Multidisciplinary management of childhood brain tumors:
a review of outcomes, recent advances, and challenges

A review

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Object. Brain tumors are the most common category of childhood solid tumors. In the 1970s and 1980s, treatment protocols for benign tumors focused almost exclusively on surgery, with radiation treatment as a salvage modality, whereas the management of malignant tumors employed a combination of surgery, radiation therapy, and chemotherapy, with therapeutic approaches such as “8-in-1” chemotherapy often applied across histological tumor subsets that are now recognized to be prognostically distinct. During the ensuing years, treatment has become increasingly refined, based on clinical and, more recently, molecular factors, which have supported risk-adapted treatment stratification. The goal of this report is to provide an overview of recent progress in the field.

Methods. A review of the literature was undertaken to examine recent advances in the management of the most common childhood brain tumor subsets, and in particular to identify instances in which molecular categorization and treatment stratification offer evidence or promise for improving outcome.

Results. For both medulloblastomas and infant tumors, refinements in clinical and molecular stratification have already facilitated efforts to achieve risk-adapted treatment planning. Current treatment strategies for children with these tumors focus on improving outcome for tumor subsets that have historically been relatively resistant to therapy and reducing treatment-related sequelae for children with therapy-responsive tumors. Recent advances in molecular categorization offer the promise of further refinements in future studies. For children with ependymomas and low-grade gliomas, clinical risk stratification has facilitated tailored approaches to therapy, with improvement of disease control and concomitant reduction in treatment sequelae, and recent discoveries have identified promising therapeutic targets for molecularly based therapy. In contrast, the prognosis remains poor for children with diffuse intrinsic pontine gliomas and other high-grade gliomas, despite recent identification of biological correlates of tumor prognosis and elucidation of molecular substrates of tumor development.

Conclusions. Advances in the clinical and molecular stratification for many types of childhood brain tumors have provided a foundation for risk-adapted treatment planning and improvements in outcome. In some instances, molecular characterization approaches have also yielded insights into new therapeutic targets. For other tumor types, outcome remains discouraging, although new information regarding the biological features critical to tumorigenesis are being translated into novel therapeutic approaches that hold promise for future improvements.

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Key Words • astrocytoma • brain tumor • ependymoma • medulloblastoma • molecular markers • oncology

Brain tumors are, as a group, the most common solid tumors of childhood, and are now the leading cause of childhood cancer-related deaths. Although advances in surgical and adjuvant therapy during the last two decades have produced significant improvements in the outcome for certain types of childhood brain tumors such as medulloblastoma, the outlook for other groups, such as malignant gliomas and diffuse intrinsic brainstem gliomas, has changed minimally, if at all. In addition, for patients with more prognostically favorable tumor types, there has been growing concern that “cure” often comes at a high price in terms of late sequelae, which can impair long-term quality of life. Accordingly, current management strategies for children with brain tumors strive to maintain high survival rates while reducing long-term sequelae of treatment for more favorable-risk tumors, and to improve the rate of disease prognosis.

Abbreviations used in this paper: CCG = Children’s Cancer Group; COG = Children’s Oncology Group; EGFR = epidermal growth factor receptor; MAPK = mitogen-activated protein kinase; MGMT = methylguanine DNA methyltransferase; mTOR = mammalian target of rapamycin; NF1 = neurofibromatosis Type 1; PBTC = Pediatric Brain Tumor Consortium; PDGFR = platelet-derived growth factor receptor; PNET = primitive neuroectodermal tumor; POG = Pediatric Oncology Group; Shh = Sonic hedgehog.
response and long-term survival in children with prognostically high-risk tumors. This report will review how these approaches are being applied in several of the most common groups of childhood brain tumors, specifically primitive neuroectodermal tumors, low- and high-grade gliomas, ependymomas, and infant tumors, and highlight instances in which advances in clinical and biological risk-based categorization and molecularly based treatment strategies have had, or may in the near term have, an impact on therapeutic trial development and outcome.

Methods

The PubMed database was searched using the terms “medulloblastoma,” “PNET,” “ATRT,” “ependymoma,” “high-grade glioma,” “malignant glioma,” “low-grade glioma,” “astrocytoma,” and “brainstem glioma,” which are the most common groups of childhood brain tumors, and the terms “infant,” “child,” and “pediatric.” Additional searches were performed of the publications of lead or senior authors of relevant articles, and of their reference lists, as well as the abstract listing of recent international pediatric neuro-oncology meetings. An attempt was made to: 1) identify articles of critical historical significance, particularly phase III randomized trials or large centrally reviewed single-arm studies, which have had a major impact on defining current surgical and post-surgical management algorithms, and 2) to identify recent studies that have led to significant advances in the molecular categorization and treatment stratification for childhood brain tumors, and new insights for therapeutic targets. The underlying goal of this analysis was to provide an up-to-date review of those studies that have provided a foundation for the management approaches historically used in pediatric neuro-oncology as well as those that have led to recent major advancements in the field and that offer evidence or clear promise for improving outcome and reducing sequelae of therapy. No attempt was made to formally grade the evidence provided in the reviewed publications, given the rapid advances in the field, which have highlighted limitations in what were originally outstanding well-conducted clinical trials, reflecting improvements in surgical, imaging, radiological, and radiotherapeutic techniques, refinements in pathological classification based on molecular data, and evolution of chemotherapy treatment options. Instead, an emphasis was placed on discussing such studies in the context of new information that has emerged to better inform interpretations of the data generated. Results are provided for each of the major tumor subgroups that were reviewed.

Results

Medulloblastoma/Primitive Neuroectodermal Tumor (PNET)

Primitive neuroectodermal tumors are the most common group of childhood malignant brain tumors. A major controversy in the 1980s and 1990s was whether the diverse group of CNS “small round blue cell” tumors encompassed distinct, location-specific entities, such as medulloblastomas, pineoblastomas, and supratentorial PNETs, or were different manifestations of a common underlying molecular pathway of tumor development. Recent gene expression and mutational analyses support the former interpretation in that the genomic profile of cerebral PNETs differs from that of medulloblastomas. Moreover, further studies have indicated that even among individual location-based entities such as medulloblastomas, there are diverse molecular subsets of tumors, with distinctive patterns of gene expression and genomic pathway alterations, which may have a significant impact on the biological behavior and treatment response of a given lesion.

This novel biological information may help to refine the well-known clinical risk stratification criteria that are currently in use for these tumors (Table 1). These clinical parameters are based on a series of cooperative group studies from the Children’s Cancer Group (CCG), Pediatric Oncology Group (POG), and Société Internationale d’Oncologie Pédiatrique (SIOP) in the 1980s and 1990s that noted significant differences in outcome based on the extent of postoperative residual tumor, metastasis status, tumor location, and age among patients treated with approximately 3600 cGy of radiation to the craniospinal axis with a boost to a dose of 5400 cGy to the tumor bed. In these early studies, 5-year progression-free survival rates were approximately 60% to 70% for children older than 3 years of age with extensively resected, nonmetastatic (M0) posterior fossa lesions (so-called “average-risk” or “standard-risk” tumors), but less than 30% to 40% for patients younger than 3 years of age and those with extensive residual disease, metastases, or tumors originating outside of the posterior fossa (so-called “high-risk” tumors). The use of chemotherapy appeared to significantly improve survival outcome for high-risk tumors, but a comparable improvement was not apparent for standard-risk tumors, potentially because the baseline survival rate was so much higher in the latter group. It also became increasingly apparent that many of the long-term survivors suffered significant long-term sequelae from their treatment, particularly those who received standard doses of radiation (3600 cGy to the neuraxis) at a young age. These observations provided an impetus for studies that stratified therapy based on these clinical risk factors, with the goal of improving survival in the high-risk group and reducing the long-term side effects of treatment in the average-risk group.

Because initial efforts to reduce sequelae in average-risk patients by reducing the craniospinal radiation dose to 2340 cGy were associated with a decrease in progression-free survival, subsequent studies attempted to augment the efficacy of reduced-dose radiation by administering adjuvant chemotherapy. These approaches were substantially more successful with rates of long-term survival exceeding 70% and potentially lower frequencies of radiation-related cognitive and endocrine sequelae than after treatment with standard doses of radiation alone. Building upon these results, the Children’s Oncology Group (COG) initiated a randomized Phase III study (A9961) that was designed to compare 2 adjuvant chemotherapy regimens, administered with radiation, for
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TABLE 1: Criteria for stratification of intracranial PNETs

<table>
<thead>
<tr>
<th>Category</th>
<th>Prognostic Factor</th>
<th>Outcome Association</th>
<th>Application*</th>
</tr>
</thead>
<tbody>
<tr>
<td>clinical/imaging</td>
<td>age</td>
<td>adverse if age &lt;3 yrs</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>extent of tumor removal</td>
<td>adverse if incomplete (or &gt;1.5 cm² residual)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>tumor location</td>
<td>adverse if outside of posterior fossa</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>metastases</td>
<td>adverse</td>
<td>1</td>
</tr>
<tr>
<td>pathology</td>
<td>anaplasia</td>
<td>adverse if diffuse</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>desmoplasmia</td>
<td>favorable, particularly in younger patients</td>
<td>2</td>
</tr>
<tr>
<td>molecular</td>
<td>Shh pathway alterations</td>
<td>favorable, particularly in younger patients</td>
<td>1, 3</td>
</tr>
<tr>
<td></td>
<td>Wnt pathway alterations</td>
<td>favorable, particularly in older patients</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>c-myc amplification</td>
<td>adverse</td>
<td>2</td>
</tr>
</tbody>
</table>

* 1 = used for stratification in current protocols; 2 = proposed for use in protocols under development; 3 = potential therapeutic target.

average-risk patients. This study confirmed that reducing the dosage of craniospinal radiation from 3600 cGy to 2340 cGy in conjunction with chemotherapy was not associated with an unacceptable drop in survival rates.76 Survival with both regimens was comparable, and was superior to results in previous studies with standard doses of radiation, possibly reflecting improved stringency in the imaging criteria used to establish tumors as average risk. These results provided a foundation for a subsequent study (ACNS0331) that is examining whether doses and volumes of radiation can be further reduced with intensification of adjuvant chemotherapy. For children between 3 and 8 years of age, one component of the study is comparing outcome in patients randomized to receive a craniospinal radiotherapy dose of 1800 cGy versus those who receive 2340 cGy, with a goal of determining whether the lower dose can maintain disease control while diminishing cognitive and endocrine sequelae, which are most severe in younger children. A second component of the study, which incorporates both the 3–8 age group as well as children between 8 and 18 years of age, will examine the safety of reducing the volume of posterior fossa irradiation using 3D imaging-based conformal delivery techniques to decrease ototoxicity.

This study also includes a battery of correlative analyses to evaluate molecular features that have been found in recent retrospective studies to identify prognostically distinct tumor subsets, as well as genome-wide screening of DNA copy number alterations and gene expression profiles to look for patterns of abnormalities that can improve upon current clinically based risk classification. The long-term objective of this effort is to identify molecular features that can highlight tumors likely to recur despite favorable clinical features, or unlikely to recur despite adverse clinical features, which would provide insights for biologically refined stratification in future studies.

The potential utility of these molecularly based risk-adapted classification schemes is supported by several recent reports. For example, Thompson et al.115 observed that medulloblastomas could be subdivided into 5 groups based on characteristic molecular patterns, including alterations of genes in the Wnt signaling pathway and mutations of those in the Sonic hedgehog (Shh) pathway. More recently, Kool et al.71 also identified 5 distinct subsets that shared similarities with the groups noted by Thompson et al., including features such as alterations in Wnt signaling, particularly mutations in the β-catenin gene, and alterations in Shh signaling associated with mutations or inactivation of PTCH1. The various molecular groups also differed significantly in their clinicopathological features in terms of disease dissemination and patient age.51 Other molecular features, such as TP53 mutations and c-myc amplification have also been linked to prognostically adverse tumor subsets.108,118

Although the above molecular subgroups of medulloblastomas may in part overlap with clinically defined subsets, the molecular data also appears to convey prognostic information that supplements clinical risk stratification.51,115 The fact that many of the above genomic and gene expression changes can be assessed on formalin-fixed paraffin-embedded samples using standardizable assays offers the possibility of tailoring therapy based on the patterns of abnormalities in the tumor, in conjunction with established clinical factors. This strategy is under consideration for implementation in future trials of the European and North American cooperative groups, particularly in average-risk patients, in whom reduction of neurotoxic therapy in the most favorable patient subgroups remains a priority.

The converse approach, specifically intensification of therapy in average-risk patients with adverse prognostic features as a way to improve outcome, is also an ongoing objective. An example in this regard is based on data from study A9961, which indicate that the subset of patients whose tumors showed anaplastic histological features had a significantly worse prognosis than those with classical histology.76 This has led to inclusion of anaplastic tumors with other high-risk PNETs in current COG medulloblastoma/PNET protocols, regardless of clinical features. Recent studies suggest that the subset of anaplastic tumors with large cell histology, which generally exhibit c-myc amplification, have a particularly poor prognosis, independent of clinical factors.115

In contrast to the underlying therapeutic philosophy for average-risk medulloblastomas, which is directed toward reduction, where feasible, of treatment-related se-
with metastatic medulloblastoma. Currently, a trial of Shh inhibitor GDC-0449 is ongoing in the Pediatric Brain Tumor Consortium (PBTC), and if response correlates with the status of Shh pathway activation in a given tumor, this will provide a basis for prospective molecular characterization as a criterion for therapy.

Based on recent studies that mutations and alterations in the histone deacetylase genes, which affect gene transcription, are present in a subset of medulloblastomas and that targeted inhibition of this pathway can block tumor growth in preclinical models, recent studies have also examined the activity of histone deacetylase inhibitors in children with recurrent tumors. Studies of other proteins involved in neural cell developmental regulation are currently in progress, including inhibitors of Notch signaling. Studies of antiangiogenic signaling inhibition, using agents such as bevacizumab, as well as targeted inhibition of pathways implicated in medulloblastoma growth, have also been undertaken.

Low-Grade Glioma

Low-grade gliomas encompass several histological subgroups of tumors, including pilocytic astrocytoma and subependymal giant cell astrocytoma, which generally are classified as Grade I lesions, and fibrillary and pilomyxoid astrocytomas, which are considered Grade II lesions. In the 1970s and early 1980s, treatment of these tumors focused almost exclusively on resection, followed by reoperation or irradiation for lesions that progressed or were believed to be at high risk for progression after initial resection. Several sizeable clinical reports based on cases treated during this era demonstrated, not unexpectedly, that deep-seated, infiltrative tumors, such as those involving the optic pathways, were much less likely than superficial lesions to be amenable to gross-total resection, and had a correspondingly worse outcome. However, the use of wide-field irradiation in these large centrally located tumors, which often occur in young children, carried a significant risk of late cognitive, endocrine, and vascular sequelae.

For superficially situated, well-circumscribed lesions in the cerebral or cerebellar cortex, resection remains the initial treatment of choice. A recent report by Wisoff et al. has strongly supported this approach, demonstrating that the factor most strongly associated with outcome in all low-grade gliomas is the extent of surgical tumor removal. In a large cooperative group natural history study (CCG9891/POG8930), 5-year progression-free survival was more than 90% in children with low-grade gliomas that had undergone gross-total resection, whereas approximately half of children with less extensive tumor removal had disease progression during that interval. In accordance with these data, a variety of surgical adjuncts are sometimes employed in an effort to enhance the likelihood of safely achieving an extensive resection. Advances in image-guided tumor localization and treatment planning, functional brain mapping, intraoperative imaging, and neurophysiological monitoring have led to theoretical improvements in the safety of extensive tumor resections, particularly for more deep-seated lesions such as thalamic tumors, although it has been difficult to design a prospective trial to prove the independent impact on outcome of any of the above approaches.
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Given the strong association between resection extent and outcome, it has also been difficult to determine conclusively whether there is a correlation between histology and prognosis. Although pilocytic astrocytomas appear to have a more favorable prognosis than fibrillary lesions, this may reflect that pilocytic tumors, particularly when superficially located, are often reasonably well circumscribed and more likely to be amenable to gross-total resection. Likewise, the contribution of tumor location to outcome is inextricably tied to the issue of the extent of resection: superficial lesions involving the cerebral cortex tend to have a better prognosis than deep lesions involving the basal ganglia, optic pathways, and brainstem, probably relating to the fact that they are more amenable to extensive removal without excessive morbidity.

Because patients whose tumors have undergone gross-total resection have a greater than 90% long-term survival rate, adjuvant therapy is usually not required for such lesions, which include the majority of cerebral hemisphere and cerebellar low-grade gliomas. In contrast, the adjuvant management considerations are much more complex for deep-seated lesions, particularly those involving sites such as the hypothalamus and optic pathways and those arising in the brainstem, which are usually not amenable to complete removal because of their involvement of critical surrounding structures. Management of optic pathway tumors is further complicated by the fact that they commonly arise in young children, who are at high risk of long-term sequelae from side effects of wide-field radiation therapy.

In a series of studies during the last 15 years, several chemotherapy regimens were noted to have efficacy in delaying or avoiding the need for radiotherapy in children with progressive or incompletely resected low-grade gliomas believed to be at high risk of progression.4,6,74 The recently completed COG A9952 study involved a Phase III randomized comparison between 2 active regimens, carboplatin and vincristine versus 6-thioguanine, procarbazine, lomustine, and vincristine, for low-grade gliomas arising in children without neurofibromatosis Type 1 (NF1) and a single-arm analysis of the results with carboplatin and vincristine in children with NF1-related low-grade gliomas. Although both regimens showed efficacy in delaying tumor progression and the need for radiation therapy, the results were slightly better with the lomustine-based regimen and significantly better in the nonrandomized cohort of patients with NF1, reflecting the often indolent growth characteristics of NF1-associated low-grade gliomas. Whereas the median time to progression in NF1 patients exceeded 8 years, most children without NF1 in both treatment arms suffered disease progression within 5 years of initial therapy, which calls attention to the importance of identifying new treatment options.

Accordingly, subsequent studies are evaluating other therapeutic approaches for these tumors. The ACNS0223 study examined the feasibility and efficacy of administering temozolomide in addition to carboplatin/vincristine. The ADVL0515 study examined the use of vinblastine, which has been observed to have independent activity for low-grade gliomas, as an alternative to vincristine in carboplatin-based regimens. Other variations on the platinum-based therapy have also been examined, including studies of cisplatin combined with etoposide, which have achieved high rates of disease control and radiation avoidance in young children with progressive low-grade gliomas. In contrast, ACNS0221 is examining the efficacy of conformal radiotherapy in children older than 10 years with progressive tumors and in younger children with chemotherapy-refractory tumors to determine whether the use of 3D treatment planning, which conforms to the shape of the tumor and minimizes the volume of surrounding normal brain that receives high doses of radiation, can achieve an acceptable level of side effects and lead to long-term disease control. More recently, a host of biological agents have been examined in these tumors, including antiangiogenic agents and growth signaling inhibitors that are directed against newly identified molecular targets in low-grade glioma.

In particular, recent studies have demonstrated that a large percentage of pilocytic astrocytomas exhibit alterations in the BRAF gene, most commonly involving translocations between BRAF and KIAA, or activating mutations, such as BRAFV600E, which induces growth signaling through mitogen-activated protein kinase (MAPK)-related pathways.50 Based on these findings, and data that BRAF inhibitors have preclinical activity against pilocytic astrocytoma xenografts, clinical trials of BRAF and MAPK pathway inhibitors have been launched for children with progressive tumors, such as the PBTC study of AZD6244. Because these tumors have been noted to have evidence of vascular proliferation histologically, studies of antiangiogenic agents, such as bevacizumab and lenalidomide, have also been launched, and have achieved encouraging rates of response or disease control in initial Phase I and Phase II trials.119

Subependymal giant cell astrocytomas are a second low-grade glioma subset for which a characteristic pattern of genomic alterations has been identified and translated therapeutically. Many of these tumors arise in the setting of tuberous sclerosis and exhibit mutations in the TSC1 and TSC2 genes, leading to deregulated activation of mammalian target of rapamycin (mTOR) signaling. As with the BRAF anomalies that characterize pilocytic tumors, these consistent genomic alterations provide a “druggable” target for molecularly directed therapy. A recent trial of one mTOR inhibitor, everolimus, showed a high rate of tumor regression and disease control for lesions that were not amenable to resection.

In contrast to the above 2 groups, the molecular basis for childhood fibrillary low-grade astrocytomas remains less well-defined. Although in adults such tumors represent an early stage in a pathway of tumorigenesis that often ends in higher grade lesions, such a phenotype is less commonly observed in childhood lesions. At present, tumor-specific molecular therapies for these lesions are lacking, although the identification of characteristic genomic alterations that may provide a basis for targeted therapies remains a subject of intense interest in the research community.

High-Grade Glioma

Malignant (high-grade) gliomas encompass Grade
III anaplastic astrocytomas, oligodendrogliomas, and oligoastrocytomas, and Grade IV glioblastomas and gliosarcomas. As with adult malignant gliomas, the prognosis for children with these tumors has historically been poor, despite advances in surgical techniques and implementation of newer protocols for administering radiation. The addition of chemotherapy with lomustine and vincristine to postoperative radiation therapy was demonstrated in the CCG-943 study to improve survival compared with the use of radiation therapy alone, which helped to establish multimodality therapy as the standard approach for these tumors. Unfortunately, subsequent studies with the more complex “8-in-1” regimen in the CCG-945 study failed to further improve outcome, and the use of more intensive chemotherapy, administered before or after radiation therapy, also failed to increase survival and in some instances was associated with prohibitively high rates of toxicity. Moreover, with the recognition that a sizeable subset of long-term survivors in historical studies actually harbored atypical low-grade gliomas, rather than malignant gliomas, the reported survival rates for children with these tumors have actually declined in the last 20 years, reflecting that recent studies have applied more consistent entry criteria and central histopathological review to exclude discordant histologies.

In studies that have used central review, two clinical factors have stood out in terms of having an association with outcome, specifically histology and extent of tumor resection. In general, patients with Grade IV lesions (glioblastoma) have had a worse prognosis than those with Grade III lesions. Anaplastic (Grade III) oligodendrogial tumors, in particular, have appeared to have a better outcome than other malignant gliomas. In addition, patients with tumors that were not amenable to extensive resection have had lower rates of long-term survival than those with more resectable lesions. Molecular studies of the CCG-945 cohort have also identified several biological factors that have been associated with a worse prognosis, including overexpression and/or mutation of TP53, high MIB-1 proliferation index, and overexpression of methylguanine DNA methyltransferase (MGMT), which counteracts the effects of alkylating agents, such as the nitrosoureas.

Based on recent studies in adults that noted superior outcomes from administering chemotherapy with temozolomide during and after radiation therapy versus treatment with radiation therapy alone, pediatric studies of this approach were initiated. The ACNS0126 study incorporated daily administration of temozolomide during radiation therapy followed by treatment on a 5-day per 28-day (5 days in a row every 28 days) schedule thereafter. Although outcome results in this study were similar to those reported in adults, they were no better than those obtained in the CCG-945 study with CCNU and vincristine. As in the CCG-945 study, MGMT overexpression proved to be adversely associated with outcome. The 2-year event-free survival rate was 17% ± 5% among patients without overexpression of MGMT versus 5% ± 4% among those with overexpression (p = 0.045). A subsequent study (ACNS0423) combined both lomustine and temozolomide, which was based on the results of a pilot study that noted a comparatively better rate of 1-year survival with this combination than with temozolomide alone. Preliminary results from ACNS0423 suggest a nominal improvement in outcome in the overall cohort of patients, compared with the results from ACNS0126, although survival rates remain disappointing.

In view of the failure of conventional chemotherapy and radiation therapy to substantially improve the prognosis of children with these tumors, there has been significant interest in exploring the applicability of molecularly targeted treatment strategies. However, compared with the extensive research that has been directed at defining the molecular pathways of tumorigenesis in adult high-grade gliomas, relatively little information is available in pediatric lesions. Adult malignant gliomas have characteristiclly been subdivided into “primary” lesions that arise de novo as Grade IV tumors, which typically exhibit amplification and often rearrangement of the epidermal growth factor receptor (EGFR) gene and deletion of PTEN; “secondary” lesions that progress from low-grade fibrillary astrocytomas to Grade III and ultimately Grade IV lesions in a stepwise fashion, which typically have mutations of TP53 and IDH1 or IDH2 as early genetic anomalies; and oligodendrogial tumors, which often exhibit deletions of chromosomes 1p and 19q. In this regard, previous studies have noted TP53 mutations in approximately half of childhood malignant gliomas, similar to the rate observed in adult secondary malignant astrocyomas. However, pediatric malignant gliomas rarely arise from apparent low-grade precursors and, apart from those occurring in adolescents, infrequently exhibit mutations in the IDH1 or IDH2 genes, suggesting that despite their similarities in terms of TP53 alterations, most childhood high-grade gliomas arise by a mechanism that is distinct from the one seen in adult secondary malignant gliomas. Childhood lesions are also biologically distinct from adult primary malignant gliomas, because they infrequently exhibit deletions or mutations of the PTEN gene or amplification of EGFR.

Similar to recent reports that highlight the existence of multiple pathways of tumorigenesis in adults, it is likely that pediatric lesions are not only genetically distinct from many adult lesions, but may themselves encompass several parallel pathways of tumorigenesis. Recent studies from several groups have identified amplification of PDGFR-α in a subset of pediatric malignant gliomas, suggesting that inhibitors of this receptor or its downstream signaling pathways may constitute a relevant targeted therapy approach. However, for most such tumors, a consistent pattern of genetic alterations has not been observed. Accordingly, molecularly directed studies to date have generally focused on targets such as EGFR signaling that are relevant in adult malignant gliomas. The results of several of these studies have been recently reported, and have unfortunately noted low rates of responses and disease control. An ongoing challenge is to identify molecular factors that may better determine prospectively which patients are likely to respond to a given approach and to identify new strategies that can achieve a higher rate of response.

In this regard, a newly opened study (ACNS0822),
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which is comparing the activity of several different agents during radiation therapy, followed by the antiangiogenic agent bevacizumab in combination with irinotecan after radiation therapy, is incorporating extensive correlative studies encompassing microarray-based genotyping and expression profiling to parallel the extensive analyses that have been recently completed in adult malignant gliomas.\textsuperscript{20,117} The goal of these correlative analyses is to define genes associated with tumor progression in pediatric malignant gliomas and to potentially identify heretofore unrecognized therapeutic targets that may be applied in future studies.

Brainstem Glioma

Brainstem gliomas are a biologically diverse group of lesions, which encompass subgroups of focal tumors that are generally benign biologically, and diffuse intrinsic tumors, which are malignant. The increasing availability of MR imaging during the 1980s and 1990s had a major impact in allowing the reliable categorization of these tumors (Fig. 1).\textsuperscript{18,94} The fact that diffuse tumors can now be identified noninvasively has diminished the role of biopsy in establishing the diagnosis,\textsuperscript{1} except in cases with atypical imaging or clinical characteristics, and has had the unintended consequence of limiting access to tumor material for molecular analysis. On the other hand, improved imaging has had undeniable benefits in terms of identifying lesions that may in selected cases be amenable to surgical intervention, such as dorsally exophytic brainstem gliomas and focal lesions of the midbrain and cervicomedullary junction, which are generally low grade histologically. Such tumors are typically managed like other low-grade gliomas in that accessible lesions, such as dorsally exophytic brainstem gliomas, are often treated using resection as the primary therapeutic modality. If an extensive resection has been achieved, adjuvant therapy is often deferred and observation alone is pursued. For more deep-seated brainstem low-grade gliomas, which may not be amenable to complete resection, the same considerations apply as noted earlier for nonbrainstem low-grade gliomas, in terms of the use of focal conformal radiation therapy or chemotherapy, depending on the age of the patient.

In stark contrast to the reasonably favorable prognosis of low-grade focal brainstem gliomas, the outcome for children with diffuse intrinsic brainstem gliomas remains exceedingly poor and has artifically worsened slightly over time, reflecting that refinements in imaging have screened out atypical low-grade lesions that may have been mistaken for diffuse tumors in early studies, leaving a more homogeneous population of prognostically adverse tumors. Historically, these tumors have been treated with radiation, which provides an interval, albeit transient, of symptomatic improvement in many patients. Cooperative group studies in the 1980s and early 1990s examined the efficacy of increasing the dose of radiation using hyperfractionated delivery approaches. Although these studies demonstrated that escalation of the radiation dose to as high as 7800 cGy was often tolerated, no improvement of progression-free or overall survival duration was observed, with 1-year progression-free survival rates clustering in the range of 15% to 20%.\textsuperscript{23,43,47,75}

Subsequently, a series of studies examined the use of pre- and/or postradiotherapy chemotherapy for these tumors, in some cases in conjunction with hyperfractionated high-dose irradiation, but disappointing results were obtained with a variety of agents, even when administered at high doses.\textsuperscript{15,42,43,54} More recent studies have attempted to build upon the activity of radiation therapy by administering chemotherapy concurrently in an effort to add to the effects of radiotherapy (chemoradiotherapy) or synergistically enhance the activity of radiation therapy (radiosensitization). Unfortunately, results to date have been discouraging. For example, the ACNS0126 study of temozolomide with irradiation, which incorporated a stratum for patients with brainstem gliomas, noted a 1-year event-free survival rate of only 14%.\textsuperscript{10} Similarly, a recent French Society of Pediatric Oncology study of topotecan during radiotherapy failed to observe a significant survival benefit,\textsuperscript{6} and a COG study of the radiosensitizer gadolinium texaphyrin during irradiation (ACNS0222), which incorporated the maximally tolerated dose determined by the A09712 Phase I study,\textsuperscript{9} also yielded disappointing results.

Studies by the PBTC have examined several molecularly targeted treatment strategies, selected predominantly because of the known involvement of the targeted pathways in adult glial tumorigenesis, in conjunction with radiation therapy. Studies with the PDGFR inhibitor imatinib (PBTC-006), the EGFR inhibitor gefitinib (PBTC-007), and the farnesyltransferase inhibitor tipifarnib (PBTC-014) have been completed, but the results, which have recently been reported, have been disappointing.\textsuperscript{31,95,96} Studies are currently in progress using conceptually different molecularly targeted strategies in conjunction with radiation therapy. One study being conducted by the COG is examining the histone deacetylase inhibitor vorinostat, which has shown promising synergy with radiation in other tumor systems. Concurrently, the PBTC is conducting a study that uses capecitabine, a prodrug of 5-fluoro-uracil, based on the rationale that this compound may be selectively metabolized to the active agent by the increased thymidine phosphorylase activity observed in gliomas, and that this effect may be further enhanced by radiation.
As noted earlier, one of the many challenges to progress in the management of diffuse intrinsic brainstem gliomas has been the lack of well-preserved tumor material to identify molecular abnormalities and potential novel therapeutic targets, reflecting that most diffuse intrinsic brainstem gliomas are now diagnosed by imaging findings alone in the context of appropriate clinical symptoms. Until recently, most biological studies involving these tumors have relied on archival biopsy specimens obtained in the era before MR imaging, cases with atypical imaging and clinical features that have undergone biopsy, and autopsy specimens. The archival nature and uncertain processing of many such specimens constrained the range of analyses that could be accomplished, which generally focused on a limited group of targets, such as EGFR and p53, which could be assayed by immunohistochemistry or DNA analysis.

More recently, a series of studies have attempted to obtain autopsy material in real time, which has allowed collection of higher-quality fresh tumor material that is amenable to whole genome microarray-based expression analysis, DNA copy number determination, and targeted gene sequencing. In addition, several groups in Europe have incorporated image-guided stereotactic biopsy of brainstem gliomas at diagnosis as a way to obtain biologically informative tumor material. The relatively low rates of morbidity reported in these studies have prompted some groups in North America to also consider the feasibility of incorporating biopsy sampling into clinical trials for brainstem gliomas. The theoretical underpinning of such studies would be to use the biopsy data to direct the selection of molecularly targeted therapeutic approaches in individual patients. Unfortunately, long-term responders have been rare in essentially all molecularly targeted studies reported to date, which has posed a quandary about which targeted agents would be included in such a clinical trial. Thus, although the rationale behind using biopsy data to direct subsequent therapy remains controversial, there is general agreement that novel approaches are critically needed to improve upon the dismal rates of response and long-term survival in children with these tumors. In this regard, pilot trials of innovative strategies, such as convection-enhanced delivery of immunotoxins and immunotherapy, are being conducted in small groups of newly diagnosed patients with these tumors in an effort to assess safety and efficacy as a basis for broader clinical trial assessments.

Ependymoma

With improvements in neuroimaging technology, there has been increasing evidence from institutional and cooperative group trials during the last two decades that the most important prognostic factor for outcome among children with ependymomas is the extent of tumor removal. Whereas children with tumors that have undergone gross-total resection have a 50%–75% chance of long-term survival after postsurgical radiation therapy, less than 30% of those with subtotal resections experience prolonged survival. Recognition of this factor has been associated with a trend toward higher rates of extensive tumor resection among children enrolled in cooperative group trials, increasing from approximately 50% in the CCG-9941 study from the 1990s to approximately 75% in the ACNS0121 study completed during the last several years. Moreover, institutional studies that have incorporated a strong emphasis on achieving extensive tumor removal have reported even higher rates of gross-total resection and, coupled with administration of carefully planned 3D conformal radiation of the tumor bed, have observed 7-year overall survival rates exceeding 80%. A second factor that has more recently been associated with outcome is tumor histology: several studies have noted that anaplastic (Grade III) ependymomas have a significantly worse prognosis than Grade II lesions. A third factor that has been less convincingly associated with outcome is tumor location, which may reflect that nonanaplastic supratentorial lesions may be more likely to undergo radiologically complete removal than infratentorial tumors and in some cases may be amenable to microscopically complete removal.

The COG ACNS0121 study, which recently completed enrollment and is currently undergoing final outcome analysis, stratified therapy based on the above 3 factors. For patients who underwent gross-total or near-total resection of infratentorial ependymomas and anaplastic supratentorial lesions, and those who underwent gross-total or near-total resection of nonanaplastic supratentorial lesions with microscopic residual disease, the study will determine the efficacy of conformal radiation to the tumor bed plus a 1-cm margin for achieving long-term disease control. For children with nonanaplastic supratentorial ependymomas who underwent microscopically complete resection, the study will define the frequency of disease control without adjuvant therapy, based on favorable results with expectant management in a previous pilot study. Finally, for patients who had an incomplete initial resection, the study will determine whether a short course of chemotherapy will achieve disease regression or permit ‘second-look’ complete resection before radiation therapy, and whether this intervention will improve long-term survival. A novel aspect of this study is the inclusion of children as young as 1 year of age. Historically, children younger than 3 years with ependymoma have had a less favorable prognosis than older children, which may reflect distinctive biological features of these tumors in terms of their invasive growth patterns around the brainstem when they arise infratentorially, and their large size and vascularity when they arise supratentorially, but may also reflect that irradiation of such tumors has often been deferred after surgery. The use of conformal radiation planning has allowed these children to be treated with tumor-directed therapy with tight margins to minimize irradiation of the surrounding brain. The sequelae of this approach, particularly in young children, are undergoing careful assessment in this cohort.

A subsequent study for ependymomas (ACNS0831), which is ongoing, is a randomized Phase III trial designed to resolve a long-standing area of controversy in the management of ependymomas, specifically whether chemotherapy has any benefit when administered in addition to radiation for postsurgical therapy. Although platinum-based chemotherapy has shown efficacy in inducing
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tumor regressions, and in that context was examined in the ACNS0121 study for the ability to promote second-stage gross-total resections among children who initially had incomplete resections, the role of chemotherapy as a
compartment of postradiation treatment has been less clear. Previous studies have had insufficient patient numbers to
tackle this issue conclusively, particularly in view of the strong association between resection extent and outcome. The current study therefore retains the stratification approach used in ACNS0121, but then adds randomization for the use of postradiation chemotherapy in the
subset of patients who have had gross-total or near-total resections, either initially or after second-look surgery. Because previous studies have indicated poor results for patients with subtotal resections that could not be converted to a minimal residual disease state by chemotherapy and second-look surgery, this subset of patients will all receive postradiation chemotherapy and their results will be compared with those from ACNS0121 without this adjuvant.

Both the ACNS0121 and ACNS0831 studies incorporate central histological review and analysis of gene expression profiles, genome-wide assessment of gene copy number alterations, and examination of telomerase activity within the tumors to determine whether histological or genomic features can identify prognostically distinct subsets of tumors, which would provide a basis for refining therapeutic stratification in subsequent studies. The potential relevance of such data is provided by recent studies that indicate the presence of several molecularly distinct subsets of ependymomas. In a recently published report, information regarding these subgroup-specific genomic alterations was then used to unravel the cellular underpinnings of ependymoma development. This work involved matching the transcriptomes of human tumors to those of mouse neural stem cells derived from different regions of the nervous system to define critical molecular substrates of tumorigenesis. These studies generated a novel mouse model of one subset of human supratentorial ependymoma, defined the molecular signaling mechanisms that contribute to tumorigenesis, and suggested a molecularly targeted therapeutic approach that could be explored to treat such tumors. Pilot studies of molecularly based approaches for these tumors are being conducted by several cooperative groups and consortia, as well as the Collaborative Ependymoma Research Network.

Brain Tumors in Young Children

The management of malignant brain tumors in children younger than 3 to 5 years of age has historically incorporated somewhat different strategies than for comparable tumors in older children, because of the particular sensitivity of the young brain to the toxic sequelae of radiation therapy. As a way to delay or avoid the need for radiation therapy, early treatment protocols in the cooperative groups examined the use of a variety of regimens for intensive postsurgical chemotherapy. Although a subset of children responded well to such treatment and did not require radiotherapy, most manifested disease progression within 1 to 2 years of diagnosis, which was generally fatal. Several of these studies used similar chemotherapy regimens for multiple distinct histologies, and not unexpectedly, there were wide differences in efficacy as a function of tumor type.

More recent studies have adopted a variety of strategies in an effort to improve on these results. One general approach, which was initially examined in the “Head Start” series of studies, involved the use of extremely intense myeloablative “consolidation” chemotherapy, often following an initial course of induction therapy. Modifications of this theme, including the use of different combinations of agents, as well as the administration of a series of submaximally intense courses of myeloablative therapy rather than a single course, have been evaluated in subsequent trials. The latter approach, examined in CCG-99703, suggested an improvement in event-free survival in the overall population of infant tumors, as well as in the subset of children with medulloblastoma, although final results from this study are pending.

A second general approach has involved the use of conformal targeting of radiation to the tumor bed for patients with localized disease, specifically nonmetastic medulloblastomas and ependymomas. This approach has been examined in the cooperative group context for medulloblastoma in the P9934 study, in which conformal radiation was administered in conjunction with pre- and postradiation chemotherapy and was well tolerated, given that radiation-induced cognitive or functional decline was not apparent. Outcome results with this approach appear to be superior to those from the prior P9233 study that used comparable chemotherapy, but did not administer focal radiation. Conformal radiation has also been applied without chemotherapy for patients older than 1 year who underwent gross-total resection of an intracranial ependymoma and with preradiation chemotherapy in patients who underwent subtotal resection of such tumors in the ACNS0121 and 0831 studies, based on favorable results with conformal radiation in a large institutional study.

A third general approach that has been pursued in children with medulloblastoma has involved the use of high-dose systemic and intraventricular methotrexate, which has been examined in the Hirntumor-Studie SKK92 protocol of the German Pediatric Oncology Group. With 3 approaches, outcome results have been superior to those of prior cooperative group studies that have employed less intensive therapy. In addition to intensification of therapy and the adoption of histology-specific treatment approaches, a further advancement that has contributed to an overall improvement in infant brain tumor management has been the refinement of tumor classification, which has encompassed new insights in molecular stratification. Until recently, malignant infant “blue cell” tumors were treated on fairly homogeneous therapeutic protocols that considered them all as “embryonal tumors” or PNET variants. During the last decade, it has been recognized that this group includes a number of prognostically distinct subsets that warrant different management approaches. One group now recognized to be an entirely separate entity encompasses the atypical teratoid/rhabdoid tumors, which char-
characteristically have mutation or inactivation of the INI1 gene.\textsuperscript{16} The immunohistochemical test for INI1 expression, supplemented by mutation analysis, has now been incorporated in the screening armamentarium to facilitate rapid identification of these tumors, some of which arise in the setting of germ-line alterations in the INI1 gene.\textsuperscript{16,46}

The relevance of distinguishing these tumors from infant PNETs is that atypical teratoid/rhabdoid tumors have a substantially lower survival rate than PNETs with comparable therapy, often exhibiting rapid progression during and after initial chemotherapy.\textsuperscript{27} As a result, current treatment protocols for these tumors are evaluating alternative highly intensive chemotherapy approaches and, in some cases, examining the use of radiation therapy early in the treatment regimen. The latter approach is based on the observation that long-term survivors in previous studies have often received highly intensive multagent chemotherapy, early radiation therapy, or a combination of the two modalities.\textsuperscript{9,20,113}

Contemporary studies of the European and North American cooperative groups for infants with medulloblastomas and other PNETs are also adapting therapy based on clinical and molecular prognostic features. For example, the P9934 study specifically focused on non-metastatic medulloblastomas, which have a much more favorable prognosis than lesions with leptomeningeal spread at diagnosis.\textsuperscript{27} Analysis of the Hirntumor-Studie SKK series, the P9934 study, and other large cohorts of medulloblastomas have highlighted the fact that, even within the well-defined group of nonmetastatic infant medulloblastomas, there are distinctive molecular sub-sets that would likely benefit from individualized treatment approaches. In particular, tumors with desmoplasmatic histological features or extensive nodularity, which commonly exhibit PTCH1 mutations, appear to have a substantially better prognosis than tumors with classical histological features, and may warrant treatment approaches that minimize the risks of late sequelae.\textsuperscript{24} Conversely, the COG ACNS0334 study focuses on infants with metastatic medulloblastoma and supratentorial PNETs, which represent a particularly high-risk subset of tumors, and uses correspondingly more intensive chemotherapy to define whether further intensification of induction therapy with the use of methotrexate as per the Hirntumor-Studie SKK regimen is tolerable and can increase the percentage of children with complete tumor regression.

Conclusions

Advancements in imaging technology, surgical techniques, strategies for precisely targeted radiation delivery, and chemotherapy regimens have led to improvements in outcome for children with several types of brain tumors, such as medulloblastoma. In addition, refinements in risk-adapted treatment planning based on the clinical and molecular features of these tumors offer the potential for reducing the morbidity of therapy while maintaining high rates of disease control. An emerging area of study that has particular relevance to children with prognostically favorable brain tumor subgroups involves strategies for toxicity remediation that can reverse the effects of radiation on cognitive function and enhance recovery from surgical morbidities, such as the posterior fossa syndrome.\textsuperscript{86,116,120} Pilot studies of various pharmacological approaches are currently in progress, and evaluating the success of these interventions will rely heavily on the implementation of validated, widely applicable testing batteries to assess the effects of these therapies. The development of improved functional imaging approaches, such as diffusion tensor imaging,\textsuperscript{48} may enhance the safety of tumor resections by helping in the selection of surgical trajectories that spare critical structures. Such modalities may also have utility when coupled with increasingly precise techniques for radiotherapy treatment planning and delivery to reduce unintended toxicity to normal structures.\textsuperscript{63–65} Advanced metabolic imaging techniques, such as MR spectroscopy and PET, are also undergoing examination for their utility in predicting tumor histology preoperatively and assessing treatment response,\textsuperscript{49,78} although further work will be needed to determine whether these adjuncts can reliably supplement the information provided by conventional MR imaging techniques.

Despite the therapeutic advances that have been achieved for some groups of childhood brain tumors, the prognosis for children with other types of tumors, such as diffuse intrinsic brainstem glioma and other high-grade gliomas, remains suboptimal. The increasing implementation of molecular characterization approaches for these lesions, as well as the more favorable risk tumors, has already yielded some novel targets for molecularly directed therapy, and as more refined tools for interrogation of gene expression patterns and genomic alterations within tumors are applied, it is likely that additional targeted treatment options will be identified that offer the hope of improving patient outcome and, ultimately, tailoring therapy more precisely to the distinguishing features of a given tumor.

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References


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36. Horbinski C, Hamilton RL, Nikiforov Y, Pollack IF: Associa-
tion of molecular alterations, including BRAF, with biology and outcome in pilocytic astrocytomas. Acta Neuropathol
119:641–649, 2010
38. Hukin J, Epstein F, Lefton D, Allen J: Treatment of intracran-
ial epidermoidoma by surgery alone. Pediatr Neurosurg 29:
40–45, 1998
treated with carboplatin during craniospinal radiotherapy (CSRT) followed by cyclophosphamide (CPM) and vincris-
zolomide (TMZ) followed by temozolomide and lomustine (CCNU) in the treatment of children with high grade glioma
(HGG): results of COG ANS0423. Neuro Oncol 12:i112,
2010 (Abstract)
in newly diagnosed high-grade gliomas of childhood. Neuro
Oncol 10:569–576, 2008
ized trial of irradiation with and without adjuvant CCNU, VCR, and prednisone. A report of the Childrens Cancer Study
43. Jennings MT, Sposto R, Boyett JM, Vezina LG, Holmes E, Berger MS, et al: Pre-radiation chemotherapy in primary high-
risk brainstem tumors: phase II study II CCG-9941 of the Chil-
matches driver mutations and cell compartments to model ep-
46. Judkins AR, Burger PC, Hamilton RL, Kleinschmidt-DeMas-
biers T, Perry A, Pomeroy SL, et al: INI1 protein expression dis-
tinguishes atypical teratoid/rhabdoid tumor from choroid plex-
dren’s Cancer Group review of 119 cases. Pediatr Neurosurg
24:185–192, 1996
inhibitor of the vascular endothelial growth factor receptor
(VEGFR) in refractory pediatric central nervous system tu-
institutional experience of integrated modality therapy:
value of image guided radiation therapy. Int J Radiat Oncol
institutional experience of integrated modality therapy:
value of image guided radiation therapy. Int J Radiat Oncol
subtypes with distinct genetic profiles, pathway signatures
geradiotherapy of childhood low-grade glioma of the brain. Part I: Treatment modalities of radiation therapy. Strahlenther
Onkol 179:509–520, 2003
ngeradiotherapy of childhood low-grade glioma of the brain. Part II: Treatment-related late toxicity. Strahlenther Onkol
54. Kretschmar CS, Tarbell NJ, Barnes PD, Krischer JP, Burger
PC, Kun L: Pre-irradiation chemotherapy and hyperfraction-
ated radiation therapy of childhood primary central nervous
oma patients with carboplatin allergic reaction. Cancer 103:
2636–2642, 2005
57. Lam C, Bouffet E, Tabori U, Mabbott D, Taylor M, Bartels U: Rapamycin (sirolimus) in tuberous sclerosis associated pedi-
catral central nervous system tumors. Pediatr Blood Cancer
54:476–479, 2010
58. Li M, Lee KF, Lu Y, Clarke I, Shih D, Eberhart C, et al: Fre-
quent amplification of a chr19q13.41 microRNA polycistron in aggressive primary neuroectodermal brain tumors. Cancer
Cell 16:533–546, 2009
59. Lonser RR, Warren KE, Butman JA, Quezado Z, Robison RA,
Walbridge S, et al: Real-time image-guided direct convec-
tive perfusion of intrinsic brainstem lesions. Technical note.
60. MacDonald TJ, Aренson EB, Ater J, Spottos R, Bevan HE,
Brunner J, et al: Phase II study of high-dose chemotherapy be-
fore radiation in children with newly diagnosed high-grade astrocytoma: final analysis of Children’s Cancer Group Study
9933. Cancer 104:2862–2871, 2005
61. Massimino M, Sprefico F, Riva D, Biassoni V, Poggi G, Sole-
ro C, et al: A lower-dose, lower-toxicity cisplatin-etoposide regi
en for childhood progressive low-grade glioma. J Neuro-
ocnol 100:65–71, 2010
to progression after irradiation for localized ependymoma in
63. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA: Conformal radiotherapy after surgery for paediatric ependy-
64. Merchant TE, Mulhern RK, Krasin MJ, Kun LE, Williams T, Li C, et al: Preliminary results from a phase II trial of conformal
radiotherapy and evaluation of radiation-related CNS effects for pediatric patients with localised ependymoma. J Clin
Oncol 22:3156–3162, 2004
65. Merchant TE, Zhu Y, Thompson SJ, Sontag MR, Heideman RL,
Kun LE: Preliminary results from a Phase II trial of confor-
mal radiotherapy for pediatric patients with localised low-grade astrocytoma and ependymoma. Int J Radiat Oncol
Biophys 52:325–332, 2002
66. Milde T, Oehme I, Korshunov A, Kopp-Schneider A, Remke
M, Northcott P, et al: HDAC5 and HDAC9 in medulloblas-
toma: novel markers for risk stratification and role in tumor
67. Miralbell R, Fitzgerald TJ, Laurie F, Kessel S, Glicksman AS,
Friedman HS, et al: Radiotherapy in pediatric medulloblas-
toma: quality assessment of Pediatric Oncology Group Trial
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