Long-term quality of life and neuropsychologic functioning for patients with CNS germ-cell tumors: From the First International CNS Germ-Cell Tumor Study

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This study evaluated the quality of life and neuropsychologic functioning among patients enrolled between 1989 and 1993 in the First International CNS Germ-Cell Tumor Study. Quality-of-life questionnaires (Short Form-36 or Child Health Questionnaire) were completed on 43 patients at median follow-up of 6.1 years after diagnosis (range, 4.5-8.8 years), and intellectual and academic testing was performed on 22 patients. Psychosocial and physical functioning of patients aged 19 years and older at follow-up was within the average range, whereas the same functioning for patients aged 18 years and younger, as reported by their parents at follow-up, was

low average and borderline, respectively. Overall psychosocial and physical health summary scores were positively correlated with age at diagnosis for both groups combined. Those who received CNS radiation therapy ($n = 29$) reported significantly worse physical health, but similar psychosocial health, compared with those treated without radiation. Neuropsychologic testing indicated full-scale and verbal IQ, reading, spelling, and math skills in the average range, and performance IQ in the low average range. Intelligence and math skills were positively correlated with age at diagnosis. Those with germinomas significantly outperformed those with nongerminomatous/mixed tumors on all neuropsychological measures administered. Younger patients diagnosed with CNS germ-cell tumors are at increased risk for psychosocial and physical problems as well as neuropsychologic deficits. Exposure to irradiation adversely affects overall physical functioning, whereas tumor pathology appears to be a salient neurocognitive risk factor. Collaborative and randomized studies are required to further elucidate the late effects arising from factors such as age at diagnosis, tumor histology, level of irradiation therapy, and chemotherapy toxicity among these young and potentially curable patients. *Neuro-Oncology* 3, 174-183, 2001 (Posted to *Neuro-Oncology* [serial online], Doc. 00-051, May 24, 2001. URL <neuro-oncology.mc.duke.edu>)

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²Abbreviations used are as follows: CHQ-PF50, Child Health Questionnaire; IQ, intelligence quotient; NGGCT, nongerminomatous; SF-36, Short Form-36 Questionnaire.

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CNS germ-cell tumors comprise 3% to 6% of all CNS tumors and occur predominantly in the suprasellar or pineal region in a patient population with a median age of 13 years (Balmaceda et al., 1998; Chao et al., 1993; Choi et al., 1998; Legido et al., 1989). Radiation therapy has been regarded as standard therapy for CNS germ-cell tumors, although strategies incorporating the addition of cisplatin-based chemotherapy with reduced CNS radiation dose have been reported (Allen et al., 1987; Baranzelli et al., 1997; Dahlborg et al., 1998; Diez et al., 1999; Fouladi et al., 1998; Herrmann et al., 1994; Jennings et al., 1985; Kiltie and Gattamaneni, 1995; Linstadt et al., 1988; Matsutani et al., 1997; Shirato et al., 1997).

The long-term neuropsychological and psychosocial effects of cranial irradiation have been well documented over recent years (Armstrong and Mulhern, 1999; Chapman et al., 1995; Copeland et al., 1999; Dennis et al., 1996; Ellenberg et al., 1987; Fletcher and Copeland, 1988; Goldwein et al., 1996; Hoppe-Hirsch et al., 1995; Jannoun and Bloom, 1990; Johnson et al., 1994; Kao et al., 1994; Morris et al., 2000; Mulhern, 1994; Mulhern et al., 1992, 1998; Packer et al., 1987; Radcliffe et al., 1992, 1994; Ris and Noll, 1994; Siffert et al., 1999; Silber et al., 1992; Walter et al., 1999). Radiation therapy is associated with long-term sequelae, including deficits within the domains of intelligence, attention, memory, and psychomotor processing speed. These deficits often reflect white matter abnormalities characterized by calcification, lacunar cysts, and atrophy, particularly in the frontal cortex, and may be associated with risk factors including age at irradiation and irradiation dosage level (Constine et al., 1988; Duffner et al., 1985). Furthermore, cranial irradiation also may lead to diminished height, neuroendocrine dysfunction, and hearing loss (Kun, 1997; Shirato and Sawamura, 1998). In contrast, the effects of chemotherapy in the absence of cranial irradiation appear to impact perceptual-motor skills and academic achievement (i.e., mathematics) in a mild-to-moderate degree with patients who are younger at treatment or from lower socio-economic backgrounds displaying significantly more difficulty in these areas (Copeland et al., 1996; Moore et al., 1992).

Health-related quality of life is defined as the extent to which a patient's usual or expected physical, emotional, and social well-being are affected by a medical condition or its treatment (Cella and Bonomi, 1995). A thorough review of previously published reports on the late effects of treatment for CNS germinoma reveals a paucity of documentation on quality-of-life and neuropsychologic outcomes. Specifically, many of the articles focus primarily on overall and event-free survival with no mention of either quality of life or neuropsychologic functioning (Glanzmann and Seelentag, 1989; Huh et al., 1992; Matsutani et al., 1987; Shibamoto et al., 1994; Shirato et al., 1997). Alternatively, other articles are limited to reporting a Karnofsky score or, more commonly, providing qualitative comments about the survivor's level of functioning with such phrases as "leading a normal and productive life," "attending University," "evidence of cognitive dysfunction," "learning difficulties," and "memory impairment" (Dattoli and Newall, 1990; Fouladi et al.,

1998; Hardenbergh et al., 1997; Jenkin et al., 1990; Kiltie and Gattamaneni, 1995; Sawamura et al., 1998).

Of the few studies that measured neuropsychologic outcome, single assessments were performed on relatively few survivors without presentation and analysis of the data (Linstadt et al., 1988; Shirato and Sawamura, 1998). Two recently published reports adequately documented the late effects secondary to treatment for CNS germ-cell tumors. Merchant et al. (2000) provided serial IQ² assessments for 8 of 12 patients with a median age at diagnosis of 12 years (range, 9-16 years). Patients enrolled in the study received a cranial radiation dose of 2560 cGy, a primary site boost to 5080 cGy, and a spinal dose of 2560 cGy. The patients were part of a small population that was given a Wechsler IQ test before receiving radiation therapy and were collectively performing within the average to low average range of intelligence. These 8 patients were each retested approximately 2 to 4 times over a median of 56 months from initial diagnosis (range, 13-110 months), and the authors demonstrated there was no significant decline in IQ scores over time. Sutton et al. (1999) analyzed quality-of-life questionnaires completed by 22 of 27 patients whose mean age at diagnosis was 16.9 years (range, 11-42 years) and were treated with 3600 cGy whole irradiation to the neuraxis with a boost to 5040 cGy to the primary site for marker-negative intracranial germinomas. The authors collected two different self-report quality-of-life measures (SF-36 and Functional Assessment of Cancer Therapy) from 22 survivors whose mean age at follow-up was 27.1 years (range, 16-47 years). There was a statistically significant decrease in overall physical quality of life compared with the control population ($P < 0.00005$), but overall mental quality of life functioning was reported to be better than with the control group ($P = 0.02$). The total amount of radiation was similar between these two latter studies; however, the patients in the Merchant et al. study received a lower dose of craniospinal radiation, whereas the patients treated on the Sutton et al. study were considerably older at diagnosis. Both of these studies are noteworthy for being the first to formally assess either quality of life or intellectual functioning in survivors of CNS germ-cell tumors.

This study addresses the lack of information on late effects of treatment on quality of life and neuropsychologic functioning for a patient population that received primarily chemotherapy but were also given radiation therapy for either residual or recurrent CNS germ-cell tumors.

Materials and Methods

Between November 1989 and December 1993, 83 subjects with newly diagnosed, previously untreated primary CNS germ-cell tumors were enrolled in the First International CNS Germ-Cell Tumor Study involving 31 institutions from 6 countries: the United States, Canada, Italy, Argentina, Brazil, and Australia (Balmaceda et al., 1996). Concerns about the delayed neurocognitive and neurodevelopmental effects of cranial irradiation in younger patients with CNS tumors prompted the development of

this international protocol to explore the feasibility of a chemotherapy-based regimen in minimizing the late effects from treatment for CNS germ-cell tumors. Consequently, patients with germinomas, mixed germ-cell tumors with malignant elements, and patients with non-germinomatous germ-cell tumors received induction therapy with 4 cycles of carboplatin, etoposide, and bleomycin. Induction chemotherapy was composed of carboplatin (500 mg/m² per day, days 1 and 2), etoposide (150 mg/m² per day, days 1 to 3), and bleomycin (15 mg/m² per day, day 3). Patients experiencing a complete response after the first 4 cycles received an additional 2 cycles, and those who achieved a partial response received 2 additional cycles intensified with cyclophosphamide (65 mg/kg). The protocol recommended that patients who did not achieve a complete response after 4 cycles of chemotherapy would receive local field radiation therapy to a maximum dose of 3000 cGy. Patients with neuraxis dissemination received 2000 cGy to the neuraxis, with an additional boost of 1000 cGy to sites of residual disease, and those who failed to achieve a partial response beyond the primary site were treated with 2500 cGy to the neuraxis.

The CHQ-PF50 and the SF-36 were the quality-of-life measures used in this late effects study. They have been well validated for assessing both the overall physical and psychologic quality of life of the general and medically ill populations (Landgraf, 1996; Levi and Drotar, 1998;

Ware and Sherbourne, 1992; Ware et al., 1997). CHQ-PF50 is a quality-of-life questionnaire that assesses a child's physical, emotional, and social well-being from the perspective of the parent or guardian (Landgraf, 1996). Specifically, the CHQ-PF50 measures 10 health concepts of children and adolescents from 6 to 18 years old: general health, physical functioning, bodily pain/discomfort, limitations in school work and activities due to physical problems or emotional/behavioral difficulties, behavior, mental health, self-esteem, and the impact of both time and emotions on the parent. The SF-36 for adults is a self-report scale for subjects 19 years and older, and it measures 8 health concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health (Ware et al., 1997). A detailed breakdown of the measurement models for both the CHQ-PF50 and the SF-36 is shown in Table 1.

Depending on the participant's age at the time of follow-up, either the CHQ-PF50 or the SF-36 (in the participant's native language) was mailed to each survivor treated in the First International CNS Germ-Cell Tumor Study. Forty-three patients of 54 survivors (80%) returned their questionnaires via mail. Twenty-four patients who were 19 years or older completed the SF-36, and parents of 19 patients aged 18 years or younger completed the CHQ-PF50. Additionally, recent neuropsychologic

Table 1. Quality of life measurement models and scores

Quality of life domain	Score	SD	Range
Child Health Questionnaire - Parent Form (aged 6-18 years)			
Overall physical health	32.57	12.27	Borderline
Physical functioning	-1.46	1.82	Borderline
Role/social limitations 2 ⁰ to physical problems	-1.78	2.02	Borderline
General health	-0.03	0.91	Average
Bodily pain/discomfort	-2.58	1.20	Impaired
Overall psychosocial health	40.36	5.17	Low Average
General behavior	-0.25	1.48	Average
Role/social limitations 2 ⁰ to emotional-behavioral problems	-1.84	2.20	Borderline
Mental health	-0.34	1.57	Average
Self-esteem	-2.19	1.44	Impaired
Included in both physical and psychosocial domains			
Parental impact of time	-0.59	1.45	Average
Parental impact of emotional distress	-1.59	1.43	Borderline
Short Form - 36 (age 19 - adulthood)			
Overall physical health	48.53	10.90	Average
Physical functioning	-0.18	1.09	Average
Role/social limitations 2 ⁰ to physical problems	-0.05	1.09	Average
Bodily pain	+0.11	0.94	Average
General health	-0.11	1.27	Average
Overall mental health	50.91	9.22	Average
Social functioning	-0.21	1.16	Average
Role/social limitations 2 ⁰ to emotional-behavioral problems	+0.13	0.84	Average
Vitality	-0.09	1.05	Average
Mental health	+0.14	0.91	Average

Overall scores are reported as T scores (mean = 50, SD = 10). Individual index scores are reported as Z scores (mean = 0, SD = 1).

Table 2. Characteristics of study population

Feature	Total	Quality of life		Neuropsychologic
		CHQ-PF50	SF-36	
No. of patients	43	19	24	22
Age at diagnosis (SD)	14.4 (7.3)	8.95 (3.2)	18.7 (6.7)	16.2 (6.5)
Months of follow-up (SD)	72.9 (12.6)	71.5 (11.6)	74 (13.5)	73.7 (10.4)
Age at follow-up (SD)	20.7 (7.5)	14.9 (3.2)	25.3 (6.6)	19.9 (6.3)
Sex				
Male	37 (86%)	15 (79%)	22 (92%)	18 (82%)
Female	06 (14%)	04 (21%)	02 (08%)	04 (18%)
Diagnosis				
Germinoma	32 (74%)	12 (63%)	20 (83%)	16 (73%)
NGGCT/mixed	11 (26%)	07 (37%)	04 (17%)	06 (27%)
Tumor location				
Pineal	20 (46%)	8 (42%)	12 (50%)	08 (36%)
Suprasellar	11 (26%)	7 (37%)	04 (17%)	09 (41%)
Both	08 (19%)	3 (16%)	05 (21%)	05 (23%)
Other	04 (09%)	1 (05%)	03 (12%)	NA
Irradiation				
Yes	29 (67%)	13 (68%)	16 (67%)	18 (82%)
No	14 (33%)	06 (32%)	08 (33%)	04 (18%)

Abbreviation: NGGCT, nongerminomatous; NA, not applicable.

evaluations were received from 22 patients (41%) through either their medical institution or their school setting. All IQ and academic achievement testing was conducted in English to English-speaking patients. The IQ tests included either the Wechsler IQ Scale (Wechsler, 1991) or the Stanford-Binet, 4th edition (Thorndike, 1986), whereas the academic achievement testing utilized either the Wechsler Individual Achievement Test (Wechsler, 1992) or the Wide Range Achievement Test, 3rd edition (Wilkinson, 1993). Clinical and demographic details for all patients enrolled in the study, broken down by the quality-of-life instrument that was completed and by those who received a neuropsychologic assessment, are documented in Table 2.

Overall, the average age at diagnosis was 14.4 years (range, 0.33–37.13 years), with a median follow-up of 73 months (range, 54–105 months), and a mean age at follow-up of 21 years (range, 4.89–41.99 years). There were 37 males (86%) and 6 females (14%), including 32 patients diagnosed with pure germinoma (75%) and the remaining 11 with nongerminomatous or mixed germ-cell tumor (26%). Most of the survivors (81%) received 6 cycles of chemotherapy during the induction phase, whereas two-thirds of the survivors subsequently required irradiation because of either residual disease or progression. The median neuraxis dose and the local/ventricular field boost were both within the range of current CNS germ-cell tumor treatment regimens. Simultaneously, it is important to note that one-third of the surviving patients were never irradiated. Table 3 itemizes the treatments provided.

The distributions of various prognostic variables—age at diagnosis, pathology type (pure germinomas versus nongerminomatous), tumor location (suprasellar, pineal, suprasellar and pineal, other), extent of disease

(localized versus disseminated), surgery type (radical versus nonradical), postsurgery residual volume (greater or less than 1.5 cm²), and exposure to radiation (ever versus never)—were compared by quality-of-life instrument using chi-square statistics, Fisher's exact test, and Wilcoxon rank-sum test where appropriate. The relationship between quality of life (both physical and psychosocial) and age at diagnosis was analyzed using Spearman rank correlation, because none of these variables were normally distributed. The effect of radiation on physical and psychosocial health, stratified by quality-of-life instrument, was assessed using the Wilcoxon rank-sum test. Ranked linear regression models were used to control for age at diagnosis. A subanalysis of the 22 subjects for whom neuropsychologic test results were available was carried out. The relationship among measures of intelligence (full scale, verbal, and performance IQs), those of academic achievement (reading, spelling, and math), and age at diagnosis was examined using Spearman rank correlation. Kruskal-Wallis tests were used to assess the relationship between neuropsychologic test results and prognostic variables.

Results

Subjects evaluated by CHQ-PF50 were younger at age of diagnosis (median, 9.4 years) than were those evaluated by SF-36 (median, 16.0 years, P value <0.001 by Wilcoxon rank-sum test). Age at follow-up was significantly correlated with age at diagnosis (Spearman rank correlation 0.97, P < 0.001). There was no difference in surgery type, postsurgery residual volume, extent of disease, exposure to radiation, or pathology type by

Table 3. Patients' chemotherapy and radiation exposure
Induction chemotherapy regimen for all 43 patients (100%)

Drug	Dosage per cycle
Carboplatin	1 g/m ²
Etoposide	300 mg/m ²
Bleomycin	15 mg/m ²
Cyclophosphamide ^a	65 mg/kg
Cycles administered	No. of patients
2	1
3	1
4	5
5	1
6	35

^aIncluded only during cycles 5 and 6 for those who achieved a partial response after 4 cycles of the other 3 drugs.

Irradiation therapy given to 29 of 43 patients (67%)

	No. of patients
Craniospinal	<i>n</i> = 23
Neuraxis dose	
Up to 2500 cGy	5
2500 to 4000 cGy	14
4000 cGy and above	4
Local/ventricular field boost to	<i>n</i> = 23
2000 to 3000 cGy	1
3000 to 5000 cGy	7
5000 to 5580 cGy	15
Local radiosurgery alone	<i>n</i> = 3
Below 2000 cGy	1
Above 4500 cGy	2
Whole-brain/ventricular field alone	<i>n</i> = 3
3500 to 5040 cGy	3

quality-of-life instrument (all *P* values >0.05 by Fisher's exact test). There was a difference in tumor location by quality-of-life instrument (*P* = 0.01). However, as there are 4 tumor location categories, the distributions of tumor location by quality-of-life instrument may be unstable. See Table 2 for details.

Quality of Life

Age at diagnosis was positively correlated with both overall physical health (Spearman rank correlation = 0.43, *P* = 0.002) as well as with overall psychosocial health (Spearman rank correlation = 0.43, *P* = 0.002) for both groups combined, so that those younger at diagnosis indicated lower quality of life by either parent- or self-report. When analyzed separately by instrument type, no statistically significant correlations between either quality-of-life measurement or age were detected. Overall, parents of children 18 years and younger at follow-up reported that their children experienced borderline overall physical functioning and low average overall psychosocial functioning. In marked contrast, patients 19 years and older at follow-up reported functioning within the average

range of overall physical and psychosocial health. Refer to Table 1 for a detailed breakdown of mean scores obtained on both quality-of-life measures.

Specifically, the overall Child Health Questionnaire-Physical Summary score for those 18 years or younger at follow-up was within the borderline range. Analyzing the 6 individual components comprising the physical summary score revealed that patients' overall health and illness were reported to be within the average range, whereas the limitations in personal time experienced by the parent/guardian were within the low average range. In contrast, the parents reported limitations in their child's schoolwork and activities, and extent of physical limitations, which were within the borderline range, whereas the intensity and frequency of their pain and discomfort were within the impaired range. Furthermore, the overall Child Health Questionnaire-Psychosocial Summary score of patients 18 years or younger was within the low average range. This was composed of average frequencies of anxious and depressive symptoms, as well as minimal behaviors, such as aggression, hyperactivity, and impulsivity. In contrast, these children displayed limitations due to emotional or behavioral difficulties and reported low levels of self-esteem that were both within the borderline range, along with a significant amount of parental distress many years after treatment.

In contradistinction, the overall SF-36 Physical Health Summary scores for those aged 19 years and older at follow-up were collectively within the average range. Specifically, they reported a general lack of problems with work or other daily activities; few limitations in performing physical activities; minimal pain; and good personal health, that were all solidly within the average range. Furthermore, the overall SF-36 Psychosocial Functioning Summary score of patients in this study was also well within the average range. Additionally, they did not report many problems with work or other daily activities because of emotional problems, nor feelings of nervousness or depression, and the degree of interference with normal social activities and feeling tired and worn out were also within the average range.

Analyses that explored the impact of irradiation on quality of life revealed that those evaluated by CHQ-PF50 (18 years and younger at follow-up, *n* = 19) experienced a marginally significant decline in physical functioning following irradiation (median 36.0 for irradiated subjects versus 45.4 for never-irradiated subjects, *P* = 0.087 by Wilcoxon rank-sum test). The decline among those evaluated by SF-36 (19 years and older at follow-up, *n* = 24) was highly statistically significant (median 48.2 versus 58.1, *P* = 0.004 by Wilcoxon rank-sum test). After controlling for age in a ranked regression model, the decline in physical functioning due to the effects of radiation became statistically significant for both groups (*P* = 0.039 and *P* = 0.004, respectively, for CHQ-PF50 group and SF-36 group). It is important to note that there was no significant impact of irradiation demonstrated by the overall psychosocial functioning of either children or adults (42.1 irradiated versus 46.5 nonirradiated, *P* = 0.47 for CHQ-PF50 group, and 53.2 irradiated versus 49.7 nonirradiated, *P* = 0.15 for SF-36 group).

Table 4. Summary of intelligence and academic achievement test results

	Mean standard score	SD
Intelligence		
Verbal intelligence	97.36	19.60
Performance intelligence	84.82	23.18
Full scale intelligence	90.45	22.21
Academic achievement		
Reading	96.12	22.78
Spelling	90.75	18.06
Math	89.41	19.00

All standard scores have a mean of 100 and an SD of 15.

Neuropsychologic functioning

Results of follow-up intellectual and academic achievement testing obtained from a subset of this population ($n = 22$) indicated that these patients (mean age = 16.2 years; range, 7-32 years) were functioning within the average range in full scale IQ, verbal IQ, reading, spelling and math abilities. In contrast, they were aggregately performing within the low average range in performance IQ. Refer to Table 4 for a summary of results for tests of intelligence and academic achievement.

Furthermore, results from correlation analyses revealed that the age at diagnosis was positively correlated with full scale IQ score (Spearman rank correlation = 0.55, $P = 0.008$), verbal IQ (Spearman rank correlation = 0.51, $P = 0.017$), performance IQ (Spearman rank correlation = 0.44, $P = 0.042$); and mathematics (Spearman rank correlation = 0.51, $P = 0.037$). The correlations between reading and age at diagnosis, and between spelling and age at diagnosis were not significant. Additional analyses of the neurocognitive data in relation to tumor pathology revealed that those with pure germinomas ($n = 16$) significantly outperformed those with NGGCT/mixed tumors ($n = 6$) on all measures of intelligence: full scale IQ (median 96.5 versus 65.5, $P = 0.006$), verbal IQ (median 100.5 versus 81.0, $P = 0.010$), performance IQ (median 87.5 versus 58.0, $P = 0.013$) as well as all measures of academic achievement: reading (median 109.0 versus 70.5, $P = 0.003$), spelling (median 98.5 versus 70.0, $P = 0.002$), math (median 99.0 versus 66.0, $P = 0.045$).

Discussion

Parents of survivors who were 18 years or younger at follow-up reported that their children experienced low average overall psychosocial functioning, while simultaneously displaying overall physical functioning within the borderline range. In contrast, survivors who were 19 and older at follow-up reported functioning well within normal limits on all 19 indices of overall physical and mental health, that range from vitality and general and mental health to bodily pain, physical and social-emotional functioning. Because of the strong correlation between age at follow-up and age at diagnosis, our results imply that disease and treatment have more adverse effects on younger patients.

The CHQ-PF50 and SF-36 were the general health status measures used in this study because of their sound psychometric qualities, along with their similar theoretical constructs for reporting quality of life. The one main limitation between these two measures, however, involved the self-report nature of the SF-36 for those aged 19 and older, in contrast to the parental-report format of the CHQ-PF50 for those aged 18 years and younger. The question of whether parents are good informants of their child's health-related quality of life is an important one. The literature suggests that parent-child agreement is acceptable with regard to the level of physical functioning; however, there tends to be less concordance with regard to the level of emotional functioning, particularly with internalizing problems (i.e., anxiety, depression) compared with more apparent externalizing symptoms, such as conduct problems, aggression, and hyperactivity (Achenbach et al., 1987; Canning, 1994; Canning et al., 1992; Levi and Drotar, 1999; Pantell and Lewis, 1987; Sawyer et al., 1999; Varni et al., 1998a, 1998b; Weissman et al., 1980). Because one of the main findings from the Child Health Questionnaire-Parent Report Form involved limitations in the physical functioning of their children, it is hypothesized that these deficits were present and exercising a negative impact on these survivors' overall level of functioning. Nonetheless, the incorporation of pediatric measures that utilize a developmentally appropriate self-report format are strongly recommended and are currently being developed through the collection of adequate normative data and publication of validation and reliability studies, i.e., PedsQL 4.0 (Varni et al., 2001), PCQL-32 version 3.0 (Seid et al., 1999), Child Health Questionnaire-Child Short Form (J. Landgraf, personal communication, 2000), and Minnesota-Manchester Quality of Life.³

Overall responses of patients who were treated on this protocol revealed that age at diagnosis was a predictive factor in both physical and psychosocial long-term quality of life when the summary scores were combined for all patients. However, analyzing the relationship between quality of life and age at diagnosis stratified by quality-of-life instrument did not yield a significant correlational relationship between physical and mental health within each instrument separately. It is unclear whether the same relationship with age at diagnosis does not exist within each quality-of-life instrument or whether the study does not have a large enough sample to demonstrate such an effect when the cohort is analyzed in smaller groups. Nonetheless, the finding that survivors under the age of 19 are reported to be experiencing both physical and psychosocial difficulties had not been previously documented in the follow-up literature of CNS germ-cell tumor patients.

Direct comparison of the quality-of-life responses from the 20 adult germinoma patients in the current study (not including the 4 patients treated for NGGCT/mixed tumors) who completed the SF-36, with the 22 germinoma patients treated from the Sutton et al. (1999) study who completed the same SF-36 survey, revealed strikingly similar profiles with generally nonsignificant differences (see Table 5).

Because the surviving patients on both protocols reported experiencing similar levels of quality of life, one could question the utility of a chemotherapy-based regimen

Table 5. Comparison of SF-36 responses for patients with CNS germinomas

	Index scores								Summary scores	
	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Current study (<i>n</i> = 20)	80	88	84	70	62	74	84	73	49	49
SD	26	25	21	26	20	29	26	18	11	10
Sutton et al. (1999) (<i>n</i> = 22)	71	89	82	58	63	90	86	78	46	54
SD	23	25	25	08	20	28	28	17	8	9
Normal (<i>n</i> = 474)	92	89	81	77	61	85	82	73	54	49
SD	16	25	20	17	20	21	31	18	7	10

Abbreviations: PF, physical function; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social function; RE, role emotional; MH, mental health; PCS, physical composite scale; MCS, mental composite scale.

for treating CNS germ-cell tumors given the high overall and event-free survival rate that is reported by most radiation protocols. An alternate interpretation of these two comparable levels of quality of life underscores the finding that 2 survivors (10%) were irradiated during treatment because of residual disease, whereas 12 survivors (60%) were irradiated at a later point in time when they subsequently relapsed after this chemotherapy-based regimen. Consequently, it is important to note that 6 survivors (30%) were disease free without ever having received radiation therapy. This treatment approach is in direct contrast to the Sutton et al. (1999) study in which chemotherapy was not administered and patients received 3600 cGy to the neuraxis, with a boost to 5040 cGy to the primary site and 4500 cGy to lumpy spinal metastatic lesions. The current authors believe that this represents a salient distinction given the significant association discovered between irradiation and decline in overall physical quality of life in the present study regardless of age at diagnosis. Moreover, parents of those 18 years and younger who were irradiated reported that their children experienced significantly lower self-esteem, in addition to limitations in their roles at school and with friends because of emotional or behavioral problems.

Results from follow-up neuropsychologic testing indicated functioning within the average range in full scale and verbal IQ, as well as in reading, spelling, and math abilities, whereas their performance IQ was within the low average range. These findings are consistent with prior research on pediatric oncology patients treated with combinations of irradiation and/or chemotherapy that identified declines in rapid visual-spatial, visual-perceptual, and visual-motor skills primarily involving right hemispheric functioning (Armstrong et al., 1999; Anderson et al., 2000; Buono et al., 1998). Additionally, age at diagnosis was a predictive factor for many aspects of neuropsychologic functioning, so that those patients treated at a younger age commonly demonstrated lower intellectual functioning and math skills.

The neurocognitive functioning of patients diagnosed with germinomas was generally within normal limits and significantly higher than those patients diagnosed with an NGGCT/mixed tumor on all the measures administered. This finding may be related in part to the significant difference in the age at diagnosis between these tumor types ($P = 0.023$), which was 15.9 years ($SD = 7.5$ years) for those with germinomas, whereas the average age for the diagnosis of NGGCT/mixed tumor

was 10.1 years ($SD = 4.8$ years). At follow-up, those treated for germinomas were on average 22 years old ($SD = 7.8$ years), compared with 16.7 years old ($SD = 5.3$ years) for those who were treated for an NGGCT/mixed tumor, which was also a significant difference ($P = 0.039$). Further analyses comparing these two pathology types with respect to location, extent of disease, and exposure to irradiation did not yield significant results; however, the sample size may have limited the ability to detect further differences.

In sum, this study has primarily demonstrated that young age at diagnosis is a risk factor for both lowered quality of life and neuropsychologic functioning, and that radiation has a negative impact on physical quality of life. However, the analyses presented were limited by the small sample size, the use of two different quality-of-life instruments, and the nonrandomized allocation of subjects to radiation treatment. In addition, as the analyses were exploratory in nature rather than hypothesis driven, multiple comparisons may be an issue. Therefore, the presence of detrimental effects from craniospinal irradiation, NGGCT/mixed tumors and young age at diagnosis can only be definitely resolved via a larger, randomized clinical trial.

Given the current dilemma regarding the role of cisplatin-based chemotherapy and the dose of radiation required to effectively treat CNS germinomas, future studies will need to simultaneously examine quality of life and neuropsychologic sequelae, in addition to overall and event-free survival. Repeated quality-of-life measurements based on multiple informants, along with neuropsychologic assessments that move beyond singular measures of intelligence and evaluate specific areas of anticipated deficit, i.e., attention/concentration, memory, psychomotor processing speed, and neurobehavioral functioning, are necessary to effectively determine whether there is a decrement in level of functioning over time with this population.

The effective documentation of late effects arising from the treatment of CNS germ-cell tumors in children and adolescents, therefore, provides important opportunities to quantify neuropsychologic, academic, social-emotional/behavioral and general health functioning in order to provide school and vocational remediation when areas of deficit are either anticipated or noted (i.e., occupational and physical therapy secondary to physical deficits), as well as to provide critical feedback regarding the optimal treatment regimen for CNS germ-cell tumors.

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