Neurocognitive Outcomes in Survivors of Childhood Cancer

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Objectives To review issues associated with neurocognitive outcome in survivors of pediatric cancer. Recommendations are made for future research directions. Methods A large body of literature pertaining to neurocognitive outcome in cancer survivors was reviewed. Brain development and methodological issues that provide challenges to conducting meaningful research in cancer outcomes also are discussed. Results Neurotoxic agents used in some cancer therapies produce permanent neurocognitive sequelae, especially in very young children. Conclusions The state of neurocognitive research for pediatric cancer survivors needs to move beyond empirical studies of neurocognitive sequelae to research that will identify individual patients at risk for neurocognitive morbidity.

Key words pediatric cancer; neurocognitive outcome; neurotoxicity.

Cancer in children is rare: only 1 or 2 children per 10,000 are diagnosed with it each year. Nevertheless, it is the leading cause of death by disease in children under 15 years old. In 2001, approximately 8,600 children were diagnosed with some form of cancer, and about 1,500 died (NCI, Cancer Facts). Advances in the early diagnosis and treatment of pediatric cancers have led to dramatic increases in survival rates, especially for diseases such as leukemia. Several decades ago, a diagnosis of acute lymphocytic leukemia (ALL) was almost always fatal, but a child diagnosed with it today has about a 90% chance of long-term survival (>5 years). The overall cure rate for children and adolescents with cancer in the United States is approximately 83% (Bleyer, 1997). The use of central nervous system (CNS) prophylaxis and multidrug regimens is largely responsible for this success. Delayed intensification and the use of maintenance intrathecal (IT) methotrexate have contributed to the dramatic improvement in survival rate (Gaynon et al., 2000).

The ultimate goal of cancer therapy is to cure the patient’s disease, and the successful development of new and more effective treatments has greatly enhanced the ability to achieve that goal. Effective treatments are not always without costs, so oncologists attempt to maintain a balance between effective therapy and acceptable toxicity. In some cases high doses of therapy (e.g., chemotherapy, radiation therapy) and aggressive surgery are associated with better cure rates yet more severe morbidity. In contrast, therapeutic regimens that seek to minimize toxicity may increase the chance of relapse or disease progression. As advances in cancer therapies have resulted in improved response rates and cure rates, more attention needs to be focused on fine-tuning those therapies that minimize treatment-related toxicity while maintaining therapeutic efficacy.

Despite the many types of pediatric cancers, brain tumors and leukemia are the focus of this review because they have the most profound effect on neurocognitive functioning owing to the direct effects of the diseases and to the indirect effects of treatment on the CNS. The purpose of this article is to provide a better understanding for the neurocognitive outcome of childhood cancer and the many factors that must be taken into account in evaluating outcome (see Figure 1). First, I discuss the vulnerability of the developing brain to the neurotoxic therapies used to treat leukemia and brain tumors—namely, surgery, chemotherapy, and radiation therapy. Further, I review studies of neurocognitive outcome in survivors of childhood leukemia and brain tumors. Subsequently, I provide a discussion of other factors that affect neurocognitive outcome, including...
the patient's sex and age, neurological complications, tumor location (for brain tumors), and time since treatment. I also examine the challenges to meaningful research in this field, including the need and difficulty of longitudinal methodology, small numbers of patients, and incomplete data sets. Finally, I speculate on the directions of future research concerning the neurocognitive outcome of pediatric cancer survivors, including the possibilities for interventions and the need to identify those patients at greatest risk for the poorest outcome.

The Typically Developing Brain
A first step to understanding the neurocognitive outcome experienced by cancer survivors is understanding brain development and the underlying effects that brain tumors, ALL, and their respective treatments have on the brain itself.

By 6 months of gestation, the human brain has most of its neurons, including the 10 billion that form the cerebral cortex (Netter, 1983). During early childhood the brain undergoes a dynamic stage of development whereby the volume of certain types of brain tissue increases and decreases. This interaction of brain growth involves an increase and a decrease in gray matter and an increase in white matter (Holland, Haas, Norman, Brant-Zawadski, & Newton, 1986). The volume of the brain's gray matter increases rapidly and peaks at around 4 years of age. During this time, neurons grow, dendritic arborization increases, and new synapses form. Thereafter,
gray matter decreases as apoptosis take place (Dekaban & Sandowsky, 1978). This is considered a normal part of brain development whereby unnecessary neurons and synaptic connections are eliminated through a process of programmed cell death, or apoptosis (Barinaga, 1993). This process results in a brain that is considered leaner and more efficient.

Myelination begins in the brain during the 3rd or 4th month of gestation and continues to increase in volume through the age of 20 years, particularly in the prefrontal cortex (Casey, Giedd, & Thomas, 2000; Pfefferbaum et al., 1994). The axons of the cortical projection and association areas finally become fully myelinated during the adult years (Netter, 1983). The areas of the cortex involved in higher order cognitive skills remain vulnerable to neurotoxic agents during the prime learning period of a child's life. Myelinated axons help speed communication between neurons (Giedd, 2003) since they, unlike unmyelinated fibers, are capable of rapid conduction velocity with little fatigue (Netter, 1983). It is this dynamic phase of white matter proliferation that places the brain at greatest risk for injury due to the ionizing radiation or chemotherapy used to treat different types of cancer.

The importance of white matter has been documented by numerous studies of traumatic brain injury in which cognitive deficits have been associated with the extent and site of white matter damage (Levin, 2003; McAllister, Sparling, Flashman, & Saykin, 2001). White matter abnormalities in aging have also been associated with the cognitive decline leading to dementia (Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000). In normal aging, deficits in processing speed, memory, and executive functions are associated with the presence of white matter lesions (Gunning-Dixon & Raz, 2000).

**How Does Cancer and Cancer Therapy Affect the Brain?**

The brain is a target for therapy not only in a child with a brain tumor but also when there is metastatic disease in the brain or when a child has a disease such as high-risk ALL, which may spread to the central nervous system. The armamentarium for treating brain cancer consists primarily of surgery, chemotherapy, and radiation therapy, either alone or in some combination. In addition, different dosing schedules and combinations of chemotherapeutic agents vary according to diagnosis, disease stage, and other factors. This complex topic is not within the scope of this article, but a brief explanation of each modality is warranted.

**Surgery Alone**

The mere presence of a brain tumor that is infiltrating or having a mass effect (i.e., pushing) on vital brain structures is an obvious concern with regard to functionality. Neurosurgical resection of the tumor may have a positive or negative effect on neurocognitive functioning postoperatively. Steinlin et al. (2003) demonstrated that children treated for benign cerebellar lesions with surgery alone had intact global intellectual abilities, though they also had significant deficits in attention, memory, processing speed, and visual-constructive copying. These results highlight the need to consider factors other than chemotherapy and cranial radiation therapy (CRT) as causes of neurocognitive decline but also that the cerebellum is involved in higher order cognitive skills, not simply motor coordination. Perioperative complications can also lead to significant neurological complications with long-term consequences (Chapman et al., 1995; Kao et al., 1994).

Young age at diagnosis is associated with severe neurological deficits, even without intensive CNS treatments (Chapman et al., 1995). Younger children are more likely to present with hydrocephalus and a dulled or reduced level of alertness or consciousness and to have had more aggressive surgery than their older counterparts. Studies have generally indicated a statistically significant inverse relationship between children's ages and neuropsychological and neurological severities. Kao et al. (1994) found that children who evidenced adverse perioperative events—such as neurological deficits, meningitis, shunt infections, or the need for additional surgery—evidenced declines in full-scale intellectual functioning of more than 15 IQ points (one standard deviation), whereas those without these adverse events lost only about 5 points (one third of a standard deviation). Packer et al. (1987) identified preoperative obtundation, the need for a permanent shunt, a younger age at diagnosis, and a complicated postoperative course as contributory factors for a negative outcome. These studies highlight the complexity of a child's medical course and why it is important to document more than just the type and intensity of therapy when evaluating risk for neurocognitive declines.

**Chemotherapy**

Treatment for brain tumors and ALL frequently involves high-dose chemotherapy administered with radiation therapy delivered to the brain. Although different mechanisms have been postulated to explain the underlying neurological basis of neurocognitive dysfunction, damage
to cortical and subcortical white matter has received the most attention (Mulhern et al., 2001). For example, Iuvone et al. (2002) reported that children with ALL who had been treated with a combination of CRT (18–24 Gy) and IT methotrexate evidenced brain calcifications on neuroimaging scans. The number of doses of IT methotrexate was associated with these calcifications and with neurocognitive decline. No difference in neurocognitive functioning was noted between those treated with CRT at either 18 Gy or 24 Gy.

Although CRT has been strongly implicated in white matter changes, chemotherapy alone may have similar effects. Wilson et al. (1991) demonstrated white matter abnormalities in patients with ALL who were treated with chemotherapy that consisted of prednisone, vincristine, L-asparaginase, and intravenous methotrexate. However these white matter changes had resolved in most of these patients after treatment.

**Radiation Therapy**

When radiation is delivered to the brain, the effects are generally described as occurring in three stages: acute, subacute (or early delayed), and late. The acute effects are generally associated with sudden neurological deterioration following radiation therapy but have also been associated with certain types of chemotherapy, including cisplatinum, L-asparaginase, ifosfamide, methotrexate, and interferon (Allen, 1992). During the subacute period (2 to 6 months after radiation therapy), the “somnolence syndrome” is often observed and is associated with fatigue or an exaggeration of the neurological signs. This is believed to be secondary to diffuse demyelination, but the clinical symptoms are generally transient. Finally, late effects of CRT are characterized by various neurological deficits and are largely believed to be responsible for the gradual neurocognitive decline often observed in young children, possibly as a result of an imbalance in the development of gray and white matter (Mulhern et al., 2001).

Event-related potential and reaction time experiments have been demonstrated to be sensitive to processing speed in other patient populations with demyelinating diseases (Tobimatsu, Fukui, Kato, Kobayashi, & Kuroiwa, 1985; Wulff & Trojaborg, 1985). Moore, Copeland, Ried, and Kopecky (1992) studied 33 long-term non–brain tumor cancer survivors treated with a variety of protocols: 11 with leukemia had received IT chemotherapy plus CRT; 9 with sarcoma, Hodgkin’s disease, or Wilms’ tumor had been treated without any CNS therapy; and 13 with leukemia or lymphoma had received only IT chemotherapy. The group receiving a combination of CNS therapies had significantly lower performance on neuropsychological tests and significantly slower reaction time compared to those treated without CRT. Compared to the survivors in the other groups, the combined-therapy participants also had significantly smaller amplitude and slower response of the P-300 (a brain-evoked potential associated with attention). Because one function of myelin (i.e., white matter) is to increase axonal conduction velocity, the results of this study suggest that the effect of CRT impeded neural transmission speed, resulting in a slowing and disorganization of cognitive processing that was manifested in neurocognitive deficits (Moore et al., 1992).

**Neurocognitive Outcome in Survivors of Leukemia**

Children with ALL who are at risk for brain metastases are often treated prophylactically with IT methotrexate in addition to standard systemic chemotherapy. For those children who have the highest risk, CRT is also used (Iuvone et al., 2002). Despite a large literature on the effects of CRT on neurocognitive outcome in children with ALL, studies of the effects of chemotherapy in isolation are far less frequent.

Brown, Madan-Swain, Pais, Lambert, Sexson, et al. (1992) reported on 48 patients with moderate-risk ALL who were treated with a 3-year course of systemic and IT chemotherapy that included cyclophosphamide, L-asparaginase, intravenous methotrexate, and IT chemotherapy (methotrexate, cytosine arabinoside, and hydrocortisone). Findings revealed that the participants had significantly poorer performance on tests of attention and memory as well as visual construction ability than did those who had recently been diagnosed. Deficits were particularly notable in computational arithmetic skills that were consistent with a learning disability (Brown, Madan-Swain, Pais, Lambert, Sexson, et al., 1992).

Von der Weid et al. (2003) compared 132 ALL survivors treated with chemotherapy alone to 100 children with non-CNS tumors who did not receive chemotherapy on standardized neuropsychological measures. Intellectual abilities were within the normal range and were comparable between the groups, suggesting that chemotherapy alone did not have an additional adverse effect on neurocognitive functioning above the cancer experience itself.

Copeland, Moore, Francis, Jaffe, and Culbert (1996) studied 99 long-term cancer survivors treated with either IT chemotherapy or no CNS therapy; no child had been treated with CRT. The sample was diverse in terms
of diagnoses: ALL, Hodgkin’s disease, osteosarcoma, Ewing’s sarcoma, and others. Of the children in the study, 73% had a diagnosis of leukemia or lymphoma. Patients treated with IT chemotherapy received methotrexate, cytarabine, and hydrocortisone. After they had been diagnosed, researchers assessed the children four times between 5 and 11 years after using a comprehensive battery of neuropsychological tests. Mean scores for the IT chemotherapy and the no-IT chemotherapy groups were within the average range, and there was no statistically significant difference between the two group. There was, however, a significant group by time interaction, whereby the group receiving IT chemotherapy declined slightly on perceptual motor skills and those in the no-IT chemotherapy group improved. Copeland et al. (1996) concluded that chemotherapy has only a slight effect on neurocognitive status.

Neurocognitive Outcome in Brain Tumor Survivors

Brain tumors in children in the United States are more common than cases of ALL and are far more lethal (Bleyer, 1999). Approximately 30,000 to 40,000 children are diagnosed with brain tumors worldwide, and many do not survive (Bleyer, 1999). Brain tumors by their very nature can have a profound impact on the neurocognitive status of children and can have a primary effect on neurocognitive status by way of their location within the brain. They also cause secondary effects, since CRT is often part of the treatment regimen.

Medulloblastomas account for approximately 30% of all pediatric brain tumors (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004) and are usually found in the posterior fossa; they are often treated with a combination of surgery, CRT, and chemotherapy. At one time treatments were mostly unsuccessful, but today, with refinements in the delivery of CRT and with the use of multiagent chemotherapies, approximately 65% to 70% of children diagnosed with medulloblastoma survive 5 or more years (Goldwein et al., 1996; Heideman et al., 1993; Hoppe-Hirsch et al., 1995).

The impact of treatment for medulloblastoma on cortical white matter and on neurocognitive outcome has been examined in a cross-sectional study of 42 children ranging in age from 2 to 16 years (M = 8.2; Mulhern et al., 2001). Each of the participants had been treated with CRT and was at least 1-year postirradiation (1.8–11.0 years, M = 4.9) with no evidence of disease progression. All patients underwent surgical resection of their tumors followed by CRT consisting of 23.4 Gy to 36.0 Gy to the whole brain, with a boost to the posterior fossa of 49.0 Gy to 54.0 Gy. Children who were the youngest at the time of treatment had the greatest severity of neurocognitive dysfunction; time since treatment was negatively associated with most neurocognitive measures, confirming the general understanding that CRT is severe in young children and that the effect becomes worse over time.

Mulhern et al. (2001) assessed the association between CRT and neurocognitive decline. Age at the time of CRT, but not time since CRT, was significantly associated with the volume of white matter. Further analyses revealed that the volume of white matter accounted for a significant amount of the variance for age at the time of CRT, IQ, factual knowledge, and verbal and nonverbal abstract thinking. No significant associations were found between age at diagnosis and sustained attention or verbal memory. Thus, the link between CRT and neurocognitive decline appears to occur through damage to cortical and subcortical white matter (Mulhern, White, et al., 2004). But unlike a progressive dementia, declines in neurocognitive functioning in children treated with CRT are probably due to a failure to learn and acquire new information rather than to a loss of previously acquired knowledge (Mulhern, Merchant, et al., 2004).

It is difficult to disentangle the effects of various treatments used for children with brain tumors since treatment is typically multimodal, employing a combination of surgery, radiation, and chemotherapy. Hoppe-Hirsch et al. (1995) compared the intellectual functioning of children with medulloblastoma to children with ependymoma of the posterior fossa. Patients with medulloblastoma (n = 59) had been treated with surgery followed by whole-brain and focal radiation, whereas patients with ependymoma (n = 37) underwent surgery followed by focal radiation only. The dose to the posterior fossa was 45 Gy to 55 Gy in all cases, and patients with medulloblastoma received an additional 25 Gy to 35 Gy. The two groups did not differ on IQ at 1 year after treatment, and the performance of the ependymoma group remained stable at 5 and 10 years. The medulloblastoma group, however, demonstrated a steep decline at the follow-up periods, reflecting, presumably, the deleterious effect of the additional dose of irradiation to the cerebellum. However, a greater percentage of patients in the medulloblastoma group (76%) had been treated with chemotherapy than those in the ependymoma group (27%), leaving open the possibility of a synergistic effect between CRT and chemotherapy. Even for children with brain tumors, treatment regimens consisting
of chemotherapy alone remain an option as an effort to spare the patient from the adverse effects of CRT or at least delay CRT until a young child is older (Ater et al., 1997; Moore, Ater, & Copeland, 1992; Lacaze et al., 2003).

Mulhern, Hancock, Fairclough, and Kun (1992) reviewed 22 studies that had assessed the neurocognitive status of children treated for brain tumors. These studies represent a total of 544 patients ranging in age from birth to 18 years. Mulhern et al. (1992) evaluated these studies for their type of design, method of selection, and risk factors. Half the studies were longitudinal, although only two made use of a comparison control group. All studies included a test of intellectual functioning; 8 studies included an assessment of academic achievement; and 9 studies focused on comprehensive neuropsychological functions. For 18 of the studies, IQ data were reported 2 or more years posttreatment, and these studies were subjected to further analysis. The mean IQ of the 403 children in these 18 studies was 91.0 (SD = 24.1). Children diagnosed when younger than 4 years of age evidenced significantly lower IQ scores than those diagnosed over 4 years of age (71.9 vs. 92.6, p < 0.0001). No significant differences on neuropsychological functions were found for tumor location (third ventricle, posterior fossa, cerebral hemispheres). Children who did not receive CRT evidenced a mean IQ score in the average range, whereas those receiving whole-brain CRT had a mean IQ score of more than one standard deviation below average. Children treated with local, but not whole-brain, CRT attained mean IQ scores between the no-treatment and whole-brain radiation treatment groups. Thus, there was a significant inverse association between brain volume that was irradiated and intellectual decline. This is especially true for children who receive whole-brain radiation. Although this review was conducted more than a decade ago and the therapies used to treat brain tumors have changed considerably, it nevertheless illustrates some of the general principles relating to neurocognitive outcome in patients with brain tumors. More recent studies continue to validate these principals (Mulhern et al., 1998; Mulhern, White, et al., 2004; Palmer et al., 2003).

Additional Factors Affecting Neurocognitive Outcome

Patient gender, neurological and perioperative factors, brain tumor location, age at the time of diagnosis and treatment, and time since treatment are additional variables that may influence the ultimate neurocognitive outcome of children with cancer.

**Gender**

Several studies have demonstrated an increased vulnerability of females to the neurocognitive morbidity associated with CNS treatment (Bleyer et al., 1990; von der Weid et al., 2003; Waber et al., 1990; Waber, Tarbell, & Kahn, 1992), although not all studies have supported this effect (e.g., Ater et al., 1996). Von der Weid et al. (2003) reported that girls with ALL who were treated with chemotherapy but not CRT had significantly low verbal and nonverbal performance IQ scores. Compared to boys, approximately three times as many females had an IQ lower than one standard deviation below average. Brown et al. (1998) reported that girls, but not boys, who had been treated for ALL had scores on nonverbal tests that were below average.

**Neurological Severity**

Ater et al. (1996) developed a neurological severity scale (NSS) to test the hypothesis that neurocognitive outcome is the product of cumulative, interactive events that affect the CNS. The NSS comprises graded scores in four areas: events before diagnosis, preexisting neurological conditions, perioperative events, and postoperative events. The scale for the study consisted of medical events occurring before diagnosis (e.g., seizures), preexisting developmental disabilities (e.g., Down’s syndrome), perioperative events (e.g., hydrocephalus), and postoperative events due to surgery (e.g., ataxia). Within 3 months of being diagnosed with gliomas, fifty-nine children (mean age = 10 years, SD = 4.08) were assessed using a comprehensive battery of neuropsychological tests.

The total NSS score was significantly correlated with visual–spatial skills, memory, attention, and performance IQ; specifically, higher NSS scores were associated with lower neuropsychological scores. Although the NSS during the acute phase of diagnosis and treatment was significantly associated with neuropsychological functioning in a number of functional domains, its true functionality for predicting long-term neurocognitive outcome remains to be documented.

**Tumor Location**

Tumors of the cerebral hemispheres have been associated with difficulty in performance IQ (but not verbal IQ), academic achievement, memory, motor skills, and attention (Ater et al., 1996). Midline tumors were associated with difficulties in memory, motor, and attention.
Children with posterior fossa tumors evidenced difficulties only in memory and motor abilities, and those with brainstem tumors were within the average range on all abilities. Researchers using the NSS have documented increased impairment for patients with supratentorial tumors. Other studies have also demonstrated that tumors of the cerebral hemispheres result in poor neurocognitive outcome (Ellenberg, McComb, Siegel, & Stowe, 1987; Kun & Mulhern, 1983). However, in a review of 22 studies, Mulhern et al. (1992) concluded that tumor location did not seem to have a significant effect on neurocognitive outcome. Most of the studies had classified tumor location based only on their being classified as supratentorial or infratentorial. A comprehensive study of tumor location within the cerebral hemispheres may result in more definitive conclusions regarding tumor location and neurocognitive functioning.

**Age at Time of Diagnosis and Therapy**

Young age has been strongly implicated in poor neurocognitive outcomes following treatment for cancers that involve the CNS (Chapman et al., 1995; Copeland, deMoor, Moore, & Ater, 1999; Moore, Ater, & Copeland, 1992; Mulhern et al., 2001; Radcliffe, Bunin, Sutton, Goldwein, & Phillips, 1994; Walter et al., 1999). This makes sense given what is known about the development of the nervous system and, in particular, cortical and subcortical white matter. Substituting or delaying the use of CRT in very young children may lessen the neurocognitive morbidity without compromising the medical outcome in infants with brain tumors (Ater et al., 1997; Moore et al., 1992). Among children with brain tumors who were under 3 years of age when diagnosed, those who were treated without CRT had scores within the average range of intellectual functioning and academic achievement, but those who were treated with CRT had significant deficits in verbal and performance IQ, academic achievement, memory, visual–spatial skills, fine motor skills, and attentional abilities (Moore et al., 1992).

Ater et al. (1997) advocated the use of MOPP chemotherapy (methotrexate, vincristine, prednisone, and procarbazine) as the primary postsurgical therapy for infants with brain tumors to delay or eliminate the need for CRT and potentially avoid its impact on neurocognitive development. CRT also can be used effectively as salvage therapy in infants initially treated with surgery or chemotherapy alone (Walter et al., 1999).

In a study of 27 children diagnosed at less than 3 years of age with a cerebellar tumor, Copeland et al. (1999) concluded that neurocognitive outcome is generally positive when treatment includes only surgery and chemotherapy. These results are in partial agreement with other studies demonstrating that chemotherapy regimens, at least those that do not include methotrexate, are fairly benign in terms of cognitive toxicity (Ellenberg et al., 1987; Packer et al., 1989). Packer et al. (1989) reported that children with primary brain tumors who were treated without CRT experienced no significant decline in their intellectual abilities 2 years following treatment. Overall, those who were managed with CRT evidenced a 14-point decline in full-scale IQ, but for those under the age of 7 years, the decline was 25 IQ points.

**Time Since Treatment**

Cross-sectional studies have provided data suggesting that neurocognitive status declines with increasing time since treatment with CRT (e.g., Mulhern et al., 2001). Only a few longitudinal studies have been conducted for children with brain tumors to determine the time course of neurocognitive sequelae and whether they resolve, plateau, or progress (Anderson, Godber, Smibert, Weiskop, & Ekert, 2000; Copeland et al., 1999; Palmer et al., 2001; Palmer et al., 2003). Copeland et al. (1999) employed growth curve analyses to characterize the change in neurocognitive functioning of 27 children diagnosed during infancy with posterior fossa tumors. Of the participants, 20 had been treated with MOPP chemotherapy only, whereas 7 were also treated with CRT. The time since diagnosis ranged from 2 to 13 years (M = 7). The results suggest that in the absence of CRT, children with cerebellar tumors can have a positive outcome. Spiegler, Bouffet, Greenberg, et al. (2004) conducted a longitudinal design that included 34 patients with posterior fossa brain tumors who were administered neuropsychological assessments. The patients were treated with either reduced-dose CRT (23.4–30.2 Gy) or standard-dose CRT (34–36 Gy) with a boost to the posterior fossa (total dose = 45.0–55.8 Gy). The patients were assessed for an average of 2.85 times each, with a median time since diagnosis to the last evaluation of 4.71 years. Intelligence declined an average of 2 points per year with a rapid decline in the early phase, especially for the younger patients, followed by a gradual decline as time since therapy increased.

The effects of CRT on the brain and on neurocognitive abilities are progressive, yet they seem to be delayed during onset. In a cross-sectional study, Moore et al. (1992) reported a negative association between time since CRT (mean interval = 85.3 months) and neurocognitive functioning in 14 young children with brain tumors. In contrast, Williams et al. (1986) found no
significant declines or differences in the neurocognitive performance of children with ALL who were treated with either IT methotrexate alone, 18 Gy CRT plus IT methotrexate, 24 Gy CRT plus IT methotrexate, or intensive systemic chemotherapy plus 24 Gy delayed CRT. Children were assessed only 1 year after diagnosis, leading the investigators to suggest that the effects of CNS therapies, including CRT, are delayed in their onset. In another study employing a cross-sectional design, children with ALL who had received a 3-year course of chemotherapy were more impaired, especially on tasks involving right-hemisphere simultaneous processing, than were sibling controls or other children with ALL who had been recently diagnosed and whose treatment had only recently begun (Brown, Madan-Swain, Pais, Lambert, Sexson, et al., 1992). The relationship between age at the time of treatment and elapsed time since treatment may be domain specific. Dennis, Spiegler, Hetherington, and Greenberg (1996) reported an age effect on nonverbal abilities, but not verbal abilities, in children with medulloblastoma treated with CRT; younger age at treatment was associated with poorer nonverbal abilities. Interestingly, for these patients it was verbal abilities, not nonverbal abilities, that declined with increasing time since treatment.

Methodological Issues

A number of methodological issues have been identified that make research complex regarding neurocognitive outcome of children treated for cancer (Ris & Noll, 1994). These include difficulties conducting longitudinal studies, characteristic small sample sizes, missing data through attrition, and determining the optimal timing of the baseline evaluation.

Longitudinal Studies

For the purpose of describing the evolution of neurocognitive changes related to treatment, longitudinal designs are far superior to cross-sectional designs but are subject to certain biases, such as the selective attrition of participants due to progressive disease and death. Longitudinal studies, by definition, take more time to complete than do cross-sectional studies. However, cross-sectional studies may have a larger number of available patients to study but are limited to indirect implications regarding time since diagnosis and age of the child at the time of treatment. New therapies and monitoring techniques are rapidly evolving so that by the time a longitudinal study is completed and published, newer therapies may have replaced the ones being studied.

Because cancer in children is rare and because an individual medical center caring for patients with cancer has only a limited population from which to select participants, studies often have insufficient statistical power to detect significant main effects. This can be mitigated by research within the large multi-institutional clinical trials groups. The Children’s Oncology Group is the largest of these collaborative groups and has an active program that studies the neurocognitive outcome of children treated with various treatment protocols for cancer. Many studies, however, have been plagued by low patient accrual and poor adherence with the demands of study participation and data collection. In one of the most successful studies within the cooperative groups (Children's Cancer Group 9892), only 66% of eligible patients had more than a single evaluation over a 4-year period, and data accrued were limited primarily to measures of intellectual functioning (Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001). The Children’s Oncology Group has recently adopted a core battery of standardized neurocognitive assessment measures in an attempt to increase accrual and compliance and to enable comparisons of outcomes across studies.

Most studies of pediatric populations, especially longitudinal studies, are hampered by attrition and missing data (Drotar & Riekert, 2000). Conventional methods for dealing with incomplete data sets and missing data (i.e., completely dropping those cases with incomplete data) may result in biased samples with insufficient power to conduct meaningful analyses and, thus, a reduction of internal and external validity (Bender, Ikle, DuHamel, & Tinkelman, 1997; Francis, Copeland, & Moore, 1994). For instance, patients who are excluded because they have incomplete data owing to death or relapse may bias a sample toward those who had a relatively good medical outcome. Contemporary statistical methodology, including the use of individual growth curve modeling, has greatly improved our ability to conduct this type of research (see, Copeland et al., 1999).

Remediation and Intervention

Clearly, survivors of cancer that involve the CNS either directly through the disease process or indirectly through treatment are at risk for neurocognitive sequelae. Although there is still much to be learned about neurocognitive outcome in cancer survivors, it is now time to shift the emphasis from simply documenting these effects on cognition and school performance to developing an effective means to prevent or remediate
these impairments. Unfortunately, only a few published articles address this important topic.

Butler and Copeland (2002) enrolled cancer survivors with documented attentional problems into a cognitive remediation program aimed at improving attention and neuropsychological abilities. The program was based on educational, psychological, and rehabilitation approaches, and it involved approximately 50 hr of therapy over a 6-month period. When reassessed at 6 months, those children in the intervention arm of the program evidenced significantly improved attention skills relative to the control group.

Because treatment-related neurocognitive sequelae of cancer therapies include symptoms associated with attention deficit hyperactivity disorder (ADHD), such as impaired concentration and sustained attention (Brouwers, Riccardi, Poplack, & Fedio, 1984), other studies have focused remediation efforts on traditional treatments for ADHD. Methylphenidate (Ritalin) and other stimulants are often used to manage inattention and impulsivity in children and adolescents diagnosed with ADHD. For survivors of brain tumor and ALL who evidence attentional problems, Thompson et al. (2001) found that methylphenidate resulted in significantly better performance on tasks of sustained attention than did survivors who received placebos. These results suggest that pharmacological interventions for cancer survivors showing signs of inattention may be as effective as they are within the general population. Ideally, a pharmacological intervention should be combined with behavioral or cognitive interventions, either through a formalized rehabilitation program or traditional school-based programs.

**Future Directions**

Advances in the treatment of childhood cancers have been made not only in the types of therapies used but also in the delivery of therapy. Chemotherapy regimens are now being fine-tuned to reduce the neurocognitive morbidity of cancer while maintaining medical efficacy. This approach includes the use of new agents, different combinations of agents, and different dosing schedules. This work is being done primarily through large cooperative group clinical trials, such as those conducted by the Children’s Oncology Group, but also at individual institutions and through limited institution consortiums.

An area of intense focus for brain tumors is discovering ways to restrict the delivery of therapy to the tumor only, without causing damage to normal tissue. Specific tumors are known to be chemoresistant or chemoresponsive; hence, designing therapies for specific genotypes may result in better treatment outcome with less neurotoxicity (Doolittle et al., 2001). Although some regimens seek to reduce therapeutic dose to an acceptable toxicity level while maintaining therapeutic efficacy, other regimens are being designed to increase the dose beyond the level of typical toxicity by the use of cytoenhancers and chemoprotectants.

Advances in neuroimaging have resulted in precise measurement of tumor shrinkage and progression. Magnetic resonance spectroscopy and positron emission tomography provide important information regarding the chemical composition and metabolic activity of a tumor, respectively. Each is especially promising because each can provide insight into a tumor’s malignant stage and response to therapy, thus helping to guide therapy and potentially avoiding unnecessary additional neurotoxic therapies. Functional magnetic resonance imaging and stereotactic neurosurgical imaging are also currently being used to guide surgeons in the precise localization of brain tumors in relation to eloquent areas of the brain, thereby allowing them to perform complete tumor resections while reducing the potential for neurocognitive morbidity as a result of surgical resection.

The use of fractionated CRT to deliver a high number of small doses is being used to reduce toxicity to surrounding tissue. Stereotactic radiosurgery precisely targets a tumor by using high-resolution neuroimaging scans with three-dimensional computer-guided radiotherapy so that the beam of ionizing radiation converges on the tumor while surrounding tissues receive only a minimum of exposure. Another approach is the use of radioenhancers to make cancer cells sensitive to the ionizing effect of radiation, allowing lower doses to be delivered and thus sparing other tissues in the process.

The most promising advance at this time is proton beam radiotherapy (Kirsch & Tarbell, 2004). Standard radiotherapy uses photon X-rays to treat tumors but often at the expense of surrounding tissues. With proton beam therapy, almost all of the energy is deposited into the tumor, thereby sparing surrounding tissues from most of the toxic effects (Schneider, Lomax, & Lombriser, 2000; Suit, 2002). This has obvious implications for the sparing of neurocognitive functioning secondary to the treatment of pediatric brain tumors. At the present, there are only four centers in the United States with proton beam facilities, with a fifth scheduled to come online in the fall of 2006 (M. D. Anderson Cancer Center, University of Texas, Houston).
Summary and Conclusions

Cancer in children, although rare, is nevertheless a significant global health problem. Improvements in treatments—including surgery, radiation therapy, and chemotherapy—have resulted in dramatic improvements in survival rates. Brain tumors are the most common form of cancer in children in the United States, and children with brain tumors have poorer survival rates than those with leukemia do (Bleyer, 1999). Numerous studies have documented the neurocognitive toxicities experienced by survivors of childhood cancer, particularly survivors of brain tumors and leukemia, owing to the direct and indirect effects of chemotherapy and radiation therapy on the CNS. In pediatric cancer survivors, CRT has been strongly implicated as contributing to neurocognitive declines whether it is administered prophylactically in patients with ALL or as a primary treatment for brain tumors or CNS leukemia. However, CRT is not typically administered in isolation as a treatment for leukemia or brain tumors. For leukemia, the doses of CRT are usually much lower than they are for brain tumors, thereby resulting in less severe neurocognitive sequelae. High-dose chemotherapy regimens (e.g., IT methotrexate) may also play a role in determining the neurocognitive outcome of cancer survivors (Butler, Hill, Steinherz, Meyers, & Finlay, 1994).

For oncologists and neuropsychologists, attention is now turning to interventions that may diminish the neurocognitive sequelae associated with survival. However, interventions in survivors occur at a point when the cognitive damage already has occurred. Two additional approaches are needed. First, prophylactic interventions that begin during or immediately after therapy may help to minimize the effects associated with neurotoxic therapies. However, not every child who is so treated will suffer the same degree of neurocognitive morbidity. Some children will remain relatively intact, whereas others will suffer marked declines in their intellectual and cognitive abilities. Second, because of this variability across patients and because intervention programs are too costly and labor intensive to use prophylactically for every child, studies are needed that will identify, early in their treatment, those patients who are at most risk for the greatest declines. Modifications in the treatment regimen for these children may then be entertained, or prophylactic interventions may then be initiated. We already know of specific risk factors that are associated with cognitive outcome—for example, young age at treatment—but there may be certain genotypes that are susceptible to the neurotoxic effects of CNS therapies. For this reason, some protocols seek to avoid CRT in very young children, and parents often are informed of the possibility of potential neurocognitive toxicities. Several other approaches are needed. One might be to retrospectively examine demographic, social, medical, and neuropsychological factors that are associated with good and poor cognitive outcome for survivors of childhood cancer. Innovative new techniques, including those being developed in neuroimaging, might also be used as early acute barometers of a child’s response to specific neurotoxic treatments. The ultimate goal of cancer therapy today is not simply medical cure but cure that results in the survivors’ healthy, long-term neurocognitive outcome and optimum quality of life.

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