Pediatric Cancers in the New Millennium: Dramatic Progress, New Challenges

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Over the past 50 years, great strides have been made in diagnosis, treatment, and survival of childhood cancer. In the 1960s the probability of survival for a child with cancer was less than 25%, whereas today it may exceed 80%. This dramatic change has occurred through significant and steady progress in our understanding of tumor biology, creation of specialized multidisciplinary care teams, incremental improvements in therapy, establishment of specialized centers with research infrastructure to conduct pivotal clinical studies, and the evolution of a cooperative group mechanism for clinical research. Most children with cancer in the United States, Europe, and Japan receive appropriate diagnosis and treatment, although access is limited in developing countries. The price of success, however, is the growing population of survivors who require medical and psychosocial follow-up and treatment for the late effects of therapy. Here we review the progress made in pediatric oncology over the past 3 decades and consider the new challenges that face us today.

Cancer is the second leading cause of death (after accidents) in children and adolescents in the United States despite significant progress in diagnosis, treatment, and survival. [1] Mortality rates have declined approximately 2% per year over the past 3 decades, and survival rates for many childhood cancers have greatly improved (Figure 1). The overall 5-year survival rate for childhood cancer now exceeds 79%. [2] Most notable is the progress in treating acute lymphoblastic leukemia (ALL), which represents about a third of all cases of pediatric cancer (Figure 2). Improved critical care, infectious disease management, and nutritional support and the widespread use of central venous catheters have increased survival overall for children with malignancies. Approximately 1 in every 250 adults is expected to be a childhood cancer survivor by 2010. The potential social, economic, and medical impact of this advance is second only to that of the treatment of adult breast cancer. [3]
Figure 1: Survival Rates for Pediatric Leukemias and Lymphomas — Trends in 5-year cancer survival rates according to diagnosis and era. (A) Pediatric leukemias and lymphomas. (B) Pediatric solid tumors. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; HL = Hodgkin’s lymphoma; NBL = neuroblastoma; NHL = non-Hodgkin’s lymphoma; STS = soft-tissue sarcomas. Adapted from Section XXVIII SEER Cancer Statistics Review 1975-2003 and pre-1975 SEER data.
Overview of Childhood Cancers
Childhood cancers comprise a spectrum of malignancies that differ in histologic type, site of origin, and incidence across age groups. Importantly, they also differ from adult cancers in significant ways. Whereas most adult cancers are epithelial and may be influenced by environmental factors (eg, smoking and diet), most pediatric cancers are dysontogenic in nature. Therefore, screening or prevention programs are less likely to be effective. Further, tolerance of therapy is quantitatively and qualitatively different in children and adults because of dissimilar host characteristics, such as physiology and organ maturation.

Because childhood cancer is rare, successful therapy depends on focused, collaborative clinical research supported by governmental agencies and public philanthropy.[4] This model is anchored in a strong clinical research infrastructure and the effective collaboration of a multidisciplinary team composed of pediatric oncologists, surgeons, radiation therapists, and other professionals. Paramount to these efforts is the contribution of basic and translational scientists who define important biologic and genetic components of childhood cancer that can guide risk-based therapy. The international community has made significant contributions to this success. Collaborative pediatric oncology research models have also laid the foundation for research alliances for the treatment of asthma, cystic fibrosis, AIDS, and other chronic childhood diseases. Further, fundamental principles gained through protocol-based treatment of pediatric cancer have translated to improved management of adult cancers. These key principles are summarized in Table 1 and further elaborated below.

Many challenges remain. Survival remains poor for children with tumors such as disseminated neuroblastoma or diffuse pontine glioma, and for others we have reached a survival plateau. There is poor understanding of the biology of some tumor subtypes. The physical, psychosocial, and financial consequences of effective therapy have created a need for specialized care for survivors and new venues for research. There is room for improvement in the collection of late effects and outcome data. There is little financial incentive or support for the development of new drugs and biologic therapies. There are disparities in outcomes in adolescents and young adults, and many children worldwide lack access to effective therapy. This article will review specific examples of progress, the challenges that remain across the spectrum of childhood cancer, and future areas of work.
Acute Leukemias and Lymphomas

Acute Lymphoblastic Leukemia

Survival of children with ALL in the 1970s was only about 50%, but today more than 90% of these children can be cured.[5] Contributing factors include a better understanding of the immunobiology...
of ALL, recognition that different chemotherapy agents and intensity are required for different disease burdens, and improved supportive care.

Clinical trials have progressively refined therapy on the basis of a multitude of prognostic factors related to the host or the leukemic cell (Table 2). These factors and the heterogeneous nature of ALL have generated a variety of complex treatment protocols.[5-7] Improved treatment has eliminated previous prognostic factors like male sex and T-cell ALL. We also now understand that some treatment failures reflect suboptimal drug dosing in patients with specific genetic polymorphisms of drug-metabolizing enzymes, transporters, receptors, or drug targets. DNA microarrays for global gene-expression profiling of leukemic cells can predict immunophenotype, treatment response, and relapse and are becoming an important tool in refining the classification of ALL. Moreover, these microarrays can be used to identify novel molecular therapeutic targets, as in the case of FLT3 inhibitors.[8]

Although very few new leukemia-specific drugs have been developed, we have learned to optimize the use of the available agents by applying pharmacokinetic and pharmacodynamic principles, by understanding the selective roles of various agents (eg, different steroids; different routes, dosages, and schedules of antimetabolites), and by developing alternative approaches to prophylaxis for the central nervous system (CNS) and other sanctuary sites. All treatment protocols now use the strategy of remission induction followed by intensification (or consolidation) therapy and continuation treatment to eliminate residual leukemia. Delayed intensification (reinduction) therapy was recently found to benefit all risk groups, and 5-year event-free-survival (EFS) was increased from 58% to 87% in the standard-risk group by double reinduction.[9]

Early CNS prophylaxis was another breakthrough in ALL therapy, as it prevented both isolated CNS relapse and combined CNS and bone marrow relapse. Although craniospinal irradiation was effective, its acute and long-term neurocognitive impact and the risk of secondary brain tumors led to its reassessment during the past decade. With careful disease staging and modification of systemic and intrathecal chemotherapy, most cases of childhood ALL can now be effectively controlled without radiation therapy.

The most important independent predictor of treatment success is the response to therapy, measured as the level of minimal residual disease (MRD). Patients whose leukemic blasts comprise < 0.01% of nucleated bone marrow cells at the end of induction fare significantly better than others. Future protocols will individualize therapy on the basis of the leukemia' genetic signature and the patient' pharmacogenetic and pharmacodynamic characteristics and will modify ongoing therapy on the basis of MRD findings.[10]

Finally, we must recognize the importance of supportive care in the management of childhood ALL, including routine empiric antibiotic therapy during periods of neutropenia, prophylaxis of Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxasole, and more recently, the use of uricolytics in the management of hyperuricemia and prevention of acute renal failure.

**Hodgkin’s Lymphoma**
Treatment of childhood Hodgkin's lymphoma is well tolerated and highly effective. However, the morbidity and long-term sequelae of therapy are of increasing concern. In the 1970s and 1980s, growth inhibition and musculoskeletal malformations were observed after high-dose, large-field radiation therapy (35-44 Gy).[11] Subsequently, low-dose radiotherapy (15-25 Gy) given with combination chemotherapy proved very effective, with 10-year survival rates of up to 90%.[12] However, the alkylating agents in these regimens heightened the risk of secondary leukemias and myelodysplastic syndromes.[13] After 10 to 15 years, survivors also developed radiation-associated tumors of the lung, skin, gastrointestinal tract, and breast. Other dose-dependent effects include an increased risk of cardiovascular disease, myocardial infarction, cardiopulmonary fibrosis, hypothyroidism, and infertility.[14]

Most contemporary Hodgkin's lymphoma regimens use a combined-modality approach with chemotherapy and radiation. There are, however, instances in which only radiation, or chemotherapy alone may be considered. Advances in treatment have reduced the prognostic importance of age, sex, histologic subtype, stage, and B symptoms. The response to initial therapy is increasingly used to determine subsequent therapy. Diagnostic imaging advances have obviated the need for staging laparotomy and lymphangiography. High-resolution computed tomography (CT) and magnetic resonance imaging (MRI) have revolutionized staging. Positron-emission tomography (PET) scans can sensitively assess the proliferative activity in tumors through the uptake of 18-fluoro-2-deoxyglucose (FDG) and assess tumor response after treatment to help guide additional therapy. (Figure 3).[15,16] Prospective trials of FDG-PET in pediatric Hodgkin's lymphoma are ongoing.

Recurrent and refractory Hodgkin's lymphoma remain the greatest challenge. Progression of the disease during induction therapy or within 1 year after therapy predicts a 5-year disease-free survival rate < 20%.(17) Patients whose relapse occurs more than 1 year after completion of therapy have a survival rate of only 20% to 50% with conventional chemotherapy and 40% to 50% with high-dose chemotherapy and autologous stem cell rescue.[18]

The sensitivity of Hodgkin's lymphoma to combined-modality therapy has been a great asset, but the paucity of Hodgkin and Reed-Sternberg (HRS) cells in the tumors has slowed research on the origin and biology of the disease. HRS cells were found to be monoclonal derivatives of germinal-center B cells only in the early 1990s. The role of the nuclear factor kappaB pathway in Hodgkin's lymphoma offers potential targets for novel therapies to reduce treatment sequelae and improve the survival of high-risk patients. Other novel possibilities for retrieval therapy incorporate proteasome inhibitors, monoclonal antibodies to Hodgkin's lymphoma-associated receptors (CD30, CD20, CD40), or radiolabeled immunoglobulin therapy.

**Non-Hodgkin's Lymphoma**

Pediatric non-Hodgkin's lymphoma (NHL) is a diverse collection of lymphoid malignancies that vary in pathogenesis, natural history, and response to therapy. Pediatric NHL originates from both mature...
and immature cells of the B- or T-lymphocyte lineage and is typically intermediate- to high-grade, whereas adult lymphomas are more indolent. With effective combination chemotherapy and supportive care, approximately 70% to 80% of children with NHL are now cured.[19] This progress reflects an understanding of the pathogenesis of pediatric NHL and the integration of immunophenotypic and genetic information into classification and staging so that therapy can be tailored to stage and histologic subtype.[20]

Although the etiology of most pediatric NHL remains unknown, patients who have congenital or acquired immune deficiency are known to be at risk. Identification of the role of Epstein-Barr virus in the pathogenesis of B-cell neoplasms and the role of tumor-specific molecular lesions such as the NPM-ALK fusion product in large-cell lymphomas has offered new diagnostic tools and potential targets for therapy. We also now know that the molecular epidemiology of Burkitt’s lymphoma differs across regions of the world, ie, Africa and North and South America.

Many of the principles of therapy for pediatric NHL have evolved from the treatment of childhood ALL: systemic combination chemotherapy for all patients, limited use of primary surgery, no irradiation except in life-threatening emergencies, and use of intravenous high-dose methotrexate for T-cell lymphomas. The treatment of childhood advanced-stage Burkitt’s lymphoma has been a particular success. Systemic combination chemotherapy based on intensive cyclophosphamide, methotrexate, and cytarabine has pushed cure rates above 85%.[21,22] However, the prognosis after relapse or primary treatment failure remains poor. Further, late effects such as anthracycline-induced cardiomyopathy or secondary myeloid leukemia can be devastating. Promising new strategies include monoclonal antibody-based immunotherapy (eg, rituximab [Rituxan] for CD20-positive NHL) and cellular approaches (targeted cytotoxic T cells).

**Solid Tumors**

Non-CNS solid tumors account for approximately 40% of malignancies in patients < 20 years of age. Risk-adapted therapy developed through clinical studies initially focused on clinical presentation features, such as patient age and extent of disease but now includes biologic and molecular features as well. A brief review of several of the more common tumor types follows.

**Neuroblastoma**

Studies by the Pediatric Oncology Group (POG) and the Children’s Cancer Group (CCG) have identified biologic tumor features (especially DNA ploidy and MYCN amplification) that allow risk-directed therapy.[23] In general, patients with resectable localized disease enjoy a > 90% chance of cure with surgery alone. Most children < 1 year old with disseminated disease also have a high likelihood of cure with surgery and chemotherapy. In contrast, survival is suboptimal for patients older than 12 months with disseminated disease, although recent studies report a subset of 12- to 18-month-old children with favorable biologic features who have a much greater chance of survival with intensive therapy.[24] Some patients with local or locoregional disease and other unfavorable features, such as tumor MYCN amplification or, in the infant group, diploidy, also have a poor prognosis.

A landmark CCG study (recently confirmed by European investigators) found that progression-free survival in high-risk disease is slightly improved by intensive induction chemotherapy followed by high-dose consolidation chemotherapy and autologous stem cell rescue, irradiation, and maintenance therapy.[25,26] New approaches being investigated include immunotherapy, multiple autologous stem cell transplants, targeted radiotherapy with iodine-131-meta-iodobenzylguanidine (MIBG), newer chemotherapy agents, such as the camptothecins, and antiangiogenic agents.[27,28]

**Wilms Tumor**

The improved outcome of Wilms tumor, one of the greatest clinical trials group successes, reflects a balanced use of radiation therapy, chemotherapy, and surgery. Survival has improved from 30% in the 1930s to more than 85% today.[29,30] The National Wilms Tumor Study Group (NWTSG, now part of the Children’s Oncology Group [COG]) clinical trials, beginning in 1969, demonstrated that vincristine, dactinomycin (Cosmegen), and doxorubicin are active against Wilms tumor and refined the use of these drugs to maximize EFS while minimizing toxicity. The role of radiation therapy has also been successively reassessed. Treatment of Wilms tumor in North America and in Europe differs in the timing of surgery. In the United States, resection with nephrectomy is done at the time of diagnosis if feasible, whereas in Europe, neoadjuvant chemotherapy is used. Both approaches yield excellent clinical outcomes.

Two major challenges remain in the treatment of Wilms tumor. One is the poorer outcome of patients with tumor anaplasia. In the NWTS-3, -4, and -5 studies, the addition of cyclophosphamide improved the 5-year relapse-free survival of patients with stage II-IV disease and diffuse anaplasia from 27% to 55%. Unfortunately, recent trials have not led to a further increment in survival.[31] The second major challenge is to minimize the late effects of therapy while maintaining a high cure
rate. Each therapeutic modality carries some risk of long-term sequelae. Through refinement of surgical techniques and addition of preoperative chemotherapy, the rate of renal failure in patients with bilateral Wilms tumor has fallen from 16.4% to 3.8%.[32] Radiation therapy can cause or contribute to damage to the remaining kidney, lungs, heart, and female reproductive organs. The NWTS-1 through -3 studies demonstrated that radiation could be safely eliminated for stage I and II disease.[33] The late effects of chemotherapy are increasingly well understood. The cardiovascular effects of doxorubicin and the congestive heart failure and subclinical cardiac abnormalities caused by anthracyclines are well known. NWTS-3 demonstrated that doxorubicin is unnecessary for stage II disease and for stage III disease (if 20 Gy abdominal irradiation is given). Despite the risks, 634 young adult survivors of Wilms tumor reported a health-related quality of life that did not differ significantly from population norms.[34] The challenge remains to find new therapies that can maintain the high cure rate with less risk or to identify patients who require less intensive therapy. NWTS-5 used surgery alone for patients < 24 months old who had small stage I tumors with favorable histology. Unfortunately, 2-year relapse-free survival was reduced from 94.9% to 86.5% (although overall survival was 100%).[35] NWTS-5 also identified loss of heterozygosity at chromosome 1p and 16q as an adverse prognostic factor.[36] Future research will focus on further therapy reduction in the absence of unfavorable genetic findings and on other ways to decrease late effects, such as use of cardioprotective agents.

Rhabdomyosarcoma

The Intergroup Rhabdomyosarcoma Study Group (IRSG, now part of COG) has significantly increased cure rates for rhabdomyosarcoma over the past 30 years. Approximately 70% of patients in the United States are now cured.[37] As with Wilms tumor, the histologic features of rhabdomyosarcoma are important prognostic factors. The favorable embryonal histologic subtype (ERMS) has an approximately 80% cure rate, and the unfavorable alveolar subtype (ARMS), approximately 30%.[38] Successive IRSG studies have refined multimodality therapy to maximize survival while decreasing early and late toxicity (Figure 4). IRS-I through IRS-III reduced or eliminated radiation therapy for a subset of patients with low-risk ERMS without compromising survival.[39] Surgery has been modified to preserve the bladder, reduce aggressive resection of vaginal rhabdomyosarcoma, and eliminate retroperitoneal lymph node dissection for boys < 10 years of age with paratesticular primary tumor and no evidence of retroperitoneal lymph node involvement.[40-42]

Advances in chemotherapy include the identification of a subset of low-risk patients who benefit from the addition of cyclophosphamide to vincristine and dactinomycin and the demonstration that addition of ifosfamide and etoposide does not improve outcome for intermediate-risk patients.[43] The Soft Tissue Sarcoma Committee of COG continues to revise risk stratification in order to better tailor therapy for each patient.
Approximately 20% of patients with rhabdomyosarcoma continue to have a poor prognosis (5-year relapse-free survival rate < 25%). In recent years, patients with ARMS and metastatic disease have been eligible for experimental therapy with new agents in the 6- to 8-week "upfront window" at the start of therapy. This approach has identified several active drugs and drug combinations, including ifosfamide/doxorubicin, melphalan (Alkeran), topotecan (Hycamtin)/cyclophosphamide, and irinotecan (Camptosar)/vincristine. Targeted therapy against the unique gene fusion products of ARMS, PAX3-FKHR and PAX7-FKHR, is being developed.[44]

Osteosarcoma
In the 1960s, localized osteosarcoma of an extremity was treated with amputation alone, and more than 80% of these patients died of distant metastatic disease.[45] In the mid-1980s, the benefit of adjuvant chemotherapy with cisplatin, doxorubicin, and high-dose methotrexate was demonstrated, and these agents form the backbone of chemotherapy today.[46] Neoadjuvant chemotherapy followed by surgical resection and additional chemotherapy results in a 3-year EFS rate of 71% for patients with localized disease and a 5-year EFS rate of 46.7% for those with metastatic disease at diagnosis.[47] The goal of surgery—en bloc tumor removal with adequate margins—initially required amputation of the involved limb. However, limb salvage can be performed in most cases, with comparable local control (Figure 5).[48,49]

Unfortunately, endoprostheses require removal or revision as patients grow. Some devices can now be lengthened without surgery as the child grows, although the lifespan of the prosthesis is limited.[50] Remaining challenges include improving therapy for metastatic disease and decreasing the need for modification of prostheses.

Ewing Sarcoma Family of Tumors
Information about the molecular pathology of the Ewing sarcoma family of tumors now allows us to recognize Ewing sarcoma of bone, extraosseous Ewing sarcoma, and peripheral primitive neuroectodermal tumor as a single tumor type. These tumors share the genetic lesion EWS-FLI1 [t(11:22)(q24;q12)], which produces a fusion protein with aberrant transcriptional activation properties that can transform NIH3T3 cells.[51,52] Some Ewing sarcomas contain other translocations involving the EWS gene on chromosome 22. Molecular tests for these abnormalities allow accurate diagnosis, sensitive detection of metastatic disease in the bone marrow, and detection of minimal residual disease. The EWS abnormalities may also offer a target for future therapies.[53]

Before the introduction of systemic chemotherapy, few patients survived Ewing sarcoma. The Intergroup Ewing Sarcoma Study (IESS) introduced the first successful combined-modality therapy.[54] Another major contribution was the principle that the primary tumor site dictates the local control measure—for example, complete surgical removal of tumors in expendable bones (rib,
clavicle, fibula). Risk-adapted irradiation of the primary site is based on the degree of resection and the response to chemotherapy. In addition, irradiation of pulmonary metastasis may improve survival in a subset of patients, as shown in Figure 6.[55] More recently, ifosfamide and etoposide were shown to benefit patients with high-risk features.[56] More than 70% of localized Ewing sarcoma is curable with combined therapy. Metastatic disease remains a challenge, and high-dose chemotherapy and immunotherapy regimens are under investigation.

Tumors of the Central Nervous System

Tumors of the CNS are the second most common malignancies in children aged 0 to 14 years.[1] Several unique features of brain tumors present therapeutic challenges, including anatomic constraints on resection, the blood-brain and blood-cerebrospinal fluid barriers, and the sensitivity of the developing brain to toxic insult. With the notable exception of germinoma, brain tumors are relatively unresponsive to chemotherapy and radiation. Consequently, survival rates have not increased dramatically. The past few decades have seen many advances in diagnosis and treatment, however, and survival rates for some pediatric brain tumors, including low-grade glioma, ependymoma, and medulloblastoma, are relatively good. Therapies targeted to the molecular characteristics of pediatric brain tumors should improve outcomes for more patients in the near future.

Many advances over the past 3 decades reflect improved technology, particularly diagnostic imaging. CT and MRI have revolutionized management through accurate diagnosis and staging, advanced neurosurgical treatment planning, and sophisticated radiation therapy.[57] Current CT- and MRI-based treatment planning can precisely identify tumor and critical normal structures to allow optimal delivery of conformal techniques such as intensity-modulated radiotherapy. Proton-beam therapy may further spare normal structures and is likely to be widely implemented.

Low-Grade Glioma

Low-grade glioma is the most common childhood brain tumor and has an excellent prognosis when completely resected. Children with completely resected cerebellar pilocytic astrocytoma, for example, have a long-term survival rate > 95%, without adjuvant radiation or chemotherapy.[58] Tumors that cannot be completely resected, including hypothalamic/optic pathway gliomas, are much more likely to recur. Although radiation can result in prolonged stable disease, it may have severe endocrine and cognitive consequences.

In recent years, chemotherapy has been used to delay radiation, particularly in young children. Effective chemotherapy regimens include the vincristine/carboplatin combination, which induced objective responses or prolonged stable disease in two-thirds of patients with low-grade astrocytoma, although long-term follow-up is needed.[59] Ongoing COG trials are testing the efficacy of additional chemotherapeutic agents, including temozolomide (Temodar) and vinblastine.

Ependymoma

Ependymoma is rare but exemplifies the advantages of enhanced imaging capability. In the late
1980s, the 5-year EFS for patients with this neoplasm was approximately 40% and 5-year overall survival, < 60%.[60] High-resolution imaging now allows complete resection, which is crucial even at the cost of cranial nerve deficits, and detection of postoperative residual disease that may require re-resection. With complete resection and focal conformal irradiation, 3-year EFS is reportedly > 75% for children with localized ependymoma.[61] Survivors have reasonable functional outcomes, as cranial nerve deficits often improve significantly. Focal conformal irradiation also allows relative sparing of cortical structures and preservation of neurocognitive function.

Remaining challenges in ependymoma management include effective risk stratification, which is impeded by the difficulty of reliably interpreting histologic grade. Insights into the biology of ependymoma, including the adverse significance of ERBB2 and ERBB4 overexpression, may ultimately improve risk stratification.[62] Patients with metastatic or recurrent disease currently fare poorly. Although ependymoma has been considered chemoresistant, current trials are reevaluating the role of chemotherapy for high-risk disease and exploring the efficacy of new agents.

**Medulloblastoma**

Medulloblastoma is the most dramatic success story in pediatric neurooncology. Overall, long-term survival for patients older than 3 years at diagnosis has improved 20% to 30% over the past 3 decades through routine conformal irradiation of the tumor bed plus craniospinal irradiation (CSI), recognition of the importance of complete resection, and neurosurgical advances that have improved the safety and feasibility of complete resection.

As shown in Figure 7, the addition of chemotherapy has provided a further survival benefit and allowed reduction of the CSI dose for average-risk disease (complete resection with no evidence of metastasis at diagnosis).[63-65] After further refinement of chemotherapy, average-risk patients had 5-year EFS rates > 80% in two recent large trials.[65,66] The SJMB96 regimen (surgical resection and radiation followed by four cycles of high-dose chemotherapy with autologous stem cell support) substantially improved survival for high-risk patients.[66] Further advances will require development of less toxic, more specific therapies based on a thorough understanding of tumor biology. Analysis of medulloblastoma tumor specimens has shown the histology to be prognostically important: Large-cell anaplastic medulloblastoma is more clinically aggressive, while nodular...
desmoplastic tumors are much more likely to be cured.[67] Some histologic characteristics are associated with specific molecular derangements (eg, the large-cell anaplastic phenotype and abnormalities of c-myc and n-myc), but even within histologically identical tumors, molecular differences can have prognostic value and may ultimately provide a basis for targeted therapy. Abnormalities of the wnt/beta-catenin pathway are associated with a relatively favorable prognosis, while overexpression of ERBB2 is associated with poor outcomes.[68,69] Microarray technology can now provide the comprehensive molecular profile of a tumor. This technology has been used to create a combined clinical and molecular risk-stratification system for medulloblastoma that will serve as a prototype for similar, but likely more complex, stratification schemes in future clinical trials.

Formidable challenges remain. One-third of patients older than 3 years at diagnosis experience relapse, and very few of these survive. For younger patients, the neurocognitive sequelae of craniospinal irradiation are unacceptable, and therefore outcomes are substantially worse in most series.[70,71] Older patients are less profoundly affected by CSI, but the cognitive, behavioral, and endocrine sequelae can still affect quality of life, school performance, and adult potential. The extent to which CSI can be safely decreased for average-risk disease, and the potential improvement in neurocognitive function, are still unresolved.

There continue to be more challenges than successes in the treatment of pediatric brain tumors. Long-term complications of treatment remain a concern even when tumors are highly curable. Several tumor types, including high-grade and diffuse pontine gliomas, are remarkably resistant to therapy. These and the recently defined atypical teratoid/rhabdoid tumor have a dismal prognosis despite decades of clinical trials.[72,73] For these patients and for those with recurrent medulloblastoma, progress will depend on the elucidation of tumor biology.

To that end, clinical trials are beginning to routinely incorporate biologic studies. To facilitate such studies, neurosurgeons should be encouraged to save frozen tissue from all pediatric brain tumor resections. As tumor-specific molecular abnormalities are identified, new drugs are being developed to target them. Many such agents are now in early pediatric clinical trials in cooperative groups such as COG and the Pediatric Brain Tumor Consortium (PBTC). The effective use of these agents should make it possible to cure a larger proportion of children with brain tumors in the future.

**Summary**

Fifty years ago, childhood cancer was almost uniformly fatal. Today, most patients survive if treated appropriately. Further progress will require greater coordinated efforts to develop less toxic therapies for the more curable pediatric cancers and novel approaches for patients at greatest risk. There is also a need to establish and support evidence-based national pediatric oncology standards of care, to develop new incentives for drug development specific to childhood cancer, to increase support for translational research, to develop comprehensive management strategies for survivors, and to develop and finance national initiatives to improve the outcome of adolescents and young adults with cancer. Because many remaining research questions will require the study of large populations and access to high-quality biologic specimens, more efficient and productive international collaborations are needed.

Whereas many early clinical trials were empirical, our growing understanding of tumorigenesis, cellular signal transduction, and tumor survival factors is rapidly providing new clues for the development of targeted agents. In addition, new diagnostic and imaging tools promise more robust measurement of disease burden and response to verify the benefits of therapy. The success we have achieved to date is gratifying. We should not be discouraged by our failures but galvanized by the remaining challenges.

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