Medical and Neurocognitive Late Effects among Survivors of Childhood Central Nervous System Tumors

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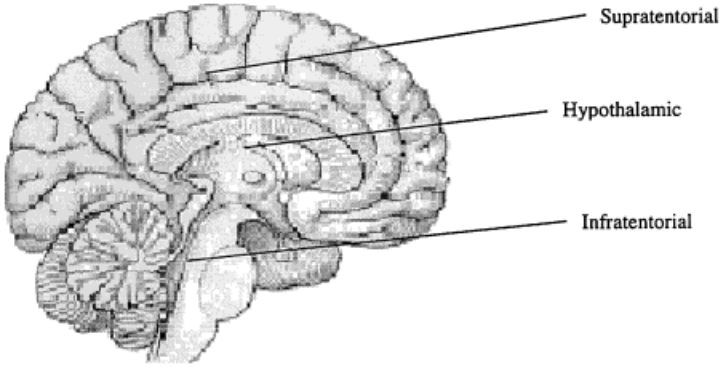
Primary brain and other central nervous system (CNS) tumors are the most common solid tumors that occur during childhood,[1] with an annual U.S. rate of approximately 3.0 cases per 100,000 persons aged 19 years or younger.[2] Incidence rates of pediatric CNS malignancies were essentially unchanging during the 1990s[3]; past concerns about trends that indicated increasing rates in the 1980s appears to be largely explainable by diagnostic and ascertainment improvements that occurred during that time period.[4,5]

The prevalence of persons alive with a previous diagnosis of a CNS malignancy is estimated by the National Cancer Institute to be 35 per 100,000 males and 29 per 100,000 females.[6] Because nonmalignant CNS tumors (such as meningiomas) are not included in this statistic, the actual prevalence of CNS tumor survivors in the U.S. is substantially higher than the National Cancer Institute estimates. As treatment improves, more children are surviving cancer into adulthood. Survival rates for those with pediatric CNS tumors differ substantially by histology, site, and age at diagnosis.[1] Overall, the 5-year survival probability for children with a CNS malignancy diagnosed between 1985 and 1994 was 67%.[1] Pediatric patients generally have a better prognosis than adults with CNS tumors, although the morbidity from these tumors and their treatment can be substantial.[7,8] As more children with CNS tumors survive and require treatment in primary care settings, it is increasingly important for health care providers to recognize long-term complications of these tumors and their treatments. The purpose of this article is to provide a concise review of the long-term effects of pediatric CNS tumors and their treatment. We hope this review will aid providers in managing CNS survivors' existing problems and in anticipating problems that survivors may face.

Pediatric CNS Tumor Classification

Tumor location plays a critical role in the type and severity of late effects.[8] Tumors frequently are categorized anatomically as supratentorial, infratentorial, or hypothalamic/parasellar (Fig. 1). In children, 50–60% of tumors arise below the tentorium, whereas in adults, most arise above it.[9] Several studies have shown that supratentorial tumors generally result in greater morbidity than infratentorial tumors in surviving children and adults.[10–12]

Tumor histology itself does not appear to be a major factor in the occurrence of late effects, but because treatments vary considerably among different tumor types, histology plays a strong indirect role in



Region	Histology (% of primary CNS tumors)	Important Associated Late Effects
Supratentorial	Low-grade astrocytoma (15-20%) High-grade astrocytoma (8-12%) Other Glioma (5-10%)	Poor cognitive function[10] Poor manual dexterity[11] Emotional Difficulties[11,12] Seizures[51,54] Poorer overall quality of life[12,30]
Hypothalamic/Parasellar	Craniopharyngioma (6-10%) Optic pathway glioma (4-8%)	Growth Hormone Deficiency with Hypothyroidism/Hypogonadism[54]
Infratentorial	PNET (20-25%) Cerebellar astrocytoma (12-15%) High-grade pontine glioma (5-10%) Ependymoma (4-8%)	Ataxia[11] Primary Thyroid Dysfunction[66] Ovarian Dysfunction[55]

FIGURE 1 Location of pediatric central nervous system tumors and associated late effects. CNS: central nervous system; PNET: primitive neuroectodermal tumor.

determining late sequelae. Central nervous system tumors often are defined to fall into the following broad histologic categories: astrocytomas and gliomas (also referred to as astroglial or astrocytic tumors), primitive neuroectodermal tumors (PNETs, including medulloblastoma), germ cell tumors, and pineal cell tumors. Of these, astroglials are the most common, accounting for more than half of all pediatric CNS tumors. Classification systems developed by the World Health Organization[13,14] and the more recent International Classification of Childhood Cancer[15] often are used for surveillance and epidemiologic purposes, but a variety of other classification systems are used more frequently by clinicians.[16,17] Although staging is important in some pediatric carcinomas, it is of little use in pediatric CNS tumors except for medulloblastomas.[17] Molecular diagnostic techniques and cytogenetic information are increasingly becoming available,[18] but such data are currently of limited clinical utility.

Treatment

Virtually all pediatric brain tumors are treated first with surgery, although surgical cure is usually limited to low-grade astroglial tumors. The two primary goals of surgery for pediatric CNS tumors are diagnosis and cytoreduction.[19] Once a child is identified as having a brain lesion, surgery normally is needed to establish a definitive diagnosis. Direct open biopsies are the preferred method of obtaining tissue and often allow for simultaneous reduction of tumor burden. Cytoreduction is a vital part of tumor therapy because for many pediatric brain tumors, unlike those in adults, surgery has been shown to improve outcome in many tumor types.[20]

Surgical mortality is generally low, with rates of approximately 1% for experienced surgeons.[17] Morbidity is variable and depends on factors such as tumor location and adjuvant therapy. Newer techniques such as the use of operating microscopes and stereotactic biopsies have aided surgeons in reducing late effects; experimental techniques such as brain mapping and intraoperative magnetic resonance imaging scanning may help further reduce operative morbidity in the future.

Radiotherapy also plays a major role in treatment of pediatric CNS tumors.[17,21] Until the 1970s, when widespread use of chemotherapy became common, radiation was the only adjuvant therapy available for CNS tumors. Unfortunately, the long-term damage that radiation imparts on brain cells has become more apparent as survival has improved.

Children treated for CNS tumors generally receive radiation either specifically to the site of the tumor itself or to the whole brain and spinal cord with a

boost given at the tumor site. Radiotherapy for primary CNS tumors in children tends to be higher in dose than those used against other malignancies, typically greater than 30 grays (Gy) and frequently as high as 50–60 Gy.[8] In contrast, children receiving therapy for acute lymphoblastic leukemia (ALL) usually receive doses in the 18–24-Gy range. The threshold dose required to produce tissue damage that results in late effects is not known.[22] Age is an important risk factor for developing late-term complications of radiotherapy; as discussed below, studies have emerged showing profound intellectual disturbances in children receiving radiation before age 3 years, and mild to moderate impairment of intellectual functioning when radiotherapy is administered before age 7 or 8 years.[8]

Advances in the administration of radiotherapy may help mitigate some of the late effects currently observed. Sophisticated computer algorithms now allow radiation oncologists to administer hyperfractionated treatments that maximize tumor exposure to radiation while minimizing exposure of normal brain parenchyma. Similarly, brachytherapy, in which high-energy, low-penetrance radioactive sources are surgically placed within or adjacent to the tumor, may allow for improved therapy of recurrent tumors with fewer late-term effects.[23]

Although chemotherapy was a relatively late addition to the modalities used to treat childhood CNS tumors, its use during the past several years has increased substantially.[24] With data available to support its use in deferring radiotherapy in children younger than age 3 years,[25] chemotherapy has now become virtually standard treatment in infants and young children. Agents used include the nitrosoureas (carmustine and lomustine), vincristine, platinum compounds, and procarbazine. Each of these agents has characteristic adverse effects. The use of intrathecal methotrexate has produced problematic late-term effects and is not commonly used today.[8] Different tumors show varying sensitivities to chemotherapy regimens. Historically, chemotherapy has been shown to have good activity against PNETs[26] and high-grade gliomas,[24] but more recently success has been shown in low-grade gliomas.[27] New research is underway using traditional agents in combination with immunotherapy in an attempt to further improve survival and reduce late-term effects.

Late Effects

Late effects are defined as any chronic or late occurring physical or psychosocial outcome persisting or developing well after diagnosis of the tumor. Some investigators have specified 5 years as the minimum time period after which an outcome can be classified as a late effect.[28] The treatment received, age at which the child developed the tumor, and tumor location all influence the late effects a child treated for a CNS tumor may experience. Table 1 provides a summary of these late effects and important associated risk factors.

TABLE 1
Common Late Effects in Childhood Brain Tumor Survivors and Their Risk Factors

Late effect	Relative prevalence	Risk factors
Cognitive dysfunction	+++[10,31]	Cranial radiation (especially young age at radiation therapy), supratentorial tumors, intrathecal methotrexate
Emotional disturbance	++[12]	Supratentorial tumors
Motor dysfunction	++[11,51,54]	Supratentorial tumors: hand–eye coordination problems, poor manual dexterity Infratentorial tumors: balance problems
Other neurologic complications		
Pain	++[30,50]	Osteopenia
Seizures	+[11,51,54]	Supratentorial tumors
Sensory loss	++[11,12,30]	Supratentorial tumors
Endocrinopathies		
Growth hormone deficiency	+++[54,55]	Cranial, spinal radiation, hypothalamic tumors
Hypothyroidism	++[65]	Spinal radiation, combined chemotherapy and radiotherapy
Gonadal dysfunction	++Females[55,66] +Males[55]	Spinal irradiation, cyclophosphamide, lomustine, carmustine
Dyslipidemia	++[70]	Growth hormone deficiency
Obesity	++[70]	
Second malignancies	None to +[57,76]	Cyclophosphamide, etoposide, radiation therapy
Pulmonary dysfunction	+[74]	Lomustine
Osteopenia	++[75]	Radiotherapy, growth hormone deficiency

+++: incidence of 60% or greater in cited series; ++: incidence of 30–60% in cited series; +: incidence of 0–30% in cited series.

Although the evidence is strong that childhood brain carcinoma survivors suffer more morbidity than survivors of other childhood cancers,[29,30] estimates as to the prevalence and severity of their morbidities are crude. Most of our knowledge is derived from single institution case series, each with differing research questions and methodologies that limit our ability to accurately characterize the problems survivors face. Currently, research is underway examining data from

larger cohorts in an attempt to improve knowledge of this important topic.

Neurocognitive Effects

Neurocognitive late effects in childhood brain tumor survivors are relatively common and can be highly debilitating. In one review of the literature,[31] cognitive deficits were reported in 40–100% of survivors included in the series examined. Although there is not a uniform neuropsychologic profile of a pediatric brain tumor survivor, deficits frequently are noted in the areas of intellectual ability, academic achievement, memory, attention, visual perceptual ability, and language.

Most studies on neuropsychologic functioning in pediatric brain tumor survivors have focused on the sequelae of radiation therapy.[32] In one study of 56 pediatric brain tumor survivors in whom 22 received radiation therapy, 68% of survivors who received radiation treatment were found to have intelligence quotient (IQ) scores less than 90, compared with 18% who were not treated with radiotherapy. Doses of radiation administered in this series were 40–56 Gy.[11] In another series of 57 medulloblastoma survivors, 89% of patients who underwent whole-brain radiation of 45–50 Gy had an IQ less than 90 after treatment, compared with 38% of survivors who did not undergo radiation therapy.[33] Moreover, survivors who were treated with radiation therapy tended to have significantly lower IQs than their siblings.[34] In a series of 120 medulloblastoma patients who received 35–50 Gy radiation therapy, only 58% of patients who underwent whole-brain irradiation for medulloblastoma had IQs higher than 80 five years after treatment.[35] At 10 years after treatment, only 15% of survivors had IQs higher than 80, whereas 46% had IQs lower than 60. In addition, survivors of medulloblastomas had significantly more intellectual impairment than astrocytoma patients who did not receive radiation therapy.[36] Collectively, these studies suggest that survivors who were treated with radiation therapy experience greater intellectual deficits than those who were not treated with radiation therapy. These studies are limited, however, because it is unclear whether the cognitive deficits are a product of the tumor itself or the treatment.

Survivors of brain tumors often experience academic difficulties. Learning disabilities in particular are common among those treated with radiation.[37] Research suggests that survivors who have academic difficulties are more likely to struggle with math than with reading.[38] Moreover, children who received whole-brain radiation have been found to have significant learning problems and tend to require special education services at school, regardless of IQ.[39] Thus, an average IQ for a pediatric brain tumor survivor does not necessarily preclude the need for special help in the classroom. Academic difficulties tend to be more evident among children who are young at the time of diagnosis.[40]

Pediatric brain tumor survivors also have been found to have attentional and memory deficits.[7,32,41] Survivors of childhood PNETs perform significantly worse on measures of immediate and prolonged attention when compared with siblings and peers.[42] Mulhern and Kun found that both selective attention and memory decreased in 68% of the 26 pediatric brain tumor survivors who they studied.[43] Moreover, children who underwent resection of cerebellar tumors without cranial radiation or methotrexate treatment were found to have verbal memory deficits.[44] Impairments in visual memory were found by other investigators.[37]

The few studies to examine visual perceptual abilities in pediatric brain tumor survivors suggest potential difficulties in perceptual motor, fine motor coordination, and visual-constructive abilities.[41,45] Deficits in visual motor and visual spatial skills[39] and perceptual-organizational skills also have been reported.[37]

Several factors place brain tumor survivors at higher risk for poor neuropsychologic outcomes.[10] Specifically, young children who undergo radiation therapy, especially those younger than age 7 years, experience greater cognitive deficits than older children. In addition, whole-brain radiation appears to lead to cognitive decline.[10] In a study of 56 brain tumor patients, radiation therapy before age 6 years resulted in subnormal IQ for all patients.[11] Younger children had greater declines in IQ than those who were older at the time of treatment.[34,35] Infants and toddlers were at highest risk for intellectual and neuropsychologic difficulties. Thus, the evidence is clear that the younger a child is at time of radiation treatment, the greater the risk for poor neuropsychologic outcomes.

Although it seems reasonable to hypothesize that children who undergo higher doses of radiation treatment will have greater cognitive deficits, evidence has not uniformly supported this notion. Some studies have reported a tendency for higher doses of radiation to be associated with lower IQ in pediatric brain tumor survivors,[46,47] whereas others have found no correlation between the two.[39]

Tumor location plays a role in long-term outcomes for pediatric brain tumor survivors. Supratentorial tumors are associated with greater cognitive impairment then infratentorial tumors, even when whole-brain radiation was not used in treatment.[48]

According to Ellenberg et al., hemispheric tumors result in greater cognitive impairment. Left hemispheric lesions were more likely to be associated with verbal- or language-based deficits, whereas right hemispheric lesions were associated with visual perceptual deficits.[10] Moreover, hemispheric tumors resulted in lower IQ than tumors of the third or fourth ventricle, although children with fourth ventricle tumors showed significant declines in their IQ over time.

In summary, several studies in recent years, typically characterized by relatively small sample sizes, have examined neurocognitive sequelae of long-term pediatric brain tumor survivors. Although the nature and severity of outcomes depend on multiple factors, it is clear that pediatric brain tumor survivors may face many cognitive effects, including declines in their intellectual functioning, academic difficulties, especially in math, visual perceptual problems, memory impairments, and attentional difficulties.

Neurologic/Sensory Late Effects

Survivors of childhood brain tumors may suffer debilitating neurologic impairment, with pain, seizures, and sensory loss among the most problematic. Various mechanisms in addition to radiotherapy and chemotherapy are hypothesized to cause neurologic damage, including endothelial cell injury, damage to glial cells, and autoimmune responses related to antigens released from damaged cells.[7] Pathologic changes resulting from treatment of CNS tumors include radionecrosis, a rare but occasionally fatal complication, necrotizing leukoencephalopathy, and mineralizing microangiopathy with dystrophic calcification. Clinically, it is important to differentiate these changes from tumor recurrence, because the treatments differ.

The clinical consequences of these pathologic changes are numerous. Mostow and colleagues, in a study of 342 adults, found 24% of brain tumor survivors suffering from visual disturbances and 8% from hearing loss.[12] Another survey of 82 children treated earlier than age 4 years for brain tumors found that 55% had significant neurologic sequelae.[49] In that series 14% had moderate to severe difficulties with ambulation, 24% had major visual defects, and 14% had moderate or severe hearing loss. The incidence of sensory loss, seizures, and motor disturbances was studied in a series of 56 Swedish survivors, with 20% found to have residual seizures and 25% of survivors to have motor disturbances of differing degrees.[11] This study investigated the relative contribution to overall morbidity of motor and cognitive effects, finding that most survivors felt that motor and sensory problems were less disabling than cognitive late effects.

Another recent study of 52 long-term survivors found that 19% of survivors experience frequent pain and 15% were blind, deaf, or mute.[30] These findings are further reinforced by a Canadian study of 44 children that reported that one-third of survivors experience chronic pain.[50] In a series of 64 children whose disease was diagnosed before they reached age 3 years, a high rate of neurologic disturbance was found, with 36% of surviving children experiencing seizures and 64% suffering motor difficulties.[51] Ischemic stroke is a rare late effect of brain tumor treatment, but some series have reported its occurrence.[52,53]

A few risk factors for neurologic late effects have been identified. Younger age at treatment appears to be a risk factor for all neurologic late effects.[49,51] Tumor location appears to be a risk for more specific late effects. Seizures were strongly associated with supratentorial tumors, as are hand–eye coordination deficits and hemiplegia.[11,51,54] Infratentorial tumors may be associated more frequently with ataxia and balance problems.[11]

Neuroendocrine Late Effects

Neuroendocrine late effects are common in survivors of CNS tumors. Some series estimate the risk of endocrinopathy to be $> 80\%$.[55] Neuroendocrine effects can be caused by damage to the hypothalamus (e.g., growth hormone deficiency) or to specific organs (thyroid, ovaries, testicles).

Growth hormone deficiency

The most frequently noted endocrinopathy in long-term survivors of CNS tumors is growth hormone deficiency. In the largest unselected series investigating endocrine dysfunction in brain tumor survivors, comprising 144 patients, Livesey and coworkers found that 86% of survivors had clinical and biochemical evidence of growth hormone deficiency at a median follow-up of 9.6 years.[55] Several smaller series corroborate this finding, with rates of 70% or higher consistently found among childhood brain tumor survivors.[55–60]

Growth hormone deficiency has been shown to occur as early as 3 months after the completion of radiation therapy[61] and as late as 6 years after treatment.[58] Most survivors, however, develop growth hormone deficiency relatively early after treatment. One prospective study found greater than 80% of patients were growth hormone deficient 1 year after treatment,[61] whereas another found that most patients treated for brain tumors became growth deficient within 2 years of therapy.[56] Radiation-induced growth hormone deficiency in survivors appears to be irreversible, because growth hormone stimulation tests

have been shown to remain abnormal 8 years after treatment.[58]

Risk factors for growth hormone deficiency appear to be most strongly related to radiotherapy. Total dose of radiation strongly correlates with the development of growth hormone deficiency[22,62] as does fewer radiation fractions for a given radiation dose.[63] Two smaller series have found young age at time of treatment to be associated with growth hormone deficiency.[57,60] Further research is needed to verify this finding.

It is also important to note that growth hormone deficiency is not the only cause of short stature in survivors of brain tumors. Spinal radiation itself has been shown to irreversibly retard growth,[64] as has precocious puberty, which can occur in CNS tumor survivors.[8]

Although growth hormone replacement may not allow brain tumor survivors to grow at a normal rate, it is still beneficial in promoting growth. Although some have expressed concern about exogenous growth hormone promoting reoccurrence of primary tumors, current data do not support this hypothesis.[8]

Hypothyroidism

Thyroid dysfunction also occurs in a substantial portion of children treated for CNS tumors. Livesey and Brook found that hypothyroidism occurred in 23% of 47 survivors who received craniospinal radiation.[65] A series investigating 20 adult survivors of PNETs who received craniospinal radiation found 20% with thyroid dysfunction.[60] Another series of 20 children and 12 adult brain tumors survivors found hypothyroidism in 28% after a mean follow-up of 7 years after treatment.[66] There are conflicting data as to whether radiation of the cranium alone confers less risk, because some show a substantial reduction in the rate of hypothyroidism in patients receiving only cranial radiation[65] whereas other data do not.[66] Addition of chemotherapy to radiotherapy does increase the risk of hypothyroidism, with studies showing a significant increase in the rate of hypothyroidism to from 20–25% to 70–75% when both are administered.[65,67] Greater fractionation in radiation dosing may reduce the development of hypothyroidism.[67]

It is important that proper treatment for hypothyroidism be received by brain tumor survivors. Hypothyroidism may further impair growth in children with existing growth hormone deficiency. Similarly, lack of thyroid function may contribute to learning disabilities that brain tumor survivors face.[8] Patients with compensated hypothyroidism face an increased risk of developing primary thyroid carcinomas, leading some to argue that patients with elevated TSH levels should receive supplemental thyroxine therapy even if such children are clinically euthyroid and have normal T4 levels.[55]

Sex hormone dysfunction

Gonadal dysfunction is yet another endocrine disorder that may occur in brain tumor survivors. Unlike growth hormone deficiency and hypothyroidism, which generally occur within 2–3 years of treatment, such disorders do not become apparent until children enter puberty or adulthood, making their incidence more difficult to quantify.[55] Livesey et al. found that spinal radiation therapy for CNS tumors was associated with a 35% rate of ovarian dysfunction in girls and a 3% rate of testicular dysfunction in boys.[55] In contrast, those receiving only cranial radiation had no gonadal dysfunction.

A study examining the effects of treatment on 32 brain carcinoma survivors of varying ages found that 70% of postpubertal, premenopausal women had oligomenorrhea, and 50% had low serum estrogen concentrations. In addition, 30% of men were found to have low serum testosterone concentrations.[66] Girls are at higher risk than boys because ovaries are more likely to be damaged by spinal radiation scatter.[8] Certain chemotherapy agents such as cyclophosphamide, carmustine, and lomustine also may produce sex hormone deficiencies in both boys and girls.[68]

Clinically these effects may translate into reduced fertility. In a series comparing fertility in 142 childhood brain tumor survivors and their siblings, the relative probability of pregnancy among survivors was estimated to be 90% that of controls.[69] This finding only includes married survivors, however, thus potentially underrepresenting the true burden of infertility among brain tumor survivors because one-third or more never marry.[12,29]

Other Endocrinopathies

Other endocrinopathies occur in brain tumor survivors as well, including dyslipidemia and cortisol deficiency. A recent European study of 26 brain tumor survivors found that LDL and total cholesterol levels were higher and HDL levels lower than in controls.[70] These differences were especially prominent in survivors with absolute growth hormone deficiency. Because both blood pressure and waist to hip ratio also were increased in brain carcinoma survivors, the authors argued that survivors are at higher risk for cardiovascular disease. Cortisol deficiency has been found in a few brain carcinoma survivors,[55,60] although the clinical implications are presently unclear.

Despite the abundance of data regarding growth hormone deficiency, little data exist regarding the

prevalence of obesity among childhood brain tumor survivors. Heikens et al. found that body mass index did not differ in 26 brain tumor survivors and age-matched controls, but that waist to hip ratio was significantly higher in the survivors.[70] In this series, waist to hip ratio was especially increased in survivors with growth hormone deficiency.

Pulmonary Dysfunction

Pulmonary dysfunction occurring as a late effect of brain tumor treatment is primarily caused from nitrosoureas. The rate of pulmonary dysfunction after administration of carmustine as a single agent has been approximately 15–20% in several large series.[71–73] Pulmonary complications appear linearly related to total dose of carmustine administered, with the highest risk occurring in individuals who have received more than 1400 mg/m^2.[73] Younger age also has been shown to be a risk factor in one series.[71]

In a study of 17 children aged 1–16 years receiving carmustine in cumulative doses ranging from 770 to 1800 mg/m^2, 6 children died of delayed pulmonary fibrosis.[74] Of these deaths, 2 occurred within the first 3 years of treatment and 4 occurred between 8 and 13 years after treatment. All survivors had restrictive pulmonary physiology, with an average vital capacity of 54%. One survivor developed symptomatic fibrosis 17 years after carmustine therapy, leading the investigators to conclude that fibrosis may become symptomatic at any time after treatment.

Osteopenia

Although osteopenia has been shown to be a problem in survivors of ALL, limited data exist on osteopenia in survivors of brain tumors. In one series of 19 survivors, all children had received radiation as part of therapy and were assessed an average of 7 years after receiving treatment.[75] Nine children (47%) were found to be osteopenic by plain X-ray. Formal bone densitometry found that 84% of survivors had negative lumbar spine Z scores and 74% had negative femoral neck scores. Scores for patients deemed osteopenic by X-ray were lower than others, and those with osteopenia were shown to have more pain than others. No correlation between growth hormone deficiency or steroid use and osteopenia was observed in this series.

Second malignancies

Second malignancies are relatively infrequent but potentially devastating consequences of treatment for childhood CNS tumors. Although primary tumor recurrence generally occurs within 5 years, second primary tumors can develop 10–20 years after initial tumor treatment.[17] Second malignancies occurring after CNS tumor treatment can originate in the CNS or other sites. With the increasing use of chemotherapy, children are developing hematopoietic malignancies as well as solid tumors.[76]

Early reports suggested that the incidence of second malignancies in survivors of childhood brain tumors was low, approximately 1–2% 2–8 years after therapy.[57] Reported cases of second malignancies included meningiomas, malignant astrocytomas, intracranial fibrosarcomas, and thyroid carcinomas, with most arising in areas of radiation therapy or radiation scatter. Subsequent series[77] have shown similar rates and confirmed that meningiomas, gliomas, and nerve-sheath tumors appear to be most common after radiation. Other tumor types noted after treatment for childhood CNS tumors include lymphomas, skin carcinomas, and soft tissue sarcomas.

The Childhood Cancer Survivor Study recently reported one of the largest series studied for the occurrence of second malignant neoplasms in childhood and adolescent brain tumor survivors.[78] Among the 1779 5-year survivors of a brain tumor, 24 developed a total of 25 malignancies consisting of leukemia (n = 2), lymphoma (n = 1), CNS (n = 6), breast (n = 3), bone (n = 2), sarcoma (n = 1), thyroid (n = 1), melanoma (n = 3), and other malignancies (n = 6). Although brain tumor survivors were found to be 10 times more likely to develop cancer compared with the general population, the cumulative incidence at 20 years was only 2.1%. Risk of developing a second malignancy was not different for survivors of astroglial tumors versus PNET. After adjusting for radiation exposure, females were 3.6 times more likely to develop a secondary malignancy, whereas age at brain tumor diagnosis, treatment era, or chemotherapy exposure did not predict overall risk.

It is now well recognized that the risk of chemotherapy-induced secondary leukemia is associated with a relatively short latency period (i.e., within 10 years)[79] in contrast with radiation-induced solid tumors.[80] In a small series specifically examining children treated for tumors before age 3 years with chemotherapy, a higher risk of second malignancies was found than in previous series, with a cumulative risk at 8 years of 11%.[76] In contrast with other series in which most second malignancies were attributed to radiation, chemotherapy appeared to contribute to development of multiple hematopoietic tumors in this series. Young age also appeared to contribute to risk of developing tumors, because four of five second tumors occurred in children who were younger than age 2 years at diagnosis. These findings have led some to argue that chemotherapy should be used cautiously in treating childhood CNS tumors[81]; however, given the

severe morbidity caused by radiation to the developing brain, its use in children younger than age 3 years will likely continue.

Social/Family

As would be expected, survivors and their families encounter numerous psychosocial stresses. Central nervous system tumor survivors have been found to have poorer overall social functioning than survivors of other childhood cancers, with family members often sharing in their problems.

A large study investigating quality of life among survivors of brain tumors involved interviews with 342 adults whose brain tumors were diagnosed when they were children and who subsequently survived for at least 5 years.[12] In this study, survivors were found to have substantially worse outcomes than matched sibling controls on several quality-of-life outcomes. For example, CNS tumor survivors were 10 times as likely to never have been employed, 28 times more likely not to be able to drive, and 8 times more likely to describe their health as poor. Survivors were also 6 times more likely to have had a health condition leading to a job change or work stoppage and 3 times as likely to have an income of less than $15,000 per year.

In examining risk factors for poor outcomes in this study, survivors of supratentorial tumors were generally at greater risk than those with infratentorial tumors. Similarly, survivors who received radiation were at higher risk for poorer health outcomes than those who received none. Male survivors generally had poorer outcomes then female survivors, with the exception of the percentage having an income less than $15,000 per year, in which there was a female preponderance.

Education and employment information from another large series of children treated during the 1970s helps to provide a context for the difficulties CNS tumor survivors face as compared with survivors of other cancers.[29] Just greater than 90% of childhood brain carcinoma survivors in this series graduated from high school, but only 10% received college degrees. For other childhood cancer survivors, rates were 97% and 25%, respectively. Roughly 54% of all brain carcinoma survivors were employed at the time of the survey, whereas 86% of other cancer survivors were working. Workplace discrimination was noted by 13% of CNS tumor survivors, but only by 2.5% of other tumor survivors. Perhaps most significantly, greater than 50% of brain carcinoma survivors had incomes less than $15,000 per year, with only 22% of other cancer survivors falling into this income group.

Family and marital interactions also seem to suffer among survivors of CNS tumors. In the same series of comparative data, 36% of brain tumor survivors were currently married and 23% divorced, compared with 62% currently married and 8% with a history of divorce among survivors of other tumors. A series of 38 survivors published in 1982 found that 39% of survivors, 59% of their mothers, and 43% of their fathers had behavioral disorders as determined by a psychologist and the Minnesota Multiphasic Personality Inventory.[57] Survivors and their families also may face difficulties in obtaining insurance, keeping jobs during treatment, and other legal and financial challenges.[82] Recent legislation such as the Americans with Disabilities Act and the Family Medical Leave act may provide survivors and their families with assistance in coping with such concerns.

Summary of Management Issues

Because of the heterogeneity of late effects among brain tumor survivors, no formal guidelines exist regarding their follow-up care. Instead, differences among individual survivors of CNS tumors require that long-term follow up be based on each person's individual circumstance. We suggest that those providing primary care to these patients consider three aspects of their care at each visit: 1) tumor surveillance status of the patient; 2) specific late-term effects of cancer treatments the patient received; and 3) the patient's cognitive status with an emphasis on maximizing functioning.

The most important step in providing care for survivors is to obtain a thorough treatment history. Because patients will likely not be able to provide such history themselves, original records detailing their treatment are preferred and should be obtained whenever possible. Relevant details of the patient's history include tumor location, histology, and treatment administered. If the patient had surgery, location of tumor and extent of resection should be noted. Radiation dosage and location (cranial vs. cranial and spinal) as well as specific chemotherapeutic agents administered also should be noted, if applicable. The worksheet included in a recent review by Oeffinger et al. regarding late effects in ALL survivors[28] may provide a useful prototype for gathering a thorough history.

Because the effects of second tumors can be devastating, it is important for clinicians to be aware of surveillance screening status of the survivor. Although routine neuroimaging has been shown to be of little value in screening for primary tumor recurrence,[83] routine scanning is still performed by some practitioners. Central nervous system imaging should be considered whenever a rapid change in mental status is observed. In addition to screening for second tumors

of the CNS, skin and soft tissue in and around radiation fields also should be carefully examined for suspicious lesions.

Endocrine late effects (e.g., growth hormone deficiency, hypothyroidism) should be monitored closely, particularly those that can be aided with replacement therapy. Primary care practitioners should maintain awareness of endocrinologic function in patients and consider referral to a specialist as needed.

Neurocognitive late effects also should be addressed specifically at each visit. Survivors and parents should be asked about school performance, if applicable, and educational status. If survivors are not receiving special educational or employment assistance, they should be offered it if appropriate. Formal neuopsychologic testing also may be of periodic benefit.

Care of childhood brain tumor survivors poses numerous challenges to providers and families alike. As more children survive CNS tumors, primary care providers will need to become more adept at addressing these challenges. Although advances in therapy may someday reduce the long-term morbidity in brain tumor survivors, primary care practitioners will likely continue to encounter survivors with substantial morbidity for years to come.

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