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Neuropsychological Status of Children Treated for Brain Tumors: A Critical Review and Integrative Analysis

Raymond K. Mulhern, PhD, Janet Hancock, PhD, Diane Fairclough, DrPH, and Larry Kun, MD

The literature on the neuropsychological status of children with primary brain tumors was reviewed to identify English-language publications reporting the results of standardized, quantitative measures of patient function. The 22 studies that met these review criteria, representing 544 patients, were evaluated to assess the relationship between traditional risk factors (age at diagnosis, tumor location, radiation therapy, and time since completion of treatment), as well as subsequent intellectual development, academic achievement, psychosocial adjustment, and neuropsychological status. The impact of other potentially salient factors, such as seizures and sensory and motor deficits, was evaluated when possible. Despite inconsistent reporting of demographic and treatment-related effects across studies

which precluded formal meta-analysis, we were able to confirm the primary importance of radiation therapy volume and age at treatment on IQ. No effects were detected for tumor location. Younger children treated with cranial (whole brain) irradiation showed a 14-point deficit in IQ as compared with their older counterparts. No significant differences were noted between older children receiving lòcal or cranial irradiation, although both groups had IQ levels 12-14 points lower than those not irradiated. The high-risk groups identified in this study require increased clinical surveillance. Definitive evaluation of potential risk factors for neuropsychological impairment will depend on more complete reporting of relevant patient characteristics and interinstitutional © 1992 Wiley-Liss, Inc.

Key words: brain tumors, neuropsychology, IQ

INTRODUCTION

Concerns have been expressed about the quality of life of children treated for malignant brain tumors for at least the past two decades, with quantitative attempts at assessment beginning with Bloom's four-stage system of ranking functional status in 1969 [1]. Several major changes have since occurred that make this issue even more salient. These include the development of new treatment approaches with less well-documented toxicities, such as hyperfractionated radiation therapy and preor postirradiation chemotherapy. Children with malignant brain tumors have now become more fully integrated into the comprehensive treatment approaches of regional pediatric cancer centers. Because brain tumors account for approximately 20% of all pediatric malignancies, ranking second only to the leukemias in incidence. children with these tumors participate in the increasingly available protocols for brain tumor management in the Pediatric Oncology Group (POG) and Children's Cancer Study Group (CCSG). The overriding incentive for accurate quantification of the functional status of children treated for brain tumors emerges from the clinician's

desire to balance the efficacy and chronic toxicity of therapies used for the developing child. In recognition of the special vulnerabilities of very young children, significant alterations of the timing and doses of irradiation and chemotherapy have evolved in contemporary protocols [2]. Careful assessment of neuropsychological sequelae of treatment is essential in judging the value of such changes in therapy.

In 1983, we reviewed 15 studies of the functional status of children surviving malignant brain tumors [3]. Fewer than one-half of these studies reported data on standardized psychological measures, although studies published after 1980 more frequently used standardized

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assessments. That review suggested the importance of radiation therapy, age at treatment, and tumor location in determining neuropsychological status. Here, we present a comprehensive evaluation of empirical studies that has been updated since our previous review. Our goal was to identify those factors that place children at greatest risk of psychological impairment following treatment for brain tumors.

REVIEW CRITERIA AND PROCEDURES

The literature review was based on searches of two data bases: PSYCH INFO (1967–June 30, 1990) and CANCER LIT (1963–June 30, 1990). PSYCH INFO permits access to 950 journals, periodicals, monographs, and technical reports; CANCER LIT provides access to 3,400 different publications. Three key word groups were used: (1) brain tumor or neoplasm; (2) child or adolescent; and (3) intelligence, IQ, or neuropsychology. Only publications in English were considered. Of the 104 references identified, we excluded book chapters, review articles, abstracts, and single case reports.

Several studies were identified that used only ad hoc measures of psychological performance. Because of the lack of established reliability and external validity for these outcome measures, six studies were excluded from consideration [4–9]. The remaining 22 studies were evaluated for study design (cross-sectional or longitudinal), method of patient selection (random, consecutive admission, or unselected), risk factors analyzed, and sample size. The sample size of the individual studies was sometimes larger than the number of patients with psychological outcome data; in these cases, we coded only the number of patients with psychological testing. Some patients were included in more than one study, but this proportion was not large enough to warrant special measures to consider them separately.

In abstracting patient and treatment data from the 22 studies that met our review criteria, we were guided by traditional and more recently implicated risk factors, with the objective of establishing a contemporary standard for reporting the results of neuropsychological studies of children with brain tumors [3,10-12]. The following patient features were recorded: (1) patient age at the time of treatment; (2) tumor location based on the classification system presented in Table I (posterior fossa, third ventricle, or cerebral hemisphere regions); (3) surgery (none, biopsy only, resection of any degree); (4) the presence or absence of hydrocephalus at diagnosis and whether a ventriculoperitoneal (V-P) shunt was placed; (5) treatment with radiation therapy, including the volume (local vs. whole brain) and dose; (6) treatment with chemotherapy; (7) time from initiation of treatment to assessment; (8) major visual, auditory and motor impairments; (9) treatment for seizures at the time of evaluation;

TABLE I. Classification Criteria for Tumor Locations

Regional designation ^a	Specific location
Posterior fossa	Brainstem Pons Cerebellum
Third ventricle	Pineal body Hypothalamus Midbrain area Thalamus Optic chiasm Pituitary body Suprasellar area
Cerebral hemisphere	Lateral ventricles Frontal lobes Temporal lobes Parietal lobes Occipital lobes

^aAdapted from the system of Ellenberg et al. [12].

and (10) presence or absence of a history of progressive or recurrent disease.

PATIENT CHARACTERISTICS AND STUDY DESIGNS

Of the 22 selected studies, all but four contained missing information for one or more features describing therapy or patient characteristics at the time of neuropsychological assessment (Table II). Descriptive statistics were computed for the available demographic and medical data. The total number of patients studied was 544. Age at treatment ranged from 0 to 18 years, with the exception of two studies that also included adults [13,14]. The greatest proportion of tumors (48.9%) were located in the posterior fossa; 23.2% were in the cerebral hemispheres and 27.9% in the third ventrical region. In the 18 studies that reported the extent of surgery, gross total, subtotal, or partial resections were performed in 78.7% of cases; 7% underwent biopsy only. V-P shunts were placed in 10.8% of the patients. Both local and whole-brain irradiation were administered in 37.3% of cases; 33% received only local irradiation, and 29.6% received no cranial irradiation. Slightly less than onefifth of the patients received chemotherapy.

The time between initiation of treatment and assessment ranged from the immediate postoperative period to 21 years (Table III). Twenty-three different standardized measures of psychological functioning were employed. All 22 studies reported some measure of intellectual functioning. Neuropsychological function beyond IQ testing was formally evaluated in nine studies, academic achievement was assessed in eight, and emotional adjustment was studied in seven. Measures of adaptive behavior (activities of daily living) were included in two studies. Sensory and motor impairments were not often

TABLE II.

Study

Bordeaux et Cavazzuti e Cavazzuti e Clopper et Danoff et a Duffner et Duffner et Ellenberg e Hirsch et a Hirsch et a Jannoun et Kun et al. Kun and M [24] LeBaron et Mulhern et Mulhern et Mulhern a [20] Mulhern e Packer et Riva et al. Silverman Spunberg

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PABLE II. Summary of Presenting Features and Therapy in Studies of Children Treated for Brain Tumor

		Patient age						Radiation therapy				
	Sample	at treatment	Tun	nor loca	ationb	Extent of	surgery	V-P	Local	Whole		
<u>Study</u>	sizea	(yr)	CH	3V	PF	Resection	Biopsy	shunt	only	brain	None	Chemotherapy
Bordeaux et al. [22]	14	5-16	5	2	. 7	6	1	NR	3	4	7	0
Cavazzuti et al. [23]	35	2-NR	0	35	0	19	16	NR	27	0	8	0
Cavazzuti et al. [13]	20	6-33	20	0	0	20	0	0	NR	NR	9	0
Clopper et al. [29]	20	2-16	0	20	0	20	0	NR	0	0	20	NR
Danoff et al. [15]	38	1-16	3	23	12	37	0	0	12	26	0	0
Duffner et al. [16]	16	2-16	4	6	6	NR	NR	NR	10	6	0	5
Duffner et al. [17]	10	1-16	0	0	10	NR	NR	NR	2	8	0	10
Ellenberg et al. [12]	43	1-15	5	16	22	39	0	9	14	23	6	12
Hirsch et al. [18]	59	0-2	0	0	59	NR	NR	0	0	28	31	28
Hirsch et al. [28]	42	1-15	42	0	0	42	0	0	0	0	42	0
Jannoun et al. [34]	62	1-16	14	25	23	38	6	7	49	. 13	0	8
Kun et al. [19]	30	2-16	7	8	15	19	2	19	14	7	9	3
Kun and Mulhern [24]	18	2-15	, 6	1	11	16	2	NR	17	7	0	0
LeBaron et al. [25]	15	1-15	0	0	15	NR	NR	NR	0	11	4	1
Mulhern et al. [2]	14	1-3	3	3	8	. 13	1	7	0	14	0	14
Mulhern et al. [30]	7	5-15	7	0	0	7	0	NR	6	. 1	0	0
Mulhern and Kun [20]	26	2-15	8	7	11	17	0	10	13	12	1	NR
Mulhern et al. [26]	6	3-8	0	0	6	6	0	4	3	3	0	0
Packer et al. [11]	32	2-18	0	. 3	29	NR	NR	NR	0	18	14	12
Riva et al. [21]	15	3-15	0	0	15	15	0	NR	0	8	7	8
Silverman et al. [14]	9	3-25	0	0	9	9	0	NR	0	9	0	0
Spunberg et al. [27]	13	0-2	2	3	8	10	1	3	12	1	6	0
Totals	544	0-33	126	152	266	325	29	59	176	199	158	101
Percent			23.2	27.9	48.9	78.7	7.0	10.8	33.0	37.3	29.6	18.5

ancludes only those patients with psychological testing.

^bCH, cerebral hemispheres; 3V, third ventricle; PF, posterior fossa; NR, not reported.

documented; seven studies reported visual, motor, auditory, or clinical seizure status at testing.

Eleven studies had cross-sectional designs, evaluating patients at a single interval, and 11 were longitudinal, with serial evaluations over several time intervals. Two studies used control or comparison groups. In 11 studies, consecutive patients were evaluated, in eight studies an unselected or convenience sample was reported, and method of subject selection was not specified in three studies. Several risk factors were examined in relationship to psychological outcome measures: radiation therapy effects in 18, surgical resection and time from treatment in 8, age at diagnosis in 10, chemotherapy and hydrocephalus in 5, tumor location in 4, sensory and motor impairments in 2, and 1 examined progressive/recurrent tumor. A detailed discussion of the risk factors cited in Table IV follows.

EFFECTS OF RISK FACTORS ON IQ Radiation Therapy

Of the 18 studies that examined the effects of radiation therapy on the intellectual development of children with

brain tumors, 12 concluded that irradiation had an adverse effect [2,11,12,14,15-21,34], whereas six studies failed to find any effects [22-27]. Among the 12 studies reporting adverse effects, eight used formal statistical procedures [2,11,12,14,16,20,21,38], whereas four based this conclusion solely on clinical judgment and descriptive data [15,17–19]. Statistical procedures were used in four of the six studies that failed to find an effect of radiation therapy on IQ [22-24,26]. Conclusions regarding adverse radiation therapy effects were based on serial studies of irradiated patients [2,11, 16,17,20], comparisons between irradiated and nonirradiated patients [12,18,19], and comparisons between irradiated patients and normal controls [14,21]. Two studies also demonstrated greater decrements among children receiving whole-brain irradiation compared with those receiving localized fields of treatment [12,19]. No studies relating irradiation dose to IQ decrements were found.

Surgical Resection

Of the eight studies that examined the relationship between surgical resection and level of intellectual func-

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TABLE III. Patient Characteristics at Time of Assessment

Study	Sample size	Time since treatment	Psychological tests administered ^a Academic Emotional Neuro- Adam						
Pordos I roos		(yr)	Intellect	achievement	adjustment	psychologic	Adapt		
Bordeaux et al. [22]	14	1-2	McC, W			payenologic	behav		
Cavazzuti et al. [23]	35	1-19	B, W						
Cavazzuti et al. [13]	20	0-1	w			WCS			
Clopper et al. [29]	20	2-20	W			WMS, WCS			
Danoff et al. [15]	38	1-21	W	WRAT		1			
Duffner et al. [16]	16	0-3	SB, McC, W	WKAI					
Duffner et al. [17]	10	1-6	SB, W	WRAT					
Ellenberg et al. [12]	43	1-4	B, McC, W	WKAI		HRNB			
Hirsch et al. [18]	59	2-11	NEMI, W						
Hirsch et al. [28]	42	1-17	NR						
Jannoun et al. [34] Kun et al. [19]	62	1-16	W						
Kun and Mulhern [24]	30	0-5	McC, W	PIAT	DIC				
LeBaron et al. [25]	18	0-10	McC, W	11/1	PIC				
Mulhern et al. [2]	15	4-9	W	PIAT	PIC				
Mulhern et al. [30]	14	0-5	B, McC	1 1/11	CBCL	WMSB, HRNB			
Mulhern and Kun [20]	7	2-7	W	WRAT	DIC		VABS		
Mulhern et al. [26]	26	0–1	McC, W	WRAT	PIC				
Packer et al. [11]	6	1-7	KABC	MAIL	PIC				
Riva et al. [21]	32	0-2	B, SB, W			LNNB			
ilverman et al. [14]	15	0-9	W			VMI			
punberg et al. [27]	9	3-8	W	WRAT	DUICCO	CPT, TMT			
	13	5-20	McC, W	WRAT	PHSCS	77.7.			
Totals	544	0-21	21		CAT, TAT	BVMGT	CQS		
Percent			95	8 38	7 33	9	2		

aB, Bayley Scales of Infant Development; BVMGT, Bender Visual-Motor Gestalt Test; CAT, Children's Apperception Test; CBCL, Child Behavior Checklist; CPT, Continuous Performance Test; CQS, Composite Quality of Survival Scale; HRNB, Halstead-Reitan Neuropsychological Battery; KABC, Kaufman Assessment Battery for Children; LNNB, Luria-Nebraska Neuropsychological Battery; McC, McCarthy Scales of Children's Abilities; NEMI, Nouvelle Echelle Metrique de l'Intelligence; NR, not reported; PHSCS, Piers-Harris TMT, Trials Making Test; VABS, Vineland Adaptive Behavior Scale; W, Wechsler Intelligence Test; TAT, Thematic Apperception Test; WCS, Wisconsin Card Sort; WMS, Wechsler Memory Scale; WMSB, Wisconsin Motor Steadiness Battery.

tioning, only two assessed the effects of extent of surgery on IQ [12,23]. Ellenberg et al. [12] found no significant differences in mean IQ for patients who had undergone gross total resection, partial surgical resection, or biopsy alone. Similarly, Cavazzuti et al. [23] found no IQ differences between patients treated with radical tumor resection compared with those who had undergone biopsy, cyst aspiration, or simply shunt insertion combined with radiation therapy. However, it was noted that memory quotient improved only among patients with more limited surgery and radiotherapy. Scores on sorting tasks were significantly lower among radically resected patients as opposed to patients with less aggressive surgery [23]. Of the seven remaining studies, two found no adverse effects on IQ [13,28], and one of these noted improvements in test scores for some patients [13]. Three investigations reported postoperative declines in intellectual functioning that are not easily separated from the effects of irradiation, chemotherapy, and/or tumor location [2,17,18].

Age at Diagnosis

Younger age at diagnosis was related to lower levels of post-treatment intellectual function in 8 of 10 investigations that examined age effects on IQ [11,12,14-16,20,30,34]. This association is difficult to evaluate because of differing definitions of "younger" age groups: below 3 years [15,21], 6 years [19,20,24], 7 years [11], 7.5 years [12], and 8 years [14]. Statistically significant age effects were found in 4 studies [11,12,20,34]; the other four investigations were purely descriptive [14,15,16,30]. Of the 2 studies that reported no overall effect of age [19,24], one described a significant relationship between age at diagnosis and selective attention, with younger children performing more poorly [24].

Time Since Treatment

The relationship between time since treatment and intellectual level was evaluated longitudinally in eight studies [2,11–13,16,19,20,23], three of which found a

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TABLE IV. Summary of Methodologic Characteristics Across 21 Studies

	Adverse effects on IQ					
Risk factors	Yes	No				
Radiation therapy	12 [2,11,12,14,15–21,34]	6 [22-27]				
Whole-brain irradiation	2 [12,19]	0				
Increased dose	0	0				
Surgery	5 [2,13,17,18,29]	3 [12,23,28]				
Degree of resection	0	2 [12,23]				
Younger age at diagnosis	8 [11,12,14-16,20,30,34]	2 [19,24]				
Increased time from treatment	7 [2,11,12,16,19,20,24]	1 [13]				
Chemotherapy	3 [2,16,21]	1 [12]				
Hemispheric tumor location	3 [12,20,24]	1 [34]				
Hydrocephalus	1 [12]	4 [15,19,20,34]				
Sensory and motor impairment	1 [20]	1 [23]				
Progressive disease	0	1 [23]				
Seizures	0	0				

VABS

Adaptive behavior

CQS 2 9.5

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statistically significant decline from pre-irradiation assessments to follow-up examinations more than 4 years later [2,11,16]. However, in one report this was only true for those patients given whole brain irradiation and those who received any irradiation at a younger age [11]. Two investigations reported declines in IQ over time but did not include statistical analyses [19,24]. The effect of time since treatment was mediated by tumor location or patient age in three studies [12,13,20]. Cavazzuti et al. [13] found postoperative improvement in verbal memory for patients with right temporal lobe tumor and improvement in nonverbal memory for patients with left temporal lobe tumors. Ellenberg et al. [12] reported increase in IQ from 1 to 4 months post-treatment with declines thereafter, but this relationship was apparently mediated by tumor location. Finally, Mulhern and Kun [20] evaluated patients before and 6 months after irradiation. Declines in scores varied with age: younger children (≤6 years) evidenced a greater interval decline in memory functioning than older children.

Chemotherapy

The relationship between chemotherapy and IQ was examined in four of the studies reviewed [2,12,16,21]; three have suggested adverse effects on IQ. One study found no significant IQ differences between patients who did and did not receive chemotherapy at the initiation of chemotherapy or at 1- to 4-year follow-up examinations [12]. Another investigation evaluated the effects of chemotherapy in combination with irradiation for meduloblastoma, astrocytoma, and control patients [21]. Children in all the tumor groups scored significantly lower on a measure of IQ than did a group of normal controls. Mulhern et al. [2] examined 14 infants receiving pre-irradiation chemotherapy and found that during chemotherapy two patients improved on tests of mental abilities, five remained stable, and one showed an interval

decline. Duffner [16] found that five of five patients treated with chemotherapy had IQ scores that declined at least 10 points over time and required special class placement, whereas only 6 of the 11 patients who did not receive chemotherapy needed such placement.

Tumor Location

Specific evaluations of the relationship between IQ and brain tumor location were done in only four studies [12,20,24,34]. Ellenberg et al. [12] examined the IQ scores of patients with tumors in the third ventricle region, posterior fossa region, and cerebral hemispheres at four time intervals. The IQ scores of patients with hemispheric tumors were lower than those for the other two groups overall, but the difference was significant only at the first postdiagnosis evaluation, perhaps due to smaller sample sizes at the later intervals. Another study [20] found a greater increase in IQ scores after surgery for patients with tumors of the posterior fossa, compared with those with third ventricle area and hemispheric tumors, but this relationship was true only for younger children. Kun et al. [24] found significant decreases in IQ in a greater proportion of children with hemispheric than posterior fossa tumors following irradiation. By contrast, Jannoun and Bloom's [34] series found no differences in IO among children with hemispheric versus nonhemispheric tumors.

Hydrocephalus

Three studies found no significant relationship between hydrocephalus and intellectual deficits [15,19, 20,34]. By contrast, Ellenberg et al. [12] reported that patients with hydrocephalus had significantly lower IQ scores both initially and at 4 months postdiagnosis. However, IQ scores improved over a subsequent 3-month interval both for patients with and without a history of hydrocephalus. This investigation also examined those

patients with hydrocephalus who did or did not have shunts. Initially, no significant IQ differences existed between these two groups. However, at the 4-month interval, a significant IQ increase was noted only for those patients who had received shunts.

Sensory and Motor Impairment

The impact of visual, auditory, and motor impairment on IQ test performance has seldom been analyzed in brain tumor patients. We identified only two such investigations [20,23]. Cavazzuti et al. assessed 35 long-term survivors of craniopharyngioma; 18 were treated with conservative surgical procedures followed by local field radiation therapy, and 17 had undergone aggressive total resection [23]. The latter group was further divided into those whose tumors never recurred, and those whose tumor recurred and required second surgery and irradiation. No permanent visual impairment was noted among patients without recurrence, but one-third of the patients who required repeat resection had clinically relevant visual impairment. No statistically significant differences among the IQ values of the three treatment groups were noted, and all group mean scores fell within the normal range for age. The sensorimotor status of 26 children with malignant tumors was evaluated [20]. Twenty-five percent of the patients had one or more significant visual, auditory, or motor deficits. Although there was no statistically reliable correlation between these deficits and IQ scores, five of the six patients with FSIQs of <80 were visually impaired; among the 20 children with FSIQs ≥80, only two had visual impairments.

Progressive/Recurrent Tumor

Only one of the 21 studies reviewed formally evaluated the effects of recurrent tumor. As described in the previous section, Cavazzuti et al. [23] found no IQ differences between those patients with or without recurrent craniopharyngioma. However, they noted an increased incidence of other neuropsychological problems, including symptoms of frontal lobe dysfunction, among patients who required retreatment.

Multivariate Analysis of IQ

The discussion of risk factors for IQ deficits has thus far assumed that these factors operate independently. Many potential risk factors are not independent. For example, dose and field of cranial irradiation are highly dependent on tumor location and histology. Only one study to date has attempted to analyze risk factors in combination, presumably because of the large sample size needed for such analyses. Ellenberg et al. [12] serially evaluated 43 consecutively diagnosed children with brain tumors and performed multiple regression analyses using IQs at 1–4 years of follow-up as the criterion variable. The following factors, listed in de-

scending order of importance, were significant univariate predictors of lower IQ: (1) lower IQ at 1 month postdiagnosis, (2) younger age at diagnosis, (3) whole-brain radiation therapy field, and (4) cerebral hemisphere tumor site. Ellenberg and colleagues also found a statistically significant interaction between age at diagnosis and radiation therapy field: younger children who had received local or no irradiation had higher IQs than comparably treated older children, whereas younger children treated with whole-brain irradiation had lower IQs than did comparably treated older children.

DEVELOPMENT OF A MULTISTUDY ANALYSIS OF IQ EFFECTS

Methods

On the basis of the literature review presented earlier, we developed the following three hypotheses regarding the primary risk factors of age at treatment, tumor location, and extent of irradiation: (1) in general, younger children at the time of treatment will exhibit lower IQs at follow-up than children who were older at treatment; (2) children with tumors located in the cerebral hemispheres should show lower IQ values than those with tumors located in the region of the third ventricle or posterior fossa; and (3) patients receiving cranial (whole-brain) irradiation should display lower IQ attainment than those receiving local or no irradiation.

Within the constraints of the completeness of reporting of patient information and IQ outcomes in the studies reviewed here, we developed a statistical approach to the quantitative analysis of IQ, which could be applied across studies. Meta-analysis is the preferred method for such an analysis [33]. However, meta-analysis depends on the reporting of an effect size for the variable of interest using similar definitions of that variable in comparable groups of patients. Since most of the studies were descriptive and did not use statistical tests of differences in IQ between groups (e.g., younger vs. older children receiving cranial irradiation for medulloblastoma) or strength of association between variables (e.g., the correlation between age at irradiation and IQ), the meta-analytic approach was prohibited because it would have excluded most of the studies in this review.

As an alternative approach, individual and group data were extracted from the 18 studies reporting IQ outcome 2 or more years from treatment. Age at treatment, tumor location, and/or extent of irradiation were also recorded. When individual IQ values were reported, an observation (Y_i) consisted of the data for that patient (N=60). When only group data was reported, an observation consisted of a measure of central tendency (Y_g) , usually the mean, and the number of patients in the group. There were 23 such groups ranging in size from 3 to 40 patients. The observations were then classified by age at treatment (<4

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TABLE V. Summary of Multistudy Analysis of IQ

Patient group ^a	N	Mean	SEb	SDc
Overall	403	91.0	2.65	24.1
Age at diagnosis				
<4 yr	48	71.9	3.08	21.4
≥4 yr	135	92.6	1.84	21.4
Tumor region				
3rd ventricle	73	94.2	2.76	23.6
Posterior fossa	101	90.2	2.34	23.6
Cerebral hemisphere	67	89.7	2.88	23.6
Radiation therapy volume				
None	54	101.2	2.85	20.9
Local	98	93.8	2.11	20.9
Cranial (whole brain)	125	82.9	1.87	20.9
Region and age				
Posterior fossa, <4 yr	10	75.0	6.18	18.6
Posterior fossa, ≥4 yr	53	88.9	2.69	18.6
Cerebral hemisphere, ≥4 yr	12	82.0	5.64	18.6
Radiation therapy volume and age				
None, ≥4 yr	10	99.3	6.10	19.3
Local, ≥4 yr	15	85.3	4.98	19.3
Cranial, <4 yr	16	73.4	4.82	19.3
Cranial, ≥4 yr	54	87.0	2.62	19.3
Region and radiation therapy volume				
3rd ventricle, none	24	100.3	4.24	20.8
3rd ventricle, local	45	93.2	3.10	20.8
Posterior fossa, none	24	103.2	4.24	20.8
Posterior fossa, local	17	93.9	5.04	20.8
Posterior fossa, cranial	60	83.9	2.68	20.8
Cerebral hemisphere, local	22	92.2	4.43	20.8

^aRestricted to those subgroups with $n \ge 10$.

years, ≥4 years), region of tumor (posterior fossa, third ventricle, cerebral hemisphere), and radiation therapy volume (none, local, cranial). Age at treatment, tumor region, and radiation therapy volume were analyzed in separate univariate analysis of variance (ANOVA) and then in separate two-way ANOVA for their effects on IQ, with each observation weighted by the number of patients represented by that observation. These separate procedures were necessary because insufficient patient numbers in some cells prohibited the concurrent analysis of all three independent variables. In each analysis, observations were excluded in which the independent variable(s) of interest were unknown or in which the grouped data consisted of a heterogeneous mix of patients. Pairwise comparisons were restricted to groups with 10 or more observations; two-tailed probabilities are reported. Because of insufficient data in some cells, interactions among risk factors could not be analyzed.

Results

The mean IQ of the entire sample of 403 children was 91.0 (Table V). Analysis of simple main effects revealed

that younger children exhibited a lower IQ overall than that of older children ($M=71.9~\rm vs.~92.6$; P<0.0001). No overall effect of tumor location was detected (P>0.10), with children treated for tumors of the posterior fossa region (M=90.2), third ventricle region (M=94.2), and cerebral hemispheres (M=89.7) having similar IQ performance. The adverse effects of radiation therapy increased significantly with treatment volume (P<0.0001); nonirradiated children had the highest performance (M=101.2), followed by children who had received local irradiation (M=93.8), and those who had received cranial irradiation (M=83.9).

Tumor region and age. Younger children with tumors of the posterior fossa displayed lower mean IQ values than older children with posterior fossa tumors (M = 75.0 vs. 88.9; P < 0.05). Among the older children, no statistically significant difference was noted between those with tumors of the posterior fossa region or cerebral hemispheres (M = 88.9 vs. 82.0; P > 0.10).

Radiation therapy volume and age. Among children who had received cranial irradiation, those who were younger had significantly lower IQs than those who were

bSE, standard error.

^cSD, standard deviation.

older (M = 73.4 vs. 87.0; P < 0.05). Among older children, those who did not receive irradiation tended to have higher IQ values than those receiving local irradiation (M = 99.3 vs. 85.3; P = 0.08) or cranial irradiation (M = 99.3 vs. 87.0; P = 0.07); however, no difference was observed between older children receiving local or cranial irradiation (M = 85.3 vs. 87.0; P > 0.10).

Tumor location and radiation volume. Children with posterior fossa tumors receiving cranial irradiation displayed lower IQ values than that of children with no irradiation (M = 83.9 vs. 103.2, P < 0.001) and also tended to have lower IQs than those receiving local irradiation (M = 83.9 vs. 93.9, P = 0.08), but no significant difference was detected between the nonirradiated children and those receiving local irradiation only (P > 0.10). For tumors of the third ventricle region, no differences were noted between children receiving no irradiation or local irradiation (M = 100.3 vs. 93.2, P > 0.10). Those receiving local irradiation for posterior fossa tumors did not differ significantly from children receiving local irradiation for tumors of the third ventricle region (M = 93.9 vs. 93.2, P > 0.10) or those receiving local irradiation for tumors of the cerebral hemispheres (M = 93.9 vs. 92.2, P > 0.10). Finally, comparison of nonirradiated children with posterior fossa and third ventricle region tumors failed to detect differences (M = 103.2 vs. 100.3, P > 0.10).

Summary

The results of the integrative analysis emphasize the risk of a young age at treatment and greater irradiation volume in adversely affecting the intellectual status of long-term survivors of pediatric brain tumors. In general, younger children and children receiving cranial irradiation had the lowest IQ values. Specifically, children under the age of 4 years who receive cranial irradiation appear to be at highest risk for impaired intellect. These results confirm the findings of Packer et al. [11], Ellenberg et al. [12], and Jannoun and Bloom [34], cited earlier. The absence of a significant effect of tumor location is in contrast to previous findings that children with hemispheric tumors show greater deterioration [12,24], although this effect has been difficult to confirm in other empirical studies [34]. Insufficient patient numbers in some groups of interest (e.g., <4 years, nonirradiated) and a 30-60% increased variability among IQ scores compared with normal expectations contributed to failure to detect some differences between groups.

OUTCOME MEASURES OTHER THAN IQ

Academic Achievement

Eight studies included academic achievement as an outcome measure in assessing children treated for brain

tumors, with statistical analyses provided in two [14,20]. Arithmetic scores, but not reading or spelling scores, were significantly decreased for brain tumor patients when compared with sibling controls in one study [14]. Another investigation found a marginal decline over time in arithmetic achievement but not reading or spelling skills [20]. The remaining studies provided only descriptive analyses. Spunberg et al. [27] found reading ability below the expected age level for most patients, and 6 of the 13 patients were enrolled in special education classes. Eight of 15 patients studied by LeBaron et al. [25] were at least one standard deviation below average in at least one area for grade level. Similarly, Mulhern et al. [30] reported problems in academic achievement for seven children with below normal IQ, five of whom were in special education classes. In another study, 10 of 30 patients were in learning disabled settings because of achievement delays or problems in selective attention [19]. Duffner et al. [17] reported learning disabilities in 4 of 10 children with *normal* IQs.

Emotional Adjustment

Seven studies have examined emotional adjustment in brain tumor patients [14,19,20,24,30]. Although none of these reports included statistical evaluations, the results generally indicate at least some increase in socialemotional problems. Mulhern and Kun [20] found that at postsurgical evaluation 50% of patients showed disturbances not representative of premorbid functioning: 42% were identified as disturbed at a second evaluation. Kun et al. [24] reported a significant trend toward psychotic symptomatology among the same patients, and observed that patients exhibited a high frequency of acute emotional adjustment problems early in their treatment. After supratentorial or whole brain irradiation [19], 9 of 12 patients had abnormal social-emotional functioning; 1 of 5 patients had abnormal functioning after local posterior fossa irradiation. In another investigation, 8 of 15 patients evidenced clinically significant disturbances and frankly psychotic symptoms were noted in four of these patients [25]. In that study, the behavior problems reported most frequently were somatic complaints, social withdrawal, and depression. One-third of the patients were disrupted enough to warrant clinical intervention. Using projective measures of emotional functioning, Spunberg et al. [27] found no severe emotional disturbances, but noted poor planning and organizational skills and a tendency toward passive-dependent and immature personality style. Finally, Mulhern et al. [30] found evidence of organic personality syndrome in 2 of 7 patients treated for temporal lobe tumors.

Neuropsychological Tests

Eight studies used formal measures of neuropsychological functioning in addition to IQ tests. These mea-

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sures can be broadly categorized into those measuring higher conceptual abilities; specific memory functions; and visuomotor, visuographic, or fine motor functions. With regard to conceptual abilities, problems with cognitive flexibility and problem-solving were noted by LeBaron et al. [25] among children treated for posterior fossa tumors that could not entirely be attributed to cranial irradiation. Cavazzuti et al. [13,23] used the Wisconsin Card Sort Test to evaluate frontal lobe cognitive functions among patients treated for craniopharyngioma. There was a high incidence of abnormal responses in patients who had undergone radical surgical excision with or without radiation therapy [23].

Memory and attentional skills were assessed by Riva et al. [21], who found selective deficits in vigilance among children with posterior fossa tumors on the Trails-Making Test but not on the computer-administered Continuous Performance Test. In the Cavazzuti et al. study [13], the Wechsler Memory Scales revealed abnormal short-term verbal memory capacity in children with right or left temporal lobe tumors; adverse effects were more frequency among children with left than right temporal lobe tumors.

Three independent investigations using the Halstead-Reitan Neuropsychological Battery [17,25] or the Luria–Nebraska Neuropsychological Battery [26] have found a high frequency of visuospatial defects as well as problems with fine and gross motor steadiness, speed, and coordination among children treated for posterior fossa tumors. Specific tests of visual-motor functions have also been given (e.g., Developmental Test of Visual-Motor Integration, Bender Visual Motor Gestalt Test). Packer et al. [11] reported poor performance on these tests among children with posterior fossa tumors with or without prior radiation therapy. Spunberg et al. [27] found that 12 of 13 children previously treated for a variety of brain tumors had deficient visuomotor skills.

Adaptive Behavior

Only 2 of the 21 studies reviewed reported quantitative measures of adaptive behavior or activities of daily living other than the Bloom [2] or Karnofsky [31] ratings. Spunberg et al. [27] developed a Composite Quality of Life Scale (CQS) to evaluate survivors of brain tumors who were younger than 2 years at diagnosis. The CQS rates of functional status from grade 1 (normal, no impairment) to grade 5 (totally disabled) based on the patient's physical, neurological, endocrinologic, psychological, and educational status. Of 14 patients studied, six received ratings of grade 1-2, two patients were rated grade 3, and six patients received ratings of grade 4-5. An inherent problem in such ad hoc measures is a lack of information concerning reliability, validity, and normative standards. Mulhern et al. [2] used the Vineland Adaptive Behavior Scales to assess functional status.

Scores for communication, social, daily living, motor domains and an adaptive behavior composite were computed. The Vineland is a standardized structured interview with norms from birth to late adulthood [32]. Patient scores clearly changed over time from diagnosis and appeared associated with the timing of various therapies (surgery, chemotherapy, radiation therapy) as well as the neurological integrity of the patient. Ultimately, 11 of the 12 survivors scored ≥1 SD below the mean score for normal age peers.

CONCLUSIONS

Defining sources of neuropsychological toxicities is a complex process, as evidenced by the wide variation across studies in reported effects of tumor location, hydrocephalus, irradiation field, and time since treatment. Nonetheless, it is possible to draw some conclusions regarding the risk of neuropsychological deficits among survivors of pediatric brain tumors. In general, these children have an increased incidence of intellectual, academic, and personal–social adjustment problems when compared with siblings, normal comparison groups, or children with other cancers. Cognitive performance appears most directly impaired by young age at treatment and full cranial irradiation, although indirect impairment may result from clinically significant sensory and motor deficits.

Relatively few empirical studies of children treated for brain tumors have used standardized methods of assessing neuropsychological status. Further, among the 22 studies we identified that met this criterion, the completeness of reporting demographic, medical and psychological data varied markedly. These limitations prohibited our use of formal meta-analysis, a statistical method of integrating the outcomes of different studies by computing standardized estimates of the effects of variables of interest [33].

Because of multiple concurrent sources of potential neuropsychological dysfunction, multivariate analyses are necessary to identify definitively the relative contributions made by separate tumor- and treatment-related factors. Such analyses have seldom been possible, however, because of the limited number of patients available in most single-institution series. The one multivariate analysis included in our review implicated tumor location, radiation therapy volume, and age at treatment as the predominant factors determining subsequent performance on IQ tests [12]. Our own analysis, based on the studies reviewed here, confirmed the negative impact of young age and whole brain irradiation. This limited analysis further suggests that tumor location does not modify the effects of local irradiation on IQ. However, two caveats are required in interpreting these findings. First, neither analysis considered the patients' sensory,

motor, or seizure status as mediating variables. Second, potential interactions among identified risk factors could not be analyzed because of limitations and inconsistencies of the reported data. For example, too few patients were available in the following subgroups for comparisons: older and younger children with tumors of the third ventricle region, older children with tumors of the cerebral hemispheres, older and younger children receiving no irradiation, younger children receiving local irradiation only, children with tumors of the cerebral hemispheres who receive cranial or no irradiation, and children with tumors of the third ventricle region receiving cranial irradiation.

Although deficient intellectual development associated with specific patient, tumor, and treatment characteristics may limit quality of life among children with brain tumors, IQ alone cannot adequately represent the scope of psychological changes observed in this population. Other outcomes include academic failure and learning disability, sometimes within the context of normal IQ, personal and social adjustment problems directly resulting from the tumor and its treatment or indirectly resulting from attempts to cope with residual disabilities, specific neuropsychological deficits in processing information such as abnormal verbal memory among some children treated for left temporal lobe tumors, and functional problems reflected in restriction of activities of daily living. Our ability to integrate these qualitatively different domains into a valid index of quality of life among children is currently limited by the lack of an acceptable unitary measure.

RECOMMENDATIONS

The significant functional deficits among survivors of pediatric brain tumors summarized in this review provide ample evidence to justify neuropsychological evaluations as a component of comprehensive patient care, especially for those high-risk subgroups previously identified. If neuropsychological evaluations are to be useful for the evaluation of toxicities associated with systematic treatment of pediatric brain tumors, changes in the reporting and analysis of outcome data are required to permit optimal integration of findings.

- 1. Evaluations should be conducted with standardized instruments. Neuropsychological and intellectual test performance in the general population is highly correlated with age, especially for children. Therefore, test scores must be adjusted for age-related changes before comparisons among patient groups are conducted. Psychological tests that provide age-corrected, general population norms should receive priority.
- 2. Prospective serial evaluations are essential to assess the relationship of changes in neuropsychological test

performance with neurological events and medical interventions. Surveillance of patient status with neuropsic chological evaluations should be planned with the same relevance as repeated neuro-imaging, if with different frequency. The intervals between evaluations will depend upon the patient's clinical course and expectations for the timing of the appearance of adverse effects of treatment.

- 3. The completeness of reporting of patient information must be improved in individual studies so that more rigorous comparisons may be made among patient samples. Essential information for each patient sample and lyzed in a given study includes: age at diagnosis, time from diagnosis, neurologic status (seizures, sensory and motor findings), tumor location, extent of surgery, volume and dose of radiation therapy, and chemotherapy details.
- 4. Resources must be pooled to allow for multivarial analyses with sufficient statistical power to address interactions among risk factors. This process can be facilitated by informal consortiums among institutions and by the more formalized structures for investigations in pediatric oncology, the Pediatric Oncology Group (POG) and Children's Cancer Study Group (CCSG).

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