, patients with increased markers and no histology were coded as having mixed germ cell disease. g, group.

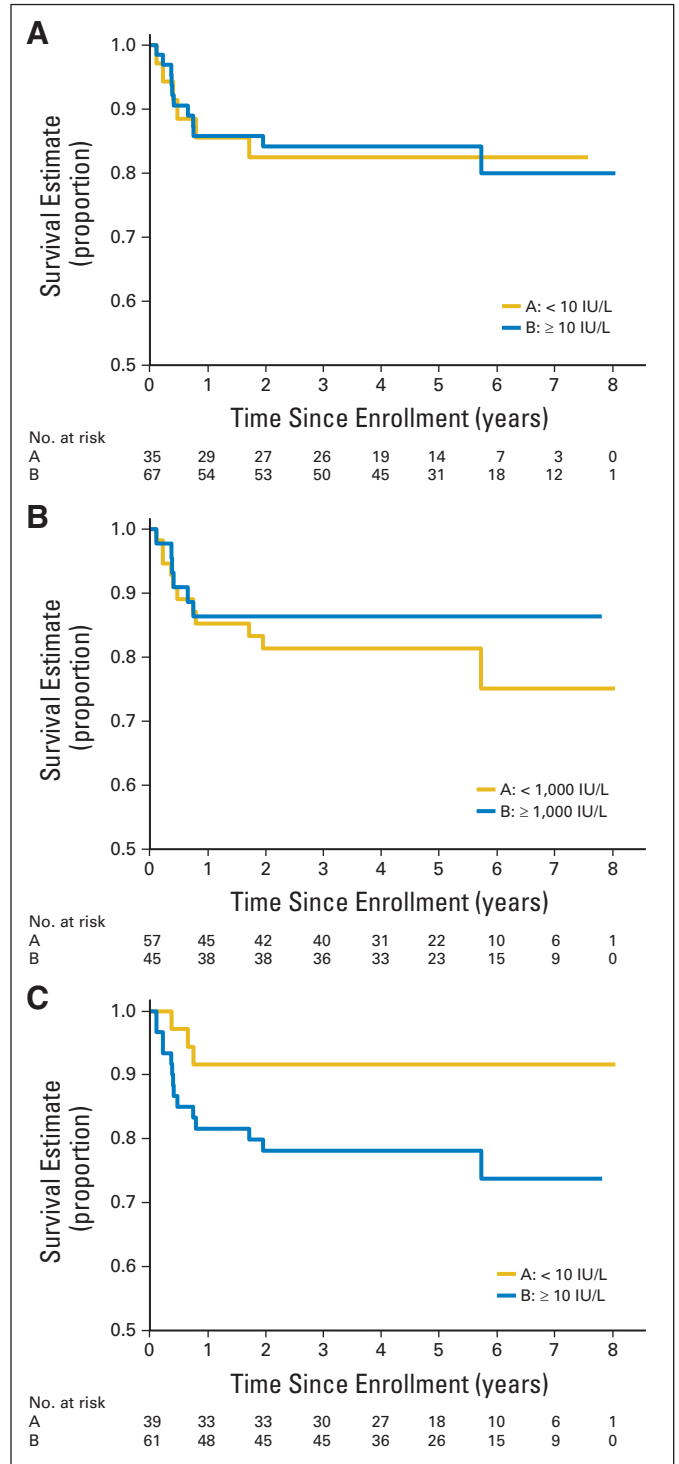


Fig 4. Event-free survival (EFS) stratified by serum or CSF markers. (A) EFS stratified by serum or CSF beta human chorionic gonadotropin less than 100 IU/L and \geq 100 IU/L. (B) EFS stratified by serum or CSF beta human chorionic gonadotropin at less than 1,000 IU/L and \geq 1,000 IU/L. (C) EFS stratified by serum or CSF α -fetoprotein at less than 10 IU/L and \geq 10 IU/L.

marker increase alone without imaging evidence of progression. Four of the patients with local failure underwent second-look surgery and were found to have only teratoma/malignant teratoma (growing teratoma syndrome), and were coded as PD on the basis of protocol

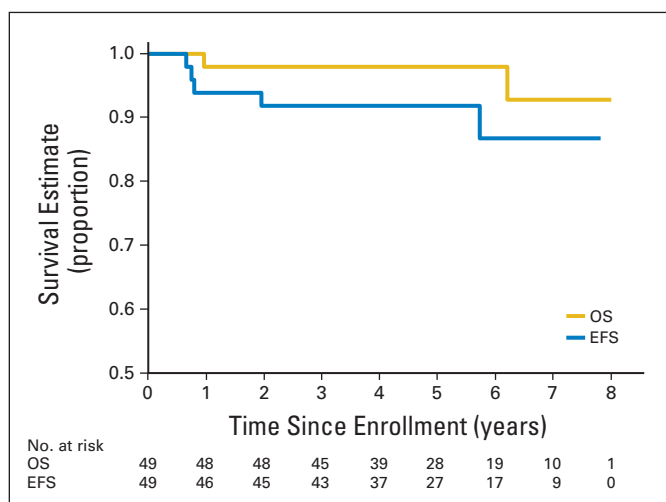


Fig 5. Overall survival (OS) and event-free survival (EFS) for patients with localized disease who achieved complete response or partial response with induction chemotherapy or second-look surgery.

criteria. Of the seven deaths subsequent to relapse, four patients had embryonal carcinoma. One of these four patients had a late recurrence that was coded pathologically as undifferentiated carcinoma.

Toxicity

Toxicities were evaluated by using the Common Toxicity Criteria Evaluation (version 4). No deaths were attributed to study treatment. The most common grade 3 and 4 toxicities consisted of transient and expected anemia (range of incidence during cycles of chemotherapy administered during induction, 17.6% to 30.3%); neutropenia (29.4% to 31.5%); thrombocytopenia (11.8% to 31.5%); and electrolyte abnormalities with hyponatremia (10.1% to 8.6%), hypernatremia (4.9% to 1.2%), and hypokalemia (6.7% to 10.3%) during induction cycles of chemotherapy. Overall, less than 5% of patients developed transient febrile neutropenia during therapy.

DISCUSSION

For children and adolescents with NGGCTs, the study regimen of six cycles of neoadjuvant chemotherapy (carboplatin/etoposide alternating with ifosfamide/etoposide) was well-tolerated with significant objective response rates and improved OS following CSI (93%). Historically, the survival rates for patients with NGGCTs have been poor compared with those for patients with germinomas. NGGCTs are less radiosensitive, and CSI alone has resulted in 5-year OS rates of only 30% to 50%. In previous studies, most relapses occurred within 18 months of diagnosis.^{1,2,8,10} Although our median follow-up was beyond 5 years, one patient recurred at 68 months, warranting further follow-up of our cohort.

The use of chemotherapy regimens for GCT was first introduced for testicular and extragonadal tumors. The cure rates for males with disseminated GCT of the testis increased from less than 10% to more than 50% after the introduction in 1974 of the Einhorn regimen of vinblastine, bleomycin, and cisplatin.^{11,12} The first trial of adjuvant chemotherapy for NGGCTs was reported in 1981 by Matsutani et al¹ from the University of Tokyo. Three trials performed by the Interna-

tional CNS GCT Study Group evaluated a chemotherapy-only approach, and although the majority of patients responded to chemotherapy, radiation was necessary to provide maximal cure rates.¹³⁻¹⁵ Robertson et al¹⁶ led a multi-institutional trial in 18 patients with NGGCTs who were treated with cisplatin and etoposide followed by irradiation. Twelve patients also underwent postirradiation chemotherapy with bleomycin, vinblastine, etoposide, and carboplatin. Nine of twelve assessable patients had an objective response to induction chemotherapy (four CR and five PR). The 4-year EFS rate was 67% and the 4-year OS rate was 74%.¹⁶ In 1999, the French Society of Pediatric Oncology combined carboplatin, ifosfamide, and etoposide followed by focal radiotherapy. Induction chemotherapy normalized tumor markers in all patients, all of whom had increased markers at diagnosis. At a median follow-up of 53 months, the OS rate was 74%.¹⁷ The German Cooperative Group MAKEI (Maligne Keimzelltumoren) 89 study reported a 67% 5-year OS for patients with NGGCTs treated with two cycles of bleomycin, etoposide, and cisplatin, followed by two cycles of vinblastine, ifosfamide, and cisplatin.^{18,19}

There is some controversy regarding the substitution of carboplatin for cisplatin for this patient population. In the treatment of systemic germ cell tumors, studies have shown superiority of cisplatin to carboplatin.^{20,21} Data from our trial revealed not only excellent response rates to a carboplatin-based induction regimen but also a 5-year EFS of 84% ± 4% and OS of 93% ± 3%, which are nominally superior to those of the previously reported French, German, and smaller American trials. Our regimen had no toxicity-related deaths and minimal grade 4 toxicities, supporting the notion that carboplatin can safely replace cisplatin for the treatment of CNS NGGCTs.

Our study protocol included standard-dose CSI. The French Society of Pediatric Oncology (SFOP) study reported a 74% OS rate with focal radiation therapy and used CSI only for those with metastatic or disseminated disease.¹⁷ In the study by Robertson et al,¹⁶ five patients received CSI and 13 received involved field irradiation; four of the six relapsing patients were in the involved field group and had isolated CNS relapses outside the radiation field. On the basis of these outcomes, we included CSI in our protocol, with the goal of moving more patients toward CR and achieving better survival outcomes. On the basis of this trial's preliminary data, current ongoing trials are evaluating CSI dose and volume reductions as part of their study design.

Growing teratoma syndrome (GTS) led to PD in four patients. GTS was first reported by Logothetis et al²² in 1982 in six patients with systemic, nonseminomatous germ cell tumors and has been estimated to occur in 2% to 7% of systemic GCTs.^{23,24} A PubMed search revealed only 10 publications involving intracranial GTS, most of which were case reports. In a review of 170 cases of intracranial germ cell tumors in South Korea, 11 patients (6.5%) developed GTS after therapy for NGGCTs.²⁵ In our study, patients underwent second-look surgery at the end of induction in an attempt to bring patients to CR or PR. Of the 15 patients who underwent second-look surgery at the end of induction, nine had teratomas with six of the nine showing no malignant elements. Of five patients who underwent resection following radiographic PD, four were found to have GTS. On the basis of this experience, the ongoing COG trial has incorporated a definition of GTS into the evaluation process.

HDCT has been investigated in patients with relapsed CNS GCTs.²⁶⁻²⁹ One aim of this trial was to determine whether patients who did not achieve PR or CR with induction chemotherapy with or

without second-look surgery would benefit from preirradiation HDCT with PBSCR. We were unable to test this hypothesis because only two patients proceeded to HDCT with PBSCR before radiation therapy. Unfortunately, data on patients with PD who underwent HDCT with PBSCR off study were not captured as part of the trial.

Previous studies have suggested that GCT histologic subtype is of prognostic importance. Matsutani et al¹ reviewed 153 histologically verified intracranial GCTs that were treated uniformly and reported that patients with pure choriocarcinoma, endodermal sinus tumor, or embryonal carcinoma fared poorly with a 5-year OS of 9.3%. In comparison, the 5-year OS was 70% for those patients with germinoma, teratoma, or teratoma with malignant elements. Results from our trial did not show a significant difference in outcomes by initial histologic subtype (Fig 3C). This may reflect that patients who met eligibility criteria with increased tumor markers without histologic confirmation were coded as mixed germ cell tumors. It is possible that the high OS rate reflects a relative although undocumented paucity of the highest-risk tumor types in our study population.

Previous studies have documented the prognostic importance of disease status after chemotherapy. The Society of Paediatric Oncology (SIOP) –CNS-GCT-96 (Combination Chemotherapy and Radiation Therapy in Treating Patients With Germ Cell Tumors in the Brain) trial reported outcomes for 34 patients with residual disease after induction chemotherapy; 47% relapsed, with a PFS rate of 37% ± 10%, which was inferior to the relapse rate for patients in CR after chemotherapy.³⁰ The Japanese Brain Tumor Study Group trial of intermediate-risk GCT found that only one of 13 patients relapsed after achieving a CR compared with progression in two of 10 patients who had less than CR.³¹⁻³³ Therefore, it is imperative that treatment regimens be designed to maximize responses to chemotherapy.

In this trial, nearly 70% of patients responded to neoadjuvant chemotherapy, based on institutional review. If we include patients

whose tumors were localized at diagnosis and those who underwent second-look surgery, the 5-year EFS was 92% and OS was 98% for these groups. This subgroup of patients is currently receiving reductions in radiotherapy volume and dose as part of the ongoing COG trial. Of note, the 14 patients who had a gross total resection at diagnosis had a 5-year EFS of 100%, raising the question of whether the potential morbidity of resection before chemotherapy is justified in patients with NGGCTs. A future publication will present our findings regarding tumor location correlated with the extent of resection and morbidity and whether more aggressive surgical procedures might be considered in these patients.

In conclusion, we showed that the neoadjuvant chemotherapy regimen, with or without second-look surgery, used in this study is not only feasible and well tolerated but also produces high response rates and OS rates for children and adolescents with NGGCTs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors

Final approval of manuscript: All authors

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¹The Matalia Group Essential Journal Study, *Medical Oncology & Hematology Oncology*, 2011

²Kantar Media, June 2013 Medical/Surgical Readership Study, *Oncology*

³Thomson Reuters 2013 Journal Citation Reports

⁴Google Scholar Top Publications



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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II Trial Assessing the Ability of Neoadjuvant Chemotherapy With or Without Second-Look Surgery to Eliminate Measurable Disease for Nongerminomatous Germ Cell Tumors: A Children's Oncology Group Study

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Appendix

Table A1. Required Observations

Observation	Induction Chemotherapy	Second-Look Surgery	Radiation Therapy	End Therapy	Follow-Up	
					Year 1	Year 2
MRI (brain with or without spine)	Before cycles 3 and 5 and after cycle 6	Post		Brain and spine	Every 3 months	Every 4 months
Tumor markers (serum and CSF)	Before each cycle	Post	Prior	Serum	Every 3 months	Every 4 months
Endocrine evaluation	Baseline				At 6 and 12 months	At 24 months
Ophthalmologic evaluation	Baseline					

NOTE. Magnetic resonance imaging (MRI) scan with gadolinium of the entire spine is required within 10 days before or at least 10 days after surgery with contrast (and without contrast if scan is postoperative). Only an MRI with contrast of the spine is required at study entry if there was no surgery (nonhistologic confirmation with markers). All brain postoperative imaging should be done within 48 hours of surgery. If imaging cannot be obtained at that time, then it should be done within 28 days after surgery. Postinduction MRI will serve as preradiation therapy evaluation. Endocrine evaluations consists of free thyroxine, thyroid-stimulating hormone, insulinlike growth factor 1, insulinlike growth factor-binding protein 3, bone age, lactate dehydrogenase (in males older than age 10 years or in females older than age 9 years), follicle-stimulating hormone (in males older than age 10 years or in females older than age 9 years), testosterone (in males older than age 10 years), estradiol (in females older than age 9 years), Tanner stage, human chorionic gonadotropin, cortisol at 8:00 to 10:00 AM cortisol.