Pediatric Oncology

Nalin Gupta
Anuradha Banerjee
Daphne A. Haas-Kogan *Editors*

Pediatric CNS Tumors

Third Edition

Springer

Pediatric Oncology

Nalin Gupta
Anuradha Banerjee
Daphne A. Haas-Kogan
Editors

Pediatric CNS Tumors

Third Edition

Springer

Editors
Nalin Gupta
San Francisco, CA
USA

Anuradha Banerjee
San Francisco, CA
USA

Daphne A. Haas-Kogan
Boston, MA
USA

ISSN 1613-5318 ISSN 2191-0812 (electronic)
Pediatric Oncology
ISBN 978-3-319-30787-9 ISBN 978-3-319-30789-3 (eBook)
DOI 10.1007/978-3-319-30789-3

Library of Congress Control Number: 2016943111

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

We dedicate this book to our children
Naya, Kavi
Shabnam, Hrittik, and Tizita
Yonatan, Shira, and Maetal

Preface

Pediatric brain tumors are a tremendous challenge for the treating physician. Their diverse biological behaviors, in the unique context of the developing nervous system, require flexible and tailored treatment plans. In the last 20 years, there has been an exponential increase in our understanding of the molecular and genetic basis of human malignancy. This is particularly true for pediatric tumors such as medulloblastoma, glioma, and neuroblastoma. The challenge for clinicians is using this array of new biologic information in a directed and rational manner to select effective and less toxic therapeutic agents.

As with previous editions, the goal of this textbook is to provide a current, biologically based perspective of the management of central nervous system tumors in children. Rather than present every tumor type in an encyclopedic manner, the common tumor types encountered in clinical practice are presented in the initial chapters. The epidemiology, pathological features, clinical presentation, diagnosis, and treatment are discussed for each tumor type. We have separated high- and low-grade glial tumors into separate chapters, mainly because the management and outcomes for these two broad groups of tumors are very different. Additional molecular and genomic data relevant to several tumor types have been added in this edition. In the final chapters, many of the diagnostic and treatment modalities common to all tumors are discussed with an emphasis on emerging and experimental techniques.

It is recognized that a variety of treatment strategies is utilized by many different practitioners and institutions. For the most part, the general management principles used by the authors, most of whom are at the University of California, San Francisco, are presented in the context of standard therapy. Although this approach may underemphasize other equally valid approaches, we believe that the reader will benefit from a coherent approach to the management of childhood tumors.

The editors acknowledge the contribution of the authors, our colleagues at the University of California, San Francisco, the editorial staff at Springer, and our many mentors in the preparation and assembly of this book.

San Francisco, CA, USA — Nalin Gupta
San Francisco, CA, USA — Anuradha Banerjee
Boston, MA, USA — Daphne A. Haas-Kogan

Contents

Contributors

Mekhail Anwar Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Kurtis I. Auguste Departments of Neurological Surgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA

Anuradha Banerjee Division of Hematology/Oncology, Departments of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

A. James Barkovich Departments of Radiology and Biomedical Imaging, Neurology, Pediatrics & Neurosurgery, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Mitchel S. Berger Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

Steve Braunstein Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Jonathan D. Breshears Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

Sean O. Bryant Departments of Radiology, Diversified Radiology of Colorado, PC, Lakewood, CO, USA

Soonmee Cha Radiology & Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

Edward F. Chang Departments of Neurological Surgery & Physiology, University of California San Francisco, San Francisco, CA, USA

Eric Chang Department of Radiation Oncology, University of California Los Angeles, Los Angeles, CA, USA

Jennifer S. Chang Department of Radiation Oncology, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Dario J. Englot Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

Craig Forester Division of Hematology/Oncology, Departments of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Robert Goldsby Division of Hematology/Oncology, Departments of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Nalin Gupta Division of Pediatric Neurosurgery, Departments of Neurological Surgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Daphne A. Haas-Kogan Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute & Boston Children's Hospital, Boston, MA, USA

Biljana Horn Blood and Marrow Transplant Program, Department of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Cassie Kline Division of Hematology/Oncology, Departments of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Tiffany F. Lin Division of Hematology/Oncology, Department of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Robert H. Lustig Department of Pediatrics & Institute for Health Policy Studies, University of California, San Francisco, CA, USA

UCSF Benioff Children's Hospital San Francisco, San Francisco, CA, USA

Mark D. Mamlouk Division of Neuroradiology, Kaiser Permanente Santa Clara, Santa Clara, CA, USA

Sean M. McBride Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Sabine Mueller Departments of Neurology, Neurosurgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Theodore Nicolaides Division of Hematology/Oncology, Departments of Pediatrics and Neurological Surgery, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

Lauren Ostling Department of Neurological Surgery, UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA

Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

Sunanda Pejavar Department of Radiation Oncology, Sharp Memorial Hospital, San Diego, CA, USA

Alexei Polishchuk Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Michael Prados Departments of Neurological Surgery & Pediatrics, University of California San Francisco, San Francisco, CA, USA

Corey Raffel Department of Neurological Surgery, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA

David Raleigh Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Peter P. Sun Department of Neurological Surgery, UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA

Low-Grade Gliomas

1

Anuradha Banerjee and Theodore Nicolaides

Contents

A. Banerjee, MD (✉)
Division of Hematology/Oncology, Departments of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th St, 4th Floor, Box 0434, San Francisco, CA 94143, USA
e-mail: anu.banerjee@ucsf.edu

T. Nicolaides, MD
Division of Hematology/Oncology, Departments of Pediatrics and Neurological Surgery, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th St, 4th Floor, Box 0434, San Francisco, CA 94143, USA
e-mail: theodore.nicolaides@ucsf.edu

1.1 Introduction

Astrocytomas are the most common subgroup of central nervous system (CNS) tumors in children. The most frequent histological types are pilocytic and fibrillary astrocytomas, which are considered low-grade astrocytomas. A variety of other, less common glial tumors are also seen in children, including pleomorphic xanthoastrocytoma (PXA), subependymal giant cell astrocytoma, high-grade gliomas, ganglioglioma and desmoplastic infantile ganglioglioma, astroblastoma, ependymoma, and oligodendroglioma. This chapter focuses on low-grade astrocytomas with an emphasis on infiltrating astrocytoma, cerebellar astrocytoma, optic pathway glioma, and oligodendroglioma.

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_1

1.2 Astrocytomas

1.2.1 Epidemiology

Supratentorial tumors account for approximately 40–60 % of all pediatric brain tumors and are almost twice as common in infants as in older children (Farwell et al. 1977; Dohrmann et al. 1985; Dropcho et al. 1987; Ostrom et al. 2015). The majority of supratentorial tumors are gliomas (astrocytoma, oligodendroglioma, and ependymoma) with the most common subtype, low-grade glioma, accounting for half of these. In contrast to the distribution of gliomas in adults, malignant gliomas account for only 20 % of all childhood supratentorial gliomas.

For the majority of gliomas, the etiology remains unknown. Children with familial cancer predisposition syndromes have an increased risk of developing both low- and high-grade gliomas. Environmental factors, such as parental smoking and residential proximity to electromagnetic field sources, have not been associated with pediatric brain tumors, although parental occupation in the chemical/electrical industry might be associated with an increased risk of astroglial tumors in the offspring (Gold et al. 1993; Rickert 1998). Conversely, prenatal vitamin supplementation in mothers may confer a slight protective effect (Preston-Martin et al. 1998; Vienneau et al. 2015). To date, the only environmental agent clearly implicated in developing glioma is exposure to ionizing radiation, which results in a 2.6-fold increased risk of developing this cancer (Ron et al. 1988). Gliomas are described as a second malignant neoplasm following cranial radiation for medulloblastoma and acute lymphocytic leukemia (Steinbok and Mutat 1999; Tsui et al. 2015). Case reports have implied that radiation-induced mutagen sensitivity of lymphocytes may be associated with an increased risk for glioma (Bondy et al. 2001). Inherited predispositions to glioma may also augment the risk of radiation-associated glioma (Kyritsis et al. 2010).

1.2.1.1 Inherited Predispositions to Glioma

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is associated with an increased risk of intracranial tumors, and approximately 15–20 % of patients with NF1 present with low-grade intracranial tumors. Low-grade gliomas arise in a variety of locations in NF1 patients, but are most commonly located in the optic nerve, optic chiasm, hypothalamus, and/or brainstem. They may also occur within the cerebral hemisphere and cerebellum (Listernick et al. 1999).

The *NF1* gene is located on chromosome 17q and encodes a GTPase-activating protein (GAP), termed neurofibromin (NF1), involved in regulating the ras-p21 signaling pathway. Mutations in the *NF1* gene produce heterogeneous signs and symptoms of the disease including dermatologic manifestations, neurofibromas, ocular and bone abnormalities, and optic pathway gliomas. Loss of neurofibromin function due to bi-allelic loss of *NF1* results in constitutive activation of the Ras/Map kinase signaling pathway and drives tumorigenesis in NF1-associated low-grade glioma (Anderson and Gutmann 2015). This mechanism raises the possibility of therapeutic biologic targeting of components of this signaling pathway with pharmacologic agents. Neurofibromatosis may arise from sporadic mutations in the *NF1* gene or through germline transmission of an established mutation (Gutmann et al. 2000). Proteomic analysis of *NF1*-deficient human and mouse brain tumors has revealed elevated levels of mammalian target of rapamycin (mTOR) activity (discussed in Sect. 1.2.5.4) and its downstream targets associated with protein translation and growth (Dasgupta et al. 2005). Neurofibromin is a GTPase that negatively regulates the G-coupled protein, Ras, whose downstream targets include Akt and mTOR (Dasgupta et al. 2005; Sabatini 2006). Therefore, mTOR may also be an attractive molecular target worth further examination. However, NF1-associated CNS tumors, such as pilocytic astrocytomas, rarely demonstrate

alterations in other known oncogenic genes such as *p53*, *EGFR*, *PDGFR*, and *p21*, and these tumors are considered to be benign (Gutmann et al. 2000; Vinchon et al. 2000).

Tuberous Sclerosis

Tuberous sclerosis is an inherited disorder of the *TSC1* and *TSC2* genes that results in a clinical phenotype of widespread hamartomas that can involve several organ systems. The TSC1 and TSC2 genes encode a protein complex that negatively regulates mTOR, an important regulator of cell proliferation and survival. Patients with tuberous sclerosis have abnormal regulation of mTOR signaling, which can result in the development of subependymal giant cell astrocytoma (SEGA) in 10 % of patients with tuberous sclerosis (Curatolo et al. 2008). SEGA is a low-grade, mixed glioneuronal neoplasm that can result in obstruction of CSF flow and hydrocephalus. Treatment is typically surgical, but recent evidence demonstrates that SEGA in the setting of tuberous sclerosis is sensitive to medical treatment with pharmacologic inhibitors of mTOR (Ouyang et al. 2014; Franz et al. 2006, 2014).

1.2.1.2 World Health Organization Grading

The recent World Health Organization (WHO) classification of CNS tumors organizes astrocytomas into four grades (I–IV) in addition to a histological classification system, based on morphologic features. Low-grade histologies are defined as grade I or II. Grades I and II lesions can be of varying histologies, but the most common WHO grade 1 histology is pilocytic astrocytoma, while diffuse astrocytomas are the most commonly observed WHO grade II histology in pediatric patients. Cerebellar astrocytomas, grades I and II, comprise approximately 70–80 % and 15 % of childhood cases, respectively (Steinbok and Mutat 1999). Experimental evidence suggests that grade I and II cerebellar astrocytomas develop from different precursor cells (Li et al. 2001; Sievert and Fisher 2009). Although the use of the WHO classification system remains in widespread use, the emerging importance of characteristic genetic changes has resulted in proposals to update the classification system to include these findings (Louis et al. 2014).

1.2.2 Pathology

1.2.2.1 Grades I and II Astrocytomas

Pilocytic astrocytoma (PA) is the most common low-grade histology in the first two decades of life. PAs can be found throughout the neuraxis (optic pathway, hypothalamus, cerebral hemisphere, brainstem, and spinal cord), although 80 % are found in the cerebellum (Dirven et al. 1997). PA has variable radiographic appearance; tumors can be well-circumscribed without infiltration of the surrounding brain, but when it occurs as an optic pathway glioma, it can have a more, diffusely infiltrative appearance. These gliomas can infiltrate widely, even extending into the posterior visual cortex. This subtype is discussed in greater detail in Sect. 1.4.

Histologically, PAs exhibit a biphasic pattern of compact, bipolar, highly fibrillated astrocytes, accompanied by Rosenthal fibers alternating with loose-textured microcystic regions of eosinophilic granular astrocytes (Fig. 1.1). Unlike malignant astrocytomas, pleomorphism, mitotic figures, hypercellularity, endothelial proliferation, and necrosis may be present, but this does not indicate malignancy or poor prognosis (Steinbok and Mutat 1999). Local leptomeningeal invasion is apparent in half of all cases and has no prognostic significance (Burger et al. 2000).

Other grade I astrocytoma, glioma, and glioneuronal histologies that are seen in pediatric patients include subependymal giant cell astrocytoma, ganglioglioma, dysembryoplastic infantile ganglioglioma, and dysembryoplastic neuroepithelial tumor (Sievert and Fisher 2009).

Grade II astrocytomas are distinct from pilocytic tumors because of their location, degree of infiltration, and presence of genetic aberrations (Kleihues et al. 1993; Louis et al. 2007). Grossly,

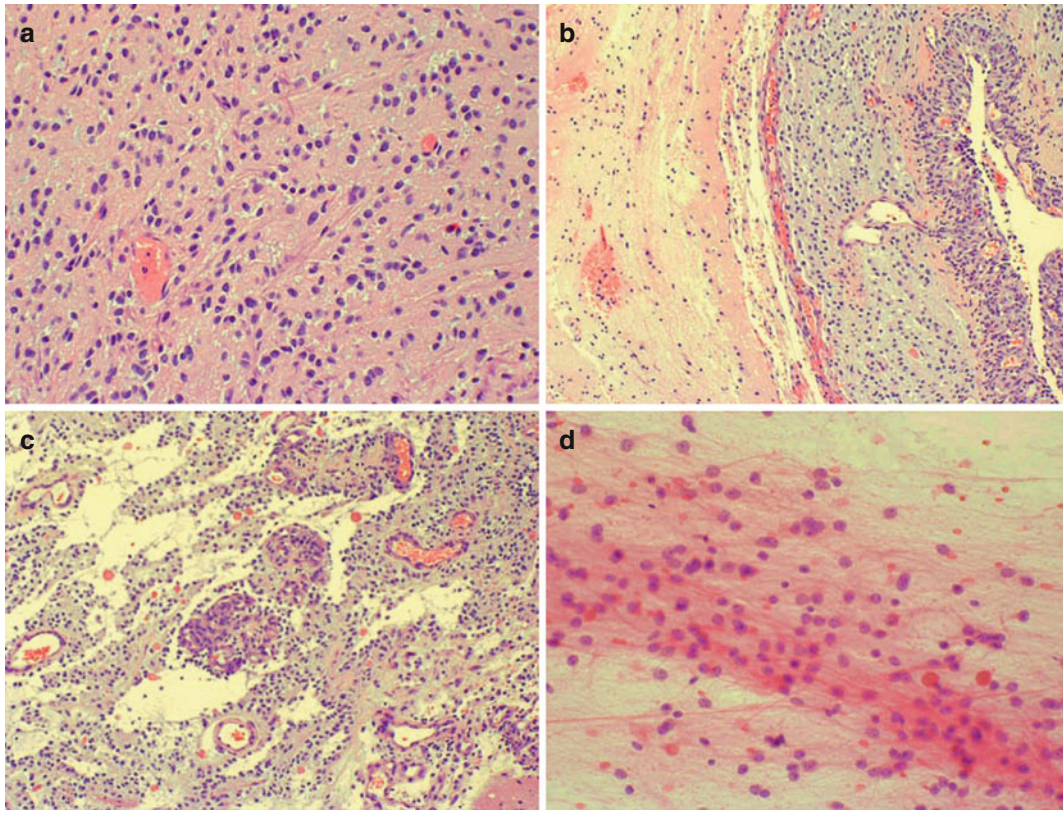

Fig. 1.1 Histopathological features of pilocytic astrocytoma. (**a**) Field of tumor cells demonstrating increased cellularity, mild nuclear atypia, and lack of mitoses. (**b**) Tumor edge with gliotic border (*left* of image) and neovascularization. (**c**) Biphasic pattern of compact, fibrillated astrocytes and loosely textured microcysts with a focus of endothelial proliferation. (**d**) Squash preparations demonstrating thin glial processes ("pili") extending from bipolar tumor cells

grade II astrocytomas are ill-defined lesions that tend to enlarge and distort involved structures. Destruction of brain tissue, however, is more characteristic of higher-grade tumors. Microscopic examination of resected grade II tumor specimens invariably shows diffuse infiltration of the surrounding gray and white matter. Low-power microscopy may show a subtle increase in overall cellularity and disruption of the orderly pattern of glial cells along myelinated fibers. Higher-power examination reveals neoplastic astrocytes with indistinct cytoplasmic features. The diagnosis is often based on the appearance of the nuclei, which are characteristically elongated. Nuclear atypia is minimal in low-grade astrocytomas and mitotic activity is infrequent.

1.2.2.2 Other Low-Grade Subtypes

Low-grade astrocytomas can be further subdivided on the basis of their microscopic appearance. The prognostic value of these subgroups is not entirely clear. Fibrillary astrocytoma is the most common grade II astrocytoma subtype and demonstrates a uniform, compact arrangement of fibrillary astrocytes with varying degrees of cellular atypia on a background of loosely structured tumor matrix (Steinbok and Mutat 1999). Gemistocytic astrocytomas are composed of neoplastic astrocytes with abundant eosinophilic, glial fibrillary acidic protein (GFAP)-positive cytoplasm with nuclei displaced to the periphery (Kaye and Walker 2000). The WHO classification identifies the gemistocytic subtype as low-grade astrocytoma, as long as cellularity and

nuclear atypia remain mild (Louis et al. 2007). The pleomorphic xanthoastrocytoma (PXA), is a rare, GFAP-positive, astrocytic tumor typically occurring in the cerebral hemispheres of children and young adults (Kepes et al. 1973).

Histologically, PXA is characterized by large, neoplastic astrocytes with substantial nuclear pleomorphism and very atypical nuclei. The borders are often infiltrative, and tumor cells may display clustering in an epithelioid fashion (Lindboe et al. 1992; Powell et al. 1996). Desmoplastic infantile astrocytoma (DIA) is a rare tumor occurring in infants 18 months or younger. These tumors are usually large, cystic, supratentorial in location, and have a dural attachment. Histologically, they are loose to dense collagenous stroma with wavy fascicles of spindle cells (Taratuto et al. 1984). The rarest subtype is the protoplasmic astrocytoma, which has prominent microcysts, mucoid degeneration, and a paucity of GFAP positivity (Kaye and Walker 2000). Some consider this a histological pattern of fibrillary astrocytoma, rather than a true variant. Diffuse cerebellar astrocytomas resemble low-grade astrocytomas of the cerebral hemispheres with poorly circumscribed borders and invasion of the surrounding parenchyma. These tumors generally occur in older children, and young adults can undergo malignant transformation (Burger et al. 2000). Regardless of subtype, all low-grade astrocytomas have low cellularity, limited nuclear atypia, and rare mitotic activity. Low-grade astrocytomas with single mitotic figures have prognoses similar to other low-grade tumors (Giannini et al. 1999). A single mitotic figure suggests that the presence of isolated mitoses may not be sufficient to transform an otherwise low-grade astrocytoma to a higher-grade lesion.

1.2.2.3 Biology

Astrocytoma cytogenetic abnormalities occur less frequently and with different patterns in children than in adults (Cheng et al. 1999). In adult low-grade astrocytomas, mutations in the *p53* tumor suppressor gene are common and may herald an early event in malignant progression (Watanabe et al. 1998; Kosel et al. 2001). In contrast, *p53* mutations are not frequently found in the pediatric population (Litofsky et al. 1994; Felix et al. 1995; Ishii et al. 1998). The majority of pediatric pilocytic astrocytomas demonstrate normal cytogenetic findings (Griffin et al. 1988; Karnes et al. 1992; Bigner et al. 1997). In a recent study of 58 pediatric patients, 70% of grade I astrocytomas had a normal cytogenetic profile (Roberts et al. 2001). In another study of 109 pediatric brain tumors, which included 33 low-grade astrocytomas, low-grade astrocytomas mostly showed changes in chromosome copy number (Neumann et al. 1993). Reported cytogenetic abnormalities include gains on chromosomes 1, 7, and 8 and losses of 17p and 17q (White et al. 1995; Wernicke et al. 1997; Zattara-Cannoni et al. 1998).

High-density single-nucleotide polymorphism-based genotyping and comparative genome hybridization (CGH) have revealed duplication or gain in chromosomes 5 and 7, with particular amplification of 7q34 in PA (Pfister et al. 2008; Sievert et al. 2008). Using CGH, *BRAF* was duplicated in 28 of 53 JPAs. In vitro inhibition of BRAF signaling, directly by lentivirus-mediated transduction of BRAF-specific shRNAs or indirectly by pharmacological inhibition of MEK1/2, the immediate downstream target of BRAF, caused G_2/M cell-cycle arrest in astrocytic cell lines (Pfister et al. 2008). The amplification of 7q34 represents a duplication of the *BRAF* gene and fusion with the *KIAA1549* gene. This *BRAF-KIAA1549* fusion results in constitutively activated *BRAF* signaling, with subsequent downstream effects on cell proliferation and survival via *MEK* and *ERK*. The *BRAF-KIAA1549* fusion transcript is detected in the majority of cerebellar pilocytic astrocytomas and less frequently in pilocytic astrocytoma in other locations as well as other low-grade glioma variants. Alternative Ras/Map kinase activating genetic changes have also been described in both pilocytic astrocytoma and other pediatric low-grade glioma histologies. The most common of these is the $BRAF^{V600E}$ mutation, described in 10% of pediatric gliomas, as well as less commonly observed alternate fusion genes involving RAF (Chen and Guttman 2014; Gajjar et al. 2015).

Thus, aberrant activation of the mitogen-activated protein kinase (MAPK) pathway, due to gene duplication or activating mutation of BRAF, is a common event in the tumorigenesis of pediatric low-grade astrocytomas and provides an opportunity for biologically targeted therapies with *BRAF* and/or *MEK* inhibitors.

Constitutive activation of the mTOR pathway is observed in pediatric low-grade glioma, through different mechanisms, in patients who develop either spontaneous or NF1-deficient PA (Dasgupta et al. 2005; Sharma et al. 2005). In tumors with Ras pathway-activating genetic lesions, mTOR, a downstream effector of the Ras pathway, is likely activated by upstream Ras activation (Chen and Guttman 2014). In patients with tuberous sclerosis-associated SEGA, mTOR is shown to be constitutively activated and responsive to treatment with mTOR inhibitors in the clinical setting (Ouyang et al. 2014; Franz et al. 2006, 2014). The identification of these markers may not only direct us to novel molecular targets for drug therapy, but may also allow rapid pathologic characterization and classification of these tumor types.

1.2.3 Clinical Features

Symptoms and signs caused by low-grade gliomas depend on the anatomic location, biological nature of the tumor, and age of the patient. These signs and symptoms may be nonspecific, such as those associated with increased intracranial pressure (ICP), or focal, related to tumor location. Nonspecific symptoms include headache, nausea, and vomiting, subtle developmental delay, and behavioral changes. Some of the behavioral changes associated with slow-growing tumors in children include alterations in personality, irritability, altered psychomotor function, apathy, and declining school performance. It is not uncommon for symptoms to have been present for months or years prior to diagnosis. In infants with open cranial sutures, a tumor may reach a massive size with a gradual increase in head circumference without signs of increased ICP or any other symptoms. Focal symptoms depend upon the location of the tumor and may include hemiparesis, monoparesis, hemisensory loss, dysphasia, aphasia, and impairment of recent memory. Tumors involving the optic pathways can present with quadrantanopia, homonymous hemianopsia, or, in cases with bilateral occipital lobe involvement, cortical blindness. Hemorrhage rarely occurs in low-grade tumors, although one report noted the presence of hemorrhage in 8 % of patients with pilocytic astrocytoma (White et al. 2008).

Epilepsy is a major presenting feature of pediatric patients with brain tumors, and seizures occur in more than 50 % of children with hemispheric tumors (Keles and Berger 2000). The majority of patients with tumor-associated epilepsy harbor slow-growing, indolent neoplasms such as low-grade gliomas. Other relatively slow-growing tumors, for example, astrocytomas, gangliogliomas, and oligodendrogliomas, may also present with a history of generalized seizures. Rapidly growing lesions are more likely to produce complex partial motor or sensory seizures, although generalized tonic-clonic seizures are also common.

1.2.4 Diagnostic Imaging

Magnetic resonance imaging (MRI) and computed tomography (CT) are essential tools in the diagnosis and treatment of brain tumors. Although CT is more commonly available, MRI provides higher sensitivity in differentiating tumor tissue from normal brain, allowing more detailed anatomic characterization of the lesion, and should be obtained in all children with a diagnosis of a brain tumor. A complete series should include the following sequences: T1-weighted axial and coronal (both before and after gadolinium), T2-weighted axial and coronal, and fluid-attenuated inversion recovery (FLAIR). In addition, sagittal plane sequences are helpful in defining anatomy of suprasellar and midline tumors. Other sequences such as fat suppression and MR angiography may also be

required in specific situations. Newer techniques, such as magnetic resonance spectroscopy (MRS), functional MRI, and perfusion measurements, offer the potential of obtaining biochemical and functional information noninvasively (see Chap. 13). It is possible that in the future a pathologic diagnosis may be reached with substantial confidence without the need for open biopsy.

Although low-grade gliomas may produce considerable mass effect upon surrounding structures, neurologic deficits may be minimal. With the exception of pilocytic astrocytoma, low-grade astrocytomas are usually nonenhancing, iso- or hypodense masses on CT scan. Calcification may be detected in 15–20 % of cases, and mild to moderate inhomogeneous contrast enhancement can be seen in up to 40 % of all cases (Lote et al. 1998; Bauman et al. 1999; Roberts et al. 2000; Scott et al. 2002). Some tumors, characteristically PAs, may have cystic changes. On MRI, T1-weighted images show an iso- to hypointense nonenhancing mass that is hyperintense on T2-weighted images. Non-PA low-grade astrocytomas have minimal to no contrast enhancement following gadolinium administration (Fig. 1.2b, d). For this reason, the tumor boundary is difficult to determine with any T1-weighted sequence. FLAIR sequence is very sensitive for defining the extent of tumor infiltration (Fig. 1.2a, c).

Because many low-grade gliomas have a risk of progression or relapse after initial therapy, surveillance MR imaging over time is recommended typically at an interval of 3–6 months, depending on the degree of clinical concern for risk of relapse. In general, for grade II astrocytoma, the two most important features are an increase in the volume of T2-weighted FLAIR signal abnormality and/or new enhancement on post-gadolinium T1-weighted images. These features are also observed in patients who have received radiation treatment, and differentiating tumor recurrence from radiation necrosis continues to present a challenge. Additional information may be obtained from MR spectroscopy and positron emission tomography (PET) scans, but at times, the only method to confirm tumor recurrence is to obtain a surgical biopsy.

1.2.5 Treatment

1.2.5.1 Surgical Indications

A surgical procedure is usually the initial step in the management of low-grade gliomas. The primary objective is to obtain tissue for pathologic diagnosis. A relative exception would be for tumors in locations not amenable to surgery, such as optic pathway/chiasmatic gliomas, although a stereotactic biopsy can safely obtain tissue for histopathologic analysis. The secondary objective is to perform as extensive a resection as possible with acceptable neurologic outcome for the patient. The two variables that must be considered are the extent and timing of resection. Extent of resection is the most important prognostic factor for 5-year overall and progression-free survival (PFS). Patients who have partial resections or residual disease often recur or experience tumor progression (Shaw and Wisoff 2003; Kim et al. 2014). The feasibility of an open surgical approach depends upon several factors. The most important is the exact location of the tumor. Deep lesions within the basal ganglia, thalamus, motor cortex, or brainstem are usually not amenable to open surgical resection, while tumors in other locations can be accessed through various standard approaches. Other factors that modify the decision to attempt surgical resection are the patient's clinical condition, age, associated hydrocephalus, and the surgeon's assessment of risk of neurologic sequelae.

Timing of resection is a controversial topic, and few conclusive studies have been published to date. There are reports questioning the value of immediate treatment when an imaging study suggests a low-grade glioma, as no definitive evidence exists which demonstrates improvement in long-term survival following early intervention (Cairncross and Laperriere 1989; Recht et al. 1992).

In addition to reducing tumor burden and providing tissue diagnosis, resection permits management of increased ICP, prevention of irreversible neurologic deficits, decompression of adjacent brain structures, and control of seizures (Berger et al. 1991, 1993; Haglund et al.

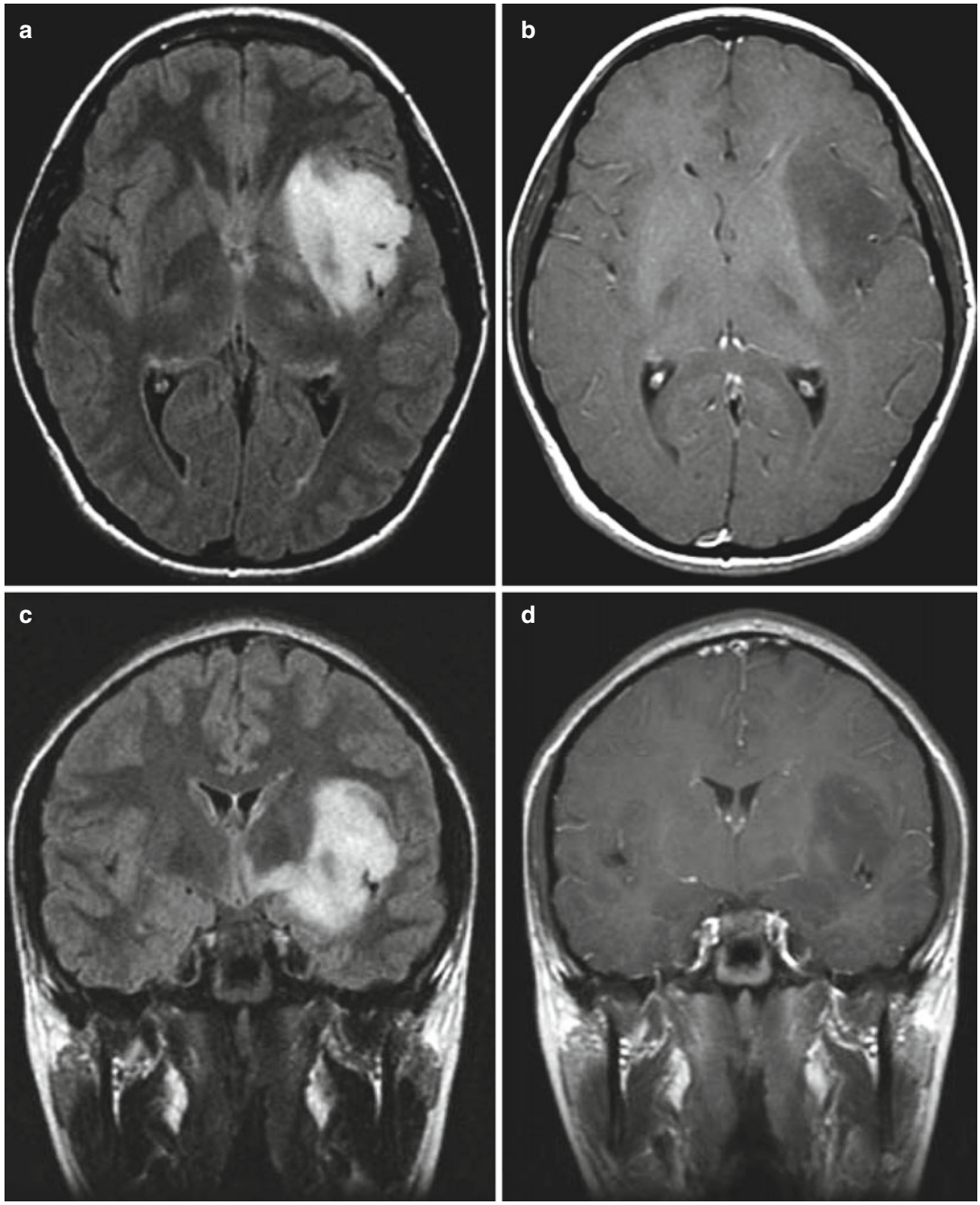

Fig. 1.2 MR images from a teenage girl with a low-grade astrocytoma of the insula who presented with a single seizure. Her neurologic exam was normal. (**a**, **c**) Axial and coronal FLAIR images showing the extent of involvement. Note the tumor infiltration medially under the lentiform nucleus toward the hypothalamus. (**b**, **d**) Corresponding T1-weighted post-gadolinium images showing no appreciable enhancement

1992; Keles and Berger 2000). For patients with discrete JPAs (WHO grade I), gross total resection (GTR), when possible, is curative. Contemporary neurosurgical methods, including ultrasonography, functional mapping, frameless navigational resection devices, and intraoperative imaging techniques enable more extensive resections with less morbidity.

1.2.5.2 Chemotherapy

Although indolent and slow growing, overall 5-year survival rates for patients with diencephalic and hemispheric tumors who have received radiation therapy vary, ranging from 40 % to 70 %. Additionally, the morbidity associated with radiation treatment can be substantial, prompting numerous investigators to explore chemotherapy as an alternative adjuvant treatment to control tumor progression. Chemotherapy effectively provides disease control in many optic pathway tumors (see below) and may improve prognosis for vision maintenance. Studies of early combination chemotherapy regimens with vincristine and actinomycin D, used in children less than 6 years of age, reported 62 % PFS without further therapy; those who did progress did so at a median of 3 years from the start of therapy. The median IQ in this group was 103 (Packer et al. 1988). It is important to recognize that prolonged periods of stable tumor size and clinical symptoms are considered a treatment "response" by many investigators. Alternative combination chemotherapy regimens have also resulted in tumor response in pilot studies. Other drug combinations that have been reported include lomustine and vincristine; 6-thioguanine, procarbazine, lomustine, and vincristine (TPCV); and combinations using cisplatin (Edwards et al. 1980; Gajjar et al. 1993). The combination regimen of carboplatin and vincristine (CV) has been associated with objective response rates (stable disease as well as tumor shrinkage) in the range of 60–70 % (Packer et al. 1997). The combination of TPCV has also been associated with a substantial response rate in a small cohort of patients (Prados et al. 1997).

A large-scale, randomized, phase III, multi-institutional clinical trial conducted by the Children's Oncology Group (COG) examined the relative effectiveness of CV versus TPCV. Four hundred and one children less than 10 years old were enrolled in COG A9952. Of these 401 eligible children, 137 were randomized to receive CV, 137 were randomized to receive TPCV, and 127 patients with NF1 and radiographically verified progressive optic pathway glioma were nonrandomly assigned to the CV arm because of the heightened leukemogenic potential of TPCV in this patient population. Tumor response rates, defined as a decrease in both enhancement and T2 signal on MRI at the end of protocol therapy, were 57 % for CV, non-NF1; 61 % for CV, NF1; and 58 % for TPCV. The 5-year overall survival rates in CV-treated, non-NF1 versus NF1 patients were 86 % and 98 %, respectively. Similarly, 5-year event-free survival (EFS) was improved in NF1 versus non-NF1 patients (69 % vs. 42 %, respectively) and no difference in EFS was found when comparing CV versus TPCV. The median time to progression for CV versus TPCV was 3.2 versus 4.9 years (Ater et al. 2012). A regimen of single-agent vinblastine demonstrated a 3- and 5-year EFS and OS of 43.2 % and 93.2 % (Bouffet et al. 2012). A phase 2 study of bevacizumab and irinotecan in patients with low-grade glioma demonstrated a 2-year PFS of 47.8 % (Gururangan et al. 2014). These findings demonstrate that both therapies can be used successfully to treat low-grade glioma with good overall EFS, thus allowing a delay in radiotherapy.

Although chemotherapy is documented to be active in low-grade glioma, conventional regimens are toxic and provide only transient tumor control. Investigators are exploring the role of mono- and combinatorial therapy to extend treatment response. The HIT-LGG 96 study examined the role of second-line chemotherapy in patients who had disease progression in the chemotherapy arm (94 patients). Of those 94 patients, 27 went on to receive a second round of chemotherapy consisting of vincristine/carboplatin and/or cyclophosphamide regimen, vinblastine alone, temozolomide alone, or other regimen. The median age in this group was 11.8 months. Best achievable response was tumor reduction in 8 patients and stable disease in 13 patients. Thirteen patients recurred 15.7 months after starting second-line chemotherapy. The overall 3-year PFS in the second chemotherapy group was 34 % (Kordes et al. 2008).

A phase II study assessed the efficacy of temozolomide in children with progressive optic pathway glioma and pilocytic astrocytoma. Thirty patients were treated with oral temozolomide for 5 days every 4 weeks. The 2-year PFS and overall

survival rates were 49% and 96%, respectively, with manageable toxicity (Gururangan et al. 2007). These findings illustrate the potential to further delay radiotherapy in this pediatric population by using chemotherapy.

1.2.5.3 Radiation Therapy

As discussed above, low-grade astrocytoma may be curable with GTR. For those patients with unresectable or incompletely resected disease, the use of radiation therapy is controversial. There is some evidence to suggest that while radiation therapy may prolong PFS, it has little impact on overall survival (Pollack et al. 1995). Its use is largely limited to patients with progressive or recurrent disease or in the setting of a highly symptomatic patient who requires tumor stabilization to avert the progression of symptoms. A large-scale multiinstitutional trial, SIOP-LGG 2004, sought to address the role of observation, adjuvant chemotherapy, and radiotherapy in order to assess their optimal therapeutic effect and toxicity on pediatric low-grade glioma after total or subtotal surgical resection. A total of 1,031 patients were enrolled and were nonrandomly assigned to one of three arms in an age-dependent manner. Six hundred sixty-eight patients were assigned to observation only, 216 to vincristine with carboplatin chemotherapy, and 147 to radiation/brachytherapy. Ten-year OS and PFS were 94% and 47%; three quarters of the chemotherapy-treated patients remain unirradiated with 9.3 years of median follow-up (Gnekow et al. 2012). In an 89 patient cohort of pediatric patients treated with conformal radiation for low-grade glioma at St. Jude's Children's Research Hospital, PFS and OS at 10 years were 75.3% and 95.9% (Merchant et al. 2009a, b). Eight-year PFS and OS in a cohort of LGG patients treated with intensity-modulated radiation therapy were 78.2% and 93.7%, with failures largely occurring in the tumor bed (Paulino et al. 2013). For the most part, these studies demonstrate the efficacy of radiation therapy in the treatment of pediatric low-grade gliomas. However, due to concerns about radiation-related side effects, an effort is generally made to delay or forgo radiation in young children.

Because of neurocognitive toxicity associated with radiotherapy, minimizing the dose and radiation fields using stereotactic radiosurgery or proton therapy may provide an effective alternative to standard conformal radiotherapy (Hadjipanayis et al. 2003; Marcus et al. 2005). One prospective trial using stereotactic radiosurgery demonstrated effective control of small, pediatric LGGs that had progressed either after surgery or chemotherapy. The 8-year PFS and overall survival rates using stereotactic radiosurgery in these patients were 65% and 82%, respectively (Marcus et al. 2005). Clinical outcomes using proton therapy in 32 pediatric patients treated for primary low-grade gliomas were comparable to standard radiotherapy. Neurocognitive exams posttreatment appeared stable, with minimal negative changes in working memory and processing speed, except in a subgroup of patients <7 years, who experienced significant declines in full scale IQ, as well as in patients who had significant dose to the left temporal lobe/hippocampus (Greenberger et al. 2014). Proton therapy appears to be safe and equally effective as IMRT or conformal therapy. Alternatively, the use of microsurgery combined with interstitial radiosurgical I-125 seed implantation (IRS) has demonstrated promising results. Nineteen children with low-grade glioma received IRS and/or microsurgery to the tumor site. With a median follow-up of 26 months, 5 tumors had a complete response, 11 tumors had reduction in size, two children developed radionecrosis requiring resection, and one child had progression and died (Peraud et al. 2008). In a cohort of pediatric patients treated with stereotactic brachytherapy, 10-year PFS and OS were 82% and 93%, respectively, again similar to other radiation strategies (Ruge et al. 2011). While this therapy appears feasible, long-term neurocognitive toxicity needs to be assessed.

1.2.5.4 Targeted Molecular Therapy

Overall prognosis and clinical outcome for patients with glioma are associated with tumor grade. Genes associated with glial cell grade and tumorigenesis continue to be identified.

Understanding the pattern of genes activated in glioma will likely provide insight into the natural history and potential clinical course of these tumors and whether they will respond to standard chemotherapeutic regimens or novel molecular targeted therapies. For this reason, the PI3K/Akt/mTOR pathway has been studied in great detail as it plays a large role in the tumorigenesis of many cancers including glial tumors (Sabatini 2006; Guertin and Sabatini 2007).

Two complexes of mTOR exist: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). The tumor suppressor genes TSC1/hamartin and TSC2/tuberin are important for the regulation of mTOR activity. Germline mutations of TSC lead to tuberous sclerosis and predisposition to a variety of benign tumors including hamartomas and lymphangioleiomyomas. Many upstream growth factor receptors and PI3K signal through the downstream mediator, mTOR. These observations make mTOR an attractive target for therapeutic intervention (Houghton and Huang 2004).

Further characterization of mTOR's signaling pathway may lead to better application of mTOR inhibitor therapy. Franz et al. used rapamycin, an mTOR inhibitor, to treat 5 TSC patients who had either subependymal giant cell astrocytoma ($n=4$) or pilocytic astrocytoma ($n=1$). In all five cases, tumor regression was observed, and in one case, tumor necrosis occurred (Franz et al. 2006). As reviewed in Sect. 1.2.1.1.2, follow-up studies demonstrated very high response rates of TS-associated SEGA to the mTOR inhibitor everolimus. Based on these observations, as well as the role of mTOR signaling in sporadic and NF1-associated PA as reviewed in Sect. 1.2.2.3, inhibition of mTOR signaling is emerging as a provocative target for treatment of LGGs. In a cohort of 19 recurrent LGG patients treated with a combination of the EGFR inhibitor erlotinib and rapamycin, 1 patient had a partial response to treatment, and 6 patients had stabilization of disease for 12 months or greater (Yalon et al. 2013). A phase 2 study of treatment with everolimus alone in a cohort of 23 patients with recurrent or progressive low-grade glioma observed that 4 subjects had a partial response and 13 subjects had prolonged stable disease (Keiran et al. 2014).

Further exploration of gene expression profiles of grade I and II gliomas have already led to the introduction of novel therapies for pediatric low-grade gliomas. As reviewed in Sect. 1.2.2.3, *BRAF* is strongly implicated in the molecular pathogenesis of pediatric low-grade astrocytoma, and open a new avenue for molecularly targeted agents. In these studies, aberrant MAPK signaling could be inhibited in low-grade astrocytoma cell lines when treated with an inhibitor of the MAPK signaling component MEK. Initial efforts to treat low-grade glioma with the BRAF inhibitor sorafenib were disappointing, with 82 % of patients demonstrating uncharacteristically rapid progressive disease on treatment (Karajannis et al. 2014). Sorafenib was demonstrated to be associated with paradoxical activation of ERK in the setting of a *BRAF-KIAA1549* fusion; hence, the drug may have driven tumor progression in this subset of patients (Sievert et al. 2013). In contrast, pediatric low-grade gliomas with $BRAF^{V600E}$ mutations have a high response rate to $BRAF^{V600E}$-specific inhibitors such as dabrafenib, with 8 out of 15 patients having an objective radiographic response (Kieran et al. 2015). A preliminary report of a phase 1 study of the MEK inhibitor selumetinib (AZD6244) in pediatric low-grade glioma patients was notable for sustained responses in 8 of 38 patients treated, suggesting that MEK inhibition may be a promising therapeutic strategy for these patients (Banerjee et al. 2014), although a larger phase II study is currently underway that will hope to identify by genotype the patients most likely to respond to MEK inhibition. In summary, targeted therapies directed at the Ras/Map kinase pathway have shown significant early promise to treat pediatric low-grade gliomas, but it is still too early to determine which specific inhibitors (BRAF vs MEK) should be used to treat tumors with which particular mutation (*NF1*, *BRAF* fusion, $BRAF^{V600E}$, *RAS*).

1.2.6 Outcome

Age and histological type are significant prognostic predictors. Although patients appear to benefit from more extensive resections, this issue remains controversial. In a majority of patients with tumor-associated epilepsy, including those patients with malignant astrocytomas, the seizures are infrequent and easily controlled with a single antiepileptic drug. In this setting, removal of the tumor alone usually controls seizure activity without the need for additional anticonvulsants. Children with indolent tumors, however, may have seizure activity that is refractory to medical therapy. Optimal seizure control without postoperative anticonvulsants in this situation is achieved when perioperative electrocorticographic mapping of separate seizure foci accompanies tumor resection. When mapping is not utilized, and a radical tumor resection includes adjacent brain, the occurrence of seizures will be lessened, but most patients will have to remain on antiepileptic drugs (Berger et al. 1991).

Dedifferentiation or malignant transformation is a well-described phenomenon in low-grade gliomas (Fig. 1.3). The incidence of recurrence as a higher histological grade ranges from 13 % to 86 % of tumors initially diagnosed as low grade (Keles et al. 2001). Similar to its broad range of incidence, the time to malignant differentiation is also variable, ranging from 28 to 60 months. However, factors resulting in change to a malignant phenotype remain unclear. In a recent study investigating the relationship between anaplastic transformation and patient's age, a strong inverse relationship was found between age at initial diagnosis and time to progression to a higher-grade glioma (Shafqat et al. 1999).

In both low- and high-grade astrocytomas, the extent of surgical resection appears to correlate with outcome and quality of life (Pollack et al. 1995; Campbell and Pollack 1996; Keles et al. 2001; Wolff et al. 2002). Patients with GTRs live longer than those with partial resections, who in turn live longer than those who have biopsies only. A further consideration is that partial resection is often accompanied by significant postoperative edema surrounding residual tumor tissue, along with increased neurologic morbidity. However, the literature regarding the prognostic impact of surgery is controversial due to a lack of randomized studies addressing the issue. An additional complicating factor is the inconsistent and less subjective methodology used in determining the extent of resection. Historically, PFS at 3 years ranges from 61 % to 75 % for patients with low-grade gliomas (Packer et al. 1997; Gururangan et al. 2002). These patients have a 10-year survival rate of 70–90 %. More recently, however, data from the Surveillance, Epidemiology, and End Results (SEER) database reported on the long-term outcome of 4,040 children with low-grade glioma. Twenty-year overall survival was 87 %, and the 20-year cumulative incidence of death due to glioma was 12 %. Prognostic features included year of diagnosis, age at diagnosis, histology, WHO grade, primary site, radiation, and degree of initial resection in univariate analysis. In multivariate analysis, the greatest risk of death was associated with the use of radiation (Bandopadhayay et al. 2014).

1.3 Cerebellar Astrocytoma

Although astrocytomas as a group represent the most common tumor of the CNS in childhood, cerebellar astrocytomas comprise 10–20 % of all pediatric brain tumors (Lapras et al. 1986; Rutka et al. 1996; Smoots et al. 1998; Reddy and Timothy 2000) and 20–40 % of all posterior fossa tumors in children (Lapras et al. 1986; Rutka et al. 1996; Morreale et al. 1997; Steinbok and Mutat 1999; Reddy and Timothy 2000; Viano et al. 2001). Infratentorial tumors comprise approximately 50 % of all intracranial tumors in childhood and include medulloblastoma/PNET (20 % of the total), cerebellar astrocytomas (15 %), ependymoma (5 %), brainstem glioma (3 %), and other miscellaneous types (5 %) (Pollack 1999). Long-term survival after surgical resection is very high, but is dependent on histological type, extent of invasion, and completeness of tumor removal.

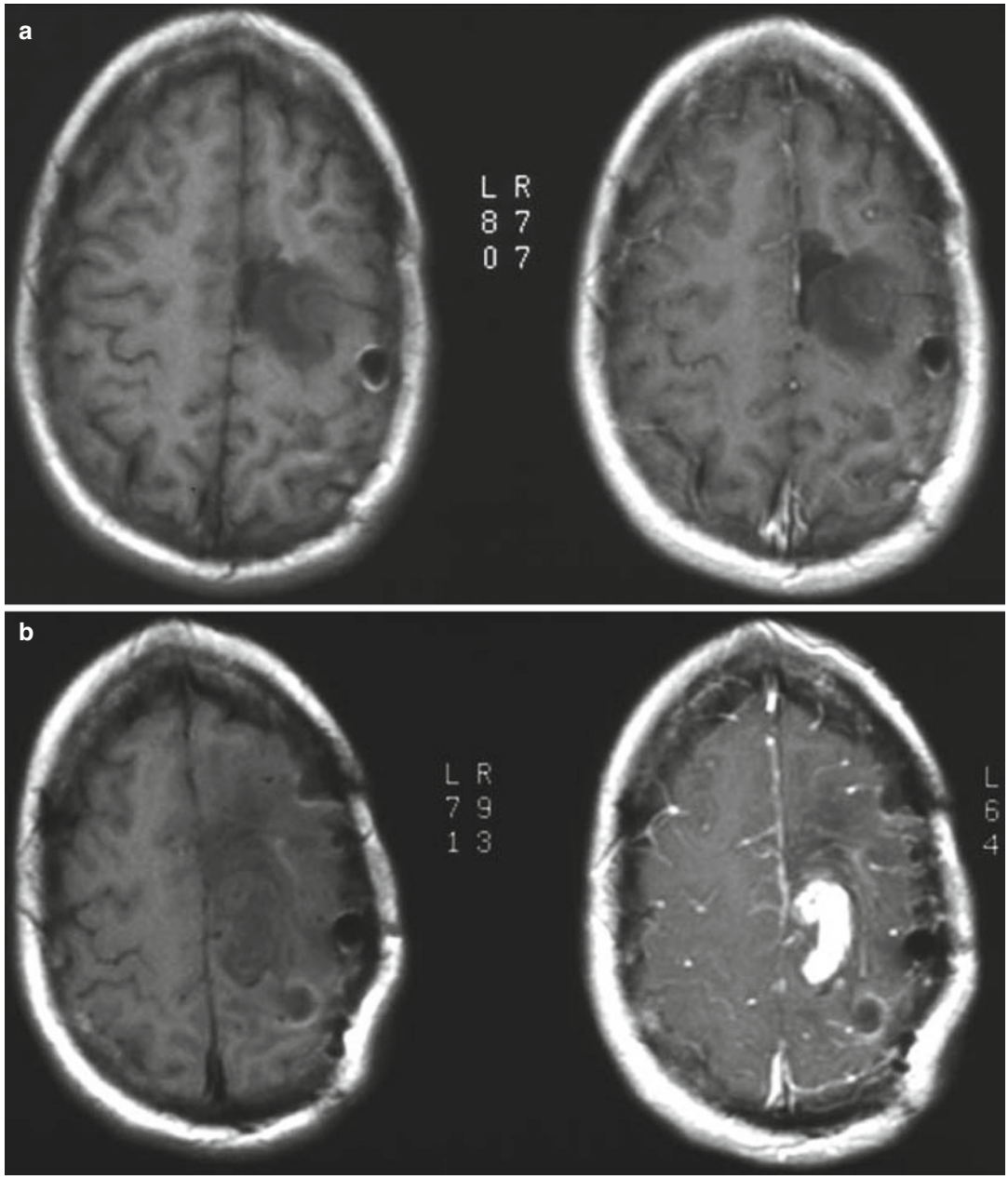

Fig. 1.3 Low-grade astrocytoma can recur at a higher grade. (**a**) Initial MRI demonstrates a nonenhancing mass in the left parietal lobe. Pathology was consistent with grade II astrocytoma. (**b**) Five years later, follow-up imaging demonstrates a new area of enhancement posterior to the original tumor. Pathology of the enhancing component was consistent with glioblastoma multiforme

Recent laboratory investigations are attempting to define the molecular features of different grades of cerebellar astrocytomas. Clinical studies have focused on approaches to the treatment of residual/recurrent tumor, the role of adjuvant therapy, functional outcomes after treatment, and the management of complications, such as pseudomeningocele, cerebrospinal fluid (CSF) shunting, and cerebellar mutism.

1.3.1 Epidemiology

The incidence of cerebellar astrocytoma is difficult to determine accurately, but is estimated to be 0.2–0.33 cases per 100,000 children per year (Berger 1996; Gjerris et al. 1998; Rosenfeld 2000). The incidence peaks between ages 4 and 10 years, with a median age at diagnosis of 6 years (Steinbok and Mutat 1999). Twenty percent of these tumors occur in children less than 3 years of age (Rickert 1998). Gender does not play a role in disease predominance, prognosis, or survival (Rickert and Paulus 2001; Viano et al. 2001). International studies do not demonstrate a geographic or ethnic propensity for the occurrence of cerebellar astrocytomas, unlike craniopharyngiomas and germ-cell tumors (Gjerris et al. 1998; Rickert 1998; Rickert and Paulus 2001).

The term "cerebellar astrocytoma" has become synonymous with a benign tumor, although a small subset are high grade and malignant. The majority (80%) of cerebellar astrocytomas in children are PAs (WHO grade I) and demonstrate a benign histology (Morreale et al. 1997). Fibrillary astrocytomas (WHO grade II) comprise 15% of the total, while anaplastic astrocytomas (WHO grade III) and glioblastoma (GBM, WHO grade IV) each represent less than 5% of the total (Steinbok and Mutat 1999). In patients who present with NF1, about 5% will develop cerebellar JPAs (Li et al. 2001).

1.3.2 Pathology

1.3.2.1 Gross Appearance

Grossly, cerebellar astrocytomas can be cystic and solid or have mixed features. JPAs (WHO grade I) are typically cystic tumors containing yellow-brown fluid and neoplastic mural nodules. The cyst wall may contain either neoplastic cells or a pseudocapsule of glial tissue (Steinbok and Mutat 1999; Bonfield and Steinbok 2015). This classic appearance occurs in less than 50% of cases. Diffuse subtypes are almost always solid tumors composed of circumscribed neoplastic cells without evidence of cysts. Very commonly, however, cerebellar astrocytomas demonstrate mixed appearance and consist of both cystic and solid portions of tumor. Cystic lesions tend to occur in the cerebellar hemispheres, while solid tumors often arise in the midline near the vermis and potentially extend to the brainstem (Abdollahzadeh et al. 1994).

1.3.3 Clinical Features

The mean age at diagnosis for cerebellar astrocytomas in children is 6.8 years, and the average duration of symptoms is 3–5 months (Steinbok and Mutat 1999; Reddy and Timothy 2000; Bonfield and Steinbok 2015). The slow-growing, indolent characteristics of these tumors allow functional compensation of adjacent brain tissue, and most cerebellar astrocytomas tend to be large at time of diagnosis. With greater availability of high-resolution neuroimaging, detection of these lesions is occurring earlier than in the past. Attempts to correlate age at diagnosis and prognosis have been inconclusive, and though patients diagnosed at younger ages tend to have better outcomes, more of these tumors tend to have a benign pathology (Morreale et al. 1997).

Initial signs and symptoms are usually mild and nonspecific and are caused by increased intracranial pressure. Headache is the most common presenting complaint (75–97%) (Abdollahzadeh et al. 1994; Berger 1996; Steinbok and Mutat 1999; Viano et al. 2001; Bonfield and Steinbok 2015) and frequently occurs with recumbency. Decreased venous return and hypoventilation during sleep and recumbency exacerbate raised ICP (Steinbok and Mutat 1999). Headaches begin frontally and may migrate to the occiput. Constant occipital headache and neck pain with hyperextension are ominous signs of tonsillar herniation into the foramen magnum. Respiratory depression, preceded by cluster or ataxic breathing, may follow shortly (Rosenfeld 2000). Vomiting, found in 64–84% of patients, is the second most frequent presenting symptom and is also caused by hydrocephalus and raised ICP (Steinbok and Mutat 1999; Viano et al. 2001). Papilledema occurs in 40–80% of patients along with cerebellar dysfunction (Rashidi et al. 2003). In the absence of tumor infiltration of the area postrema, vomiting is usually not accompanied by nausea,

unlike ependymomas and other lesions arising from the fourth ventricle itself.

Signs of cerebellar dysfunction include ataxia (88%), gait disturbance (56%), appendicular dysmetria (59%), and wide-based gait (27%) (Abdollahzadeh et al. 1994; Pencalet et al. 1999; Steinbok and Mutat 1999; Viano et al. 2001). Lesions of the cerebellar hemisphere produce ataxia and dysmetria in the ipsilateral limbs, while midline lesions produce truncal and gait ataxia (Berger 1996). Other clinical features include behavioral changes (32%), neck pain (20%), and papilledema (55–75%) (Abdollahzadeh et al. 1994; Steinbok and Mutat 1999; Bonfield and Steinbok 2015). Some degree of hydrocephalus occurs in 92% of cases, while seizures are extremely rare (2–5%) (Abdollahzadeh et al. 1994). Cranial nerves and descending motor tracts are usually not affected, unless there is significant tumor extension, and involvement indicates probable brainstem infiltration. The only clinical feature related to poor prognosis is the presence of brainstem dysfunction (level of consciousness, motor-tract signs) regardless of histology (Sgouros et al. 1995).

1.3.4 Natural History

Cerebellar astrocytomas were once considered congenital posterior fossa brain tumors, requiring treatment only when symptomatic. Patients would typically report long-standing headaches and emesis, with occasional periods of relief. Patients with cerebellar symptoms often developed symptoms of syringomyelia, indicating unrelieved hydrocephalus. It was commonly believed that the cyst wall and cyst fluid were the cause of the patients' symptoms. Thus, early treatment consisted of cyst-fluid decompression and cyst-wall removal. Symptoms were relieved temporarily, but patients often returned within months to years with cyst recurrence and sometimes tumors with malignant progression. Not until Cushing reported his surgical experience with 76 cerebellar astrocytomas in 1931 did it become clear that the true pathology lay in the mural nodule. If left untreated, patients would experience increasing bouts of cerebellar fits, become blind, and ultimately succumb to coma and death.

1.3.5 Diagnosis and Neuroimaging

1.3.5.1 Computed Tomography and Magnetic Resonance Imaging

The classic radiographic appearance of a PA, observed in 30–60% of cases, is a large cyst with a solid mural nodule (Fig. 1.4) localized to one of the cerebellar hemispheres (Steinbok et al. 1996; Reddy and Timothy 2000; Bonfield and Steinbok 2015). On CT, the cyst is hypodense to brain and hyperdense to CSF due to its high protein content, while on MRI, the cyst appears hypointense to brain on T1-weighted images and hyperintense on T2-weighted images. The mural nodule is hypo- to isodense to brain on CT and hyperintense to brain on T1-weighted images. The mural nodule enhances uniformly following contrast administration on both CT and MRI, while the cyst is not affected by contrast. The cyst wall, however, may demonstrate contrast enhancement if neoplastic cells are present (Fig. 1.4). In certain cases, the compressed glial reactive tissue surrounding a cyst may also show limited enhancement (Fig. 1.5). Other variations include multiple mural nodules; a single, large nodule filling in a portion of the cyst; and/or an irregular cyst contour.

Cerebellar astrocytomas can also appear as solid lesions in 17–56% of cases, with 90% arising from or involving the vermis (Pencalet et al. 1999; Reddy and Timothy 2000). The CT shows a lesion hypo- to isodense to brain, and MRI demonstrates a solid mass hyperintense to brain. The solid tumor enhances uniformly following contrast administration in the majority of cases, but variations include regions of nonenhancement and small intratumoral cysts in up to 30% of solid tumors (Campbell and Pollack 1996). Quite often, cerebellar astrocytomas will appear with both cystic and solid features and may have a rind-like enhancement pattern with varying degrees of cyst formation. Brainstem involvement is seen in 8–30% (Steinbok and Mutat 1999; Reddy and Timothy 2000; Viano et al. 2001; Bonfield and Steinbok 2015) of cases, while the cerebellar peduncles are affected in 34% (Hayostek et al. 1993; Pencalet et al. 1999). Calcifications are present in 10–17% of tumors

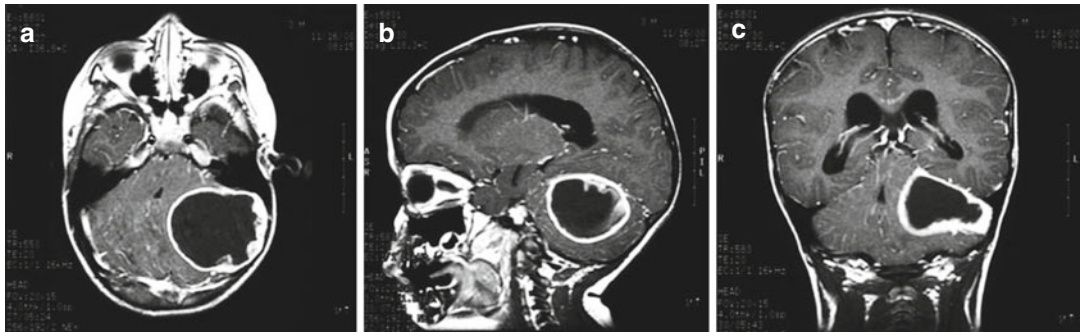

Fig. 1.4 Magnetic resonance (MR) images of a typical pilocytic cerebellar astrocytoma. (**a**) Axial, (**b**) sagittal, and (**c**) coronal T1-weighted MR images with gadolinium contrast demonstrating a cystic hemispheric lesion with mural nodule. In this case, the cyst wall enhances brightly following gadolinium and does represent tumor

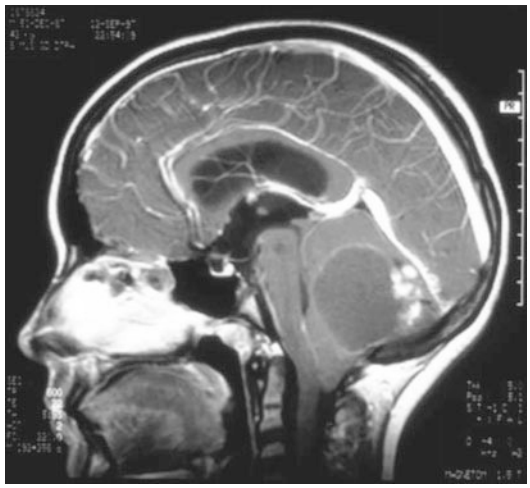

Fig. 1.5 Sagittal magnetic resonance image of a cerebellar astrocytoma showing an irregular enhancing nodule located posterior to a large cyst. The cyst wall appears to enhance slightly, but this represents gliotic brain tissue

and hemorrhage in only 4.5 % (Berger 1996). Edema may be evident in some cases, but does not indicate malignancy or poor prognosis.

1.3.5.2 Magnetic Resonance Spectroscopy

Unfortunately, neither classic tumor appearance nor location on neuroimaging can confidently distinguish cerebellar astrocytoma from PNET or ependymoma. Biopsy with histological examination is necessary to establish a definitive diagnosis. Recently, MRS has been used to distinguish various pediatric cerebellar tumors based on differential levels of tumor metabolites and macromolecules. Pilocytic astrocytomas demonstrate increased choline:*N*-acetyl-aspartate (CHO:NAA) ratios and elevated lactate levels when compared to normal brain, similar to many other tumor types (Wang et al. 1995; Hwang et al. 1998; Warren et al. 2000). In one study, low-grade astrocytomas had higher NAA:CHO ratios than PNETs, but lower ratios than ependymomas, while creatine:CHO ratios were highest for ependymoma and lowest for PNET (Wang et al. 1995; Hwang et al. 1998). MRS may be useful to identify posterior fossa tumors in children after initial CT or MRI scanning. Other metabolites differentially detected in PNET and astrocytoma in vitro include glutamate, glycine, taurine, and myoinositol. One study examined subtotally resected low-grade astrocytomas and reported that higher normalized CHO levels significantly related to tumor progression 2 years following resection (Lazareff et al. 1998). Alternatively, high levels of lactate in pilocytic astrocytoma carry no indication of malignancy and may reflect aberrant glucose utilization in these tumors (Wang et al. 1995).

1.3.6 Treatment

1.3.6.1 Preoperative Management

Preoperative management depends on the clinical presentation of the patient. An asymptomatic, incidentally discovered lesion can be treated with

an elective surgical intervention. More commonly, patients present with signs of increased ICP and cerebellar dysfunction and warrant urgent intervention. High-dose dexamethasone can relieve headache, nausea, and vomiting within 12–24 h and allow for several days of relief prior to a surgical procedure. An initial loading dose of 0.5–1.0 mg/kg given intravenously followed by a dose of 0.25–0.5 mg/kg/day divided every 6 h is the typical regimen (Rosenfeld 2000). In a patient who is stuporous and lethargic, with cardiorespiratory instability, relief of elevated ICP is of utmost importance and should be performed immediately. This is done by placing an external ventricular drain. In less urgent situations, an endoscopic third ventriculocisternostomy (ETV) can also be considered (Sainte-Rose et al. 2001). This procedure consists of placing a fenestration in the floor of the third ventricle to allow CSF to bypass an obstructive lesion in the posterior fossa. The ETV, although not always successful, can avoid permanent shunt placement. Currently, most surgeons will promptly proceed with tumor resection in the hope that relief of the obstructing mass will also treat associated hydrocephalus.

Ventriculoperitoneal (VP) shunting has been shown to improve survival after surgical resection of posterior fossa tumors. This procedure carries the risk of upward herniation and subdural hematoma from overshunting, while also rendering the patient shunt dependent for life with all of its associated complications. The risk of upward herniation is estimated at 3 % and presents with lethargy and obtundation around 12–24 h after shunt placement, with the potential for compression of the PCA at the tentorial hiatus, causing occipital lobe ischemia (Steinbok and Mutat 1999). Postoperative CSF diversion (with VP shunting) following complete tumor removal and unblockage of the aqueduct and fourth ventricle are required in 10–40 % of cases (Imielinski et al. 1998).

1.3.6.2 Surgical Treatment

GTR is the treatment goal and is achieved in 60–80 % of operative cases (Campbell and Pollack 1996; Gajjar et al. 1997). GTR is defined as the removal of all identifiable tumor tissue during surgery and is accomplished only when both the surgeon's report and postoperative neuroimaging are concordant. An MRI with gadolinium enhancement is recommended within 24–48 h after resection. Postoperative changes, including swelling, edema, and gliosis appear by 3–5 days following surgery and may interfere with identification of residual tumor (Berger 1996). Residual tumor after GTR as noted by imaging is detected in 15 % of cases, while postoperative imaging fails to demonstrate known residual tumor as reported by the surgeon in 10 % of cases (Dirven et al. 1997). The clear presence of residual tumor is managed by reoperation to achieve complete resection.

Cystic tumors with a mural nodule may only require removal of the nodule to achieve complete resection, but removal of the cyst wall is dependent upon whether tumor is present. In some cases, contrast enhancement of the cyst wall on postcontrast MRI scans is clearly visualized (Fig. 1.4) and complete removal of all enhancing portions is considered essential to prevent recurrence. Nonenhancing areas do not require resection, and recent studies have shown that enhancement of the cyst wall does not always indicate tumor and may only represent vascularized reactive gliosis (Fig. 1.5) (Steinbok and Mutat 1999; Burger et al. 2000). There is also some evidence to suggest that patients who undergo complete cyst wall removal may have a poorer prognosis at 5 years than those with cyst walls left intact (Sgouros et al. 1995). Some support biopsy of the cyst wall during resection for frozen section; however, pathologic assessment is usually indeterminate and the sampling error is high, making biopsy of little value. Surgeons may choose conservative management of an enhancing cyst wall, especially if wall enhancement is thin (suggesting gliosis rather than tumor), biopsy samples do not demonstrate clear pathology, and gross appearance is benign (Steinbok and Mutat 1999).

Resection of cerebellar tumors can be associated with neurological deficits, although they are typically improved postoperatively (Steinbok et al. 2013). Subtotal resection (STR) is recommended when GTR would result in unacceptable

morbidity and neurologic dysfunction, usually in the setting of brainstem invasion, involvement of the floor of the fourth ventricle, leptomeningeal spread, or metastasis. Involvement of the cerebellar peduncles was once thought to preclude GTR, but several authorities contend that GTR can be achieved in this circumstance (Berger 1996; Steinbok and Mutat 1999; Bonfield and Steinbok 2015), as postoperative deficits from resection involving the cerebellar peduncles tend to be transient. Management of incompletely resected tumors remains controversial and depends upon clinical circumstances.

1.3.6.3 Follow-Up Neuroimaging

Postoperative surveillance imaging in children with benign cerebellar astrocytomas depends on the extent of initial resection and the histology of tumor. While no standard schedule for surveillance imaging exists, large centers tend to obtain MRI scans at 3 and 6 months, then annually for 3–4 years. Routine imaging after confirmed GTR for a typical PA can be stopped 3–5 years following resection if there is no evidence of recurrence. However, due to the well-documented late recurrence behavior of a small percentage of benign cerebellar astrocytomas, sometimes decades after GTR, clinical changes should warrant reimaging. STR requires closer serial neuroimaging due to higher rates of tumor recurrence. Diffuse/fibrillary histology (grade II) is associated with STRs; however, GTRs of this histological subtype seem to demonstrate prognosis and recurrence rates rivaling those of juvenile pilocytic cerebellar tumors (grade I). Regardless of the extent of resection, most practitioners tend to follow grade II lesions more closely with serial exams and neuroimaging.

1.3.6.4 Management of Recurrence

Recurrence following GTR is rare and can occur after several years to decades from the initial operation. Reoperation with the goal of GTR is the recommended treatment for recurrence following STR, although this is usually not possible because the primary reason for incomplete resection is usually due to involvement of vital structures such as the brainstem (Akyol et al. 1992; Bonfield and Steinbok 2015). At reoperation, only 30 % of recurrences result in GTR, while 70 % continue to have residual tumor (Dirven et al. 1997). An interesting biologic feature of low-grade astrocytomas is the spontaneous regression or involution of residual tumors. For this reason, many authors advocate a period of observation for residual disease prior to reoperation. This approach is favored at our institution, particularly because a second procedure is associated with increased morbidity (Dirven et al. 1997).

Following STR, 30–40 % of patients have recurrence within 3 years (mean 54 months), while >60 % have recurrence by 5–6 years (Schneider et al. 1992). Tumors with diffuse/fibrillary histology are more prone to recurrence, but this association is not reported consistently in all series. Of all recurrent tumors, 65 % are pilocytic; 31 % are diffuse/fibrillary; 48 % are cystic; and 52 % are solid (Sgouros et al. 1995; Gjerris et al. 1998). Recurrences are found more often in the midline or vermis. Smoots et al., using multivariate analysis, noted that the only factor that predicted disease progression was the volume of residual disease (Smoots et al. 1998). This study also showed that only fibrillary histology, and not brainstem invasion or postoperative radiation therapy, significantly affects postoperative tumor volume. Unfortunately, the relationship between STR, brainstem invasion, residual tumor volume, and histology confound each other in almost all other series.

1.3.6.5 Adjuvant Therapy for Recurrence

Radiation therapy after resection plays an important role in the control of PNET and ependymoma, but its utility in cerebellar astrocytoma is incompletely understood. Postoperative radiation in subtotally resected tumors of any grade improves local control and recurrence rates, but survival rates seem to be unaffected (Garcia et al. 1990; Herfarth et al. 2001). One retrospective, nonrandomized study comparing patients with recurrence of grade I and II cerebellar astrocytoma found no significant difference in survival at both 5 and 9 years follow-up (Akyol et al.

1992). Radiation doses range from 30 to 54 Gy over 3–6 weeks, and some evidence suggests that doses greater than 53 Gy are necessary to see beneficial effects (Tamura et al. 1998; Herfarth et al. 2001). However, detrimental effects on the developing nervous system preclude its use in patients less than 3 years of age, and current trends favor delaying radiation therapy as long as possible to allow for maximal cognitive development prior to radiation therapy. The risks of radiation therapy include decreased cognitive function (Chadderton et al. 1995) and an increased risk of malignant transformation (Herfarth et al. 2001).

Currently, there is no consensus for the use of radiation therapy for the treatment of benign recurrent cerebellar astrocytoma, though some authors suggest its use if the recurrent tumor displays more aggressive growth features (Garcia et al. 1990; Akyol et al. 1992). Experience with Gamma Knife radiosurgery for the treatment of small-volume residual or recurrent tumors is still too limited at this time, although it may have a role for the treatment of very limited disease (Campbell and Pollack 1996; Somaza et al. 1996).

Chemotherapy has a limited role in the treatment of benign cerebellar astrocytoma, but is used in the setting of inoperable recurrent disease, multifocal disease, leptomeningeal spread, and malignant transformation (Castello et al. 1998; Tamura et al. 1998; Ater 2012). Combination chemotherapy has been used in adjuvant management of inoperable low-grade astrocytomas. The most widely used regimens are CV (Packer et al. 1993) and TPCV (Prados et al. 1997). Both regimens have been associated with complete and partial responses in a subgroup of tumors. Chronic etoposide treatment showed stable tumor lesions at 7 months in patients with recurrent, nonresectable cerebellar astrocytomas in one study (Chamberlain 1997). Cyclophosphamide has been applied in the treatment of cerebellar astrocytoma with leptomeningeal spread (McCowage et al. 1996). The frequent occurrence of the *BRAF-KIAA1549* fusion in cerebellar astrocytoma may provide new treatment avenues (reviewed in Sect. 1.2.5.4).

1.3.7 Outcome

1.3.7.1 Prognostic Factors

Few clinical characteristics at time of presentation contribute to overall outcome. Gender and age at diagnosis do not correlate with survival (Gilles et al. 1995; Campbell and Pollack 1996; Smoots et al. 1998), though younger age at presentation might indicate earlier progression of disease in those with recurrences (Gajjar et al. 1997). A short duration of symptoms at time of presentation is generally associated with a more rapidly growing tumor and, therefore, more likely to be a higher grade. Longer preoperative symptomatology may indicate progressed disease and larger tumor volume (Pencalet et al. 1999). Patients with NF sometimes present with malignant histology; the majority of cerebellar astrocytomas in NF patients appear to have a quiescent course (Freeman et al. 1998; Smoots et al. 1998), though absolute numbers are small.

The only clinical feature related to poor prognosis and survival is the evidence of brainstem dysfunction. Long-tract signs, nystagmus, apnea, and decreased consciousness indicate brainstem invasion by tumor, but also can result from raised ICP and mass effect. Brainstem invasion carries a poor prognosis with only 40 % of patients alive at 5 years after diagnosis (Sgouros et al. 1995). Conversely, 84 % of patients with no evidence of brainstem involvement are alive at 5 years (Sgouros et al. 1995). Brainstem invasion significantly impacts survival regardless of histology, as noted in several large series (Campbell and Pollack 1996). However, after multivariate analysis, Smoots et al. contend that residual tumor volume within the brainstem is the only prognostic factor for disease progression (Smoots et al. 1998).

The impact of histology on outcome and PFS has been controversial (Pencalet et al. 1999). Hayostek et al. showed that pilocytic cerebellar astrocytoma has 5-, 10-, and 20-year survival rates of 85 %, 81 %, and 79 %, respectively, while diffuse subtypes have a dramatically reduced survival rate of 7 % at 5, 10, and 20 years each (Hayostek et al. 1993). Unfortunately, the mean age of patients in both groups differed greatly

(14 years for pilocytic, 51 years for diffuse), making any meaningful comparison difficult. Also, diffuse tumors in this study had more malignant histology (mitosis, necrosis, etc.), which suggests that higher-grade lesions might have been included inappropriately. More recent series have reported 78 % overall survival and 89 % PFS for pilocytic histology and 44 % overall survival and 52 % PFS for diffuse subtypes at 5 years (Sgouros et al. 1995). Diffuse/fibrillary histology is reported as the single most important determinant for residual tumor volume, which in turn is the only predictor of tumor recurrence at any site after multivariate analysis in one study (Smoots et al. 1998). Comparing GTR and STR between grade I and grade II tumors has been difficult because grade II tumors are more likely to be subtotally resected due to tumor location and invasion. Two authors, after multivariate analyses, suggest that only the extent of resection contributes to outcome in children with grades I and II cerebellar astrocytomas (Sgouros et al. 1995; Smoots et al. 1998).

1.3.7.2 Gross Total and Subtotal Resection

The prognosis for patients with grade I tumors and GTR is excellent with 5- and 10-year PFS of 80–100 % in nearly all studies. Thirty-year PFS is not uncommon with long-term follow-up in these patients. Patients with grade II tumors after total resection have 5-year survival rates of 50–80 % (Morreale et al. 1997). As expected, grades III and IV lesions continue to have poor survival despite GTR. In one study, a small group of EGFR-negative cerebellar GBMs demonstrated improved overall survival compared to supratentorial GBMs. Saito et al. hypothesized that the lack of EGFR was the reason for increased chemo-radiosensitivity and the resultant improved overall survival (Saito et al. 2006). GTR is more commonly reported in tumors of pilocytic histology with cystic morphology and peripheral/hemispheric location. Recurrence after confirmed GTR is rare and occurs in less than 5 % of grade I cases, though recurrences have been reported as far as 45 years after initial resection (Boch et al. 2000). GTR is reported in 53 % of patients operated on with pilocytic cerebellar astrocytomas, but only in 19 % of those with nonpilocytic cerebellar tumors (Campbell and Pollack 1996).

In general, STR is associated with future tumor recurrence and poorer outcome (Pencalet et al. 1999). Approximately 75 % of patients will have recurrence during follow-up. The 5-year survival rate varies from 29 to 80 %, and 10-year survival ranges from 0 to 70 % (Sgouros et al. 1995; Campbell and Pollack 1996). These variations in survival are explained by inconsistent study designs. STR is more commonly reported with solid, midline tumors that are usually grade II or higher. A number of reports demonstrate that patients with STRs remain stable, both clinically and on serial imaging, without any evidence of progression for several years (Krieger et al. 1997). In one prospective study, only 50 % of patients with STRs and no brainstem involvement demonstrated progression of disease at 8 years follow-up (Sutton et al. 1996).

An interesting biologic feature of low-grade astrocytomas is the spontaneous regression or involution of residual tumors (Steinbok et al. 2006). In one study of cerebellar pilocytic astrocytomas, nearly 50 % of patients with STRs were noted to have spontaneous regression (Gunny et al. 2005). Specific factors that would predict regression or stability are not known (Palma et al. 2004). The biologic reasons behind tumor quiescence or regression are unknown. For this reason, many authors advocate a period of observation for residual disease prior to reoperation (Benesch et al. 2006). This approach is favored at our institution, particularly because a second procedure is associated with increased morbidity (Dirven et al. 1997).

1.3.7.3 Metastasis

Leptomeningeal dissemination (LMD) of low-grade astrocytomas occurs and is associated mainly with hypothalamic and brainstem tumor location (Pollack et al. 1994; Morikawa et al. 1997; Tamura et al. 1998; Von Hornstein et al. 2011; Chamdine et al. 2016). Metastatic disease is associated with a worse 10- and 15-year survival

prognosis. Therapies for dissemination include chemotherapy, isolated resection of metastasis, and radiation treatment (von Hornstein et al. 2011; Chamdine et al. 2016). CSF sampling appears insensitive in detecting early LMD (Pollack et al. 1994; Chamdine et al. 2016).

1.3.7.4 Survival

PFS and overall outcome depend on several factors including extent of resection, brainstem involvement, and histological subtype. Patients with complete tumor removal enjoy 10-year PFS in greater than 90 % of cases (Gajjar et al. 1997; Steinbok and Mutat 1999). Incomplete tumor resection results in only about 50 % 5-year survival in most series, but with reoperation to remove residual tumor, outcome may improve to 80 % PFS at 5 years, 74 % at 10 years, and 40 % at 20 years (Gajjar et al. 1997). Twenty-five percent of patients with subtotally resected tumors are progression-free at 5 years from the time of recurrence, and reoperation tends to lower subsequent recurrence rates, but does not affect overall survival (Sgouros et al. 1995). Radiation therapy in the setting of STR or recurrence has not been shown to confer any benefit on overall survival in nearly all studies, but some do report lower rates of local progression following radiation.

Although the functional outcome for most children is considered to be good, some data suggest that permanent deficits can occur in language function, visual-spatial ability, and behavior in up to 25 % of patients (Aarsen et al. 2004; Zuzak et al. 2008). In another large group of children ($n = 103$) with cerebellar tumors removed surgically, but not treated with radiation, there was an elevated risk of decline in cognitive and adaptive function (Beebe et al. 2005; Lassaletta et al. 2015).

1.3.8 Conclusion

Among pediatric brain tumors, cerebellar astrocytomas have the most favorable prognosis. The great majority of cerebellar astrocytomas are low-grade neoplasms (pilocytic/grade I tumors) with excellent cure rates and long-term survival following surgery. High-grade tumors, although rare, have dismal outcomes. Tumor recurrence, when it does occur, is a challenging management problem and most often seen with grade II tumors, STR, and brainstem invasion. There is no consensus among authorities regarding the optimal method in treating recurrence, though many advocate reoperation for first recurrence, followed by chemotherapy or radiation therapy for subsequent recurrence. Other management considerations encountered with cerebellar astrocytomas include pre- or postoperative CSF diversion to control hydrocephalus and perioperative steroid administration. Surgical removal of cerebellar astrocytomas may be complicated by cerebellar dysfunction, cranial nerve palsies, and mutism. These risks need to be discussed preoperatively with the patient and parents. Fortunately, the majority of adverse events resolve completely.

1.4 Optic Pathway Gliomas

Optic pathway gliomas, a large subset of pediatric low-grade glioma, occur in some or all anatomical compartments of the optic pathway (optic nerve, chiasm, tract, or radiations). They grow as infiltrative lesions, although large expansile masses are also seen. Their borders are often poorly defined radiolographically, and a surgical plane is rarely observed. Because of their infiltrative nature, these tumors are often not confined to a single anatomic area and can extend into adjacent structures, most commonly into the hypothalamus. For this reason, naming these lesions according to their exact anatomical location may be misleading especially for tumors with radiologically ill-defined borders. As only 10 % of optic nerve gliomas are confined to one optic nerve, and approximately 30 % are bilateral, the majority of optic nerve gliomas involve the chiasm or the hypothalamus (Hoffman and Rutka 1999). Optic chiasmatic and hypothalamic gliomas are often considered as a single entity because of their potential to infiltrate both anatomical sites regardless of the original location of the tumor.

1.4.1 Epidemiology

Optic pathway gliomas account for 4–6% of all CNS tumors in the pediatric age group, 2% in adults, and 20–30% of all pediatric gliomas (Farwell et al. 1977; Borit and Richardson 1982; Alvord and Lofton 1988; Packer et al. 1999). The peak incidence is during the first decade of life with no sex predilection. Overall, NF1 is present in 25–60% of patients with optic pathway tumors (Lewis et al. 1984; Riccardi 1992; Ater et al. 2012). Fifteen to 20% of patients with NF1 will have an optic glioma on MR scan, but only 1–5% become symptomatic (Ruggieri 1999). There is a higher likelihood of NF1 in patients who have multicentric optic gliomas and a relatively lower incidence of NF1 in patients with chiasmatic tumors (Housepian 1977). The natural history of optic pathway gliomas is related to the presence of neurofibromatosis and to the location of the tumor. Patients with optic pathway gliomas who have NF1 appear to have a better overall prognosis than those without NF1 (Rush et al. 1982; Deliganis et al. 1996). However, this view is opposed by other studies showing that patients with neurofibromatosis had a similar prognosis as patients without neurofibromatosis following irradiation for chiasmatic gliomas (Alvord and Lofton 1988). Approximately two thirds of optic gliomas associated with NF1 are indolent lesions with minimal progression. Although any location within the optic pathway from the retrobulbar area to the optic radiation may be affected, chiasmatic gliomas tend to have a more aggressive course both by invading the hypothalamus and by occluding the foramen of Munro causing obstructive hydrocephalus. It is also reported that optic and hypothalamic gliomas that are large at the time of presentation and present in children age less than 5 years are poor prognostic features (Oxenhandler and Sayers 1978; Dirks et al. 1994; Ater et al 2012).

1.4.2 Pathology

Most tumors of the diencephalon and the optic pathways are histopathologically low-grade gliomas, typically pilocytic or fibrillary astrocytomas, although other histological subtypes such as ganglioglioma and pilomyxoid astrocytoma have been described (Daumas-Duport et al. 1988; Ito et al. 1992; Ater et al. 2012). Locally, hypothalamic and optic gliomas may extend laterally invading the perivascular space along the arteries of the circle of Willis, as well as posterior expansion toward the brainstem with rostral invagination into the third ventricle. Patients with chiasmatic/hypothalamic gliomas have an increased risk for disease dissemination along the neuraxis (Gajjar et al. 1995). It has been reported that the risk of multicentric dissemination is approximately 20-fold higher in this group of patients than in those with low-grade gliomas located elsewhere, and dissemination is associated with a poor long-term prognosis (Mamelak et al. 1994; von Hornstein et al. 2011; Chamdine et al. 2016).

1.4.3 Clinical Features

Most optic pathway gliomas present with visual loss. Identifying the exact type of visual loss may be difficult early in the course of the disease, especially in very young children. The typical deficits are incongruent field deficits, at times restricted to one eye. Optic atrophy is commonly seen with large tumors. Children less than 3 years of age are usually first brought to medical attention because of strabismus, proptosis, nystagmus, or loss of developmental milestones. Tumors that involve the hypothalamus will often result in endocrine disturbances, including precocious puberty. Hypothalamic tumors may reach a large size before diagnosis and may result in diencephalic syndrome characterized by failure to thrive despite apparent normal appetite in an otherwise healthy child. Tumors that extend upward into the third ventricle can cause hydrocephalus. Tumors with thalamic involvement may cause unilateral motor deficits on the side contralateral to the lesion.

1.4.4 Diagnostic Imaging

Optic pathway gliomas are usually well visualized on MRI. In children with NF1, there is often

extensive streaking along the optic pathway and/or optic nerve involvement at the time of diagnosis, in addition to nonspecific white matter abnormalities on T2-weighted sequences (Fig. 1.6). The use of diffusion-weighted MRI in NF1 patients may be useful to differentiate between optic gliomas, hamartomas, and myelin vacuolization (Sener 2002). Optic pathway gliomas in children without NF1 tend to be more globular and somewhat more restricted to one anatomic location. The mass itself enhances homogeneously following gadolinium administration, although cysts are frequently seen (Fig. 1.6). On FLAIR sequences, the infiltrative component of the tumor can be seen extending along the optic tracts. Detailed fine cuts through the sella should be obtained. In these sequences, the optic nerve becomes continuous with the mass, a finding that helps to establish the radiologic diagnosis.

1.4.5 Treatment

1.4.5.1 Surgical Indications

Regardless of whether a patient has NF1, the diagnosis of optic pathway glioma can be made based on the presence of intrinsic chiasmatic/hypothalamic mass if the appearance is characteristic on MRI. Diagnostic radiographic characteristics include an expanded sella and/or involvement of the chiasm, optic nerve(s), and/or optic tracts. For patients without NF1 who present with an atypical chiasmatic hypothalamic mass, surgical biopsy may be needed to define the pathologic diagnosis. If mass effect is present with neurologic symptoms, debulking of a large tumor may provide clinical benefit (Magli et al. 2013; Goodden et al. 2014). Some neurosurgeons limit surgical indications to a subset of exophytic or cystic tumors with significant mass effect and hydrocephalus. However, a progressive visual deficit or progression depicted on follow-up MR scans necessitates surgical intervention if there is an exophytic or cystic component. These exophytic tumors can remain stable for extended periods after resection (Tenny et al. 1982; Magli et al. 2013). Ten to twenty percentage of children younger than 10 years with NF1 may have a low-grade glioma of the optic pathways that can be diagnosed radiographically (Lewis et al. 1984; Ruggieri 1999). Asymptomatic patients may be followed with serial clinical and visual examinations and MRI scans; endocrine replacement and CSF shunting should be instituted if necessary.

Resection of a unilateral optic nerve tumor is indicated when vision is absent or nonfunctional in the affected eye. A relative indication is extreme proptosis with exposure keratitis caused by a large intraorbital optic nerve tumor. In addition, it is generally agreed that the exophytic portion of the lesion should be removed if vision is reasonable and that nonresectable unilateral optic nerve lesions should be decompressed. Any surgery that may result in permanent neurologic morbidity should be compared with alternative treatment modalities, in terms of potential benefits and risks. For instance, although a limited resection on an optic nerve glioma extending to the optic chiasm may be indicated, a major chiasmatic resection resulting in visual compromise is virtually never indicated.

The role of biopsy for histological confirmation in optic pathway glioma is controversial. In all likelihood, as biologically targeted therapies expand the options for these patients, it will become increasingly important to obtain tissue for histopathologic and molecular characterization.

1.4.5.2 Surgical Technique

For tumors involving one optic nerve, a frontal or frontotemporal approach may be used. With either technique, intraorbital and intracranial portions of the affected nerve as well as the chiasm are exposed. The optic chiasm and the intracranial portion of the affected optic nerve are inspected to determine a site for division that should be more than 6 mm from the chiasm so as to avoid a contralateral superior temporal field defect. The orbital canal is drilled open allowing decompression of the optic nerve. After closure of the annulus and periorbita, the orbital roof and supraorbital rim are reconstructed if needed. If the orbital roof is not repaired, one associated complication is pulsatile exophthalmos.

For chiasmatic/hypothalamic tumors, surgical goals should be balanced against risks of increased visual loss and hypothalamic dysfunction. Improved

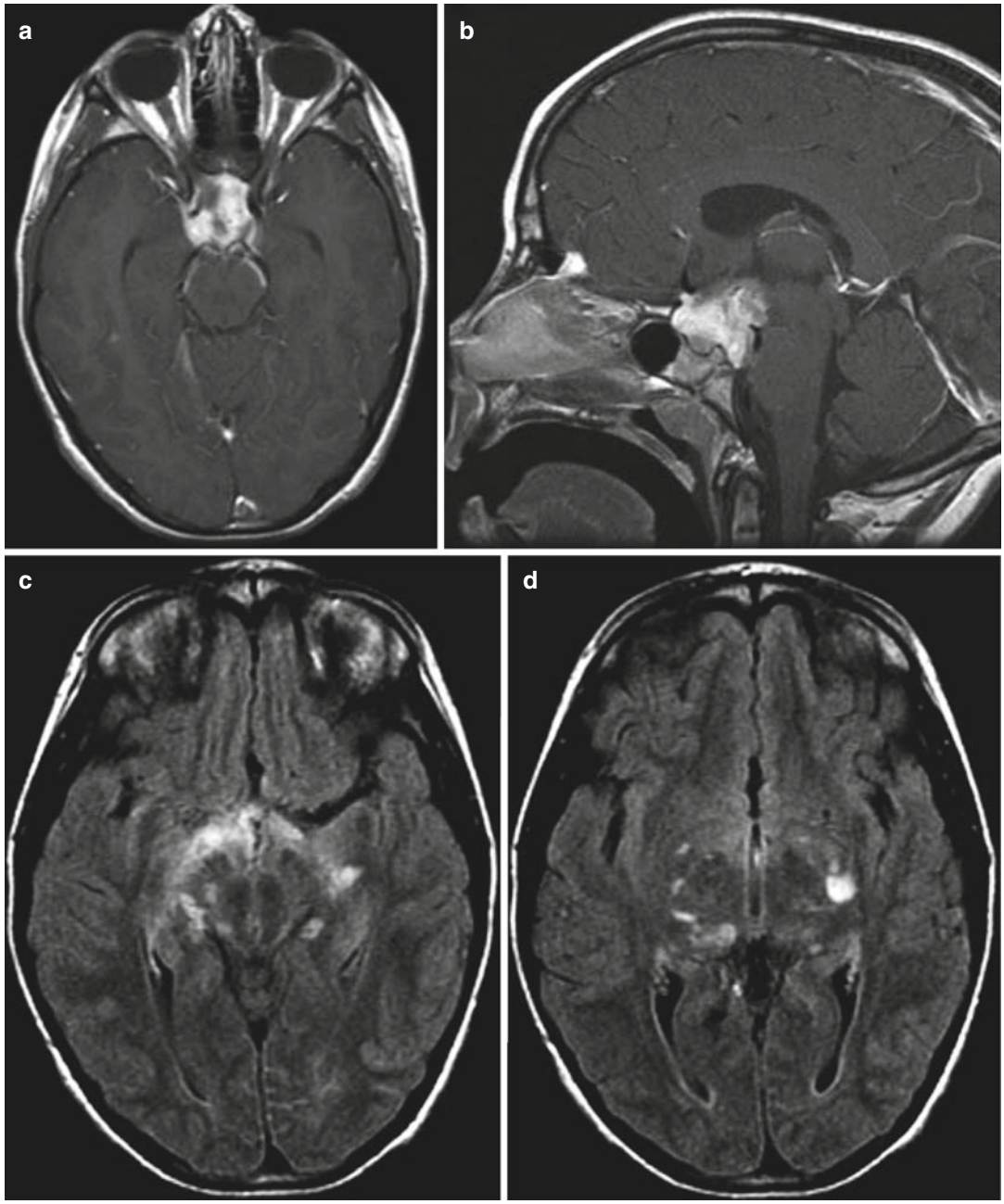

Fig. 1.6 A chiasmatic/hypothalamic pilocytic astrocytoma in a 10-year-old girl who presented with headaches. (**a**) The axial T1-weighted image shows the right optic nerve entering the enhancing portion of the tumor. A distinct boundary does not exist between the nerve and tumor. (**b**) The sagittal plane image clearly shows that the enhancing portion of the tumor is continuous with the hypothalamus. (**c**) FLAIR image shows indistinct increased signal intensity along the optic tracts extending posteriorly from the chiasm. (**d**) FLAIR image slightly superior to (**c**) shows additional abnormalities along the optic tract with a localized area of signal abnormality likely within the lateral geniculate nucleus on the left side

visual and neurologic outcome following surgery has been reported for chiasmatic/hypothalamic gliomas (Bynke et al. 1977; Baram et al. 1986; Wisoff et al. 1990). Meticulous tumor debulking from the exophytic portion of a chiasmatic tumor may improve vision by relieving external pressure on adjacent optic nerves (Oakes 1990). There are several surgical approaches to the chiasmatic hypothalamic region, each with certain advantages (Apuzzo and Litofsky 1993; Litofsky et al. 1994; Hoffman and Rutka 1999). Regardless of the approach, the aim is tumor debulking without causing additional deficit.

1.4.5.3 Radiation Therapy

The use of radiotherapy for the treatment and control of optic pathway gliomas provides long-term tumor control in the majority of patients and may result in improvement in visual outcomes (Taveras et al. 1956; Merchant et al. 2009a; Awdeh et al. 2012). However, current practice aims to delay radiotherapy either by implementing watchful waiting, surgery, or chemotherapy, especially in young patients. Alternative treatment options include follow-up without intervention until clinical deterioration, irradiation of all lesions with or without biopsy, biopsy for all lesions followed by radiation only of those located in the hypothalamus or posterior chiasm, and chemotherapy. Each of these options can be considered for certain subgroups of patients. For example, standard initial treatment for patients with chiasmatic gliomas who have progressive visual symptoms is regional radiotherapy. These tumors are typically sensitive to chemotherapy, and this modality is therefore used often in infants and children prior to or instead of radiation therapy. An option for NF1 patients harboring optic pathway gliomas is follow-up with no treatment as long as the tumor remains quiescent on serial imaging studies, and visual function is stable.

If radiation therapy is to be used, the most favorable outcome has been observed with doses of 45–56 Gy (Pierce et al. 1990; Bataini et al. 1991; Tao et al. 1997). Flickenger demonstrated that patients receiving doses >43.2 Gy delivered over 1.8 Gy fractions had statistically superior overall survival and PFS (Flickinger et al. 1988). These findings are corroborated by another study in which doses <40 Gy were associated with poorer PFS (Kovalic et al. 1990). Because of the concern for dose constraint to surrounding normal tissues, radiotherapeutic modalities under investigation include intensity-modulated radiation therapy, Gamma Knife radiosurgery, stereotactic radiosurgery (Combs et al. 2005; Marcus et al. 2005), conformal radiation therapy (Merchant et al. 2009a), and proton therapy (Greenberger et al. 2014). Because of concerns of radiation-related, long-term toxicity in very young children, the current recommended first-line treatment in patients younger than 7–10 years old is chemotherapy. Patients over 10 years of age can be treated with 50–54 Gy in 1.8 Gy daily fractions with tolerable neurocognitive outcomes (Horwich and Bloom 1985; Halperin et al. 1999; Di Pinto et al. 2012).

1.4.5.4 Chemotherapy

As the risk for late sequelae of partial brain radiation is greatest for young children, chemotherapy prior to radiotherapy as a means of delaying the use of radiation in young children has come into widespread use. In order to spare young pediatric patients' early radiotherapy, alternative chemotherapeutic trials have been explored. One study examined vincristine and carboplatin in 113 children (median age of 3.7 months). Overall response to treatment was observed in 92% of patients, and the median time to progression was 22.5 months observed in 42% of patients (Gnekow et al. 2012). Similarly, at the Hospital for Sick Children in Toronto, a retrospective analysis of 26 adolescents diagnosed with optic pathway gliomas and treated with radiotherapy or carboplatin-based chemotherapy as first-line adjuvant therapy demonstrated successful disease control using chemotherapy (Chong et al. 2008). Based on the COG A9952 results described in the previous section, the use of either TPCV or CV provides adequate tumor control that allows delay of radiotherapy (Ater et al.

2012). Alternative regimen that seems to provide at least short-term disease control in the phase 2 setting includes bevacizumab with irinotecan and vinblastine (Bouffet et al. 2012; Gururangan et al. 2014).

1.4.5.5 Molecular Targeted Therapies

As reviewed in Sect. 1.2.5.4, biologic therapeutic targets such as mTOR, NF1, and BRAF are of increasing interest in pediatric low-grade glioma. A comprehensive understanding of the spectrum of biologic aberrations in optic pathway glioma is limited by the large number of tumors that are diagnosed radiographically. As described earlier in this chapter, mTOR inhibitors and inhibitors of Ras/Map Kinase signaling, such as BRAF and MEK inhibitors, show early promise in pediatric low-grade gliomas.

1.4.6 Outcome

GTR is often impossible due to the critical location of diencephalic and optic gliomas. Patients with unilateral optic nerve tumors who undergo complete surgical resection have a good postoperative prognosis, with 92 % surviving 15 years irrespective of NF status (Jenkin et al. 1993). However, regardless of their histologically benign features, chiasmatic-diencephalic gliomas carry a worse prognosis.

The operative procedures for chiasmatic/hypothalamic gliomas carry significant morbidity. Surgical morbidity may be in the form of immediate endocrinologic or neurologic deficits. Resulting sequelae may include hypothalamic/hypophyseal dysfunction, increased visual impairment, memory loss, altered consciousness, and coma (Wisoff et al. 1990). Following an intraorbital approach, CSF leak may occur if the frontal sinus or any opened ethmoid sinus is not adequately reconstructed. Inadequate reconstruction of the orbital roof may result in pulsatile proptosis. Failure to repair a sectioned levator origin will result in ptosis. Surgical injury to the superior ophthalmic vein and to the nerves supplying the extraocular muscles will result in functional deficits (Housepian 1993). These complications are avoidable with appropriate surgical technique. In a large series of patients treated with intraorbital procedures, no significant CSF leaks, proptosis, infection, or extraocular problems were reported (Maroon and Kennerdel 1976).

Endocrine dysfunction is common in this patient population. The most common manifestations of hypopituitarism following radiotherapy are growth hormone deficiency or growth retardation (Wong et al. 1987; Bataini et al. 1991; Tao et al. 1997; Merchant et al. 2009b). Diabetes insipidus, precocious puberty, and testosterone deficiency are also reported. Furthermore, patients are reported to have significant cognitive deficits, the severity of which may be proportional to age at diagnosis (Ellenberg et al. 1987; Merchant et al. 2009).

The influence of NF1 on prognosis in patients with optic pathway gliomas is unclear. Although Rush et al. reported a better outcome for optic glioma patients with NF1, several other studies failed to show differences in survival (Imes and Hoyt 1986; Alvord and Lofton 1988; Kovalic et al. 1990). The 5- and 10-year survival rates for patients with optic gliomas and NF1 were 93 % and 81 %, respectively, compared with 83 % and 76 %, respectively, for patients without NF1 (Deliganis et al. 1996). However, a significant difference in time to tumor progression (first relapse) was observed in favor of patients with NF1. In a study including mostly diencephalic low-grade gliomas, Packer et al. did not find any prognostic differences related to the presence of NF1 (Packer et al. 1997). In this study, the only statistically significant prognostic factor was age, and children 5 years old and younger had a 3-year PFS rate of 74 % compared with a rate of 39 % in older children. In a large retrospective study of optic pathway/hypothalamic gliomas from the Hospital for Sick Children in Toronto, a large proportion of patients with NF1 were managed with observation only and did not require treatment (Nicolin et al. 2009).

Multiple studies examining clinical characteristics and consequences of chemotherapy of children with hypothalamic/chiasmatic gliomas showed frequent tumor progression despite a

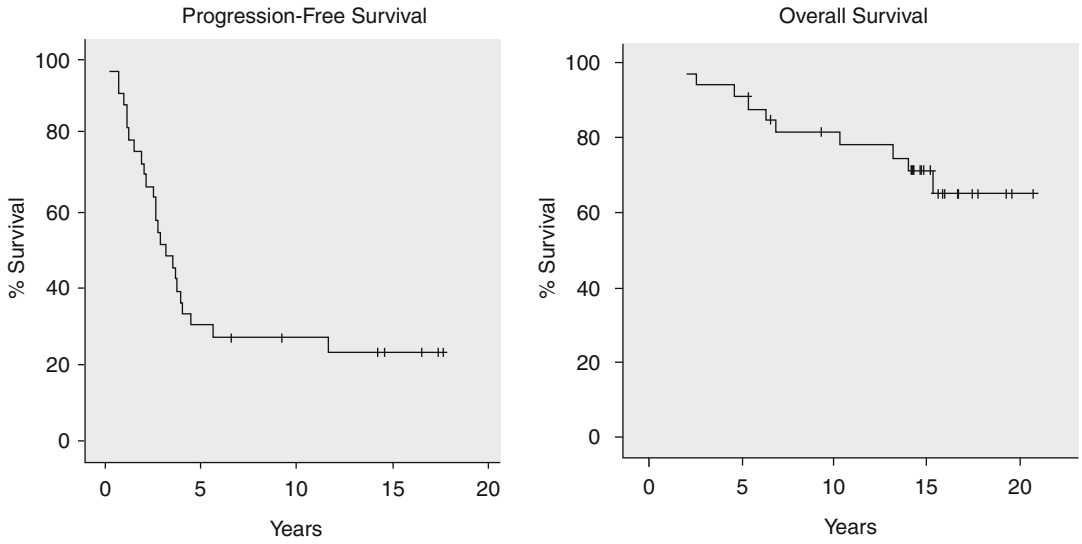

Fig. 1.7 Kaplan-Meier plots of progression-free survival and overall survival of a phase II protocol evaluating an outpatient TPDCV chemotherapy regimen as primary treatment for pediatric low-grade gliomas. The plots demonstrate favorable long-term survival and highlight the finding that most events occurred in the first 6 years with only one event occurring later than 6 years

high survival rate. Although the 5-year survival rate was 93 %, more than 80 % of the children required surgery, chemotherapy, or radiotherapy within 2 years of diagnosis, and all but 9 % eventually required radiation or chemotherapy within a median follow-up period of 6 years (Janss et al. 1995). In the cohort from the hospital for sick children, however, only 16 of a total of 133 patients were treated with radiation; more importantly, however, 58 % of these patients had NF1. A retrospective review of 36 patients with optic pathway/hypothalamic gliomas described 6-year progression-free survival of 69 % for patients who were treated with irradiation, 11 % in patients treated with chemotherapy, and 37 % of patient managed with observation alone (Fouladi et al. 2003). In a report of 33 children with hypothalamic/chiasmatic low-grade gliomas who underwent primary chemotherapy, long-term results were favorable: 5-year overall survival was 90.9 % and 15-year overall survival was 71.2 %, indicating that salvage therapy consisting of radiation, surgery, and/or chemotherapy is successful in many patients (Fig. 1.7). Five-year PFS was 30.3 % and 15-year PFS was 23.4 %, with most patients (24 of 25 patients who progressed) experiencing their first progression event within 6 years of diagnosis (Fig. 1.7). Finally, younger patients had much poorer prognoses, and many could not be successfully treated with salvage therapy. Younger age was significantly associated with poorer overall survival and PFS ($p = 0.037$, 0.004, respectively). Of the 18 children who were 3 years or younger at diagnosis, 17 progressed and of these, 10 died. Comparatively, 15 of the children who were older than 3 years at diagnosis, 8 progressed and none died (Mishra et al. 2010).

Conclusion

In low-grade tumors, GTR is associated with better long-term survival. However, many infiltrative astrocytomas cannot be resected completely. For these tumors, the use of chemotherapy to help control disease as a means to delay radiotherapy is actively being investigated and is the subject of ongoing clinical trials. Newer chemotherapy regimens, the use of stereotactic radiosurgery, and targeted biological agents offer new, promising treatment avenues for glioma therapy.

References

Aarsen FK, Van Dongen HR, Paquier PF, Van Mourik M, Catsman-Berrevoets CE (2004) Long-term sequelae in children after cerebellar astrocytoma surgery. Neurology 62:1311–1316

Abdollahzadeh M, Hoffman HJ, Blazer SI, Becker LE, Humphreys RP, Drake JM, Rutka JT (1994) Benign cerebellar astrocytoma in childhood: experience at the Hospital for Sick Children 1980–1992. Childs Nerv Syst 10:380–383

Akyol FH, Atahan IL, Zorlu F, Gurkaynak M, Alanyali H, Ozyar E (1992) Results of post-operative or exclusive radiotherapy in grade I and grade II cerebellar astrocytoma patients. Radiother Oncol 23:245–248

Alvord EC Jr, Lofton S (1988) Gliomas of the optic nerve or chiasm. Outcome by patients' age, tumor site, and treatment. J Neurosurg 68:85–98

Anderson JL, Gutmann DH (2015) Neurofibromatosis type 1. Handb Clin Neurol 132:75–86

Apuzzo MLJ, Litofsky NS (1993) Surgery in and around the anterior third ventricle. In: Apuzzo MLJ (ed) Brain surgery: complication avoidance and management, vol 1. Churchill Livingstone, New York, p 541

Ater JL, Zhou T, Holmes E, Mazewski CM, Booth TN, Freyer DR, Lazarus KH, Packer RJ, Prados M, Sposto R, Vezina G, Wisoff JH, Pollack IF (2012) Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. J Clin Oncol 30:2641–2647

Awdeh RM, Kiehna EN, Drewry RD, Kerr NC, Haik BG, Wu S, Xiong X, Merchant TE (2012) Visual outcomes in pediatric optic pathway glioma after conformal radiation therapy. Int J Radiat Oncol Biol Phys 84:46–51

Bandopadhayay P, Bergthold G, London WB, Goumnerova LC, Morales La Madrid A, Marcus KJ, Guo D, Ullrich NJ, Robison NJ, Chi SN, Beroukhim R, Kieran MW, Manley PE (2014) Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. Pediatr Blood Cancer 61:1173–1179

Banerjee A, Jakacki R, Onar-Thomas A, Wu S, Nicolaides T, Turner D, Richardson S, Young-Poussaint T, Phillips J, Prados M, Packer R, Qaddoumi I, Gururangan S, Goldman S, Pollack I, Doyle LA, Stewart C, Boyett J, Fouladi M (2014) A phase 1 study of AZD6244 in children with recurren or refractory low-grade gliomas: a Pediatric Brain Tumor Consortium Report. J Clin Oncol 32:5s, suppl: abstr 10064

Baram TZ, Moser RP, Van Eyes J (1986) Surgical management of progressive visual loss in optic gliomas of childhood. Ann Neurol 20:398

Bataini JP, Delanian S, Ponvert D (1991) Chiasmal gliomas: results of irradiation management in 57 patients and review of literature. Int J Radiat Oncol Biol Phys 21:615–623

Bauman G, Lote K, Larson D, Stalpers L, Leighton C, Fisher B, Wara W, MacDonald D, Stitt L, Cairncross JG (1999) Pretreatment factors predict overall survival for patients with low-grade glioma: a recursive partitioning analysis. Int J Radiat Oncol Biol Phys 45:923–929

Beebe DW, Ris MD, Armstrong FD, Fontanesi J, Mulhern R, Holmes E, Wisoff JH (2005) Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: evidence of diminished cognitive and adaptive functioning in National Collaborative Research Studies (CCG 9891/POG 9130). J Clin Oncol 23:5198–5204

Benesch M, Eder HG, Sovinz P, Raith J, Lackner H, Moser A, Urban C (2006) Residual or recurrent cerebellar low-grade glioma in children after tumor resection: is re-treatment needed? A single center experience from 1983 to 2003. Pediatr Neurosurg 42:159–164

Berger MS (1996) Chapter 119: cerebellar astrocytoma. In: Becker DP, Dunsker SB, Friedman WA, Hoffman HJ, Smith RR, Wilson CB (eds) Tumors, vol 4. Saunders, Philadelphia, pp 2593–2602

Berger MS, Ghatan S, Geyer JR, Keles GE, Ojemann GA (1991) Seizure outcome in children with hemispheric tumors and associated intractable epilepsy: the role of tumor removal combined with seizure foci resection. Pediatr Neurosurg 17:185–191

Berger MS, Ghatan S, Haglund MM, Dobbins J, Ojemann GA (1993) Low-grade gliomas associated with intractable epilepsy: seizure outcome utilizing electrocorticography during tumor resection. J Neurosurg 79:62–69

Bigner SH, McLendon RE, Fuchs H, McKeever PE, Friedman HS (1997) Chromosomal characteristics of childhood brain tumors. Cancer Genet Cytogenet 97:125–134

Boch AL, Cacciola F, Mokhtari K, Kujas M, Philippon J (2000) Benign recurrence of a cerebellar pilocytic astrocytoma 45 years after gross total resection. Acta Neurochir 142:341–346

Bondy ML, Wang LE, El-Zein R, de Andrade M, Selvan MS, Bruner JM, Levin VA, Alfred Yung WK, Adatto P, Wei Q (2001) Gamma-radiation sensitivity and risk of glioma. J Natl Cancer Inst 93:1553–1557

Bonfield CM, Steinbok P (2015) Pediatric cerebellar astrocytoma: a review. Childs Nerv Syst 31:1677–1685

Borit A, Richardson EP Jr (1982) The biological and clinical behaviour of pilocytic astrocytomas of the optic pathways. Brain 105:161–187

Bouffet E, Jakacki R, Goldman S, Hargrave D, Hawkins C, Shroff M, Hukin J, Bartels U, Foreman N, Kellie S, Hilden J, Etzl M, Wilson B, Stephens D, Tabori U, Baruchel S (2012) Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol 30:1358–1363

Burger PC, Scheitauer BW, Paulus W, Szymas J, Gianni C, Kleihues P (2000) Chapter 1: pilocytic astrocytoma. In: Cavenee PKW (ed) Tumors of the nervous system: pathology & genetics. IARC, Lyon

Bynke H, Kagstrom E, Tjernstrom K (1977) Aspects on the treatment of gliomas of the anterior visual pathway. Acta Ophthalmol (Copenh) 55:269–280

Cairncross JG, Laperriere NJ (1989) Low-grade glioma. To treat or not to treat? Arch Neurol 46:1238–1239

Campbell JW, Pollack IF (1996) Cerebellar astrocytomas in children. J Neuro-Oncol 28:223–231

Castello MA, Schiavetti A, Varrasso G, Clerico A, Cappelli C (1998) Chemotherapy in low-grade astrocytoma management. Childs Nerv Syst 14:6–9

Chadderton RD, West CG, Schuller S, Quirke DC, Gattamaneni R, Taylor R, Schulz S (1995) Radiotherapy in the treatment of low-grade astrocytomas. II. The physical and cognitive sequelae. Childs Nerv Syst 11:443–448

Chamberlain MC (1997) Recurrent cerebellar gliomas: salvage therapy with oral etoposide. J Child Neurol 12:200–204

Chamdine O, Broniscer A, Wu S, Gajjar A, Qaddoumi I (2016) Metastatic low-grade gliomas in children: 20 years' experience at St. Jude Children's Research Hospital. Pediatric Blood and Cancer 63:62–70

Chen, Guttman (2014) The molecular and cell biology of pediatric low-grade gliomas. Oncogene 33: 2019–2026

Cheng Y, Ng HK, Zhang SF, Ding M, Pang JC, Zheng J, Poon WS (1999) Genetic alterations in pediatric high-grade astrocytomas. Hum Pathol 30:1284–1290

Chong A, Bouffet E, Huang A, Bartels U (2008) Optic path-way gliomas in adolescence. In: The 13th international symposium on pediatric neuro-oncology. Society for Neuro-Oncology, Chicago, p 449

Combs SE, Schulz-Ertner D, Moschos D, Thilmann C, Huber PE, Debus J (2005) Fractionated stereotactic radiotherapy of optic pathway gliomas: tolerance and long-term outcome. Int J Radiat Oncol Biol Phys 62:814–819

Curatolo P, Bombardieri R, Jozwiak S (2008) Tuberous sclerosis. Lancet 372:657–668

Dasgupta B, Yi Y, Chen D, Weber J, Gutmann D (2005) Proteomic analysis reveals hyperactivation of the mammalian target of rapamycin pathway in neurofibromatosis 1-associated and mouse brain tumors. Cancer Res 65:2755–2760

Daumas-Duport C, Scheithauer B, O'Fallon J, Kelly P (1988) Grading of astrocytomas. A simple and reproducible method. Cancer 62:2152–2165

Deliganis AV, Geyer JR, Berger MS (1996) Prognostic significance of type 1 neurofibromatosis (von Recklinghausen disease) in childhood optic glioma. Neurosurgery 38:1114–1118; discussion 1118–1119

Di Pinto M, Conklin HM, Li C, Merchant TE (2012) Learning and memory following conformal radiation therapy for pediatric craniopharyngioma and low-grade glioma. Int J Radiat Oncol Biol Phys 84: e363–e369

Dirks PB, Jay V, Becker LE, Drake JM, Humphreys RP, Hoffman HJ, Rutka JT (1994) Development of anaplastic changes in lowgrade astrocytomas of childhood. Neurosurgery 34:68–78

Dirven CM, Mooij JJ, Molenaar WM (1997) Cerebellar pilocytic astrocytoma: a treatment protocol based upon analysis of 73 cases and a review of the literature. Childs Nerv Syst 13:17–23

Dohrmann GJ, Farwell JR, Flannery JT (1985) Astrocytomas in childhood: a population-based study. Surg Neurol 23:64–68

Dropcho EJ, Wisoff JH, Walker RW, Allen JC (1987) Supratentorial malignant gliomas in childhood: a review of fifty cases. Ann Neurol 22:355–364

Edwards MS, Levin VA, Wilson CB (1980) Brain tumor chemotherapy: an evaluation of agents in current use for phase II and III trials. Cancer Treat Rep 64:1179–1205

Ellenberg L, McComb JG, Siegel SE, Stowe S (1987) Factors affecting intellectual outcome in pediatric brain tumor patients. Neurosurgery 21:638–644

Farwell JR, Dohrmann GJ, Flannery JT (1977) Central nervous system tumors in children. Cancer 40:3123–3132

Felix CA, Slavc I, Dunn M, Strauss EA, Phillips PC, Rorke LB, Sutton L, Bunin GR, Biegel JA (1995) p53 gene mutations in pediatric brain tumors. Med Pediatr Oncol 25:431–436

Flickinger JC, Torres C, Deutsch M (1988) Management of low-grade gliomas of the optic nerve and chiasm. Cancer 61:635–642

Fouladi M, Hunt DL, Pollack IF, Dueckers G, Burger PC, Becker LE, Yates AJ, Gilles FH, Davis RL, Boyett JM, Finlay JL (2003) Outcome of children with centrally reviewed low-grade gliomas treated with chemotherapy with or without radiotherapy on Children's Cancer Group high-grade glioma study CCG-945. Cancer 98:1243–1252

Franz DN, Leonard J, Tudor C, Chuck G, Care M, Sethuraman G, Dinopoulos A, Thomas G, Crone KR (2006) Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol 59:490–498

Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, Witt O, Kohrman MH, Flamini JR, Wu JY, Curatolo P, de Vries PJ, Berkowitz N, Anak O, Niolat J, Jozwiak S (2014) Everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study. Lancet Oncol 15:1513–1520

Freeman CR, Farmer JP, Montes J (1998) Low-grade astrocytomas in children: evolving management strategies. Int J Radiat Oncol Biol Phys 41:979–987

Gajjar A, Heideman RL, Kovnar EH, Langston JA, Sanford RA, Douglass EC, Jenkins JJ, Horowitz ME, Kun LE (1993) Response of pediatric low grade gliomas to chemotherapy. Pediatr Neurosurg 19:113–118; discussion 119–120

Gajjar A, Bhargava R, Jenkins JJ, Heideman R, Sanford RA, Langston JW, Walter AW, Kuttesch JF, Muhlbauer M, Kun LE (1995) Low-grade astrocytoma with neuraxis dissemination at diagnosis. J Neurosurg 83:67–71

Gajjar A, Sanford RA, Heideman R, Jenkins JJ, Walter A, Li Y, Langston JW, Muhlbauer M, Boyett JM, Kun LE

(1997) Low-grade astrocytoma: a decade of experience at St Jude Children's Research Hospital. J Clin Oncol 15:2792–2799

Gajjar A, Bowers DC, Karajannis MA, Leary S, Witt H, Gottardo NG (2015) Pediatric brain tumors: innovative genomic information is transforming the diagnostic and clinical landscape. J Clin Oncol 33:2986–2998

Garcia DM, Marks JE, Latifi HR, Kliefoth AB (1990) Childhood cerebellar astrocytomas: is there a role for postoperative irradiation? Int J Radiat Oncol Biol Phys 18:815–818

Giannini C, Scheithauer BW, Burger PC, Christensen MR, Wollan PC, Sebo TJ, Forsyth PA, Hayostek CJ (1999) Cellular proliferation in pilocytic and diffuse astrocytomas. J Neuropatholol Exp Neurol 58:46–53

Gilles FH, Sobel EL, Tavare CJ, Leviton A, Hedley-Whyte ET (1995) Age-related changes in diagnoses, histological eatures, and survival in children with brain tumors: 1930–1979. The childhood brain tumor consortium. Neurosurgery 37:1056–1068

Gjerris F, Agerlin N, Borgesen SE, Buhl L, Haase J, Klinken L, Mortensen AC, Olsen JH, Ovesen N, Reske-Nielsen E, Schmidt K (1998) Epidemiology and prognosis in children treated for intracranial tumours in Denmark 1960–1984. Childs Nerv Syst 14:302–311

Gnekow AK, Falkenstein F, von Hornstein S, Zwiener I, Berkefeld S, Bison B, Warmuth-Metz M, Driever PH, Soerensen N, Kortmann RD, Pietsch T, Faldum A (2012) Long-term follow-up of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade glioma in children and adolescents of the German Speaking Society of Pediatric Oncology and Hematology. Neuro Oncol 14:1265–1284

Gold EB, Leviton A, Lopez R, Gilles FH, Hedley-Whyte ET, Kolonel LN, Lyon JL, Swanson GM, Weiss NS, West D et al (1993) Parental smoking and risk of childhood brain tumors. Am J Epidemiol 137:620–628

Goodden J, Pizer B, Pettorini B, Williams D, Blair J, Didi M, Thorp N, Mallucci C (2014) The role of surgery in optic pathway/hypothalamic gliomas in children. J Neurosurg Pediatr 13:1–12

Greenberger BA, Pulsifer MB, Ebb DH, MacDonald SM, Jones RM, Butler WE, Huang MS, Marcus KJ, Oberg JA, Tarbell NJ, Yock TI (2014) Clinical outcomes and late endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas. Int J Radiat Oncol Biol Phys 89:1060–1068

Griffin CA, Hawkins AL, Packer RJ, Rorke LB, Emanuel BS (1988) Chromosome abnormalities in pediatric brain tumors. Cancer Res 48:175–180

Guertin D, Sabatini D (2007) Defining the role of mTOR in cancer. Cancer Cell 12:9–22

Gunny RS, Hayward RD, Phipps KP, Harding BN, Saunders DE (2005) Spontaneous regression of residual low-grade cerebellar pilocytic astrocytomas in children. Pediatr Radiol 35:1086–1091

Gururangan S, Cavazos CM, Ashley D, Herndon JE 2nd, Bruggers CS, Moghrabi A, Scarcella DL, Watral M, Tourt-Uhlig S, Reardon D, Friedman HS (2002) Phase II study of carboplatin in children with progressive low-grade gliomas. J Clin Oncol 20:2951–2958

Gururangan S, Fisher MJ, Allen JC, Herndon JE 2nd, Quinn JA, Reardon DA, Vredenburgh JJ, Desjardins A, Phillips PC, Watral MA, Krauser JM, Friedman AH, Friedman HS (2007) Temozolomide in children with progressive lowgrade glioma. Neuro Oncol 9:161–168

Gururangan S, Fangusaro J, Poussaint TY, McLendon RE, Onar-Thomas A, Wu S, Packer RJ, Banerjee A, Gilbertson RJ, Fahey F, Vajapeyam S, Jakacki R, Gajjar A, Goldman S, Pollack IF, Friedman HS, Boyett JM, Fouladi M, Kun LE (2014) Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas-a Pediatric Brain Tumor Consortium study. Neuro Oncol 16:310–317

Gutmann DH, Donahoe J, Brown T, James CD, Perry A (2000) Loss of neurofibromatosis 1 (NF1) gene expression in NF1-associated pilocytic astrocytomas. Neuropathol Appl Neurobiol 26:361–367

Hadjipanayis CG, Kondziolka D, Flickinger JC, Lunsford LD (2003) The role of stereotactic radiosurgery for low-grade astrocytomas. Neurosurg Focus 14:e15

Haglund MM, Berger MS, Kunkel DD, Franck JE, Ghatan S, Ojemann GA (1992) Changes in gamma-aminobutyric acid and somatostatin in epileptic cortex associated with lowgrade gliomas. J Neurosurg 77:209–216

Halperin E, Constine L, Tarbell N, Kun L (1999) Pediatric radiation oncology. Lippincott Williams & Wilkins, Philadelphia

Hayostek CJ, Shaw EG, Scheithauer B, O'Fallon JR, Weiland TL, Schomberg PJ, Kelly PJ, Hu TC (1993) Astrocytomas of the cerebellum. A comparative clinicopathologic study of pilocytic and diffuse astrocytomas. Cancer 72:856–869

Herfarth KK, Gutwein S, Debus J (2001) Postoperative radiotherapy of astrocytomas. Semin Surg Oncol 20:13–23

Hoffman H, Rutka J (1999) Optic pathway gliomas in children. In: Albright L, Pollack I, Adelson D (eds) Principles and practice of pediatric neurosurgery. Thieme, New York, pp 535–543

Horwich A, Bloom HJ (1985) Optic gliomas: radiation therapy and prognosis. Int J Radiat Oncol Biol Phys 11:1067–1079

Houghton PJ, Huang S (2004) mTOR as a target for cancer therapy. Curr Top Microbiol Immunol 279:339–359

Housepian E (1977) Management and results in 114 cases of optic glioma. Neurosurgery 1:67–68

Housepian E (1993) Complications of transcranial orbital surgery. In: Post K, Friedman E, McCormick P (eds) Postoperative complications in intracranial neurosurgery. Thieme, New York, pp 87–90

Hwang JH, Egnaczyk GF, Ballard E, Dunn RS, Holland SK, Ball WS Jr (1998) Proton MR spectroscopic characteristics of pediatric pilocytic astrocytomas. AJNR Am J Neuroradiol 19:535–540

Imes RK, Hoyt WF (1986) Childhood chiasmal gliomas: update on the fate of patients in the 1969 San Francisco Study. Br J Ophthalmol 70:179–182

Imielinski BL, Kloc W, Wasilewski W, Liczbik W, Puzyrewski R, Karwacki Z (1998) Posterior fossa tumors in children – indications for ventricular drainage and for V-P shunting. Childs Nerv Syst 14:227–229

Ishii N, Sawamura Y, Tada M, Daub DM, Janzer RC, Meagher-Villemure M, de Tribolet N, Van Meir EG (1998) Absence of p53 gene mutations in a tumor panel representative of pilocytic astrocytoma diversity using a p53 functional assay. Int J Cancer 76:797–800

Ito S, Hoshino T, Shibuya M, Prados MD, Edwards MS, Davis RL (1992) Proliferative characteristics of juvenile pilocytic astrocytomas determined by bromodeoxyuridine labeling. Neurosurgery 31:413–418; discussion 419

Janss AJ, Grundy R, Cnaan A, Savino PJ, Packer RJ, Zackai EH, Goldwein JW, Sutton LN, Radcliffe J, Molloy PT et al (1995) Optic pathway and hypothalamic/chiasmatic gliomas in children younger than age 5 years with a 6-year follow-up. Cancer 75:1051–1059

Jenkin D, Angyalfi S, Becker L et al (1993) Optic glioma in children: surveillance, resection, or irradiation? Int J Radiat Oncol Biol Phys 25:215–225

Karajannis MA, Legault G, Fisher MJ, Milla SS, Cohen KJ, Wisoff JH, Harter DH, Goldberg JD, Hochman T, Merkelson A, Bloom MC, Sievert AJ, Resnick AC, Dhall G, Jones DT, Korshunov A, Pfister SM, Eberhart CG, Zagzag D, Allen JC (2014) Phase II study of sorafenib in children with recurrent or progressive low-grade astrocytomas. Neuro Oncol 16:1408–1416

Karnes PS, Tran TN, Cui MY, Raffel C, Gilles FH, Barranger JA, Ying KL (1992) Cytogenetic analysis of 39 pediatric central nervous system tumors. Cancer Genet Cytogenet 59:12–19

Kaye AH, Walker DG (2000) Low grade astrocytomas: controversies in management. J Clin Neurosci 7:475–483

Keiran M, Yao X, Macy M, Leary S, Cohen K, MacDonald T, Allen J, Boklan J, Smith A, Nazemi K, Gore T, Trippett J, DiRenzo J, Narendran A, Perentesis J, Prabhu S, Pinches N, Robison N, Manley P, Chi S (2014) Final results of a prospective multi-institutional phase II study of everolimus (RAD001), an mTOR inhibitor, in pediatric patients with recurrent of progressive low –grade glioma, A POETIC consortium trial. Neuro Oncol 16(suppl3):iii–27

Keles G, Berger M (2000) Seizures associated with brain tumors. In: Bernstein M, Berger M (eds) Neuro-oncology essentials. Thieme, New York, pp 473–477

Keles GE, Lamborn KR, Berger MS (2001) Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. J Neurosurg 95:735–745

Kepes JJ, Kepes M, Slowik F (1973) Fibrous xanthomas and xanthosarcomas of the meninges and the brain. Acta Neuropathol 23:187–199

Kieran MW, Hargrave DR, Cohen KJ, Aerts I, Dunkel IJ, Hummel TR, Jimenez I, Pearson ADJ, Pratilas CA, Whitlock J, Bouffet E, Shen WPV, Broniscer A, Bertozzi AI, Sandberg JL, Florance AM, Suttle BB, Haney P, Russo MW, Geoerger B (2015) Phase 1 study of dabrafenib in pediatric patients (pts) with relapsed or refractory *BRAF* V600E high- and low-grade gliomas (HGG, LGG), Langerhans cell histiocytosis (LCH), and other solid tumors (OST). J Clin Oncol 32:5s, suppl; abstr 10056

Kim AH, Thompson EA, Governale LS, Santa C, Cahll K, Kieran MW, Chi SN, Ullrich NJ, Scott RM, Goumnerova LC (2014) Recurrence after gross-total resection of low-grade pediatric brain tumors: the frequency and timing of postoperative imaging. J Pediatr Neurosurg 14:356–364

Kleihues P, Burger PC, Scheithauer BW (1993) The new WHO classification of brain tumours. Brain Pathol 3:255–268

Kordes U, Von Hornstein S, Thieme B, Breitmoser-Greiner S, Gnekow A (2008) Second chemotherapy for relapsed pediatric low-grade glioma: the HIT-LGG 96 experience. In: The 13th international symposium on pediatric neuro-oncology. Society for Neuro-Oncology, Chicago, p 452

Kosel S, Scheithauer BW, Graeber MB (2001) Genotype-phenotype correlation in gemistocytic astrocytomas. Neurosurgery 48:187–193

Kovalic JJ, Grigsby PW, Shepard MJ, Fineberg BB, Thomas PR (1990) Radiation therapy for gliomas of the optic nerve and chiasm. Int J Radiat Oncol Biol Phys 18:927–932

Krieger MD, Gonzalez-Gomez I, Levy ML, McComb JG (1997) Recurrence patterns and anaplastic change in a long-term study of pilocytic astrocytomas. Pediatr Neurosurg 27:1–11

Kyritsis AP, Bondy ML, Rao JS, Sioka C (2010) Inherited predisposition to glioma. Neuro Oncol 12:104–113

Lapras C, Palet J, Lapras C Jr, Mottolese C (1986) Cerebellar astrocytomas in the childhood. Childs Nerv Syst 2:55–59

Lassaletta A, Bouffet E, Mabbott D, Kulkarni AV (2015) Functional and neuropsychological late outcomes in posterior fossa tumors in children. Childs Nerv Syst 31:1877–1890

Lazareff JA, Bockhorst KH, Curran J, Olmstead C, Alger JR (1998) Pediatric low-grade gliomas: prognosis with proton magnetic resonance spectroscopic imaging. Neurosurgery 43:809–817; discussion 817–808

Lewis R, Gerson L, Axelson K et al (1984) von Recklinghausen neurofibromatosis: II. Incidence of optic gliomata. Ophthalmology 91:929–935

Li J, Perry A, James CD, Gutmann DH (2001) Cancer-related gene expression profiles in NF1-associated pilocytic astrocytomas. Neurology 56:885–890

Lindboe CF, Cappelen J, Kepes JJ (1992) Pleomorphic xanthoastrocytoma as a component of a cerebellar ganglioglioma: case report. Neurosurgery 31:353–355

Listernick R, Charrow J, Gutmann DH (1999) Intracranial gliomas in neurofibromatosis type 1. Am J Med Genet 89:38–44

Litofsky NS, Hinton D, Raffel C (1994) The lack of a role for p53 in astrocytomas in pediatric patients. Neurosurgery 34:967–972

Lote K, Egeland T, Hager B, Skullerud K, Hirschberg H (1998) Prognostic significance of CT contrast enhancement within histological subgroups of intracranial glioma. J Neuro-Oncol 40:161–170

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) (2007) WHO classification of tumors of the central nervous system. International Agency for Research on Cancer, Lyon

Louis DN, Perry A, Burger P, Ellison DW, Reifenberger G, von Deimling A, Aldape K, Brat D, Collins VP, Eberhart C, Figarella-Branger D, Fuller GN, Giangaspero F, Giannini C, Hawkins C, Kleihues P, Korshunov A, Kros JM, Beatriz Lopes M, Ng HK, Ohgaki H, Paulus W, Pietsch T, Rosenblum M, Rushing E, Soylemezoglu F, Wiestler O, Wesseling P, International Society Of Neuropathology – Haarlem (2014) International Society Of Neuropathology – Haarlem consensus guidelines for nervous system tumor classification and grading. Brain Pathol 24:429–435

Magli A, Forte R, Cinalli G, Esposito F, Parisi S, Capasso M, Papparella A (2013) Functional changes after treatment of optic pathway paediatric low-grade gliomas. Eye 27:1288–1292

Mamelak AN, Prados MD, Obana WG, Cogen PH, Edwards MS (1994) Treatment options and prognosis for multicentric juvenile pilocytic astrocytoma. J Neurosurg 81:24–30

Marcus KJ, Goumnerova L, Billett AL, Lavally B, Scott RM, Bishop K, Xu R, Young Poussaint T, Kieran M, Kooy H, Pomeroy SL, Tarbell NJ (2005) Stereotactic radiotherapy for localized low-grade gliomas in children: final results of a prospective trial. Int J Radiat Oncol Biol Phys 61:374–379

Maroon JC, Kennerdel JS (1976) Lateral microsurgical approach to intraorbital tumors. J Neurosurg 44:556–561

McCowage G, Tien R, McLendon R, Felsberg G, Fuchs H, Graham ML, Kurtzberg J, Moghrabi A, Ferrell L, Kerby T, Duncan-Brown M, Stewart E, Robertson PL, Colvin OM, Golembe B, Bigner DD, Friedman HS (1996) Successful treatment of childhood pilocytic astrocytomas metastatic to the leptomeninges with high-dose cyclophosphamide. Med Pediatr Oncol 27:32–39

Merchant TE, Kun LE, Wu S, Xiong X, Sanford RA, Boop FA (2009a) Phase II trial of conformal radiation therapy for pediatric low-grade glioma. J Clin Oncol 27:3598–3604

Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X (2009b) Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol 27:3691–3697

Mishra KK, Squire S, Lamborn K, Banerjee A, Gupta N, Wara WM, Prados MD, Berger MS, Haas-Kogan DA (2010) Phase II TPDCV protocol for pediatric low-grade hypothalamic/chiasmatic gliomas: 15-year update. J Neuro-Oncol 100:121–127

Morikawa M, Tamaki N, Kokunai T, Nagashima T, Kurata H, Yamamoto K, Imai Y, Itoh H (1997) Cerebellar pilocytic astrocytoma with leptomeningeal dissemination: case report. Surg Neurol 48:49–51

Morreale VM, Ebersold MJ, Quast LM, Parisi JE (1997) Cerebellar astrocytoma: experience with 54 cases surgically treated at the Mayo Clinic, Rochester, Minnesota, from 1978 to 1990. J Neurosurg 87:257–261

Neumann E, Kalousek DK, Norman MG, Steinbok P, Cochrane DD, Goddard K (1993) Cytogenetic analysis of 109 pediatric central nervous system tumors. Cancer Genet Cytogenet 71:40–49

Nicolin G, Parkin P, Mabbott D, Hargrave D, Bartels U, Tabori U, Rutka J, Buncic JR, Bouffet E (2009) Natural history and outcome of optic pathway gliomas in children. Pediatric Blood and Cancer 53:1231–1237

Oakes W (1990) Recent experience with the resection of pilocytic astrocytomas of the hypothalamus. In: Marlin A (ed) Concepts in pediatric neurosurgery, vol 10. Karger, Basel, p 108

Ostrom QT, de Blank PM, Kruchko C, Petersen CM, Liao P, Finlay JL, Stearns DS, Wolff JE, Wolinsky Y, Letterio JJ, Barnholtz-Sloan JS (2015) Alex's Lemonade Stand Foundation Infant and Childhood Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007–2011. Neuro-Oncology 16(Suppl 10):iv1–iv62

Ouyang T, Zhang N, Benjamin T, Wang L, Jiao J, Zhao Y, Chen J (2014) Subependymal giant cell astrocytoma: current concepts, management, and future directions. Childs Nerv Syst 30:561–570

Oxenhandler DC, Sayers MP (1978) The dilemma of childhood optic gliomas. J Neurosurg 48:34–41

Packer RJ, Sutton LN, Bilaniuk LT, Radcliffe J, Rosenstock JG, Siegel KR, Bunin GR, Savino PJ, Bruce DA, Schut L (1988) Treatment of chiasmatic/hypothalamic gliomas of childhood with chemotherapy: an update. Ann Neurol 23:79–85

Packer RJ, Lange B, Ater J, Nicholson HS, Allen J, Walker R, Prados M, Jakacki R, Reaman G, Needles MN et al (1993) Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. J Clin Oncol 11:850–856

Packer RJ, Ater J, Allen J, Phillips P, Geyer R, Nicholson HS, Jakacki R, Kurczynski E, Needle M, Finlay J, Reaman G, Boyett JM (1997) Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive lowgrade gliomas. J Neurosurg 86: 747–754

Packer R, Vezina G, Nicholson H, Chadduck W (1999) Child-hood and adolescent gliomas. In: Albright L, Pollack I, Adelson D (eds) Principles and practice of pediatric neurosurgery. Thieme, New York, pp 689–701

Palma L, Celli P, Mariottini A (2004) Long-term follow-up of childhood cerebellar astrocytomas after incomplete resection with particular reference to arrested growth or spontaneous tumour regression. Acta Neurochir 146:581–588

Paulino AC, Mazloom A, Terashima K, Su J, Adesina AM, Okcu MF, Teh BS, Chintagumpala M (2013) Intensity-modulated radiotherapy (IMRT) in pediatric low-grade glioma. Cancer 119:2654–2659

Pencalet P, Maixner W, Sainte-Rose C, Lellouch-Tubiana A, Cinalli G, Zerah M, Pierre-Kahn A, Hoppe-Hirsch E, Bourgeois M, Renier D (1999) Benign cerebellar astrocytomas in children. J Neurosurg 90:265–273

Peraud A, Grau S, Tonn J, Kreth F (2008) Treatment concepts for pediatric low grade gliomas in critical locations. In: The 13th international symposium on pediatric neuro-oncology. Society for Neuro-Oncology, Chicago, pp 473–474

Pfister S, Janzarik W, Remke M, Ernst A, Werft W, Becker N, Toedt G, Wittmann A, Kratz C, Olbrich H, Ahmadi R, Thieme B, Joos S, Radlwimmer B, Kulozik A, Pietsch T, Herold-Mende C, Gnekow A, Reifenberger G, Korshunov A, Scheurlen W, Omran H, Lichter P (2008) BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. J Clin Investig 118:1739–1749

Pierce SM, Barnes PD, Loeffler JS, McGinn C, Tarbell NJ (1990) Definitive radiation therapy in the management of symptomatic patients with optic glioma. Survival and long-term effects. Cancer 65:45–52

Pollack IF (1999) Pediatric brain tumors. Semin Surg Oncol 16:73–90

Pollack IF, Hurtt M, Pang D, Albright AL (1994) Dissemination of low grade intracranial astrocytomas in children. Cancer 73:2869–2878

Pollack IF, Claassen D, Al-Shboul Q, Janosky JE, Deutsch M (1995) Low-grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases. J Neurosurg 82:536–547

Powell SZ, Yachnis AT, Rorke LB, Rojiani AM, Eskin TA (1996) Divergent differentiation in pleomorphic xanthoastrocytoma. Evidence for a neuronal element and possible relationship to ganglion cell tumors. Am J Surg Pathol 20:80–85

Prados MD, Edwards MS, Rabbitt J, Lamborn K, Davis RL, Levin VA (1997) Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. J Neuro-Oncol 32:235–241

Preston-Martin S, Pogoda JM, Mueller BA, Lubin F, Modan B, Holly EA, Filippini G, Cordier S, Peris-Bonet R, Choi W, Little J, Arslan A (1998) Prenatal vitamin supplementation and pediatric brain tumors: huge international variation in use and possible reduction in risk. Childs Nerv Syst 14:551–557

Rashidi M, Reis DaSilva V, Minagar A, Rutka J (2003) Nonmalignant pediatric brain tumors. Curr Neurol Neurosci Rep 3:200–205

Recht LD, Lew R, Smith TW (1992) Suspected low-grade glioma: is deferring treatment safe? Ann Neurol 31: 431–436

Reddy ATM, Timothy B (2000) Chapter 74: cerebellar astrocytoma. In: McLone DG (ed) Pediatric neurosurgery: surgery of the developing nervous system, 4th edn. Saunders, New York, pp 835–843

Riccardi V (1992) Type 1 neurofibromatosis and the pediatric patient. Curr Probl Pediatr 22:66–106

Rickert CH (1998) Epidemiological features of brain tumors in the first 3 years of life. Childs Nerv Syst 14:547–550

Rickert CH, Paulus W (2001) Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst 17:503–511

Roberts HC, Roberts TP, Brasch RC, Dillon WP (2000) Quantitative measurement of microvascular permeability in human brain tumors achieved using dynamic contrast-enhanced MR imaging: correlation with histologic grade. AJNR Am J Neuroradiol 21:891–899

Roberts P, Chumas PD, Picton S, Bridges L, Livingstone JH, Sheridan E (2001) A review of the cytogenetics of 58 pediatric brain tumors. Cancer Genet Cytogenet 131:1–12

Ron E, Modan B, Boice JD Jr, Alfandary E, Stovall M, Chetrit A, Katz L (1988) Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med 319:1033–1039

Rosenfeld JV (2000) Chapter 37: cerebellar astrocytoma in children. In: Kaye AH, Black PM (eds) Operative neurosurgery, vol 2. Churchill Livingstone, New York, pp 447–463

Ruge MI, Simon T, Suchorska B, Lehrke R, Hamisch C, Koerber F, Maarouf M, Treuer H, Berthold F, Sturm V, Voges J (2011) Stereotactic brachytherapy with iodine-125 seeds for the treatment of inoperable low-grade gliomas in children: long-term outcome. J Clin Oncol 29:2151–2159

Ruggieri M (1999) The different forms of neurofibromatosis. Childs Nerv Syst 15:295–308

Rush JA, Younge BR, Campbell RJ, MacCarty CS (1982) Optic glioma. Long-term follow-up of 85 histopathologically verified cases. Ophthalmology 89:1213–1219

Rutka J, Hoffman H, Duncan J (1996) Astrocytomas of the posterior fossa. Blackwell Science, Cambridge

Sabatini D (2006) mTOR and cancer: insights into a complex relationship. Nat Rev Cancer 6:729–734

Sainte-Rose C, Cinalli G, Roux FE, Maixner R, Chumas PD, Mansour M, Carpentier A, Bourgeois M, Zerah M, Pierre-Kahn A, Renier D (2001) Management of hydrocephalus in pediatric patients with posterior fossa tumors: the role of endoscopic third ventriculostomy. J Neurosurg 95:791–797

Saito T, Hama S, Kajiwara Y, Sugiyama K, Yamasaki F, Arifin MT, Arita K, Kurisu K (2006) Prognosis of cerebellar glioblastomas: correlation between prognosis and immunoreactivity for epidermal growth factor receptor compared with supratentorial glioblastomas. Anticancer Res 26:1351–1357

Schneider JH Jr, Raffel C, McComb JG (1992) Benign cerebellar astrocytomas of childhood. Neurosurgery 30:58–62

Scott JN, Brasher PM, Sevick RJ, Rewcastle NB, Forsyth PA (2002) How often are nonenhancing supratentorial gliomas malignant? A population study. Neurology 59:947–949

Sener R (2002) Diffusion MRI in neurofibromatosis type 1: ADC evaluations of the optic pathways, and a comparison with normal individuals. Comput Med Imaging Graph 26:59–64

Sgouros S, Fineron PW, Hockley AD (1995) Cerebellar astrocytoma of childhood: long-term follow-up. Childs Nerv Syst 11:89–96

Shafqat S, Hedley-Whyte ET, Henson JW (1999) Age-dependent rate of anaplastic transformation in low-grade astrocytoma. Neurology 52:867–869

Sharma M, Zehnbauer B, Watson M, Gutmann D (2005) RAS pathway activation and an oncogenic RAS mutation in sporadic pilocytic astrocytoma. Neurology 65:1335–1336

Shaw EG, Wisoff JH (2003) Prospective clinical trials of intracranial low-grade glioma in adults and children. Neurooncology 5:153–160

Sievert AJ, Fisher MJ (2009) Pediatric low-grade gliomas. J Child Neurol 24:1397–1408

Sievert A, Jackson E, Gai X, Hakonarson H, Judkins A, Resnick A, Shaikh T, Biegel J (2008) Duplication of 7q34 in pediatric low-grade astrocytomas detected by high-density SNP-based genotyping. In: The 13th international symposium on pediatric neuro-oncology. Society for Neuro-Oncology, Chicago, p 379

Sievert AJ, Lang SS, Boucher KL, Madsen PJ, Slaunwhite E, Choudhari N, Kellet M, Storm PB, Resnick AC (2013) Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas. Proc Natl Acad Sci 10: 5957–5962

Smoots DW, Geyer JR, Lieberman DM, Berger MS (1998) Predicting disease progression in childhood cerebellar astrocytoma. Childs Nerv Syst 14: 636–648

Somaza SC, Kondziolka D, Lunsford LD, Flickinger JC, Bissonette DJ, Albright AL (1996) Early outcomes after stereotactic radiosurgery for growing pilocytic astrocytomas in children. Pediatr Neurosurg 25:109–115

Steinbok P, Mutat A (1999) Chapter 35: cerebellar astrocytoma. In: Albright AL, Pollack IF, Adelson PD (eds) Principles and practice of pediatric neurosurgery. Thieme, New York, p xxiii; 1300

Steinbok P, Hentschel S, Cochrane DD, Kestle JR (1996) Value of postoperative surveillance imaging in the management of children with some common brain tumors. J Neurosurg 84:726–732

Steinbok P, Poskitt K, Hendson G (2006) Spontaneous regression of cerebellar astrocytoma after subtotal resection. Childs Nerv Syst 22:572–576

Steinbok P, Mangat JS, Kerr JM, Sargent M, Suryaningtyas W, Singhal A, Cochrane D (2013) Neurological morbidity of surgical resection of pediatric cerebellar astrocytomas. Childs Nerv Syst 29:1269–1275

Sutton LN, Cnaan A, Klatt L, Zhao H, Zimmerman R, Needle M, Molloy P, Phillips P (1996) Postoperative surveillance imaging in children with cerebellar astrocytomas. J Neurosurg 84:721–725

Tamura M, Zama A, Kurihara H, Fujimaki H, Imai H, Kano T, Saitoh F (1998) Management of recurrent pilocytic astrocytoma with leptomeningeal dissemination in childhood. Childs Nerv Syst 14:617–622

Tao ML, Barnes PD, Billett AL, Leong T, Shrieve DC, Scott RM, Tarbell NJ (1997) Childhood optic chiasm gliomas: radiographic response following radiotherapy and longterm clinical outcome. Int J Radiat Oncol Biol Phys 39:579–587

Taratuto AL, Monges J, Lylyk P, Leiguarda R (1984) Superficial cerebral astrocytoma attached to dura. Report of six cases in infants. Cancer 54:2505–2512

Taveras JM, Mount LA, Wood EH (1956) The value of radiation therapy in the management of glioma of the optic nerves and chiasm. Radiology 66:518–528

Tenny R, Laws E Jr, Younge B et al (1982) The neurosurgical management of optic glioma: results in 104 Patients. J Neurosurg 57:452–458

Tsui K, Gajjar A, Li C, Srivastava D, Broniscer A, Wetmore C, Kun LE, Merchant TE, Ellison DW, Orr BA, Boop FA, Klimo P, Ross J, Robison LL, Armstrong GT (2015) Subsequent neoplasms in survivors of childhood central nervous system tumors: risk after modern multimodal therapy. Neuro Oncol 17:448–456

Viano JC, Herrera EJ, Suarez JC (2001) Cerebellar astrocytomas: a 24-year experience. Childs Nerv Syst 17:607–610; discussion 611

Vienneau D, Infanger D, Feychting M, Schüz J, Schmidt LS, Poulsen AH, Tettamanti G, Klæboe L, Kuehni CE, Tynes T, Von der Weid N, Lannering B, Röösli M (2015) A multinational case-control study on childhood brain tumours, anthropogenic factors, birth characteristics and prenatal exposures: a validation of interview data. Cancer Epidemiol 40:52–59

Vinchon M, Soto-Ares G, Ruchoux MM, Dhellemmes P (2000) Cerebellar gliomas in children with NF1: pathology and surgery. Childs Nerv Syst 16:417–420

von Hornstein S, Kortmann RD, Pietsch T, Emser A, Warmuth-Metz M, Soerensen N, Straeter R, Graf N, Thieme B, Gnekow AK (2011) Impact of chemotherapy on disseminated low-grade glioma in children and adolescents: report from the HIT-LGG 1996 trial. Pediatr Blood Cancer 56:1046–1054

Wang Z, Sutton LN, Cnaan A, Haselgrove JC, Rorke LB, Zhao H, Bilaniuk LT, Zimmerman RA (1995) Proton MR spectroscopy of pediatric cerebellar tumors. AJNR Am J Neuroradiol 16:1821–1833

Warren KE, Frank JA, Black JL, Hill RS, Duyn JH, Aikin AA, Lewis BK, Adamson PC, Balis FM (2000) Proton magnetic resonance spectroscopic imaging in children with recurrent primary brain tumors. J Clin Oncol 18:1020–1026

Watanabe K, Peraud A, Gratas C, Wakai S, Kleihues P, Ohgaki H (1998) p53 and PTEN gene mutations in gemistocytic astrocytomas. Acta Neuropathol 95:559–564

Wernicke C, Thiel G, Lozanova T, Vogel S, Witkowski R (1997) Numerical aberrations of chromosomes 1, 2, and 7 in astrocytomas studied by interphase cytogenetics. Genes Chromosomes Cancer 19:6–13

White FV, Anthony DC, Yunis EJ, Tarbell NJ, Scott RM, Schofield DE (1995) Nonrandom chromosomal gains in pilocytic astrocytomas of childhood. Hum Pathol 26:979–986

White JB, Piepgras DG, Scheithauer BW, Parisi JE (2008) Rate of spontaneous hemorrhage in histologically proven cases of pilocytic astrocytoma. J Neurosurg 108:223–226

Wisoff JH, Abbott R, Epstein F (1990) Surgical management of exophytic chiasmatic-hypothalamic tumors of childhood. J Neurosurg 73:661–667

Wolff JE, Gnekow AK, Kortmann RD, Pietsch T, Urban C, Graf N, Kuhl J (2002) Preradiation chemotherapy for pediatric patients with high-grade glioma. Cancer 94:264–271

Wong JY, Uhl V, Wara WM, Sheline GE (1987) Optic gliomas. A reanalysis of the University of California, San Francisco experience. Cancer 60:1847–1855

Yalon M, Rood B, MacDonald TJ, McCowage G, Kane R, Constantini S, Packer RJ (2013) A feasibility and efficacy study of rapamycin and erlotinib for recurrent pediatric low-grade glioma (LGG). Pediatric Blood and Cancer 60:71–76

Zattara-Cannoni H, Gambarelli D, Lena G, Dufour H, Choux M, Grisoli F, Vagner-Capodano AM (1998) Are juvenile pilocytic astrocytomas benign tumors? A cytogenetic study in 24 cases. Cancer Genet Cytogenet 104:157–160

Zuzak TJ, Poretti A, Drexel B, Zehnder D, Boltshauser E, Grotzer MA (2008) Outcome of children with low-grade cerebellar astrocytoma: long-term complications and quality of life. Childs Nerv Syst 24:1447–1455

High-Grade Gliomas

2

Jennifer S. Chang, Daphne A. Haas-Kogan,
and Sabine Mueller

Contents

J.S. Chang, MD, PhD (✉)
Department of Radiation Oncology, University of California San Francisco & UCSF Benioff Children's Hospital, 1600 Divisadero Street, Suite H1031, San Francisco, CA 94115, USA
e-mail: jennifer.s.chang@ucsf.edu

D.A. Haas-Kogan, MD
Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston Children's Hospital, 450 Brookline Ave. D1622, Boston, MA 02215-5418, USA
e-mail: dhaas-kogan@lroc.harvard.edu

S. Mueller, MD, PhD, MAS
Departments of Neurology, Neurosurgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, 625 Nelson Rising Lane, Room 402C, Sandler Neuroscience Building, San Francisco, CA 94158, USA
e-mail: sabine.mueller@ucsf.edu

2.1 Introduction

This chapter focuses on pediatric high-grade gliomas, with the exception of diffuse intrinsic pontine gliomas, which will be covered in a different chapter of this text. Gliomas arise from glial cells, which support and protect neurons and are most commonly differentiated along the astrocytic or oligodendroglial lineage. The World Health Organization (WHO) classification divides gliomas into low (WHO grade I and II)- and high-grade subgroups (Luis et al. 2007). High-grade pediatric central nervous system (CNS) tumors are comprised primarily of anaplastic astrocytomas (AA, WHO grade III) and glioblastoma multiforme (GBM, WHO grade IV), as anaplastic tumors with an oligodendroglial component are very uncommon in children (Hyder et al. 2007). High-grade gliomas can either present as high-grade disease, or they can result from transformation

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_2

of a low-grade tumor, although the latter is less common in children. In contrast to the adult population, high-grade gliomas in children are relatively infrequent, representing less than 20 % of cases (Pollack 1994; Packer 1999). The etiology for most pediatric CNS tumors is unknown, although some genetic syndromes are associated with an increased risk. Despite advances in treatment for other childhood tumors, patients with high-grade gliomas invariably have a poor outcome, and 5-year survival rates remain less than 20 %.

2.2 Epidemiology

Malignant gliomas represent 6.5 % of all newly diagnosed childhood intracranial neoplasms (Tamber and Rutka 2003), and high-grade gliomas account for 15–20 % of all pediatric brain tumors (Pollack 1994; Packer 1999). No clear link has been established between any environmental factor and the occurrence of high-grade gliomas, except for prior radiation exposure (Pettorini et al. 2008). There are several genetic syndromes associated with high-grade gliomas in children, including neurofibromatosis type 1 (NF1), Turcot syndrome, and Li-Fraumeni syndrome. NF1 is an autosomal dominant disorder that is most commonly associated with optic pathway gliomas but also carries an increased risk for developing high-grade gliomas. Turcot syndrome refers to the combination of colorectal polyposis and primary tumors of the CNS, typically divided into two groups: mutations in mismatch repair genes *hMSH2*, *hMSH6*, *hMLH1*, and *hPMS2* associated with astrocytomas and in the *APC* gene associated with medulloblastomas (Turcot et al. 1959; Hamilton et al. 1995; Hegde et al. 2005). Li-Fraumeni syndrome is a clinically and genetically heterogeneous inherited cancer syndrome associated with a high incidence of childhood brain tumors and mutations in the tumor suppressor gene *TP53* (Li et al. 1988; Varley et al. 1997).

2.3 Pathology

2.3.1 Histopathology

AA and GBM are diffusely infiltrative, malignant gliomas. In addition to high mitotic activity, the main cellular feature of malignant glial cells is local tissue invasion that typically occurs along deep white matter tracts such as the corpus callosum, anterior commissure, fornix, and internal capsule. Gliomatosis cerebri refers to an unusual pattern of growth in which malignant astrocytomas demonstrate diffuse infiltration as a primary feature, often throughout the entire hemisphere.

Compared to a low-grade astrocytoma, AA exhibits nuclear atypia, greater cellularity, multiple mitotic figures, and a high degree of cellular pleomorphism. The diagnosis of GBM is usually made by the additional presence of necrosis or microvascular proliferation. As the name implies, the character of GBM is heterogeneous; firm areas alternate with soft or cystic regions, and mottled areas of hemorrhage and necrosis give the gross specimen an overall moth-eaten appearance. The borders are often poorly defined. Significant variation in cellularity is often seen in different parts of the tumor and can lead to misdiagnosis if the tumor is sampled incompletely.

GBMs often have three zones. Confluent areas of tissue necrosis and degeneration correspond to the central area of low attenuation on neuroimaging studies. This central region is often surrounded by an irregular zone of denser, more vascular tissue that corresponds to areas of higher attenuation and contrast enhancement. Finally, there is a peripheral zone of lesser cell density, edema, and microscopic tumor infiltration. This peripheral zone may vary in contour, with fingerlike projections extending from the main tumor bulk.

Other less common tumor types included in the high-grade glioma category according to WHO criteria are anaplastic oligodendrogliomas (AO), anaplastic mixed gliomas (AMG), and anaplastic variants of pleomorphic xanthoastrocytoma, ganglioglioma, and pilocytic astrocytoma. Diagnosis of AO and AMG have been shown to be especially

challenging. In an analysis of the Children's Cancer Group (CCG) 945 study of 250 children with malignant gliomas, central review confirmed only 35 % of the 26 cases initially diagnosed as AMG and 25 % of the four initially diagnosed as AO (Hyder et al. 2007).

2.3.2 Molecular Biology

Pediatric high-grade gliomas differ in molecular characteristics from their adult counterparts, despite histological similarities. Not only do the mutation patterns differ, but the prognostic implications differ as well. Table 2.1 summarizes key genetic alterations in pediatric high-grade gliomas.

A strong association between proliferation index and outcome was found using samples derived from the multi-institutional CCG 945 study (Pollack et al. 2002b). MIB-1 labeling was lower for tumors classified as AA compared to GBM. Furthermore, there was a significant inverse correlation between proliferative index and PFS. Five-year progression-free survival (PFS) was 33 ± 7 % in 43 patients whose tumors had MIB-1 indices of less than 18 %, 22 ± 8 % in the 27 patients whose tumors had indices between 18 % and 36 %, and 11 ± 6 % in the 28 patients whose tumors had indices greater than 36 % ($p = 0.003$) (Pollack et al. 2002a). These results suggest MIB-1 index is a prognostic factor.

Studies have shown that pediatric high-grade gliomas have a high incidence (40.5 %) of mutations in the tumor suppressor gene *TP53* (Pollack et al. 2006a). Although p53 mutations have not been linked to prognosis in adults, low p53 expression has been shown to correlate with improved 5-year PFS in children. Those with low p53 expression by immunohistochemistry had a 44 % PFS rate compared to 17 % in patients with p53 overexpression (Pollack et al. 2001, 2002a). Several other mutations and altered expression patterns have been identified in pediatric high-grade gliomas, although for many of them, the prognostic significance remains less well defined. Compared with adults, children with high-grade gliomas have been found to have less frequent amplification of the epidermal growth factor receptor (*EGFR*) gene and less frequent mutations in the tumor suppressor *PTEN* (Bredel et al. 1999; Finlay et al. 1995; Nakamura et al. 2007; Pollack et al. 2006a). Despite the low rate of *PTEN* mutations, however, about 80 % demonstrate activation of the PI3-kinase/Akt/mTOR pathway, potentially through altered *PTEN* promoter methylation (Pollack et al. 2010; Mueller et al. 2012). Overexpression of Y-box-protein 1 (YB1) has been observed in many pediatric GBMs, a subset of which shows Ras and Akt pathway activation (Faury et al. 2007). Also, high-resolution genomic analysis of *de novo* pediatric high-grade gliomas revealed the tyrosine kinase receptor gene *PDGFRA* to be a target of focal amplification (Paugh et al. 2010).

In more recent studies, somatic mutations in H3F3A, encoding histone H3.3, have been identified in a third of non-brainstem pediatric glioblastomas (Schwartzentruber et al. 2012; Sturm et al. 2012; Wu et al. 2012). The mutations affect either amino acid K27 or G34, and the two mutations have been found to define different epigenetic subgroups, with distinct global methylation patterns. The K27 cluster has a median age of 10 and includes tumors that are typically midline (thalamus, brainstem, spinal cord), often with *TP53* mutations and with a poor prognosis. The G34 cluster has a higher median age of 18, is localized to the cortex, and is associated with improved prognosis.

In addition to the two H3F3A-mutant subgroups for childhood glioblastoma, a third, non-overlapping subgroup has been defined as having mutations in the isocitrate dehydrogenase (IDH) 1 gene (Sturm et al. 2012). Those tumors showed global hypermethylation and had improved overall survival. Previous analysis of CCG 945 samples had shown IDH1 mutations to be more prevalent in older children, including 7 of 20 tumors from children 14 years or older but 0 of 23 tumors from younger

Table 2.1 Key molecular and genetic alterations in pediatric and adult gliomas

	Occurrence in pediatric HGG (%)	Occurrence in pediatric AA (%)	Occurrence in pediatric GBM (%)	Occurrence in adult HGG (%)	Reference
Akt overexpression	79 (42/53)				Pollack et al. (2010)
BRAF V600E mutation		33 (3/9)	0 (0/11)		Schiffman et al. (2010)
CDKN2A inactivation		22 (2/9)	27 (3/11)		Schiffman et al. (2010)
	19				Paugh et al. (2010)
EGFR amplification		10 (1/10)	11 (2/18)	30–40	Nakamura et al. (2007)
	2.9 (1/34)				Pollack et al. (2006a)
		0 (0/17)	0 (0/15)		Raffel et al. (1999)
	7.4 (2/27)				Bredel et al. (1999)
	0 (0/24)				Cheng et al. (1999)
EGFR overexpression	80 (17/22)			30–40	Thorarinsdottir et al. (2008)
	58 (23/40)				Liang et al. (2008)
	28 (8/28)				Nakamura et al. (2007)
			36 (14/38)		Pollack et al (2006a)
	25.9 (13/54)				Ganigi et al. (2005)
	81 (22/27)				Bredel et al. (1999)
			11 (2/19)		Sure et al. (1997)
EGFRvIII expression	2.5 (1/40)			10–67	Liang et al. (2008)
	17 (6/35)				Bax et al. (2009)
IDH1 mutation		0 (0/9)	0 (0/11)		Schiffman et al. (2010)
		36 (5/14)	18 (6/33)		Setty et al. (2010)
MGMT overexpression	11 (12/109)				Pollack et al. (2006b)
MGMT methylation			40 (4/10)	45	Donson et al. (2007)
PDGFR-α amplification		0 (0/28)		10–15	Nakamura et al. (2007)
	12				Paugh et al. (2010)
			17		Bax et al. (2010)
PTEN mutation/deletion/alteration	33 (13/39)			20–30	Liang et al. (2008)
			11 (2/18)		Nakamura et al. (2007)
			28 (7/25)		Pollack et al. (2006a)
Rb mutation/loss of expression			7.4 (4/54)	70–85	Ganigi et al. (2005)
TP53 mutation		30 (3/10)	33 (6/18)	30–35	Nakamura et al. (2007)
		33 (3/9)	36 (4/11)		Schiffman et al. (2010)
	33 (40/121)				Pollack et al. (2002a)
	38 (9/24)				Cheng et al. (1999)
		24 (4/17)	20 (3/15)		Raffel et al. (1999)
			25 (5/20)		Sure et al. (1997)
p53 overexpression	35 (14/40)				Liang et al. (2008)
	35 (41/115)				Pollack et al. (2002a)
			53.7 (29/54)		Ganigi et al. (2005)

Genetic alterations in pediatric gliomas. Percentages are given for anaplastic astrocytoma (AA) and glioblastoma (GBM) separately if included in the analysis; otherwise AA and GBM are grouped into high-grade glioma (HGG). *BRAF* B rapidly accelerated fibrosarcoma, *CDKN* cyclin-dependent kinase inhibitor, *EGFR* epidermal growth factor receptor, *IDH* isocitrate dehydrogenase, *MGMT* O^6-methylguanine–DNA methyltransferase, *PDGFR* platelet-derived growth factor receptor, *PTEN* phosphatase and tensin homologue, *Rb* retinoblastoma

children ($p = 0.0024$) (Pollack et al. 2011). No mutations in IDH2 were observed in either group. Both 1-year event-free survival and overall survival were significantly better for the older children with IDH1 mutations.

Other chromatin regulators are mutated in high-grade gliomas in children. The α-thalassaemia/mental retardation syndrome X-linked (*ATRX*) and death-domain-associated protein (*DAXX*) genes were found to be mutated in 31% of pediatric GBMs (Schwartzentruber et al. 2012). The genes encode two proteins in a chromatin-remodeling complex that is required for H3.3 histone incorporation at pericentric heterochromatin and telomeres. Furthermore, the mutations are associated with a telomerase-independent mechanism of lengthening their telomeres.

Mutations in the serine/threonine protein kinase B-Raf have been found in many cancers, and a genome-wide search detected BRAF mutations in several malignant astrocytoma samples in children (Schiffman et al. 2010). On further analysis, about 10% of malignant astrocytomas have been found to harbor $BRAF^{V600E}$ mutations (Nicolaides et al. 2011), although the mutation is rare in adult gliomas. Individual case reports have demonstrated encouraging results with targeted agents in BRAF-mutant pediatric glioblastoma (Robinson et al. 2014), and clinical trials are in progress.

Current studies aim to further delineate the underlying molecular biology of high-grade gliomas in children. Given the rarity of these tumors, however, significant sample sizes can only be obtained through multi-institutional studies.

2.4 Clinical Features

Exact signs and symptoms caused by high-grade supratentorial gliomas depend upon the anatomic location, biologic aggressiveness, and patient age. These signs and symptoms may be nonspecific, such as those resulting from the effects of increased intracranial pressure, or they may be directly related to the location of the tumor. Nonspecific symptoms include headache, nausea, and vomiting. Focal symptoms may include hemiparesis, monoparesis, hemisensory loss, dysphasia, aphasia, and impairment of recent memory.

Worrisome features of headaches that should alert the clinician are those that wake the child up from sleep, occur on awakening in the morning, involve nausea and vomiting, cause consistent focal pain, worsen with Valsalva maneuvers, progress in severity, fail to respond to any therapy, or occur in the setting of an abnormal neurologic exam (Duffner 2007). In infants with open cranial sutures, tumors may reach a massive size with gradual increase in head circumference without signs of increased intracranial pressure. Subtle symptoms such as increased irritability, change in feeding pattern, and failure to thrive are often misinterpreted.

The time from first symptom to diagnosis is shorter in high-grade gliomas than in low-grade tumors (Mehta et al. 2002; Duffner 2007). Malignant gliomas are less frequently associated with seizures and are more likely to cause focal neurologic deficits, mainly due to infiltration of normal tissue or local mass effect. Disseminated disease at presentation is rare, in contrast to cases involving other malignant pediatric brain tumors such as supratentorial primitive neuroectodermal tumors and medulloblastomas (Benesch et al. 2005).

2.5 Diagnostic Imaging

Magnetic resonance imaging (MRI) and computerized tomography (CT) are essential tools in the diagnosis and treatment of brain tumors. Although CT is more commonly available and can be performed quickly in children, MRI provides higher sensitivity in differentiating tumor tissue from normal brain, allowing for more detailed anatomic characterization of the lesion. MRI should therefore be obtained in all children with a suspected brain tumor. A complete series should include the following sequences:

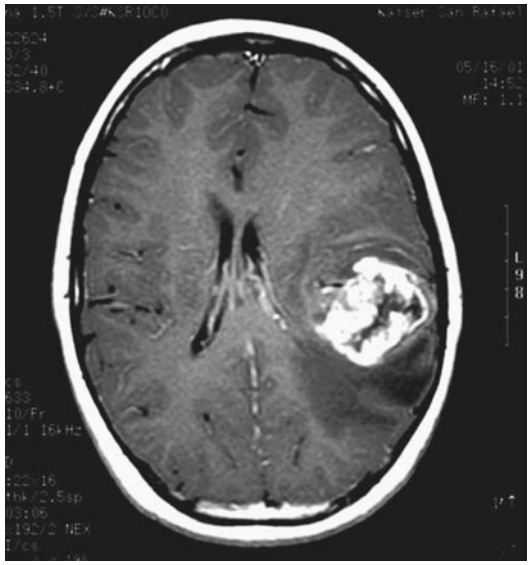

Fig. 2.1 A post-contrast T1-weighted axial MR image of a teenage boy with a glioblastoma who presented with dysphasia. A large tumor in the left frontoparietal area is visible. The margin of the tumor enhances, a central necrotic area is visible, and the low signal region surrounding the mass represents tumor-associated edema

T1-weighted axial and coronal (both before and after gadolinium), T2-weighted axial and coronal, and fluid-attenuated inversion recovery (FLAIR). In addition, sagittal plane sequences are helpful in defining the anatomy of suprasellar and midline tumors. Other sequences such as fat suppression and MR angiography may also be required in specific situations. Contrast-enhanced neuroimaging of the entire neuraxis should be considered if there is a high index of suspicion for the presence of disseminated disease at the time of evaluation. Newer techniques, such as MR spectroscopy, functional MRI, and perfusion measurements offer the potential for obtaining biochemical and functional information noninvasively (see Chap. 13 for more details).

Compared to other malignant brain tumors, high-grade gliomas do not have specific MR imaging features. In general, they appear hypointense on T1-weighted images and hyperintense on T2-weighted sequences. Enhancement occurs after contrast administration with gadolinium, but the degree of enhancement does not correlate with tumor grade (Fig. 2.1). For example, many pilocytic astrocytomas (WHO grade I) demonstrate variable degrees of enhancement. On T1-weighted images, GBMs are typically poorly circumscribed and often demonstrate central areas of low density corresponding to necrosis. This area is surrounded by an area of high density that enhances with contrast, corresponding to actively dividing and proliferating tumor cells. A third, low-attenuation area around the tumor is often seen representing tumor-associated

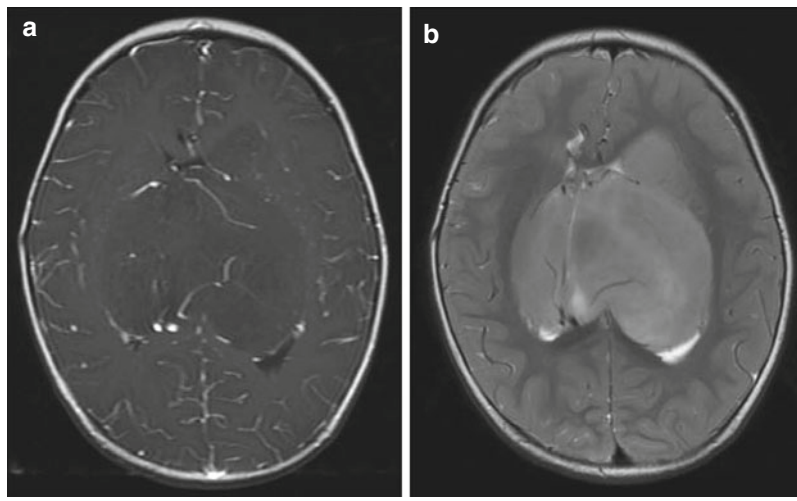

Fig. 2.2 A diffusely infiltrating bilateral thalamic astrocytoma (grade III) in a 2-year-old boy. The tumor does not enhance on T1-weighted images (**a**). The extent of the tumor is better appreciated on T2-weighted images (**b**)

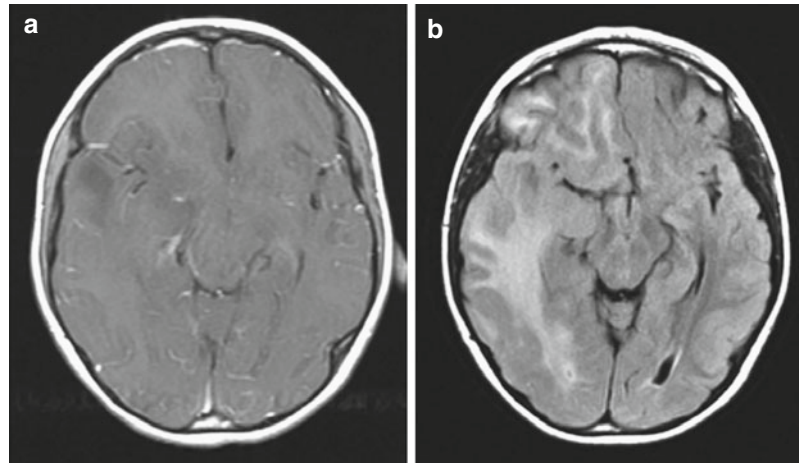

Fig. 2.3 Gliomatosis cerebri. The tumor is difficult to appreciate on T1-weighted images (**a**). An axial fluid-attenuated inversion recovery (FLAIR) image (**b**), however, clearly shows a diffuse infiltrative process extending from the frontal lobe into the occipital lobe. Distortion of the cerebral peduncle is seen from the enlarged temporal lobe

vasogenic edema but also containing infiltrating tumor cells. Peritumoral edema surrounding most high-grade astrocytomas appears as a hyperintense region of signal abnormality on T2-weighted images. The extent of peritumoral edema is underestimated on T1-weighted images. High-grade tumors demonstrate increased blood flow on perfusion studies and elevated choline/N-acetylaspartate (NAA) ratios on MR spectroscopy (see Chap. 13). Thalamic tumors can present as diffuse swelling of the entire thalamus, with or without significant edema (Fig. 2.2).

The differential diagnosis based purely on imaging appearance includes other malignant supratentorial hemispheric tumors, such as ependymoma, supratentorial primitive neuroectodermal tumor (PNET), and pleomorphic xanthoastrocytoma. Gliomatosis cerebri is usually diagnosed by widespread infiltration of tumor throughout the hemisphere. A focal lesion is usually not present, although the mass effect can be substantial (Fig. 2.3).

Recurrence is an unavoidable feature of most glial neoplasms. For this reason, serial imaging is often the only method to determine whether tumor progression has occurred. Grade II astrocytomas often recur as higher-grade lesions, which usually have imaging features consistent with GBM. Most patients with high-grade gliomas are treated as part of a clinical trial, and the frequency of screening MRIs is generally included in the study design and is frequently performed every 3 months in the first year after diagnosis.

2.6 Treatment

2.6.1 Surgery

Aggressive resection, with preservation of neural function, is the cornerstone of initial management of children with high-grade astrocytomas. The primary objectives are to obtain tissue for pathologic diagnosis, to relieve increased intracranial pressure if present, and to decrease tumor burden. The secondary objective is to perform as extensive a resection as possible with acceptable neurologic outcome. However, high-grade gliomas are diffusely infiltrative lesions, and therefore it remains challenging for the neurosurgeon to define the tumor boundaries during the resection process. For deep lesions or those in eloquent cortex, a stereotactic needle biopsy may be the only surgical option.

Multiple studies have shown gross total resection (GTR) to be linked to longer survival (Finlay et al. 1995; Heideman et al. 1997; Wolff et al. 2002; Yang et al. 2013). In the CCG 945 study, children with high-grade gliomas who underwent GTRs (defined as >90 %) had a 5-year PFS rate of 35 ± 7 % compared to 17 ± 4 % in the group with subtotal resections (STR) ($p = 0.006$) (Wisoff et al.

1998). This association persisted in subgroup analyses based on histology. Furthermore, the HIT-GBM-C study of multi-agent chemotherapy found 5-year event-free survival to be 13 % overall, but this was improved to 48 % for children with complete resection (Wolff et al. 2010). Complicating the interpretation of data on resection, however, is the inconsistent and subjective methodology used in determining extent of resection.

The feasibility of an open surgical approach depends upon several factors, the most important of which is the exact location of the tumor. Deep lesions within the basal ganglia, thalamus, motor cortex, or brainstem are not amenable to open surgical resection, while tumors in other locations can be accessed through various standard approaches. Thalamic tumors in general are considered unfavorable for resection and therefore carry a dismal prognosis (Fig. 2.2). Other factors that modify the decision to attempt surgical resection are the patient's clinical condition, age, associated hydrocephalus, and the surgeon's assessment of risk of neurologic sequelae.

Contemporary neurosurgical methods, including ultrasonography, functional mapping, frameless navigational resection devices, and intraoperative imaging techniques enable more extensive resections with less morbidity. These techniques and intraoperative considerations specific to the pediatric age group are discussed in detail in Chap. 14.

2.6.2 Radiation Therapy

Radiation therapy is the only adjuvant therapy that has been proven to improve survival of children with brain tumors, and it remains the standard of therapy after surgical resection for older children. Children older than 3 years are treated with 50–60 Gy of external beam radiation delivered with standard daily fractions of 1.8–2.0 Gy. Conformal techniques that allow treatment planning based on three-dimensional reconstructions have dramatically advanced the area of radiation oncology (see Chap. 16). Attempts at dose intensification by dose escalation (to a cumulative total dose of 72 Gy) in conjunction with hyperfractionation have failed to improve outcome in the setting of high-grade gliomas (Fulton et al. 1992; Packer et al. 1993). Hyperfractionated radiotherapy utilizes lower doses of radiation per fraction (usually 1–1.1 Gy) administered more than once daily. Decreasing the dose per fraction theoretically spares healthy tissue more than it spares tumor cells, allowing for higher total doses to the tumor, while limiting long-term side effects.

Long-term side effects of radiotherapy include neurocognitive decline, vasculopathies, endocrine abnormalities, as well as secondary malignancies (Armstrong et al. 2004). The effects of radiation are particularly harmful to the developing brain, and therefore the aim of postsurgical therapy has been to limit the use of radiotherapy in children less than 3 years of age. Two multi-institutional studies reported that outcome at younger age was better without the use of radiation therapy compared to older children (Geyer et al. 1995; Duffner et al. 1996). Children less than 2 years were treated with an "8-in-one-day" chemotherapy regimen after surgical resection without the use of radiation and had a PFS rate of 36 ± 8 % and an overall survival rate of 51 ± 8 % at 3 years. Analyzed by histological grade, patients with AA had more favorable outcomes than those with GBMs, as expected; PFS rates were 44 ± 11 % and 0 %, respectively (Geyer et al. 1995). Another study demonstrated that children less than 3 years of age treated for high-grade gliomas with vincristine and cyclophosphamide after surgical resection had a 3-year PFS rate of 43 ± 16 % and a 5-year overall survival rate of 50 ± 14 % (Duffner et al. 1996). Whether and why the younger child has a better response to chemotherapy without radiation remains to be elucidated. Currently, children less than 3 years of age are treated with chemotherapy after resection, seeking to delay radiotherapy until at least 3 years of age.

2.6.3 Chemotherapy

The effectiveness of adjuvant cytotoxic chemotherapy in conjunction with radiation for high-grade glioma is uncertain. A Phase III trial

conducted by the CCG evaluated postoperative radiation therapy with or without chemotherapy with prednisone, lomustine, and vincristine. Children who received postradiation chemotherapy had better PFS (46 %) than those who did not (26 %) (Sposto et al. 1989). However, concerns have since been raised that some low-grade gliomas may have been included in the study, confounding interpretation of the results. In a subsequent CCG study, patients were randomized to receive one of two chemotherapy regimens comparing an intensive "8-drugs-in-one-day" regimen to the more standard regimen of prednisone, vincristine, and lomustine. No difference in 5-year PFS was seen between these regimens (33 vs. 36 %) (Finlay et al. 1995). Based on these data, adding adjuvant chemotherapy to radiation may provide a small survival benefit, and standard agents are lomustine and vincristine in combination with procarbazine (PCV).

Since these early studies, chemotherapy has been added to radiation therapy in different schedules including a "sandwich" protocol (prior to and after radiation therapy), concomitant administration, and maintenance therapy. Agents including etoposide, cyclophosphamide, irinotecan, platinum compounds, PCV, and topotecan have been studied in Phase II trials with marginal effects on overall survival. Since concomitant temozolomide (TMZ) and radiation therapy for adult GBM patients led to prolonged survival (Stupp et al. 2002, 2005), several studies have tested the efficacy of this drug in pediatric brain tumors. Multiple studies including high-grade gliomas and recurrent gliomas have shown minimal effects of TMZ on survival in the pediatric population (Estlin et al. 1998; Lashford et al. 2002; Nicholson et al. 2007; Cohen et al. 2011). Additional trials have evaluated TMZ in combination with O^6-benzylguanine, an inhibitor of the DNA repair protein O^6-alkylguanine-DNA alkyltransferase (Warren et al. 2011). However, no significant benefit was seen. These studies suggest that TMZ is less effective in pediatric patients with high-grade astrocytomas than it is in adults.

High-dose myeloablative chemotherapy with autologous hematopoietic stem cell rescue (ASCR) has also been explored, and its role in the treatment of high-grade glioma remains unproven. The CCG 9922 study using thiotepa, BCNU, and etoposide followed by ASCR and focal radiation therapy resulted in a 2-year PFS rate of 46 ± 14 % (Grovas et al. 1999). This study was closed early after 5 of the 11 treated patients developed significant pulmonary complications. Another study using thiotepa in patients with newly diagnosed high-grade gliomas showed a 4-year survival rate of 46 % (Massimino et al. 2005). The most appropriate candidates for myeloablative therapy are those with complete or near-complete resection prior to myeloablative therapy (Marachelian et al. 2008). The use of high-dose chemotherapy with ASCR may contribute to long-term disease control, but at the expense of significant morbidity and mortality as a consequence of the regimens themselves. The associated side effects and resultant poor quality of life have led many investigators to question the benefit of high-dose chemotherapy with ASCR, despite the potential for better disease control.

With the development of molecular tumor analysis, several promising treatment approaches have emerged for targeted therapies. Especially promising are agents for $BRAF^{V600E}$-mutant astrocytomas that comprise about 10 % of high-grade gliomas. The kinase inhibitor vemurafenib has been shown to improve overall survival in patients with other $BRAF^{V600E}$-mutant cancers, such as melanoma (Chapman et al. 2011). Although studies in other diseases have shown tumors to develop escape mechanisms months after an initial response period (Chapman et al. 2011), addition of a second agent such as the mitogen-activating protein kinase pathway (MEK) inhibitor trametinib has been found to improve PFS (Flaherty et al. 2012). The Pacific Pediatric Neuro-Oncology Consortium (PNOC) is currently conducting a Phase I clinical trial of vemurafenib for $BRAF^{V600E}$-mutant astrocytomas in children.

Another recent line of investigation involves immunomodulation, in which different strategies are used to generate an immune response against the patient's tumor cells. In many cases, tumor-directed vaccines have been created. A

subcutaneous vaccine made with several glioma-associated antigen (GAA) peptides showed anti-GAA responses in 13 of 21 children with diffuse brainstem and other high-grade gliomas, without any dose-limiting non-CNS toxicity (Pollack et al. 2014). Other groups are investigating high-grade glioma vaccines that specifically target dendritic cells, which are professional antigen-presenting cells that link the innate and adaptive immune responses (Palucka and Banchereau 2012). Additional childhood high-grade glioma trials have been initiated with natural killer cells, which are cytotoxic lymphocytes that can function in both the innate and adaptive immune response.

Clinical trials are also investigating different mechanisms to more selectively target therapies to tumor cells. In one trial, modified herpes simplex virus (HSV) 1716 was injected into the resection cavity of high-grade gliomas (Harrow et al. 2004). The virus lyses dividing cells in the area but not the non-replicating normal tissue. Preliminary studies have been performed in adults, and additional clinical trials in children are in progress. Another tumor targeting approach has been to conjugate glioma-specific monoclonal antibodies to radioactive substances such as iodine-131, causing beta emission to be concentrated in areas of tumor. Further studies of other drug delivery mechanisms, such as intranasal delivery and convection-enhanced delivery, are in progress.

Currently, a combination of surgery, radiation, and chemotherapy is the standard therapy for children with high-grade gliomas who are older than 3 years. For children less than 3 years, chemotherapy after surgical resection is the mainstay of therapy. Several promising trials are underway for targeted agents and immunomodulatory approaches. However, the best regimens still need to be determined, and newer strategies are urgently needed to improve the overall outcome.

2.7 Outcome

Outcomes for childhood high-grade gliomas remain poor, although many published studies show outcomes to be generally better than for adults. It is unclear if this survival difference is due to differences in underlying pathology and molecular mechanisms, therapeutic approaches, inherent tumor resectability, or other factors. One hypothesis is that earlier trials of high-grade pediatric gliomas may have included patients who would currently be classified as having low-grade tumors. This misclassification could have biased trial outcomes.

Within the pediatric population, certain molecular characteristics such as low p53 expression, IDH1 mutation in older children, and lower MIB-1 index have been associated with improved outcome, as outlined above. Other factors linked to better outcome are histological grade and extent of resection. Patients with GTRs live longer than those with STRs, who in turn live longer than those who have only biopsies. Patients with GBMs have a 20 % survival rate after GTR and adjuvant therapy. Patients with partially resected GBMs rarely survive (Finlay et al. 1995). However, the literature regarding the prognostic impact of surgery is controversial, mainly due to a lack of well-controlled, randomized studies addressing the issue. The prognosis for children with recurrent high-grade glioma is dismal, and most children die within 1 year.

Children treated for brain tumors have long-term consequences owing to their tumors and treatments. Standard use of radiation therapy is associated with well-known risks of late cognitive and neuropsychological sequalae, endocrine abnormalities, as well as vasculopathies. Current strategies aim to target more precisely the tumor cells while minimizing the volume of normal brain irradiated. Such novel technologies can significantly spare key structures such as the hippocampus and neural stem cell compartments and thus may translate into decreased radiation-induced cognitive dysfunction (Barani et al. 2007; Gutierrez et al. 2007; Merchant et al. 2008). The often devastating consequences of radiation therapy in children less than 3 years of age led to substantial attention to refining strategies that either delay or avoid radiotherapy entirely in this population, by first administering an extended course of intensive chemotherapy. Children who receive treatment for a brain tumor should undergo regular neurocognitive

assessments and, if indicated, specific cognitive-behavioral training. Furthermore, these patients require long-term follow-up in specialized clinics. Secondary malignancies in brain tumor survivors have been reported. Among others, alkylating agents, etoposide, and radiation are causative agents for further malignancies.

2.8 Future Directions

The main goal of ongoing investigations is to improve overall survival as well as to enhance long-term quality of life and reduce treatment-related toxicities. The role of radiation and surgery is well established in the treatment of high-grade gliomas in children, but the optimal chemotherapy regimen still warrants further research.

Current studies tackle several aspects of treatment and examine new combinations of drugs, optimal chemotherapy dose intensities, and radiosensitizing agents to enhance the efficacy of proven therapies while limiting side effects. Novel targeted therapies aim to interfere with the molecular pathways associated with AA and GBM, as listed in Table 2.2. These small-molecule inhibitors are tested as single agents as well as in combination with conventional chemotherapy and radiation. Additional pilot studies attempt to harness the immune system in targeting cancer cells. Studies are underway for vaccines targeting tumors expressing the human lymphocyte antigen (HLA) A2-restricted glioma antigens or for using activated natural killer cells or dendritic cells to target cancer cells.

Technologies to improve local drug delivery are currently part of intensive research and

Table 2.2 Current clinical trials using small-molecule inhibitors for newly diagnosed or recurrent high-grade glioma in children

	Drug	Type of study	Intracellular target	Disease indication
ALK inhibitor	Crizotinib[a]	Phase I/II	c-Met, ALK	RE/REF
Antiangiogenic agents	Bevacizumab	Phase I/II	VEGF-A	RE/REF
	Dasatinib[a]	Phase I	PDGFRA, B	New/RE/PRO
Cell cycle	Cabazitaxel	Phase I/II	Microtubule	RE/REF
	Palbociclib[a]	Phase I	CDK4, CDK6	RE/PRO/REF
EGFR inhibitor	Cetuximab	Phase I/II	EGFR	RE/REF
Histone deacetylase inhibitor	Vorinostat	Phase I/II	HDAC	REF
mTOR inhibitor	Everolimus[a]	Phase I	mTOR	RE/REF
Monoclonal antibody	3F8-^{131}I[a]	Phase II	GD2	RE/REF
	8H9-^{131}I	Phase I		RE/REF
Oncolytic virus	HSV-1716[a]	Phase I	Immunomodulatory	RE/REF
Protein kinase inhibitor	Dabrafenib	Phase I	BRAF	RE/REF
	Erlotinib[a]	Feasibility	EGFR	RE/REF
	PLX3397	Phase I/II	Kit, CSF1R/FMS, Flt3	RE/REF
	Sorafenib[a]	Feasibility	VEGFR, PDGFR, RAF	RE/REF
	Trametinib	Phase I	MEK	RE/REF
	Vemurafenib[a]	Phase II	BRAF V600E	RE/REF
ALK inhibitor	Crizotinib	Phase I/II	c-Met, ALK	RE/REF
Histone deacetylase inhibitor	Vorinostat	Phase I/II	HDAC	REF

[a]Studies specific to high-grade gliomas

Ab antibody, *CDK* cyclin-dependent kinase, *EGFR* epidermal growth factor receptor, *HDAC* histone deacetylase, *MGMT* O^6-methylguanine–DNA methyltransferase, *mTOR* mammalian target of rapamycin, *New* newly diagnosed tumors, *PDGFR* platelet-derived growth factor receptor, *PRO* progressive disease, *RE* recurrent disease, *REF* refractory disease, *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor, *MEK* mitogen-activated protein kinase kinase

include convection-enhanced delivery, antibody- or ligand-mediated targeting of tumor cells, and radionuclide conjugates specifically designed to bind directly to tumor cells. Gene therapy using toxin-producing viral vector constructs to induce selective killing of rapidly proliferating tumor cells is also under current investigations.

Conclusions

High-grade gliomas are less common in the pediatric population compared to adults but cause significant morbidity and mortality. In children greater than 3 years of age, high-grade tumors are treated aggressively with surgery, radiation, and adjuvant chemotherapy, although the role of chemotherapy remains uncertain. For the child less than 3 years of age, the goal is to delay radiation therapy, using chemotherapy regimens to avoid significant side effects of radiation on the developing brain. Children with high-grade gliomas have poor prognoses, and the long-term outcome remains poor. Current research focuses on elucidating the underlying molecular pathways to better direct the development of new therapies.

References

Armstrong CL, Gyato K et al (2004) A critical review of the clinical effects of therapeutic irradiation damage to the brain: the roots of controversy. Neuropsychol Rev 14(1):65–86

Barani IJ, Cuttino LW et al (2007) Neural stem cell-preserving external-beam radiotherapy of central nervous system malignancies. Int J Radiat Oncol Biol Phys 68(4):978–985

Bax DA, Gaspar N et al (2009) EGFRvIII deletion mutations in pediatric high-grade glioma and response to targeted therapy in pediatric glioma cell lines. Clin Cancer Res 15:5753–5761

Bax DA, Mackay A et al (2010) A distinct spectrum of copy number aberrations in pediatric high-grade gliomas. Clin Cancer Res 16(13):3368–3377

Benesch M, Wagner S et al (2005) Primary dissemination of high-grade gliomas in children: experiences from four studies of the Pediatric Oncology and Hematology Society of the German Language Group (GPOH). J Neurooncol 72(2):179–183

Bredel M, Pollack IF et al (1999) Epidermal growth factor receptor expression and gene amplification in high-grade non-brainstem gliomas of childhood. Clin Cancer Res 5(7):1786–1792

Chapman PB, Hauschild A et al (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364(26):2507–2516

Cheng Y, Ng HK, Zhang SF et al (1999) Genetic alterations in pediatric high-grade astrocytomas. Hum Pathol 30:1284–1290

Cohen KJ, Pollack IF et al (2011) Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro-Oncology 13:317–323

Donson AM, Addo-Yobo SO, Handler MH, Gore L, Foreman NK (2007) MGMT promoter methylation correlates with survival benefit and sensitivity to temozolomide in pediatric glioblastoma. Pediatr Blood Cancer 48:403–407

Duffner PK (2007) Diagnosis of brain tumors in children. Expert Rev Neurother 7(7):875–885

Duffner PK, Krischer JP et al (1996) Treatment of infants with malignant gliomas: the Pediatric Oncology Group experience. J Neuro-Oncol 28(2–3):245–256

Estlin EJ, Lashford L et al (1998) Phase I study of temozolomide in paediatric patients with advanced cancer. United Kingdom Children's Cancer Study Group. Br J Cancer 78(5):652–661

Faury D, Nantel A et al (2007) Molecular profiling identifies prognostic subgroups of pediatric glioblastoma and shows increased YB-1 expression in tumors. J Clin Oncol 25(10):1196–1208

Finlay JL, Boyett JM et al (1995) Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. Childrens Cancer Group. J Clin Oncol 13(1):112–123

Flaherty KT, Infante JR et al (2012) Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 367:1694–1703

Fulton DS, Urtasun RC et al (1992) Increasing radiation dose intensity using hyperfractionation in patients with malignant glioma. Final report of a prospective phase I–II dose response study. J Neurooncol 14(1):63–72

Ganigi PM, Santosh V, Anandh B, Chandramouli BA, Sastry Kolluri VR (2005) Expression of p53, EGFR, pRb and bcl-2 proteins in pediatric glioblastoma multiforme: a study of 54 patients. Pediatr Neurosurg 41:292–299

Geyer JR, Finlay JL et al (1995) Survival of infants with malignant astrocytomas. A report from the Childrens Cancer Group. Cancer 75(4):1045–1050

Grovas AC, Boyett JM et al (1999) Regimen-related toxicity of myeloablative chemotherapy with BCNU, thiotepa, and etoposide followed by autologous stem cell rescue for children with newly diagnosed glioblastoma multiforme: report from the Children's Cancer Group. Med Pediatr Oncol 33(2):83–87

Gutierrez AN, Westerly DC et al (2007) Whole brain radiotherapy with hippocampal avoidance and simultaneously integrated brain metastases boost: a planning study. Int J Radiat Oncol Biol Phys 69(2):589–597

Hamilton SR, Liu B et al (1995) The molecular basis of Turcot's syndrome. N Engl J Med 332(13):839–847

Harrow S, Papanastassiou et al (2004) HSV1716 injection into the brain adjacent to tumour following surgical resection of high-grade glioma: safety data and long-term survival. Gene Ther 11:1648–1658

Hegde MR, Chong B et al (2005) A homozygous mutation in MSH6 causes Turcot syndrome. Clin Cancer Res 11(13):4689–4693

Heideman RL, Kuttesch J Jr et al (1997) Supratentorial malignant gliomas in childhood: a single institution perspective. Cancer 80(3):497–504

Hyder DJ, Sung L et al (2007) Anaplastic mixed gliomas and anaplastic oligodendroglioma in children: results from the CCG 945 experience. J Neuro-Oncol 83:1–8

Lashford LS, Thiesse P et al (2002) Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. J Clin Oncol 20(24):4684–4691

Li FP, Fraumeni JF Jr et al (1988) A cancer family syndrome in twenty-four kindreds. Cancer Res 48(18):5358–5362

Liang M-L, Ma J et al (2008) Tyrosine kinase expression in pediatric high grade astrocytoma. J Neuro-Oncol 87:247–253

Luis DN, Ohgaki H et al (2007) The WHO classification of tumors of the nervous system. Acta Neuropathol 114(2):97–109

Marachelian A, Butturini A et al (2008) Myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for childhood central nervous system tumors. Bone Marrow Transplant 41(2):167–172

Massimino M, Gandola L et al (2005) Sequential chemotherapy, high-dose thiotepa, circulating progenitor cell rescue, and radiotherapy for childhood high-grade glioma. Neuro-Oncology 7(1):41–48

Mehta V, Chapman A et al (2002) Latency between symptom onset and diagnosis of pediatric brain tumors: an Eastern Canadian geographic study. Neurosurgery 51(2):365–372; discussion 372–373

Merchant TE, Hua CH et al (2008) Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatr Blood Cancer 51(1):110–117

Mueller S, Phillips J et al (2012) PTEN promoter methylation and activation of the PI3K/Akt/mTOR pathway in pediatric gliomas and influence on clinical outcome. Neuro-Oncology 14(9):1146–1152

Nakamura M, Shimada K et al (2007) Molecular pathogenesis of pediatric astrocytic tumors. Neuro-Oncology 9(2):113–123

Nicholson HS, Kretschmar CS et al (2007) Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. Cancer 110(7):1542–1550

Nicoliades TP, Li H et al (2011) Targeted therapy for BRAF V600E malignant astrocytoma. Clin Cancer Res 21(6):7595–7604

Packer RJ (1999) Primary central nervous system tumors in children. Curr Treat Options Neurol 1(5):395–408

Packer RJ, Boyett JM et al (1993) Hyperfractionated radiation therapy (72 Gy) for children with brain stem gliomas. A Childrens Cancer Group phase I/II trial. Cancer 72(4):1414–1421

Palucka K, Banchereau J (2012) Cancer immunotherapy via dendritic cells. Nat Rev Cancer 12:265–277

Paugh BS, Qu C et al (2010) Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. J Clin Oncol 28(18):3061–3068

Pettorini BL, Park YS et al (2008) Radiation-induced brain tumours after central nervous system irradiation in child-hood: a review. Childs Nerv Syst 24(7):793–805

Pollack IF (1994) Brain tumors in children. N Engl J Med 331(22):1500–1507

Pollack IF, Finkelstein SD et al (2001) Age and TP53 mutation frequency in childhood malignant gliomas: results in a multiinstitutional cohort. Cancer Res 61(20):7404–7407

Pollack IF, Finkelstein SD et al (2002a) Expression of p53 and prognosis in children with malignant gliomas. N Engl J Med 346(6):420–427

Pollack IF, Hamilton RL et al (2002b) Impact of proliferation index on outcome in childhood malignant gliomas: results in a multi-institutional cohort. Neurosurgery 50(6):1238–1244; discussion 1244–1245

Pollack IF, Hamilton RL et al (2006a) Rarity of PTEN deletions and EGFR amplification in malignant gliomas of childhood: results from the Children's Cancer Group 945 cohort. J Neurosurg 105(5 Suppl):418–424

Pollack IF, Hamilton RL et al (2006b) O^6-methylguanine-DNA methyltransferase expression strongly correlates with outcome in childhood malignant gliomas: results from the CCG-945 cohort. J Clin Oncol 24(21):3431–3437

Pollack IF, Hamilton RL et al (2010) Akt activation is a common event in pediatric malignant gliomas and a potential adverse prognostic marker: a report from the Children's Oncology Group. J Neuro-Oncol 99:155–163

Pollack IF, Hamilton RL et al (2011) IDH1 mutations are common in malignant gliomas arising in adolescents: a report from the Children's Oncology Group. Childs Nerv Syst 27(1):87–94

Pollack IF, Jakacki RI et al (2014) Antigen-specific immune responses and clinical outcome after vaccination with glioma-associated antigen peptides and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in children with newly diagnosed malignant brainstem and nonbrainstem gliomas. J Clin Oncol 32(19):2050–2058

Raffel C, Frederick L, O'Fallon JR et al (1999) Analysis of oncogene and tumor suppressor gene alterations in pediatric malignant astrocytomas reveals reduced survival for patients with PTEN mutations. Clin Cancer Res 5:4085–4090

Robinson GW, Orr BA, Gajjar A (2014) Complete clinical regression of a BRAF B600E-mutant pediatric glioblastoma multiforme after BRAF inhibitor therapy. BMC Cancer 14:258

Schiffman JD, Hodgson JG et al (2010) Oncogenic *BRAF* mutation with *CDKN2A* inactivation is characteristic of a subset of pediatric malignant astrocytomas. Cancer Res 70:512–519

Schwartzentruber J, Korshunov A et al (2012) Driver mutations in histone H3.3 and chromatin remodeling genes in paediatric glioblastoma. Nature 482(7384):226–231

Setty P, Hammes J et al (2010) A pyrosequencing-based assay for the rapid detection of *IDH1* mutations in clinical samples. J Mol Diagn 12(6):750–756

Sposto R, Ertel IJ et al (1989) The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Children's Cancer Study Group. J Neurooncol 7(2):165–177

Stupp R, Dietrich PY et al (2002) Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol 20(5):1375–1382

Stupp R, Mason WP et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352(10):997–1003

Sturm D, Witt H et al (2012) Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. Cancer Cell 22(4):425–437

Sure U, Ruedi D, Tachibana O et al (1997) Determination of p53 mutations, EGFR overexpression, and loss of p16 expression in pediatric glioblastomas. J Neuropathol Exp Neurol 56:782–789

Tamber MS, Rutka JT (2003) Pediatric supratentorial high grade gliomas. Neurosurg Focus 14(2):e1

Thorarinsdottir HK, Santi M et al (2008) Protein expression of platelet-derived growth factor receptor correlates with malignant histology and PTEN with survival in childhood gliomas. Clin Cancer Res 14(11):3386–3394

Turcot J, Despres JP et al (1959) Malignant tumors of the central nervous system associated with familial polyposis of the colon: report of two cases. Dis Colon Rectum 2:465–468

Varley JM, McGown G et al (1997) Germ-line mutations of TP53 in Li-Fraumeni families: an extended study of 39 families. Cancer Res 57(15):3245–3252

Warren KE, Gururangan S et al (2011) A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: a Pediatric Brain Tumor Consortium study. J Neuro-Oncol 106(3):643–649

Wisoff JH, Boyett JM et al (1998) Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. J Neurosurg 89(1):52–59

Wolff JE, Gnekow AK et al (2002) Preradiation chemotherapy for pediatric patients with high-grade glioma. Cancer 94(1):264–271

Wolff JE, Driever PH et al (2010) Intensive chemotherapy improves survival in pediatric high-grade glioma after gross total resection: results of the. HIT-GBM-C Protoc 116(3):705–712

Wu G, Broniscer A et al (2012) Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet 44(3): 251–253

Yang T, Temkin N et al (2013) Gross total resection correlates with long-term survival in pediatric patients with glioblastoma. World Neurosurg 79(3–4):537–544

Brainstem Gliomas

3

Tiffany F. Lin and Michael Prados

Contents

T.F. Lin, MD
Division of Hematology/Oncology, Department of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th Street Box 0434, San Francisco, CA 94143, USA
e-mail: tiffany.lin@ucsf.edu

M. Prados, MD (✉)
Departments of Neurological Surgery & Pediatrics, University of California San Francisco, Hellen Diller Cancer Center Building, Room HD 487 D, 1450 3rd Street, San Francisco, CA 94143-0520, USA
e-mail: michael.prados@ucsf.edu

3.1 Introduction

Pediatric brainstem gliomas are a heterogeneous group of tumors that arise from either the midbrain, pons, or medulla. These tumors make up between 10 and 20 % of all pediatric central nervous system tumors (Jallo et al. 2004; Gilbertson et al. 2003). In the United States, this means that there are approximately 350 new cases each year (Khatua et al. 2011). The serious symptoms and signs produced by these tumors, which range from isolated specific cranial nerve palsies to quadriparesis, are a consequence of the many important neurologic pathways that originate or pass through the brainstem.

In general, brainstem gliomas can be divided into focal or diffuse subtypes based upon differences in their anatomic location, clinical presentation, available treatment options, treatment response, and outcome (Table 3.1). Focal brainstem gliomas usually occur in the midbrain or medulla, present with a much longer latency period, and can be either observed or effectively treated by surgical removal. The majority of brainstem gliomas, unfortunately, arise in the pons, are diffusely infiltrative in nature, and demonstrate aggressive biologic behavior. Despite the use of high-dose radiation therapy, intensive chemotherapy, and newer biologic chemotherapies, the outcome remains very poor for this subtype. During the last

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_3

Table 3.1 Overview of the brainstem glioma subtypes

Tumor type	Approximate frequency (%)	Clinical characteristics	Imaging characteristics	Predominant pathology
Diffuse intrinsic	75–85	Multiple bilateral CN deficits LTS Ataxia Short clinical history	Diffuse pontine enlargement T1 hypointensity T2 variable intensity Little contrast enhancement	Astrocytoma (grades II–IV)
Focal midbrain	5–10	Signs and symptoms of raised ICP Isolated CN deficit Ataxia Hemiparesis (rarer) Torticollis	Small, well circumscribed No edema T1 hypointensity T2 hyperintensity Variable enhancement Ventriculomegaly	Low-grade astrocytoma (grades I and II) Ganglioglioma
Dorsally exophytic	10–20	Signs and symptoms of raised ICP CN dysfunction Prominent nystagmus Torticollis FTT (infants) LTS typically absent	Arise from floor of fourth ventricle T1 hypointensity T2 hyperintensity Bright enhancement	Pilocytic astrocytoma (grade I) Grade II astrocytoma
Cervicomedullary	5–10	Lower CN dysfunction LTS Apnea Sensory loss Torticollis Hydrocephalus (rarer)	Arise from lower medulla/upper cervical cord Bulges dorsally toward fourth ventricle T1 hypointensity T2 hypointensity Commonly enhances	Low-grade astrocytoma (WHO grade I or II) Ganglioglioma

Adapted from Freeman and Farmer (1998)
CN cranial nerve, *ICP* intracranial pressure, *LTS* long tract signs, *FTT* failure to thrive

10 years, new data regarding the molecular biology of these tumors has led to a far more detailed understanding of their pathogenesis, although targeted therapeutics are still under development.

The differential diagnosis of brainstem gliomas can include vascular malformations, multiple sclerosis, and brainstem encephalitis, although high-quality MR imaging will frequently distinguish these. Rare tumors that can arise in the brainstem include primitive neuroectodermal tumor (PNET), atypical teratoid-rhabdoid tumor, lymphoma, ganglioglioma, and oligodendroglioma. Hemangioblastomas can present in association with von Hippel-Lindau disease (Jallo et al. 2004; Donaldson et al. 2008).

3.2 Focal Brainstem Gliomas

3.2.1 Epidemiology

Focal brainstem gliomas account for 20–35 % of childhood brainstem gliomas (Ramos et al. 2013; Guillamo et al. 2001). Because of their pathology and clinical features, they tend to have a longer latency period prior to clinical presentation; on average, the symptom duration prior to diagnosis is more than a year. In addition, the age at presentation tends to be older than diffuse brainstem gliomas with a mean age of 9 years and 11 months in one case review (Farmer et al. 2001). Focal brainstem gliomas occur more frequently in patients with neurofibromatosis type 1 (NF1)

although their clinical features may be more benign than similar appearing lesions in patients without NF1 (Ramos et al. 2013; Ullrich et al. 2007; Pollack et al. 1996). The overall survival of these lower-grade gliomas is close to 80 % although substantial morbidity can occur depending upon their exact location within the brainstem and whether surgical resection is possible.

3.2.2 Pathology

The majority of the focal brainstem gliomas occur outside of the pons and are almost always low-grade astrocytomas. As with other glial tumors, the degree of cellularity and presence of nuclear atypia is used to further refine the histologic grade. Rosenthal fibers and microcystic structures support the diagnosis of pilocytic astrocytoma (WHO grade I), whereas WHO grade II tumors can lack these histologic signs and usually demonstrate higher degree of infiltrative behavior (Cillekens et al. 2000). Paradoxically, pilocytic astrocytomas can harbor features, such as mitotic activity and vascular proliferation, that would typically be associated with higher-grade glial tumors. Careful neuropathologic evaluation and correlation with imaging features are required to reach the correct diagnosis.

Focal brainstem gliomas are classified into three subtypes depending on their location: focal midbrain, dorsally exophytic from the pons, and cervicomedullary (Fig. 3.1). Midbrain and

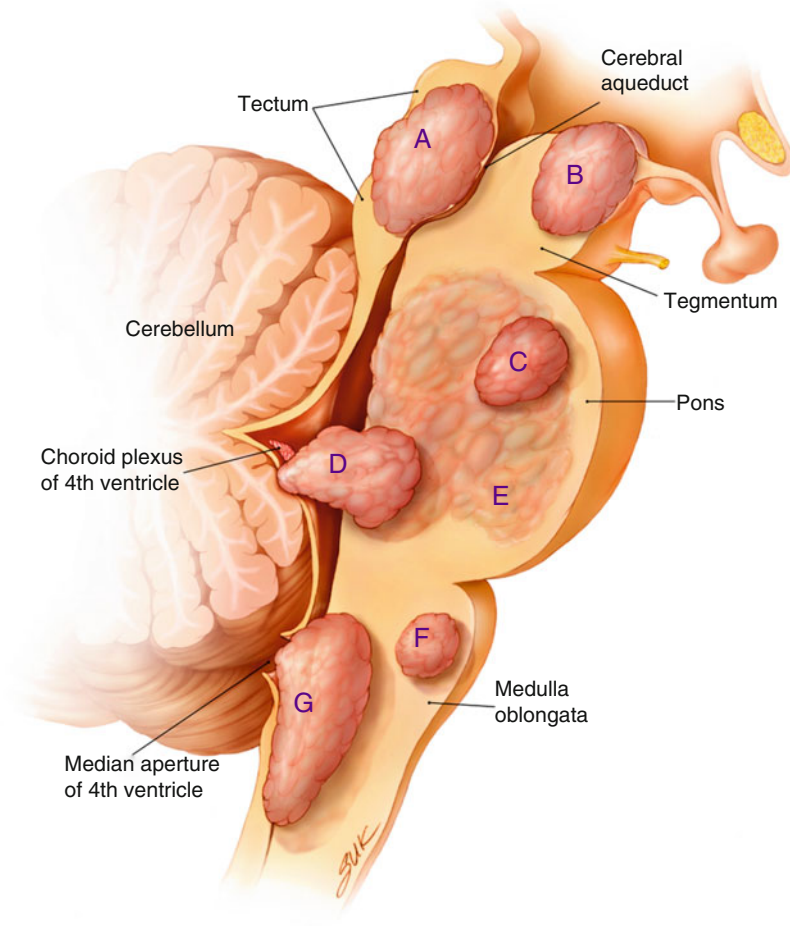

Fig. 3.1 Location of brainstem glioma subtypes (Reprinted with permission from Frazier et al. 2009)

cervicomedullary tumors tend to be WHO grade I, whereas dorsally exophytic tumors tend to be WHO grade II. The reason for this variability depending on location in the brainstem is not known.

Similar to other lower-grade glial tumors such as fibrillary astrocytomas, gangliogliomas, and pleomorphic xanthroastrocytomas, low-grade brainstem gliomas can also harbor the *BRAF*^{V600E} mutation (Schindler et al. 2011). They can also frequently harbor *BRAF-KIAA1549* gene fusions, a hallmark feature of pilocytic astrocytomas (Jones and Baker 2014).

Isocitrate dehydrogenase 1 (*IDH1*) mutations have been identified in adolescents and young adults who present with brainstem astrocytomas. Patients with this mutation have tumors that exhibit less-aggressive biologic behavior, and those patients have a prolonged survival (Qi et al. 2014; Roberson et al. 2011).

3.2.3 Clinical Features

The clinical presentation of focal brainstem tumors can often be attributed to the site of origin (Table 3.1 and Fig. 3.1). Focal midbrain tumors tend to remain within the tectum of the midbrain, although they distort and compress the surrounding structures such as the cerebral aqueduct. Obstruction of the aqueduct of Sylvius will cause hydrocephalus leading to a common group of symptoms including headache, vomiting, visual disturbance, and gait instability. Figure 3.2 Dorsally exophytic tumors can either grow into the fourth ventricle causing obstructive hydrocephalus or, if they extend in the anterolateral direction into the cerebellopontine angle, cranial neuropathies. If the tumor is bulky and causes mass effect upon the cerebellum, symptoms of ataxia, nystagmus, and dysmetria can occur. Cervicomedullary tumors originate from the medulla and also tend to grow in a dorsal direction (Fig. 3.3). Their location leads to lower cranial nerve neuropathies.

3.2.4 Imaging

The radiologic features of focal brainstem gliomas can help differentiate it from diffuse gliomas and help further classify the extent of extension of the tumor beyond what the clinical signs may demonstrate. The tumors tend to be smaller and can contain cystic components. They are well demarcated without signs of infiltration and without associated edema (Ramos et al. 2013).

On computed tomography, focal midbrain tumors are isodense with the gray matter, whereas magnetic resonance imaging (MRI) typically shows an isointense or hypointense tumor on

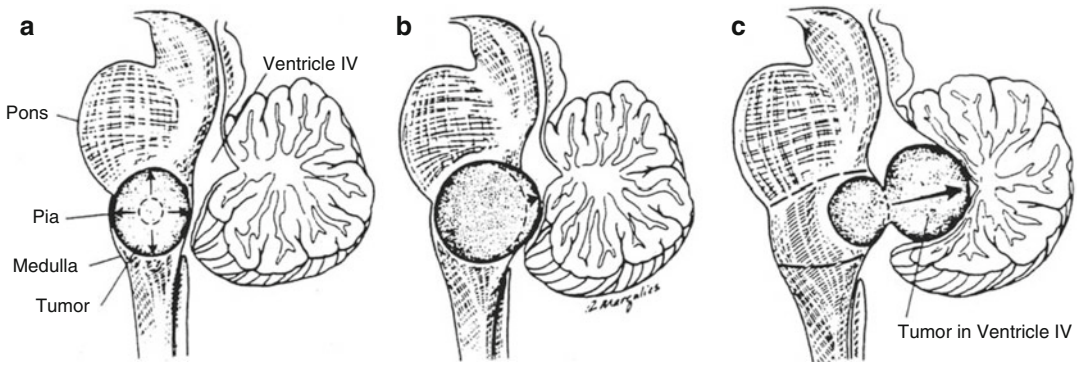

Fig. 3.2 (**a**–**c**) Illustrations of growth patterns of benign medullary tumors. (**a**) Focal medullary tumor displaces axially oriented fibers as it grows (*arrows*). (**b**) Larger focal medullary tumor tends to grow subependymally (*arrowhead*) because barriers limit its axial growth. (**c**) Subependymal lesion becomes dorsally exophytic (*arrow*) because of the limited resistance to growth offered by the ependyma (Reprinted with permission from Epstein and Farmer 1993)

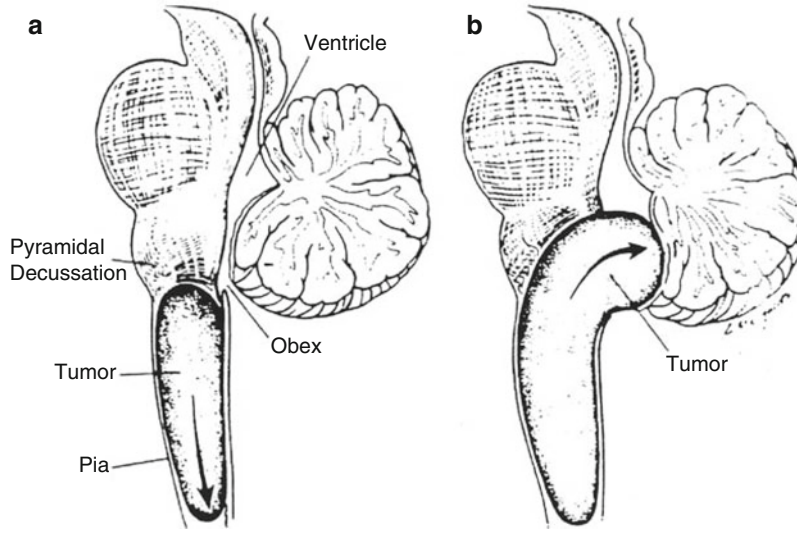

Fig. 3.3 (**a**, **b**) Illustrations of growth patterns of cervicomedullary lesions. (**a**) Caudal growth is cylindrical, as for spinal cord tumors (*arrow*). (**b**) Rostral growth is directed toward the obex (*arrow*) as a result of hindrance from pial elements and decussating fibers (Reprinted with permission from Epstein and Farmer 1993)

T1-weighted sequences and hyperintense on T2-weighted sequences (Fig. 3.4). Although focal midbrain tumors can extend beyond the tectum toward the thalamus or rostrally toward the pons, the edges of the tumor usually remain well defined. These tumors can contain calcifications and enhance poorly. They are uniform in appearance and typically do not enhance following administration with gadolinium.

Dorsally exophytic tumors tend to grow only toward the ventricle rather than infiltrating or extending further into the brainstem (Fig. 3.5). The overwhelming majority of these tumors show either focal growth or exophytic growth (Farmer et al. 2001). In one case study, 50 % of the focal brainstem gliomas had uniform enhancement, which typically is not observed in diffuse pontine tumors where patchy enhancement is observed (Farmer et al. 2001). Future contrast enhancement may suggest local progression or growth during the course of monitoring for these tumors. Magnetic resonance spectroscopy has been evaluated for prognostic value. Of those tumors with a higher choline to N-acetylaspartate (Cho:NAA) ratio (greater than 1), there was a higher proportion that showed progression (Lazareff et al. 1998).

Cervicomedullary tumors appear as solid masses within the lower medulla and upper cervical cord that frequently extend into the fourth ventricle. Like the other brainstem tumors, they are hypointense on T1-weighted and hyperintense on T2-weighted images. They often enhance homogeneously with gadolinium (Fig. 3.6).

3.2.5 Treatment

As these low-grade tumors progress slowly over time, symptomatic management is the mainstay of therapy, although surgical resection is indicated in specific circumstances. Focal midbrain tumors of the tectum can usually be identified with confidence by the MR imaging features. Initial symptom management includes treatment of hydrocephalus by endoscopic third ventriculostomy (preferred) or placement of a VP shunt. Since these tumors have an intrinsic location within the tectum, complete resection is usually not feasible without resulting in substantial morbidity. Following treatment of the hydrocephalus, observation with regular imaging studies is the primary management plan, and the tumor often remains stable for years. If there is late progression, a surgical biopsy may be needed to confirm the diagnosis prior to initiation of therapy. Of note, as cystic structures can often produce a

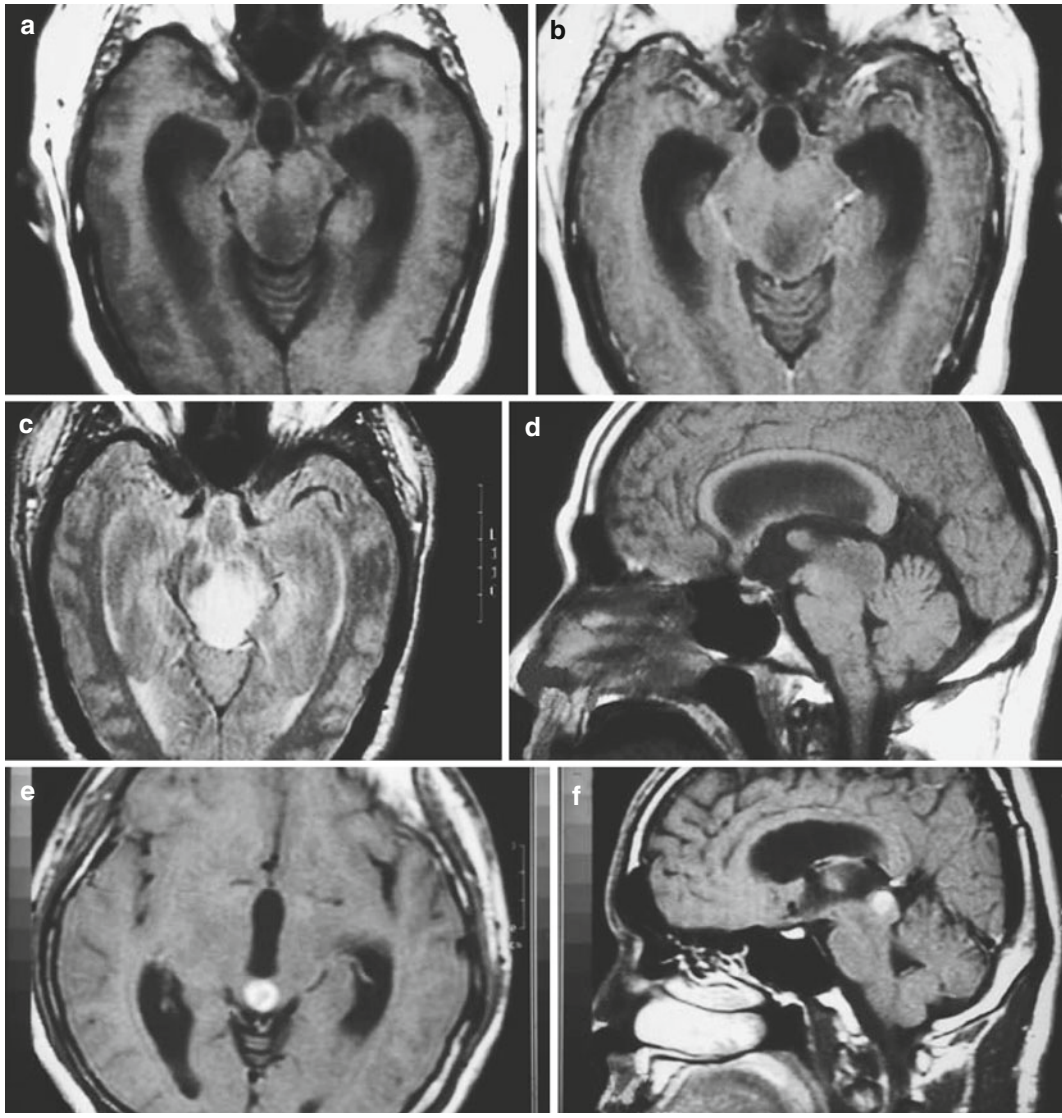

Fig. 3.4 (**a**–**f**) Magnetic resonance (MR) images of tectal gliomas. (**a**) Axial T1-weighted image without contrast: the lesion is small, is well circumscribed, and produces no edema. (**b**) Axial T1-weighted image following contrast: note the lack of enhancement. (**c**) Axial proton density image: the lesion is notably hyperintense, which contrasts with the hypointense signal of the lesion on T1-weighted pre-contrast images. (**d**) Sagittal T1-weighted image without contrast: the lesion is hypointense and does not produce significant edema. (**e**) Axial T1-weighted image following contrast: this tectal glioma exhibits obvious contrast enhancement, illustrating the enhancement variability of tectal gliomas. (**f**) Sagittal T1-weighted image following contrast: the lesion is well circumscribed and enhances brightly, which contrasts with the lesion noted in image (**b**)

more rapid onset of symptoms and cause morbidity, cyst removal can be a therapeutic option for these otherwise indolent tumors.

Dorsally exophytic tumors have a variable relationship to the adjacent brainstem. In some cases, the tumor-brain interface is well defined and the tumor can be resected with acceptable or minimal morbidity. Other tumors in this category have a poorly defined boundary and only subtotal resection can be performed. If there is an accessible location, an attempt at surgical resection is usually indicated. Subtotal resection will usually

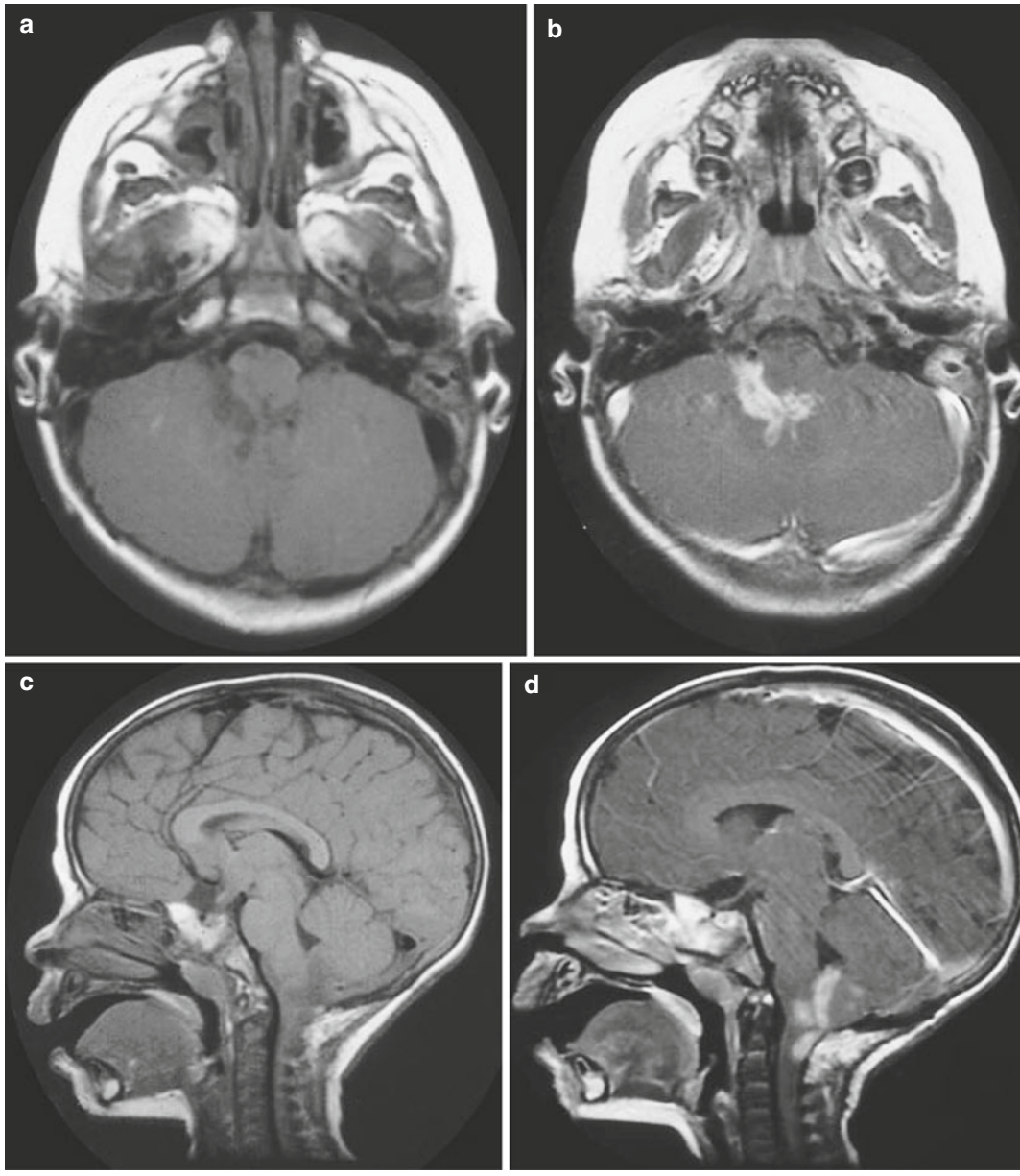

Fig. 3.5 (**a**–**d**) Magnetic resonance (MR) images of dorsally exophytic tumors. (**a**) Axial T1-weighted image without contrast: the lesion arises from the medulla and is hypointense on T1-weighted images. (**b**) Axial T1-weighted image with contrast: the lesion enhances brightly with contrast, which is a typical characteristic for dorsally exophytic tumors. (**c**) Sagittal T1-weighted image without contrast: the lesion does not invade the intrinsic tissue of the lower brainstem. (**d**) Sagittal T1-weighted with contrast: the enhancing lesion extrinsically involves the posterior upper cervical cord, medulla, and fourth ventricle

prompt further adjuvant. Cervicomedullary tumors are typically pilocytic astrocytomas (astrocytoma, WHO grade I) and as such often have a better plane between the tumor and the neural tissue. If the tumor reaches or is close to the dorsal pial surface, then resection should be considered. The surgical morbidity should be carefully considered prior to any surgery in view of the potential complications that would result in permanent injury to structures in this location.

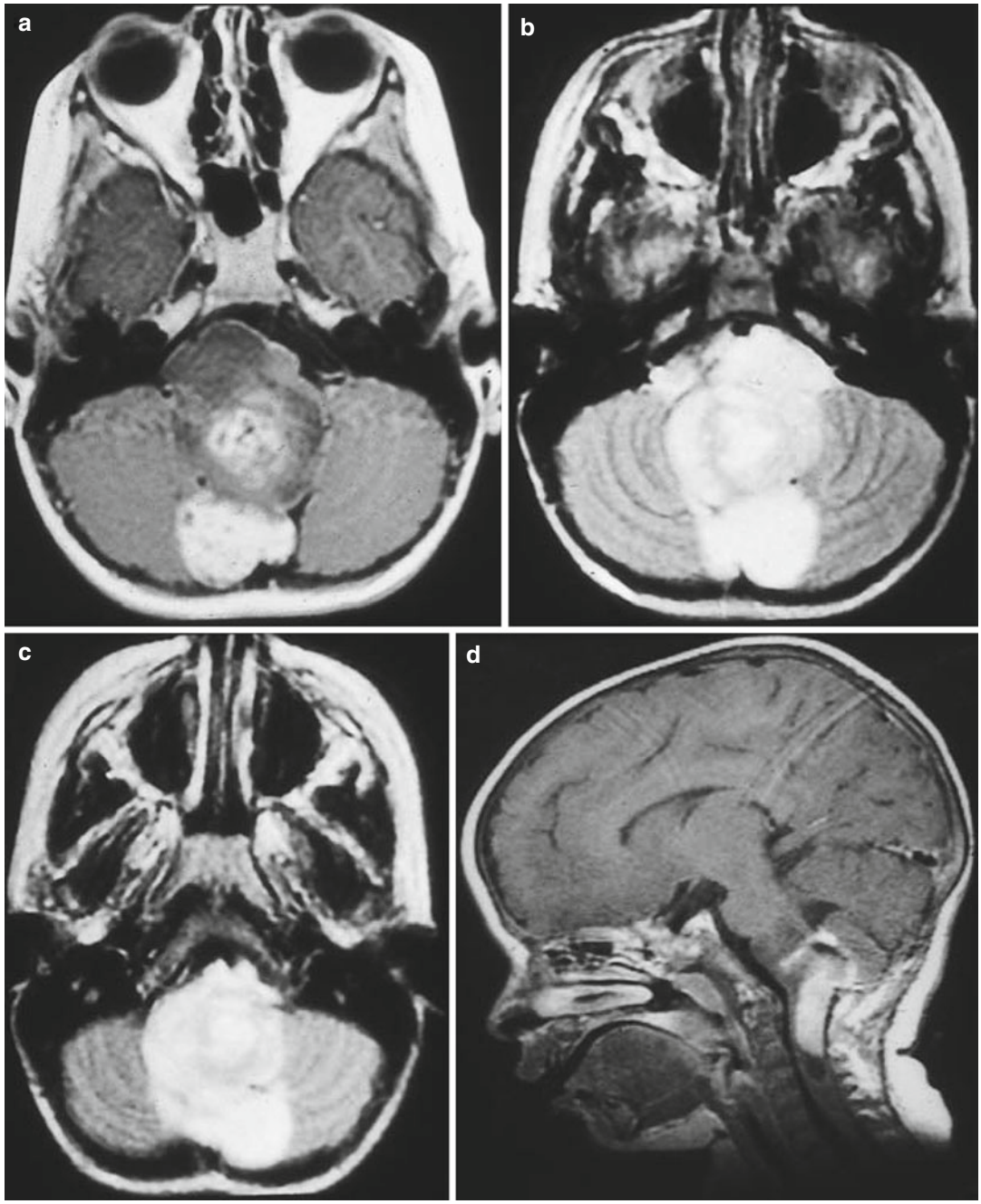

Fig. 3.6 Magnetic resonance (MR) images of cervicomedullary tumors. (**a**) Axial T1-weighted image with contrast: the lesion enhances heterogeneously and arises from the upper cervical cord. (**b**, **c**) Axial proton density images: the lesion is hyperintense. (**d**) Sagittal T1-weighted image following contrast: the lesion bulges dorsally into the fourth ventricle

Radiation therapy with 54 Gy in once daily fractions can control these focal lesions but carry a significant morbidity in pediatric patients despite the fact that focal glioma patients are older than those with diffuse gliomas. Chemotherapy options have been investigated including nitrosourea-based regimens, vinblastine-containing regimens, and carboplatin-containing regimens

all with a high proportion showing disease stabilization (Gururangan et al. 2002; Bouffet et al. 2012; Jackacki et al. 2011). Temozolomide, which has been used in adult gliomas, has been used in this patient population showing tolerability and most patients having stable disease (Nicholson et al. 2007; Khaw et al. 2007). More recently, antiangiogenic therapy with irinotecan and bevacizumab produced disease control in those with recurrence of their focal brainstem tumors (Gururangan et al. 2014). Chemotherapeutic options can be used as a bridge to delay radiation.

3.3 Diffuse Brainstem Gliomas

3.3.1 Epidemiology

Virtually all gliomas in the diffuse category occur as expansile mass lesions within the ventral pons and are known as diffuse intrinsic pontine gliomas (DIPG). The incidence of DIPG in children in the United States is 300 cases a year in children, with an additional 100 arising in adults. The median age of presentation is between 5 and 9 years (Walker et al. 2004), and the incidence is equal among males and females (Jallo et al. 2004). They account for 80 % of all brainstem gliomas (Guillamo et al. 2001).

The average overall survival is 9–12 months from the time of diagnosis with the median time to death approximately 10 months (Kaplan et al. 1996). At 2 years, the overall survival is 20 %. A coexisting diagnosis of NF1 leads to an improved prognosis in tumors meeting similar diagnostic criteria – just as focal brainstem tumors carry an improved prognosis in these patients. Lack of cranial nerve involvement and a long latency period between the onset of symptoms and diagnosis carry an improved prognosis although retrospective data may suggest that the diagnosis in these patients is not that of DIPG (Kaplan et al. 1996). Lastly, children who are diagnosed with DIPG at less than 3 years of age can have a prolonged survival. These younger patients receiving similar therapy (including radiation therapy) have a 3-year progression free survival of 45 ± 19 % (Broniscer et al. 2008). There have been case reports of similarly appearing diffuse pontine lesions in neonates with spontaneous remissions (Schomerus et al. 2007). In most cases though, the high mortality rate of DIPG has presented a challenge to researchers and clinicians (Bredlau and Korones 2014). Further research in recent years has started to expand the knowledge base about the molecular biology of this tumor hopefully leading to better therapeutic targets in the future.

3.3.2 Pathology

Since the late 1970s, stereotactic biopsy was being performed (Farmer et al. 2001) for patients with DIPG. With the arrival of MR, the characteristic imaging appearance served as a surrogate for diagnosis by tissue confirmation. This position was supported by a report in 1993 from the Children's Cancer Group recommending against surgical biopsy because of the potential risk (Jones and Baker 2014). Early biopsy results usually demonstrated high-grade glial tumors, although there was variation in grade with a range from WHO grades II to IV (Farmer et al. 2001). Presumably this represented sampling error from the overall tumor, since the majority of these patients demonstrated the relentless phenotype of a high-grade tumor.

3.3.3 Molecular Biology

As techniques have advanced, molecular pathology of diffuse brainstem lesions has been explored further. Only recently a mouse xenograft model has been developed using human high-grade gliomas. Since then, multiple models have been developed including one from a pediatric DIPG biopsy sample (Aoki et al. 2012; Hashizume et al. 2012). In addition, a viable cell line has been developed from a pediatric DIPG biopsy sample (Hashizume et al. 2012). Tissue availability has been limited in the past in the era of imaging-based diagnosis, although rapid autopsy protocols at various institutions have also contributed to tissues available for detailed

analyses. A recent review of 300 patients who underwent surgical biopsy showed that stereotactic biopsy could be performed without significant morbidity. The biopsy was aimed either toward clear areas of enhancement on imaging or an area just deep to the cerebellar peduncle in these patients (Cage et al. 2013). In addition, a pediatric neurosurgery consensus conference held in Paris in 2011 agreed that biopsy "was recommended to ascertain biological characteristics to enhance understanding and targeting of treatments, especially in clinical trials" (Walker et al. 2013; Jones and Baker 2014).

Global sequencing and evaluation of gene expression have been performed on samples of high-grade gliomas including diffuse pontine gliomas showing that mutation burdens in DIPG are much higher than in other pediatric cancers. These changes range from structural variants to complicated chromosomal changes caused by chromothripsis (rearrangements with multiple breakpoints that can lead to segments of varying copy numbers) (Kebudi and Cakir 2013).

Among the DIPG tumor samples, more than half the cases have fusion genes detectable by RNA sequencing (Jones and Baker 2014). This is an incidence similar to that of other high-grade gliomas found in the non-brainstem region. Most gene fusions of diffuse brainstem gliomas involved the kinase domain of the three known neurotrophic receptor genes (NTRK).

Growth factor binding to various receptor tyrosine kinases is hypothesized to be a major portion of the oncogenic targets in DIPG. Fusion genes causing activation of the RTK/RAS/PI3K pathway occurred in 69 % of DIPGs. Amplification of platelet-derived growth factor receptor-α (*PDGFRA*) and *c-Met* and activation of PI3K have been found in many tumors as well (Grill et al. 2012; Paugh et al. 2011, 2012). This has been of interest given the clinical availability of therapeutic agents that also disrupt PDGF/PDFR ligand activation. Epidermal growth factor receptor (EGFR) has been a subject of interest for inhibition as it is often found as activated in adult high-grade gliomas. In one study, *ERBB1* amplification and overexpression were found at an increased amount in escalating grades of brainstem glioma pediatric samples (Gilbertson et al. 2003). In other reports, the activating mutation to produce kinase EGFRvIII expression was rarely observed in DIPG as opposed to other high-grade gliomas.

Chromatin regulation and remodeling have been a subject of interest in potential oncogenesis of various tumors, and histone modifications play a part in this process. Sequencing of diffuse pontine gliomas revealed that this disease was the first example of disease linked to histone mutations. The genomes of 57 patients with DIPG were analyzed by transcriptome sequencing and whole exome sequencing. Histone H3 mutations (specifically *H3F3A*, encoding the histone H3.3 variant, and *HIST1H3B* mutations, encoding the histone H3.1 variant) were found to exist in pediatric brain tumors, but not in DIPGs in adults (Wu et al. 2012; Fig. 3.7). These mutations were as common as 80 % of the DIPGs examined (the most common were lysine-to-methionine alterations at position 27; K27M). By sequestering the polycomb repressive complex 2 (PRC2), the effect of these mutations is to reduce the overall levels of normal posttranslational methylation. As a result of this lack of methylation, there is repression of transcription of some target genes (Hashizume et al. 2014; Lewis et al. 2013; Jones and Baker 2014), although other genes show increased transcription (Chan et al. 2013). The *HIST1H3B* mutation is found more often in younger patients who have slightly longer median survival times (15 months) although the long-term outcome is unchanged. The high prevalence of histone abnormality in DIPGs has led to clinical trials with histone deacetylase inhibitor use after it was shown to have in vitro effect (Hashizume et al. 2014).

As in other cancers, there is unchecked cell cycle progression seen in diffuse gliomas. mRNA of WEE1 kinase, a main regulator of the G_2 checkpoint, is expressed in significantly higher levels in DIPG as compared to other gliomas of the brainstem. There have been trails with a WEE1 kinase inhibitor, MK-1775, as a radiosensitizer (Caretti et al. 2013; Mueller et al. 2014). Other checkpoint regulator mutations have been

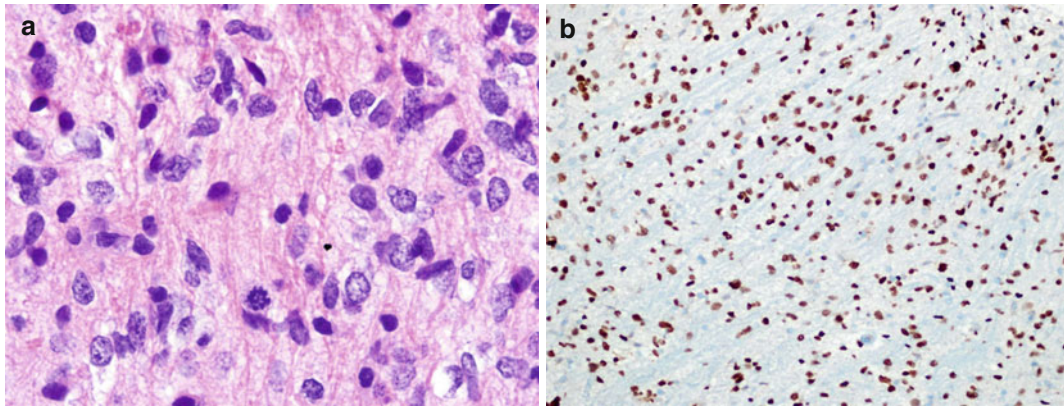

Fig. 3.7 Histopathologic images from a patient with a DIPG. (**a**) A high-power hematoxylin and eosin (H&E)-stained image shows a highly cellular tumor with marked nuclear atypia. A mitotic figure is located just below the center of the image. (**b**) An immunohistochemical stain using an antibody specific for the histone 3.3 K27M mutation shows a background of neuropil with some normal cell nuclei in pale blue and a large population of infiltrating neoplastic cells straining strongly in *brown*

found in DIPG including the G_1 checkpoint regulators cyclin D1 (CCND1), D2, and D3 with amplification of CDK4 and CDK6. The TP53 pathway also is affected with 20 % of tumors having TP53 nuclear immunoreactivity. Retinoblastoma protein phosphorylation amplification is not as often present but has been reported. Of note, the tumors with TP53 mutations do not have concurrent EGFR gene amplification. This is a shared characteristic with adult supratentorial glioblastomas that affect younger patients (Louis et al. 1993). Mutations that impact cell cycle regulation were in total found in 59 % of pediatric high-grade gliomas (Wu et al. 2014; Jones and Baker 2014).

Specific for DIPGs, a clonal mutation in *ACVR1* (also known as *ALK2*) is present in about one third of the samples analyzed. This gene encodes a bone morphogenic protein type 1 receptor, and downstream of this receptor are growth-promoting genes acting through transcription of SMAD proteins. This mutation is found in patients who have an earlier age of diagnosis and a longer survival time and often coexist with *HIST1H3B* mutation (Jones and Baker 2014).

The varied and complex mutation spectrums found in diffuse brainstem gliomas have shown its uniqueness in comparison with other high-grade gliomas. This spectrum of mutations has provided opportunities for therapeutic trials, especially with the advent of increased availability of medications against receptor kinase domains (Cohen 2009; Finlay and Zacharoulis 2005). The tumorigenesis of DIPG and specific oncogenic mutations is still undergoing detailed study to provide improved therapeutic targets for this highly morbid disease.

3.3.4 Clinical Features

As with focal brainstem tumors, location of the tumor affects the array of symptoms that the patient presents with. Since most diffuse tumors arise in the pons, involvement with the sixth and seventh cranial nerves is common causing diplopia and peripheral facial nerve palsy. These symptoms typically have presented 1–2 months prior to diagnosis (Guillamo et al. 2001; Khatua et al. 2011; Donaldson et al. 2008). Classically, diffuse gliomas present with a triad of cranial nerve deficits, cerebellar involvement with ataxia, and long tract signs (extremity weakness, Babinski sign, and hyperreflexia) (Khatua et al. 2011; Donaldson et al. 2008). There rarely can be associated with hydrocephalus and signs of increased intracranial

pressure although these symptoms usually present later in the clinical course.

3.3.5 Imaging

DIPGs have been diagnosed by characteristic imaging findings over the past two decades. These tumors demonstrate diffuse enlargement of the entire pons and are frequently large at the time of presentation. The margins of the tumors are often indistinct which reflects their infiltrative nature. Often, the ventral surface of the pons encases the basilar artery (Ramos et al. 2013; Guillamo et al. 2001; Jallo et al. 2004; Donaldson et al. 2008). Hydrocephalus is less frequent at presentation for DIPGs, as compared to focal brainstem tumors (Donaldson et al. 2008). Leptomeningeal dissemination will occur in one third of the patients with this tumor at the time of presentation (Ramos et al. 2013; Guillamo et al. 2001; Khatua et al. 2011).

Although computed tomography is rarely used for diagnosis, DIPG appears as hypodense to isodense in this modality with variable degrees of enhancement. On MRI, DIPGs are hypointense on T1-weighted sequences and hyperintense on T2-weighted sequences (Fig. 3.8) (Kornreich et al. 2005; Ramos et al. 2013). There can be heterogeneous enhancement but the tumors typically progress from patchy or no enhancement to increasing enhancement. The prognostic significance of enhancement at diagnosis is still unclear (Ramos et al. 2013; Jallo et al. 2004).

Magnetic resonance imaging with spectroscopy has been studied as a modality to monitor DIPG (Fig. 3.9). Increased ratios of choline to N-acetylaspartate or choline to creatinine ratios suggest a worse prognosis. A choline to N-acetylaspartate of greater than 4.5 had a median survival of 22 weeks with a 100 % mortality at 63 weeks, whereas a ratio of less than 4.5 had a 50 % survival at 63 weeks. MRI with spectroscopy has been used postradiation therapy to help distinguish areas of progression (as evidenced by increased choline to N-acetylaspartate ratio) from areas that signal necrosis from radiation (Ramos et al. 2013). Other radiologic findings have not been associated with significant prognostic value (Kornreich et al. 2005).

3.3.6 Treatment

Radiotherapy has been the backbone of therapy for DIPGs, and the addition of various chemotherapeutic agents targeting different possible methods of tumorigenesis has been trialed. The poor prognosis of this disease has prompted many clinical trials that have evaluated the safety and compared outcome with historical cohorts. Unfortunately, no agent or regimen has significantly improved overall survival.

Control of peritumoral swelling can be achieved with corticosteroid use. Implementation of corticosteroid use can transiently improve symptoms at the time of patient presentation, and corticosteroid use is generally continued until radiation therapy enables weaning of steroids.

Radiation therapy has shown benefits with a clinical response seen in about 70 % of patients after radiotherapy (Khatua et al. 2011). The clinical response is not long standing but can often provide symptomatic relief in patients and their families. The radiologic response to radiation therapy can be less significant than the clinical findings perhaps due to the infiltrative nature of the disease. Radiation therapy encompasses the tumor and 1–2 cm of the adjacent brainstem tissue (Walker et al. 1999). Treatment failures still usually occur locally and within the radiotherapy field.

Standard radiotherapy is once daily radiation therapy with 1.8 Gy for 5 days/week to a total dose of 54–59 Gy (Mandell et al. 1999). Multiple trials have explored the use of hyperfractionated therapy in an attempt to increase total radiation doses but have not shown improvement in survival (Packer et al. 1994; Freeman et al. 1993; Donaldson et al. 2008; Farmer et al. 2001). Radiation doses between 20 and up to 78 Gy have been given. In a summary of the clinical trials involving radiation starting in the mid-1980s, more than 900 patients with DIPG have been

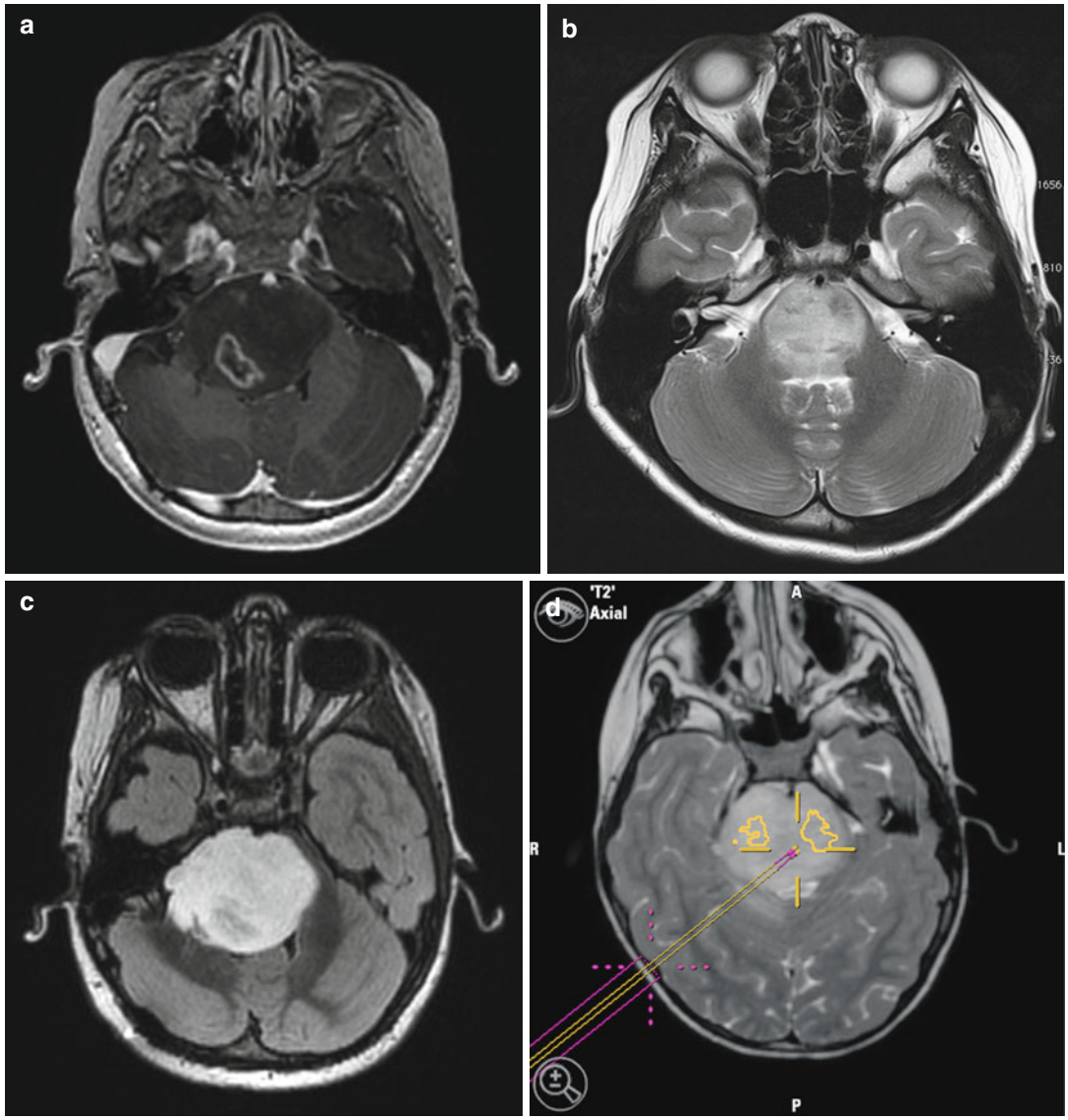

Fig. 3.8 (**a**–**d**) Magnetic resonance (MR) images of diffuse pontine gliomas. (**a**) Axial T1-weighted image contrast. The majority of the lesion is hypointense compared with the normal pons. An irregular area of enhancement is seen within the hypointense center. Many DIPGs do not have any enhancement at presentation. (**b**) An axial T2-weighted image. The lesion is hyperintense, demonstrating the large area of involvement with preservation of the internal structure of the pons. (**c**) A FLAIR image most clearly demonstrates the extent of the lesion in relationship to the surrounding tissues. The imaging abnormality is likely less than the infiltrative extent of the tumor. (**d**) An axial T2-weighted image taken from a neuronavigation system during a biopsy procedure. The tip of the biopsy needle is shown as a magenta color, while the corticospinal tracts are outlined in *yellow*. The infiltrative nature of the tumor through functional tissues is clearly shown in this image

evaluated for their response to radiotherapy at various doses both with and without concurrent chemotherapy (Donaldson et al. 2008). The highest doses were given in CCG 9882 and at UCSF with a total of 105 patients receiving 78 Gy in 1 Gy fractions using hyperfractionated therapy. Their median survival time measured at 9.5 and 10.8 months, respectively (Packer et al. 1994;

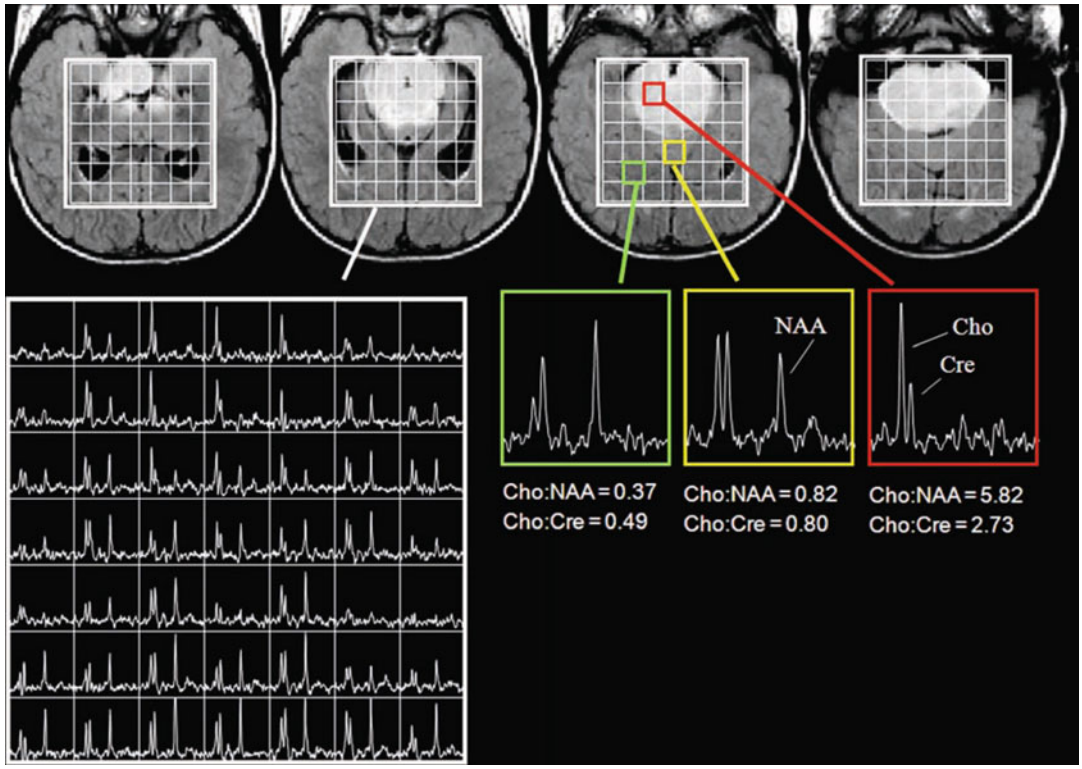

Fig. 3.9 High-quality magnetic resonance spectroscopy imaging (MRSI) data that can be acquired from a child with a brainstem glioma. The four MRSI slices cover both the tumor (bright lesion on T2 MRI) and surrounding normal brain. The spectral peaks in each voxel are highly resolved with little or no artifacts. Spectra from tumor (far *right*) are distinguished from normal brain spectra (far *left*) by high choline and low N-acetylaspartate (NAA). Peritumoral spectra (*middle*) show a mixture of both normal and tumor spectral signatures

Prados et al. 1995). Because of the poor prognosis, hypofractionated therapy has been reported to be used to improve quality of family life with up to 3.0 Gy tolerated at a time.

Initial combination chemoradiotherapy treatment of DIPGs followed the treatment used in non-brainstem high-grade gliomas with radiation with or without concurrent vincristine followed by cycles of prednisone, cisplatin, and vincristine but again, no difference was seen. Preradiation therapy was also trialed. Its use was initially studied for its possibility to help delay use of radiation in the younger patients. Despite the use of high-dose chemotherapy regimens including a comparison between cyclophosphamide and cisplatin versus ifosfamide and carboplatin, there was no favorable impact on survival. High-dose chemotherapy followed by autologous bone marrow transplant both with and without radiation therapy has also been studied with no increase in median survival. Chemotherapies trialed have included combinations including carboplatin, etoposide, busulfan, thiotepa, bradykinin with carboplatin, etanidazole, temozolomide, and lomustine (Korones et al. 2003).

The clinical benefit of radiation has led to phase I and II trials with various radiosensitizers including topotecan and motexafin gadolinium (Sanghavi et al. 2003; Bradley et al. 2013). These too have not shown clinical benefits. Other types of chemotherapy have been trialed including immunotherapy with pegylated interferon alpha and the angiogenesis inhibitor bevacizumab (Gururangan et al. 2014; Warren et al. 2012; Zaky et al. 2013). While these drugs are well tolerated and have shown some benefits in other high-grade (and low-grade) gliomas, the response in DIPGs is limited. Thalidomide also

has antiangiogenesis properties and has been evaluated without significant benefit.

The blood-brain barrier is perceived as an obstacle for drug delivery contributing to the lack of chemotherapeutic effect. New approaches, such as convection-enhanced delivery with surgically microcatheters, have been tested on an anecdotal level in an effort to achieve much higher local drug levels. The safety of the system has been established although the volume of distribution of the drug has been variable and the therapeutic index required is not clear. Carboplatin has been given via convection-enhanced delivery without change in outcome (Lonser et al. 2007; Barua et al. 2013).

The recent molecular findings in DIPG have prompted use of targeted therapy. EGFR inhibitors have been used despite the fact that EGFR amplification is less common in pediatric high-grade gliomas. These inhibitors include nimotuzumab, erlotinib, and gefitinib. Targeted inhibition against the active Ras pathway with a farnesyl transferase inhibitor in these tumors was trialed in a phase II trial concurrently with radiation therapy for newly diagnosed patients. This phase II trial offered no clinical advantage over prior therapies (Haas-Kogan et al. 2011). PDGFRA inhibitor with imatinib and dasatinib has been trialed in a phase 1 study and also was tolerated well but offered no clinical advantage (Pollack et al. 2007). The high prevalence of histone mutations led to a retrospective evaluation of patients who received valproic acid, a histone deacetylase inhibitor showing tolerance with suggestion of improved effect in combination with chemotherapy. This study was performed retrospectively in patients with high-grade glioma but not specifically DIPG (Masoudi et al. 2008). A Children's Oncology Group is examining the use of vorinostat and that study has reached accrual with results pending (Children's Oncology Group, 2016).

Conclusion

Brainstem gliomas can be separated by their nature and presentation and are treated differently. Focal brainstem tumors have been successfully followed with symptoms treated surgically or with surgical removal. Chemotherapy and radiation therapy are reserved for progressive or recurrent tumors with success. Among focal brainstem tumors, the presentation and longer-term neurologic sequelae change based on the location and slow growth patterns of the tumor. On the other hand, diffuse brainstem tumors have a short latency period and cause long tract signs, cranial nerve dysfunction, and ataxia and generally arise from the ventral pons. Conventional radiotherapy remains the standard of care for these highly morbid tumors despite multiple early-phase clinical trials to study a variety of combinations of chemoradiotherapy options including newer molecularly targeted chemotherapy. Novel techniques and research should be employed to attempt to find some amelioration for the diffuse glioma, which remains a uniformly fatal disease.

References

Aoki Y, Hashizume R, Ozawa T, Banerjee A, Prados M, James CD et al (2012) An experimental xenograft mouse model of diffuse pontine glioma designed for therapeutic testing. J Neuro-Oncol 108(1):29–35

Barua NU, Lowis SP, Woolley M, O'Sullivan S, Harrison R, Gill SS (2013) Robot-guided convection-enhanced delivery of carboplatin for advanced brainstem glioma. Acta Neurochir (Wien) 155(8):1459–1465

Bouffet E, Jakacki R, Goldman S et al (2012) Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol 30(12):1358–1363

Bradley KA, Zhou T, McNall-Knapp RY, Jakacki RI, Levy AS, Vezina G et al (2013) Motexafin-gadolinium and involved field radiation therapy for intrinsic pontine glioma of childhood: a children's oncology group phase 2 study. Int J Radiat Oncol Biol Phys 85(1):e55–e60

Bredlau AL, Korones DN (2014) Diffuse intrinsic pontine gliomas: treatments and controversies. Adv Cancer Res 121:235–259

Broniscer A, Laningham FH, Sanders RP, Kun LE, Ellison DW, Gajjar A (2008) Young age may predict a better outcome for children with diffuse pontine glioma. Cancer 113(3):566–572

Cage TA, Samagh SP, Mueller S et al (2013) Feasibility, safety, and indications for surgical biopsy of intrinsic brainstem tumors in children. Childs Nerv Syst 29(8):1313–1319

Caretti V, Hiddingh L, Lagerweij T, Schellen P, Koken PW, Hulleman E et al (2013) WEE1 kinase inhibition enhances the radiation response of diffuse intrinsic pontine gliomas. Mol Cancer Ther 12(2):141–150

Chan KM, Fang D, Gan H, Hashizume R, Yu C, Schroeder M, Gupta N, Mueller S, James CD, Jenkins R, Sarkaria J, Zhang Z (2013) The histone H3.3K27M mutation in pediatric glioma reprograms H3K27 methylation and gene expression. Genes Dev 27:900–910

Children's Oncology Group, National Cancer Institute. Vorinostat and radiation therapy followed by maintenance therapy with vorinostat in treating younger patients with newly diagnosed pontine glioma. ClinicalTrials.gov identifier NCT01189266. Accessed March 2016.

Cillekens JM, Beliën JA, van der Valk P et al (2000) A histopathological contribution to supratentorial glioma grading, definition of mixed gliomas and recognition of low grade glioma with Rosenthal fibers. J Neuro-Oncol 46(1):23–43

Cohen KJ (2009) Current clinical management of children diagnosed with Diffuse Intrinsic Pontine Glioma (DIPG). In: Joint Meeting of the Pediatric and Oncologic Drugs Advisory Committees, 27 April 2009

Donaldson SS, Laningham F, Fischer PG (2008) Advances towards an understanding of brainstem gliomas. J Clin Oncol 24(8):1266–1272

Epstein FJ, Farmer JP (1993) Brain-stem glioma growth patterns. J Neurosurg 78(3):408–412

Farmer JP, Montes JL, Freeman CR, Meagher-Villemure K, Bond MC, O'Gorman AM (2001) Brainstem gliomas. A 10-year institutional review. Pediatr Neurosurg 34(4):206–214

Finlay JL, Zacharoulis S (2005) The treatment of high grade gliomas and diffuse intrinsic pontine tumors of childhood and adolescence: a historical – and futuristic – perspective. J Neuro-Oncol 75(3):253–266

Frazier JL, Lee J, Thomale UW et al (2009) Treatment of diffuse intrinsic brainstem gliomas: failed approaches and future strategies. Journal of neurosurgery. Pediatrics 3(4); 259–269

Freeman CR, Farmer JP (1998) Pediatric brain stem gliomas: a review. International journal of radiation oncology, biology, physics, 40(2): 265–271

Freeman CR, Krischer JP, Sanford RA, Cohen ME, Burger PC, del Carpio R, Halperin EC, Munoz L, Friedman HS, Kun LE (1993) Final results of a study of escalating doses of hyperfractionated radiotherapy in brain stem tumors in children: a Pediatric Oncology Group study. Int J Radiat Oncol Biol Phys 27:197–206

Gilbertson RJ, Hill DA, Hernan R, Kocak M, Geyer R, Olson J et al (2003) ERBB1 is amplified and overexpressed in high-grade diffusely infiltrative pediatric brain stem glioma. Clin Cancer Res 9(10 Pt 1):3620–3624

Grill J, Puget S, Andreiuolo F et al (2012) Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. Pediatr Blood Cancer 58:489

Guillamo JS, Doz F, Delattre JY (2001) Brain stem gliomas. Curr Opin Neurol 14(6):711–715

Gururangan S, Cavazos CM, Ashley D et al (2002) Phase II study of carboplatin in children with progressive low-grade gliomas. J Clin Oncol 20(13):2951–2958

Gururangan S, Fangusaro J, Poussaint TY et al (2014) Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas – a Pediatric Brain Tumor Consortium study. Neuro-Oncology 16(2):310–317

Haas-Kogan DA, Banerjee A, Poussaint TY et al (2011) Phase II trial of tipifarnib and radiation in children with newly diagnosed diffuse intrinsic pontine gliomas. Neuro Oncol 13(3):298–306

Hashizume R, Smirnov I, Liu S et al (2012) Characterization of a diffuse intrinsic pontine glioma cell line: implications for future investigations and treatment. J Neuro-Oncol 110(3):305–313

Hashizume R, Andor N, Ihara Y et al (2014) Pharmacologic inhibition of histone demethylation as a therapy for pediatric brainstem glioma. Nat Med 20:1394–1396

Jakacki RI, Bouffet E, Adamson PC et al (2011) A phase 1 study of vinblastine in combination with carboplatin for children with low-grade gliomas: a Children's Oncology Group phase 1 consortium study. Neuro-Oncology 13(8):910–915

Jallo GI, Biser Rohrbaugh A, Freed D (2004) Brainstem gliomas. Childs Nerv Syst 20(3):143–153

Jones C, Baker SJ (2014) Unique genetic and epigenetic mechanisms driving paediatric diffuse high-grade glioma. Nat Rev Cancer 14(10):651–661

Kaplan AM, Albright AL, Zimmerman RA et al (1996) Brainstem gliomas in children. A Children's Cancer Group review of 119 cases. Pediatr Neurosurg 24(4):185–192

Kebudi R, Cakir FB (2013) Management of diffuse pontine gliomas in children: recent developments. Pediatr Drugs 15(5):351–362

Khatua S, Moore KR, Vats TS et al (2011) Diffuse intrinsic pontine glioma – current status and future strategies. Childs Nerv Syst 27:1391–1397

Khaw SL, Coleman LT, Downie PA et al (2007) Temozolomide in pediatric low-grade glioma. Pediatr Blood Cancer 49(6):808–811

Kornreich L, Schwarz M, Karmazyn B, Cohen IJ, Shuper A, Michovitz S et al (2005) Role of MRI in the management of children with diffuse pontine tumors: a study of 15 patients and review of the literature. Pediatr Radiol 35(9):872–879

Korones DN, Kretschmar CS, Freeman CR, Fisher PG, Zhou T, Kepner J (2003) Treatment of children with diffuse intrinsic brain stem glioma with standard dose irradiation and vincristine plus oral VP-16. A Pediatric Oncology Group study. Eighth Annual meeting of Society for Neuro-Oncology, Keystone, Colorado, November 13–16, 2003. Neuro-Oncology 5(4):359

Lazareff JA, Bockhorst KH, Curran J et al (1998) Pediatric low-grade gliomas: prognosis with proton magnetic resonance spectroscopic imaging. Neurosurgery 43(4):809–817; discussion 817

Lewis PW, Müller MM, Koletsky MS et al (2013) Inhibition of PRC2 activity by a gain-of-function H3 mutation found in pediatric glioblastoma. Science 340:857

Lonser RR, Warren KE, Butman JA et al (2007) Real-time image-guided direct convective perfusion of intrinsic brain stem lesions. J Neurosurg 107:190–197

Louis DN, Rubio MP, Correa KM, Gusella JF, von Deimling A (1993) Molecular genetics of pediatric brain stem gliomas. Application of PCR techniques to small and archival brain tumor specimens. J Neuropathol Exp Neurol 52(5):507–515

Mandell LR, Kadota R, Freeman C, Douglass EC, Fontanesi J, Cohen ME et al (1999) There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys 43(5):959–964

Masoudi A, Elopre M, Amini E et al (2008) Influence of valproic acid on outcome of high-grade gliomas in children. Anticancer Res 28:2437–2442

Mueller S, Hashizume R, Yang X et al (2014) Targeting Wee1 for the treatment of pediatric high-grade gliomas. Neuro-Oncology 16(3):352–360

Nicholson HS, Kretschmar CS, Krailo M et al (2007) Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. Cancer 110(7):1542–1550

Packer RJ, Boyett JM, Zimmerman RA et al (1994) Outcome of children with brain stem gliomas after treatment with 7800 cGy of hyperfractionated radiotherapy. A Childrens Cancer Group Phase I/II Trial. Cancer 74(6):1827–1834

Paugh BS, Broniscer A, Qu C et al (2011) Genome-wide analyses identify recurrent amplifications of receptor tyrosine kinases and cell-cycle regulatory genes in diffuse intrinsic pontine glioma. J Clin Oncol 29:3999

Pollack IF, Shultz B, Mulvihill JJ (1996) The management of brainstem gliomas in patients with neurofibromatosis 1. Neurology 46(6):1652–1660

Pollack IF, Jakacki RI, Blaney SM et al (2007) Phase I trial of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas: a Pediatric Brain Tumor Consortium report. Neuro Oncol 9:145–160

Prados MD, Wara WM, Edwards MSB et al (1995) The treatment of brain stem and thalamic gliomas with 78 Gy of hyperfractionated radiation therapy. Int J Radiat Oncol Biol Phys 32:85–91

Puget S, Philippe C, Bax DA et al (2012) Mesenchymal transition and PDGFRA amplification/mutation are key distinct oncogenic events in pediatric diffuse intrinsic pontine gliomas. PLoS ONE 7, e30313

Qi S, Yu L, Li H et al (2014) Isocitrate dehydrogenase mutation is associated with tumor location and magnetic resonance imaging characteristics in astrocytic neoplasms. Oncol Lett 7(6):1895–1902

Ramos A, Hilario A, Lagares A et al (2013) Brainstem gliomas. Semin Ultrasound CT MRI 34:104–112

Robertson T, Koszyca B, Gonzales M (2011) Overview and recent advances in neuropathology. Part 1: central nervous system tumours. Pathology 43(2):88–92

Sanghavi SN, Needle MN, Krailo MD, Geyer JR, Ater J, Mehta MP (2003) A phase I study of topotecan as a radiosensitizer for brainstem glioma of childhood: first report of the Children's Cancer Group-0952. Neuro-Oncology 5(1):8–13

Schindler G, Capper D, Meyer J et al (2011) Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extracerebellar pilocytic astrocytoma. Acta Neuropathol 121(3):397–405

Schomerus L, Merkenschlager A, Kahn T et al (2007) Spontaneous remission of a diffuse brainstem lesion in a neonate. Pediatr Radiol 37(4):399–402

Ullrich NJ, Raja AI, Irons MB et al (2007) Brainstem lesions in neurofibromatosis type 1. Neurosurgery 61(4):762–766; discussion 766

Walker DA, Punt JA, Sokal M (1999) Clinical management of brain stem glioma. Arch Dis Child 80:558–564

Walker DA, Punt JAG, Sokal M (2004) Brainstem tumors. Arnold, London

Walker DA, Liu J, Kieran M et al (2013) A multidisciplinary consensus statement concerning surgical approaches to low-grade, high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood (CPN Paris 2011) using the Delphi method. Neuro-Oncology 15(4):462–468

Warren K, Bent R, Wolters PL, Prager A, Hanson R, Packer R et al (2012) A phase 2 study of pegylated interferon alpha-2b (PEG-Intron((R))) in children with diffuse intrinsic pontine glioma. Cancer 118(14):3607–3613

Wu G, Broniscer A, McEachron TA et al (2012) Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet 44:251

Wu G, Diaz AK, Paugh BS et al (2014) The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet 46(5):444–450

Zaky W, Wellner M, Brown RJ et al (2013) Treatment of children with diffuse intrinsic pontine gliomas with chemoradiotherapy followed by a combination of temozolomide, irinotecan, and bevacizumab. Pediatr Hematol Oncol 30(7):623–632

Ependymoma

4

Cassie Kline, Craig Forester,
and Anuradha Banerjee

Contents

C. Kline, MD (✉) • C. Forester, MD, PhD
A. Banerjee, MD
Division of Hematology/Oncology, Departments of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th St, 4th Floor, Box 0434, San Francisco, CA 94143, USA
e-mail: cassie.klein@ucsf.edu; craig.forester@ucsf.edu; anu.banerjee@ucsf.edu

4.1 Epidemiology

4.1.1 Incidence

Ependymomas comprise approximately 10 % of all pediatric central nervous system (CNS) tumors and are the third most common brain tumor in children less than 20 years of age (Ries et al. 1999). Ependymomas are gliomas that originate from the lineage of cells that give rise to the differentiated ependymal cell layer lining the ventricular system and central canal of the spinal cord. The majority of those arising in the brain, up to two-thirds, arise in the posterior fossa. The percentage of ependymomas arising from the posterior fossa is greatest in children less than 3 years old (Horn et al. 1999). Data from the SEER group (Surveillance, Epidemiology, and End Results) suggest that the annual incidence of ependymoma is 2.6 per million for the 0–14 age group and 2.2 per million for the 0–20 age group (Linet et al. 1999; Ries et al. 1999). Another recent SEER data review from 2012 identified that ependymomas make up about 20 % of spinal cord tumors in patients less than 20 years old. This study also revealed

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_4

that spinal cord ependymoma diagnoses as a whole have increased over time since 1990, likely due to increased histological precision (Hayden Gephart et al. 2012).

4.1.2 Age, Race, and Sex Distribution

The incidence of intracranial ependymoma peaks in the 0–4 age group (5.2 cases per million) and decreases thereafter to 1.5 per million in the 5–14 age group and 0.9 per million in the 15–19 age group. Incidence increases up to 4.1 cases per million between the ages 20 and 44, further increases up to 5.9 per million between 45 and 64, and downtrends in incidence thereafter. Ependymomas are up to twice as common in males than in females; however, this ratio varies according to ependymoma subtype. The overall average annual incidence is 3 per million in males and 1.5 per million in females. The incidence of occurrence among races is highest among Caucasians followed by African-Americans, Asian Pacific Islanders, and lastly American Indians (Villano et al. 2013; Linet et al. 1999; Ries et al. 1999).

4.1.3 Environmental and Viral Causes

The etiology of ependymoma formation remains obscure. In most epidemiologic studies, ependymomas are grouped with other brain tumors, thus making it impossible to identify risk factors that are specific for ependymoma.

There was previously thought to be a role for polyomaviruses in the etiology of ependymoma. From 1955 to 1963, pools of poliovirus and adenovirus vaccines were contaminated with simian virus 40 (SV40), raising concern about possible increases in overall cancer incidence and the incidence of rare tumors such as ependymoma in patients inoculated with contaminated vaccines (Carbone et al. 1997). The SV40 genome can be detected in a majority of ependymomas and choroid plexus carcinomas and also in astrocytoma, meningioma, glioblastoma multiforme, and medulloblastoma (Bergsagel et al. 1992; Martini et al. 1996). However, large epidemiologic studies that evaluated the incidence of neoplasms in patients inoculated with contaminated vaccines, with surveillance up to 30 years, did not detect an increased overall incidence of ependymoma or other neoplasms (Strickler et al. 1998).

One epidemiologic study evaluating Swedish birth cohorts investigated potential maternal or perinatal risk factors leading to childhood brain tumors. Fifty-four ependymomas were included in this population, and factors such as oral contraceptive and narcotic exposure, asphyxia, neonatal instability (such as those requiring supplemental oxygen or tube feedings), and neonatal infections were shown to be linked to increased tumor occurrence. However, there were no factors that specifically linked to ependymomas or other tumor subtypes alone (Linet et al. 1996).

4.1.4 Genetic Predisposition

Neurofibromatosis type 2 (NF2) is the only known genetic disorder associated with a predisposition for developing ependymoma. Patients with NF2 typically develop intramedullary spinal tumors (Lee et al. 1996). *NF2* mutations have been found in 25–70 % of patients with sporadic intraspinal ependymomas. No *NF2* mutations were found in patients with ependymomas of other locations (Birch et al. 1996; Lamszus et al. 2001). Although familial intracranial ependymoma is very rare, in a family in which four cousins developed ependymoma, a suspected tumor-suppressor gene locus was located by a segregation analysis to chromosome region 22pter-22q11.2 (Hulsebos et al. 1999). A familial cohort of nine family members has been reported in which five members developed intramedullary spinal ependymoma. Eight of the family members (including all five with tumors) were found to have a deletion of exon 9 of *NF2* (Zemmoura et al. 2014). Although there is a case report of a child with a germline mutation in the *p53* gene and intracranial ependymoma, ependymoma is usually not considered one of the

cancers of the Li–Fraumeni syndrome (Hamilton and Pollack 1997).

One large population study indicated that parents of children with ependymoma might be at an increased risk of colon cancer (relative risk 3.7) (Hemminki et al. 2000). However, another large study did not identify increased risk of any cancer in families of children with brain tumors (Gold et al. 1994).

4.2 Pathology

4.2.1 Histopathology

Ependymomas arise from ependymal epithelium that lines the ventricles of the brain and central canal of the spinal cord. The most common sites for this tumor are the fourth, third, and lateral ventricles and the lumbosacral spinal cord. Ependymomas are usually well-demarcated tumors that often display areas of calcification, hemorrhage, and cysts. Ependymomas vary from well-differentiated tumors with no anaplasia and little polymorphism to highly cellular lesions with significant anaplasia, mitotic activity, and necrosis that may resemble glioblastoma multiforme. The World Health Organization (WHO) classification of brain tumors (Louis et al. 2007) distinguishes four subtypes of ependymoma: myxopapillary (grade I), subependymoma (grade I), classic (grade III), and anaplastic (grade III). Two histological entities are considered as WHO grade I ependymoma: subependymoma and myxopapillary ependymoma.

Subependymoma is a slow-growing, rare tumor usually located in the wall of the ventricular system, especially the fourth ventricle. A recent, large population review in Beijing identified subependymoma incidence of only about 0.07 % of nearly 60,000 investigated brain tumors (Bi et al. 2015). In contrast, The Central Brain Tumor Registry of the United States (CBTRUS) reports about 12.9 % of all ependymoma diagnoses are due to subependymomas (Villano et al. 2013). Histologically, subependymomas are characterized by clustering of monomorphic cells arranged against a fibrillary background, frequently showing the presence of focal cystic degeneration, vascular hyalinization, hemosiderin deposition, and calcifications. Subependymomas usually show strong immunopositivity for glial fibrillary acidic protein (GFAP) and S-100 antigens. Compared to other ependymal tumors, subependymomas have the lowest rate of cell proliferation, as demonstrated by MIB-1 immunostaining (Prayson and Suh 1999). Subependymomas do not show any cytogenetic changes and are considered to be hamartomatous lesions by many authors (Debiec-Rychter et al. 2000). Most subependymomas are incidental tumors discovered at autopsy, but occasionally grow large enough to cause symptoms. Following surgical resection, these tumors rarely recur, and the long-term prognosis is excellent, although one recent review has shown that poorer outcomes are seen in patients with poorly defined tumor borders and in patients less than 14 years old (Bi et al. 2015).

Myxopapillary ependymoma is found almost exclusively in the region of the cauda equina where it originates from the filum terminale. These tumors more frequently affect adult patients with one population-based study illustrating median age of 35 years at time of diagnosis (Tsai et al. 2014). Myxopapillary ependymomas are slow-growing tumors that may eventually erode into the adjacent bone and soft tissues. Common presenting symptoms include back pain, nerve pain, and extremity weakness (Kukreja et al. 2014). Grossly, myxopapillary ependymomas appear as well-circumscribed masses that typically occur within the filum terminale. The microscopic features resemble the normal filum terminale. Cuboidal to columnar cells, sometimes with clear cytoplasm, are arranged in a perivascular papillary pattern around central cores whose stroma is comprised of connective tissue and blood vessels (Fig. 4.1) (Louis et al. 2007). Although rare, myxopapillary ependymoma can recur, spread along the central nervous system (CNS) axis, and occur outside the CNS in ectopic sites such as the sacrum and presacral tissues, where embryonically derived ependymal rests may be found (Woesler et al. 1998; Smyth et al. 2000; Ciraldo et al. 1986). Children may have a higher recurrence risk as described in

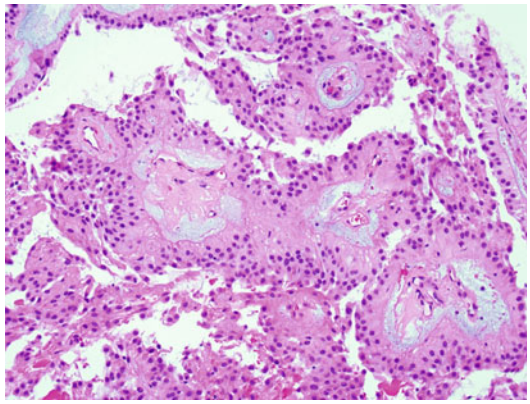

Fig. 4.1 Myxopapillary ependymoma, WHO grade I, demonstrates centrally placed hyalinized blood vessels, surrounded by mucinous microcystic degeneration and collars of small epithelioid ependymal cells (courtesy of Dr. A. Perry)

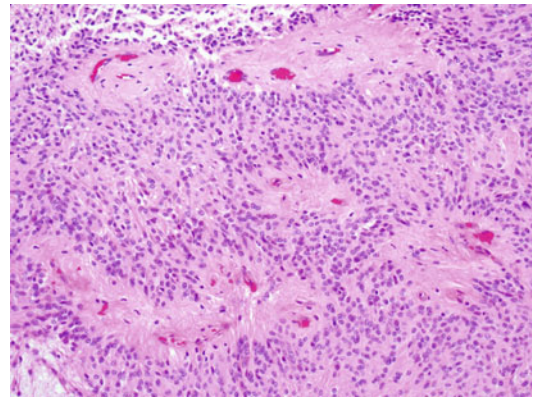

Fig. 4.2 Ependymoma, WHO grade II, demonstrates prominent perivascular pseudorosettes composed of fibrillar nuclear-free zones surrounding centrally placed blood vessels. The mitotic index is low and there is no microvascular proliferation (courtesy of Dr. A. Perry)

one meta-analysis including 475 patients, which found pediatric patients to have recurrence rates of 40.5 %, nearly twice the recurrence rate of 23.4 % in adults, independent of resection status (Feldman et al. 2013).

WHO grade II ependymomas consist of four histologic subclasses: cellular, papillary, clear cell, and tanycytic. These tumors are usually solid and well demarcated, with limited infiltration of surrounding structures. Histologic hallmarks include perivascular pseudorosettes, which consist of neoplastic cells encircling a blood vessel with cytoplasmic processes extending between their nuclei and the vessel wall (Fig. 4.2). Less commonly, true ependymal rosettes may form, which consist of neoplastic cells forming a central space reminiscent of ependymal canals. Grade II ependymomas are moderately cellular with low mitotic activity, but may demonstrate nuclear atypia, occasional mitoses, and foci of necrosis and calcification. Interestingly, a review of 134 patients with spinal ependymomas of all grades illustrated a better progression-free survival in patients with WHO grade II ependymomas when compared with WHO grade I ependymomas (Tarapore et al. 2013). Cellular ependymoma is a variant with conspicuous cellularity, but often less prominent pseudorosette or rosette formation. Papillary ependymoma histologically mimics the pattern of choroid plexus papilloma (Louis et al. 2007). Clear cell ependymomas consist of cells with swollen, clear cytoplasm, and well-defined plasma membranes (Louis et al. 2007). This subtype has been shown to demonstrate necrosis and microvascular proliferation with higher clear cell percentage corresponding to higher proliferation (Ishizawa et al. 2012; Fouladi et al. 2003). Tanycytic ependymoma is the rarest ependymoma subtype, occurs mostly within the spinal cord, and is derived from a subpopulation of ependymal cells titled tanycytes. Tanycytic ependymomas tend to contain low-to-moderate cellularity with dense nuclear zones of spindle cells and hypocellular fibrillary zones. These tumors tend to lack the stereotypical rosettes commonly seen in ependymomas, but may contain less organized perivascular rosettes. This subtype appears to show a significant male predominance (Agarwal et al. 2014).

WHO grade III anaplastic (malignant) ependymoma has histological evidence of anaplasia, including high cellularity, variable nuclear atypia and hyperchromatism, and marked mitotic activity (Fig. 4.3). Vascular proliferation is often prominent, and necrosis may be widespread (Louis et al. 2007).

Ependymoblastomas are highly malignant rare tumors of embryonic origin that consist of elements resembling primitive embryonic ependymal cells. Despite their name, these tumors are not ependymal tumors, but highly malignant primitive neuroectodermal tumors.

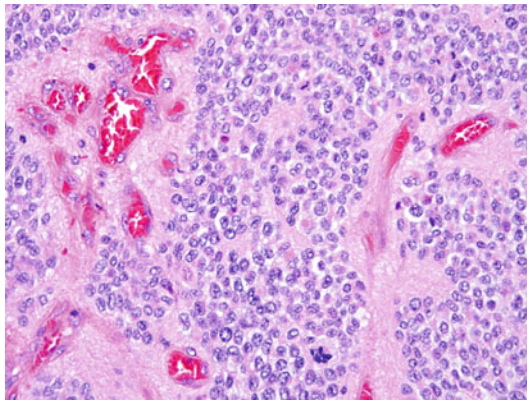

Fig. 4.3 Ependymoma, WHO grade III, demonstrates similar perivascular pseudorosettes to those of lower-grade ependymomas, but also features frequent mitoses and early microvascular proliferation (courtesy of Dr. A. Perry)

The considerable variation in histopathology among the tumor subtypes of ependymomas can result in discordance among pathologists in grading and diagnosis. The rate of misclassification can be as high as 69 % (Robertson et al. 1998), and the criteria for distinction between grades II and III are not highly reproducible. The WHO guidelines delineate grade II from grade III tumors based on increased mitotic activity, microvascular proliferation, and pseudopalisading necrosis (Louis et al. 2007). Many studies, even with central review, could not confirm the correlation between histology and patients' outcomes (Ross and Rubinstein 1989; Schiffer et al. 1991; Perilongo et al. 1997; Robertson et al. 1998). Ellison and others completed a histopathological comparison study among five neuropathologists using 229 ependymoma tissue samples. This study found that five out of five concordance on grading based on WHO schema were present only 42 % of the time, and even with consensus, grade was not consistently associated with survival outcomes (Ellison et al. 2011).

Immunohistochemistry (IHC) may be difficult to interpret in ependymomas. IHC varies according to ependymoma subtype and location and may prove to be applicable as a prognostic indicator. GFAP appears to be the most consistent immunohistochemical stain among ependymomas. Multiple studies have shown variable vimentin, synaptophysin, EMA, and S-100 staining among and within ependymoma subtypes and within individual tumors, depending on sampling size (Agarwal et al. 2014; Koperek et al. 2004; Lamzabi et al. 2013; Vege et al. 2000). IHC patterns may also change according to anatomic location of ependymoma. For example, higher expression of neuronal marker, NeuN, appears to occur in supratentorial tumors, whereas GFAP may prove to have higher concentrations in infratentorial tumors (Hagel et al. 2013).

Electron microscopy can be useful in confirming the diagnosis of ependymoma when there is atypical appearance under light microscopy. This is true regarding visualization of rosettes, which are found in more than 90 % of cases, but present in only 30–40 % of cases by light microscopy. Typical ependymoma morphology reveals microvilli and cilia on the apical surface with fragmented microtubules and cellular processes within the intracellular space (Balovannis and Balovannis 2014; Sara et al. 1994). Papillary ependymomas also show a basement membrane, and myxopapillary ependymomas reveal elongated cells within the intracellular space (Balovannis and Balovannis 2014). Higher-grade ependymomas differ from lower grades by lacking cilia and basal bodies (Alfaro-Cervello et al. 2015).

4.2.2 Genetics and Molecular Biology

Ependymomas may arise in any of three anatomic locations including the cerebral hemispheres, the spinal cord, and the posterior fossa. Over 90 % of pediatric ependymomas arise in the brain with approximately 70 % of these cases in the posterior fossa (Mack and Taylor 2009). When ependymomas are examined as a whole, genetic abnormalities have been identified in varying frequencies within the tumors. Chromosomal losses have been described in 1p, 3, 6q, 9p, 10q, 13q, 16p, 17, 21, and 22q. Chromosomal gains have been seen in 1q, 4q, 5, 7, 8, 9, 12q, and 20 (Mack et al. 2009). Abnormalities of chromosome 22 are most often seen including partial loss, monosomy 22, and translocations with a frequency ranging from 26 % to 71 % (Taylor et al. 2005). Loss of *NF2*, located on chromosome 22, suggests that it is acting as a tumor-suppressor gene in this setting.

Indeed, patients with NF2 have a higher incidence of ependymoma (in addition to schwannomas and meningiomas) (Evans et al. 2000). *NF2* abnormalities have only correlated with spinal ependymoma and are rare in childhood intracranial ependymoma (Pezzolo et al. 2008). More pertinent to pediatric CNS tumors chromosome 1q gain has been found in up to 22% of childhood ependymoma (Mack et al. 2009). Gain of 1q is correlated with pediatric age, posterior fossa, high grade, and recurrence (Mendrzyk et al. 2006; Carter et al. 2002; Godfraind et al. 2012). Although these translocations have been informative in describing this disease and patterns of location where it arises, it is important to recognize that a large proportion of pediatric, intracranial disease possesses a balanced comparative genetic hybridization (CGH) profile (Mack et al. 2009).

More detailed studies found specific gene expression patterns and chromosomal translocations in each region (Taylor et al. 2005). Array comparative genetic hybridization (aCGH) recapitulated prior findings such as gains in 1q correlating with pediatric age, intracranial location, and high grade, as well as widespread chromosome 22 loss in intracranial tumors (Taylor et al. 2005; Modena et al. 2006). This high-resolution hybridization study revealed specific losses in chromosome 9p (p16INK4a) and gains in chromosome 7p (*TWIST1*) and chromosome 20 (Notch pathway signaling) (Taylor et al. 2005; Modena et al. 2006). These analyses reconfirmed results obtained from studies using less sensitive methods suggesting that approximately half of posterior fossa ependymomas have a balanced karyotype (Taylor et al. 2005).

Gene expression analyses demonstrated characteristic networks associated with ependymoma tumors arising from individual sites (Taylor et al. 2005). Ephrin and Jagged signaling pathways and cell cycle mediators (Cdk2, 4 and CyclinB2, D1, G2) are upregulated in supratentorial ependymomas. This is in contrast to spinal cord ependymomas which upregulate Hox transcription factors and IGF signaling and posterior fossa tumors which upregulate ID (bind/inhibit HLH transcription factors) and aquaporin family proteins (Taylor et al. 2005).

Alterations of classic oncogenes associated with other CNS tumors such as astrocytomas and oligodendrogliomas (such as *TP53*, *CDKN2A*, and *EGFR*) are rare in ependymomas (Bijlsma et al. 1995; Ohgaki et al. 1991; Sato et al. 1996). An exception are *ErbB2* and *ErbB4* which are reported to be overexpressed in the majority of ependymomas (Gilbertson et al. 2002). Clues to a different mechanism of genetic alteration stemmed from work focused on hypermethylation of a p53-dependent transcription repressor, HIC-1 (Waha et al. 2004). Epigenetic methylation acts to transcriptionally repress target genes by placing methyl group on cytosines found within CpG dinucleotides by DNA methyltransferase enzymes (Bird and Wolffe 1999). Decreased expression of HIC-1 is correlated with hypermethylation and astrocytic gliomas, medulloblastomas, and hepatocellular carcinomas in human patient-derived samples (Waha et al. 2004). Of all ependymal tumors analyzed, 83% showed hypermethylation of *HIC-1* which correlated with decreased expression of HIC-1 in 81% of ependymomas (Waha et al. 2004). Subsequent studies on epigenetic changes employed genome-wide methylation array experiments (Rogers et al. 2011). This approach demonstrated a hypermethylation phenotype in supratentorial and spinal tumors and a hypomethylation pattern in posterior fossa tumors (Rogers et al. 2011). Genes repressed in supratentorial/spinal cord tumors included those involved in cell growth (*MAPK10*, *PPARG*) and the immune response (*NOD2*, *IRF7*, *IRAK3*, *OSM*, *PI3*) (Rogers et al. 2011).

Microarray expression data from two independent cohorts of posterior fossa ependymomas were able to segregate all tumors into three classifications: supratentorial, posterior fossa and posterior fossa + spinal tumor (Witt et al. 2011). These posterior fossa ependymomas could be further divided into a Group A and Group B (Witt et al. 2011). Whereas Group A tended to occur in younger patients, it was more likely to invade into the cerebellum, had multiple increased cancer-related signaling networks, and

had increased recurrence and mortality in 5 years; there was no difference in histology or grade between the groups (Witt et al. 2011). In comparison to Group B, these Group A tumors had a predominantly balanced karyotype with the exception of 1q gain.

Unbiased large-scale methods have led to the discovery of mechanistic differences between ependymoma subgroups. Whole genomic and exomic sequencing showed a strikingly low number of single nucleotide variants (SNV) in both Group A and Group B posterior fossa (PF) ependymomas (Mack et al. 2014). Analysis of the DNA CpG island methylome across all ependymomas yielded three methylome patterns corresponding to supratentorial, posterior fossa, and mixed spinal/posterior fossa (MSPF) tumors (Mack et al. 2014). Posterior fossa Group A (PFA) corresponded to the PF group, and posterior fossa Group B (PFB) tumors corresponded to the MSPF tumors. The methylome of PFA tumors was markedly different from PFB tumors and exhibited significantly higher numbers of CpG hypermethylation, thus conferring a "CpG island methylator" (CIMP) phenotype (Mack et al. 2014). These PFA tumors display a hypermethylation signature, which acts to silence *PRC2* target genes. Silencing of these genes prevents differentiation, thus keeping cells in a more "stemlike" program. Most excitingly, treatment of PFA tumors with demethylating agents and repressors of *PRC2* was able to restore gene expression signatures. In addition, these agents were active against xenografted PFA tumors and reduce their tumor-initiating capability (Mack et al. 2014).

Overexpression of *EZH2* (enhancer of zeste homolog 2) is another recently identified molecular marker that may have prognostic significance. This gene is located along the long arm of chromosome 21 at position 21.2. EZH2 leads to chromatin remodeling by adding a methyl group to histone protein H3K27 and ultimately silencing cyclin-dependent kinases responsible for limiting cell division and pluripotency. Overproduction of EZH2 has previously been implicated in other solid tumors including breast and prostate and other brain tumors such as glioblastoma and atypical rhabdoid teratomas. In the ependymoma population, EZH2 overexpression has been associated with poorer 5-year progression-free and overall survival. This effect appears especially pronounced when combined with AKT (activated protein kinase B) overexpression. Expression of p16 (tumor protein 16) appears to offer a protective role leading to overall improved survival (Li et al. 2015).

4.3 Clinical Features

Data from the Surveillance, Epidemiology and End Results study (SEER) illustrates that nearly half of primary ependymomas occur in the brain and the other half occur within the spinal cord or cauda equina. Spinal cord ependymomas are common in adult patients, although the incidence of ependymomas within the ventricles and cerebellum also increases with age. In children, however, ependymomas occur more frequently in the brain. Histology, too, changes with age; the anaplastic subtype is more common in children and adolescents, while adults are more frequently diagnosed with grade I ependymomas (Villano et al. 2013).

Approximately 35 % of patients have WHO grade III histology at diagnosis. Seven to 15 % of patients with ependymoma have disseminated disease at diagnosis (Perilongo et al. 1997; Robertson et al. 1998). Supratentorial ependymomas grow as intraparenchymal tumors, typically adjacent to the lateral ventricles. Infratentorial ependymomas arise from the fourth ventricle and typically invade adjacent structures or extend into the aqueduct of Sylvius, foramen of Magendie, foramen of Luschka, or to the upper cervical cord. Extraneural ependymomas have been rarely described, usually after progression of intracranial disease. The sites of extraneural spread include peritoneum, lymph nodes, lungs, pleura, bone, and liver (Newton et al. 1992). Extraneural metastases can be seen with both the low- and high-grade ependymoma subtypes (Cimino et al. 2014; Pachella et al. 2015; Perez-Bovet et al. 2013). WHO grade 1 myxopapillary tumors,

specifically, have been shown to have a high predilection for metastasis, both within the CNS and in extraneural spaces. Metastatic disease appears to be more common in the pediatric population (Cimino et al. 2014; Fassett et al. 2005). Chang's staging system for posterior fossa tumors (Table 4.1) can be applied to categorize ependymomas, although this is less commonly used in clinical practice.

Posterior fossa ependymomas typically present with signs and symptoms of obstructive hydrocephalus including vomiting, headache, and ataxia (Ilgren et al. 1984; Nazar et al. 1990). Infiltration into the brainstem and growth through the foramina of Luschka or central canal may result in cranial nerve palsies, torticollis, or meningismus. Children less than 2 years of age tend to present with nonspecific signs such as irritability, vomiting, lethargy, macrocephaly, or gait disturbance (Nazar et al. 1990). The duration of symptoms is usually less than 6 months at the time of diagnosis (Coulon and Till 1977), with 50 % of children presenting with duration of symptoms of 1 month or less (Horn et al. 1999). Symptoms of spinal cord ependymoma from an adult series included pain in 75 % of patients, sensory changes in 71 %, and weakness in 68 %. The average duration of symptoms was 13 months prior to diagnosis (Waldron et al. 1993). Ependymomas of the cauda equina present with limited spinal motion in 50 % of patients, paravertebral spasm in 32 %, and motor deficits and abolition of reflexes in 34 % of patients (Wager et al. 2000).

Table 4.1 Modified Chang's staging system for posterior fossa tumors

		Definition
Tumor	T1	Tumor confined to the fourth ventricle
	T2	Tumor of the fourth ventricle with contiguous extension inferiorly through the foramen Magendie and extending to the upper cervical canal
	T3	Tumor of the fourth ventricle with lateral extension through the foramen of Luschka into the cerebellomedullary or cerebellopontine cistern
	T4	Tumor of the fourth ventricle with invasion of other structures such as the cerebellar peduncle, medulla, pons, midbrain, etc.
Metastases	M0	No evidence of metastases
	M1	Microscopic tumor found in cerebrospinal fluid
	M2	Gross nodule seedings in the cerebellar or cerebral subarachnoid space or in the third or lateral ventricles
	M3	Gross nodule seedings in the spinal subarachnoid space
	M4	Extraneuroaxial metastases

4.4 Natural History and Risk Factors

In a small retrospective series of 11 untreated intracranial ependymomas, all patients died within 3 years of symptom onset (Mork and Loken 1977). In an older series, surgery alone was shown to be curative only in a small proportion of patients. For example, in one pediatric series of patients diagnosed between 1935 and 1973, 4/12 patients with intracranial ependymomas and three out of three of patients with spinal cord ependymomas were alive 5 years after surgery (Dohrmann et al. 1976). In another series of patients diagnosed between 1953 and 1974, 2/12 patients with intracranial ependymomas treated with surgery alone were alive 5 years after the surgery, and 10/17 patients with intramedullary ependymomas were alive 10 years after the surgery (Mork and Loken 1977). Another series using better diagnostic imaging indicated that if complete resection was achieved, surgery alone might be curative in a subgroup of children with low-grade intracranial ependymoma. In that study, five out of seven patients treated with gross total resection (GTR) alone remained in remission 24–70 months following surgery (Awaad et al. 1996). Similarly, Hukin et al. reported ten cases of ependymoma treated with complete resection alone. Seven out of ten patients were free of disease and three recurred, with median follow-up of 48 months. Two of the recurrences were salvaged with repeat surgery and radiation

therapy (Hukin et al. 1998). Notably, a longer period of observation of patients with ependymoma is necessary, since recurrences continue even after 5 years from diagnosis.

While most studies demonstrate that achievement of GTR of intracranial and intramedullary spinal cord ependymoma correlates with superior outcomes, other risk factors, including location of tumor, histology, and use of adjuvant chemotherapy, have not been unequivocally confirmed to predict outcome (Cervoni et al. 1994; Rousseau et al. 1994; Perilongo et al. 1997; Robertson et al. 1998). Younger children with ependymoma historically have had worse outcomes. It is not clear if age alone, or a combination of risk factors such as unfavorable location, which may preclude GTR, and withholding radiation therapy, may have contributed to poor outcomes in younger age groups. Current therapeutic studies use age, histology, and location of ependymoma for stratification of treatment, despite conflicting literature reports on their validity as prognostic factors.

4.5 Diagnosis

Evaluation of a patient with ependymoma should include a comprehensive history and physical examination, pre- and post-operative magnetic resonance imaging (MRI) of the brain, MRI of the spine, and cerebrospinal fluid evaluation. The spine MRI should ideally be performed prior to surgery, because post-operatively, blood in the spinal subarachnoid space may be confused with drop metastases.

Radiographically, supratentorial ependymomas appear as large, heterogeneous, periventricular, or, less commonly, intraventricular masses. Calcifications are present in approximately 50 % of tumors examined by computerized tomography. Most supratentorial ependymomas have cystic components and enhance after the administration of intravenous contrast (Furie and Provenzale 1995). Infratentorial ependymomas appear as heterogeneous lesions that grow into the fourth ventricle and cause dilation of its upper part. Usually, the tumor is separated from the vermis by a cleavage plane. In most cases, the solid part of the tumor is intense with gray matter on T1- and T2-weighted MR images, and this enhances with contrast (Tortori-Donati et al. 1995) (Figs. 4.4, 4.5, and 4.6).

The typical picture of an intramedullary ependymoma on MRI consists of segmental or diffuse cord expansion with intramedullary intensity abnormalities and prominent nodular gadolinium enhancement (see Fig. 10.2). Intramedullary cysts and hydrosyringomyelia are common, particularly in childhood cases. Gadolinium enhancement may distinguish solid tumor from cord edema and from cyst or syrinx (Slasky et al. 1987). Cauda equina ependymomas usually demonstrate homogeneous hypointense signal on T1-weighted MRI sequences, hyperintense signal on T2-weighted sequences, and homogeneous enhancement after gadolinium injection (Wager et al. 2000).

4.6 Treatment

4.6.1 Surgery

The goals of surgery are to make a definitive tissue diagnosis, achieve a GTR of the tumor, and re-establish cerebrospinal fluid flow. The location of the ependymoma may be a limiting factor to surgical resection, particularly when within the upper spinal cord or posterior fossa and abutting midbrain structures (Safaee et al. 2014).

Based on retrospective studies, the extent of surgery is considered as the most important prognostic factor. In a retrospective analysis of 96 pediatric posterior fossa ependymomas from the Children's Oncology Group, extent of resection and older age were significantly correlated with better overall survival. They went on to review 1,444 patients from 32 manuscripts from 1990 to 2005 and determined that the extent of resection was a significant factor in 21 studies, age in 12, and histological grading in 9 of the studies (Tihan et al. 2008). In a study of 55 patients with anaplastic ependymoma, patients with a complete surgical resection followed by other treatments had an 83 % disease-free

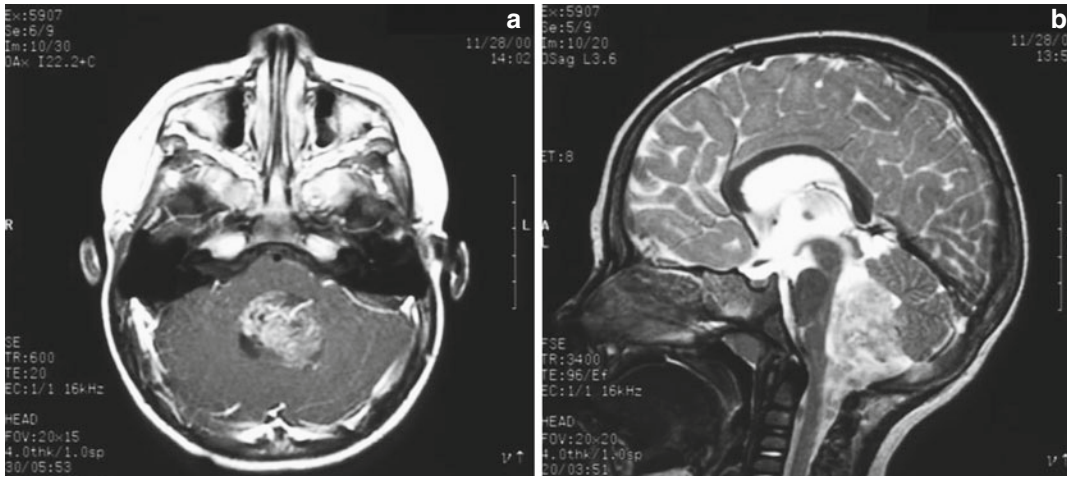

Fig. 4.4 Typical imaging features of a posterior fossa grade II ependymoma showing heterogeneous enhancement following gadolinium administration (**a**). The T2-weighted image (**b**) shows the typical extension of the tumor through the foramen magnum into the upper cervical spinal canal

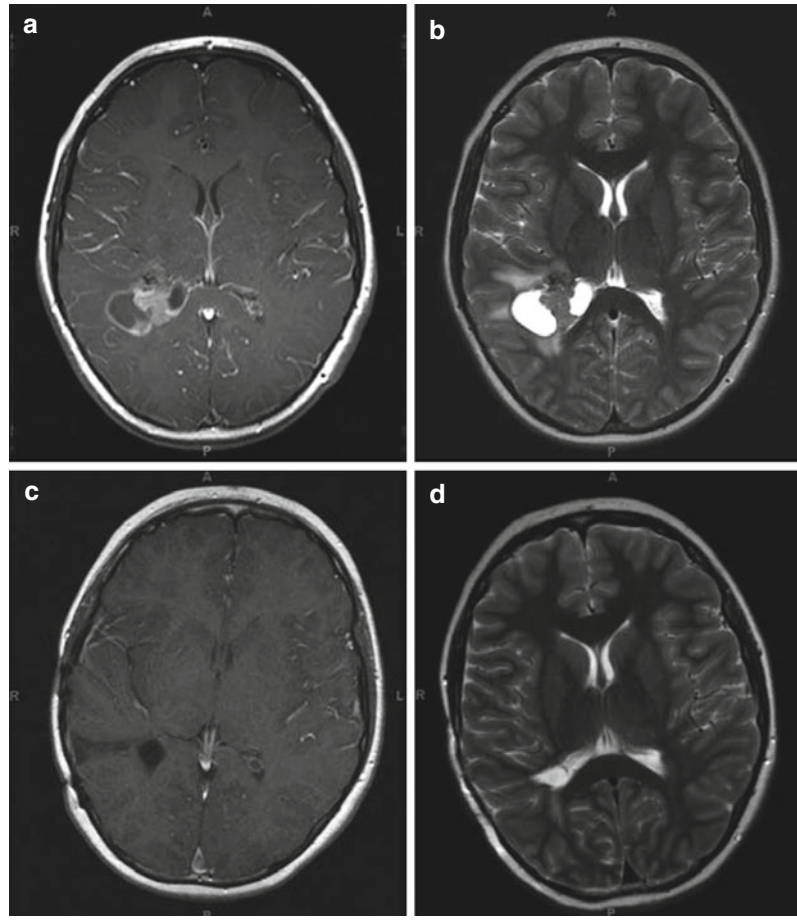

Fig. 4.5 Preoperative T1- (**a**) and T2-weighted (**b**) MR images of a supratentorial ependymoma in a 9-year-old boy arising adjacent to the right trigone and periventricular area. The grade III ependymoma was grossly resected and after external beam radiation therapy, he remains progression-free for 3 years. The postoperative T1-weighted image with contrast (**c**) and T2-weighted image (**d**) show no evidence of tumor recurrence

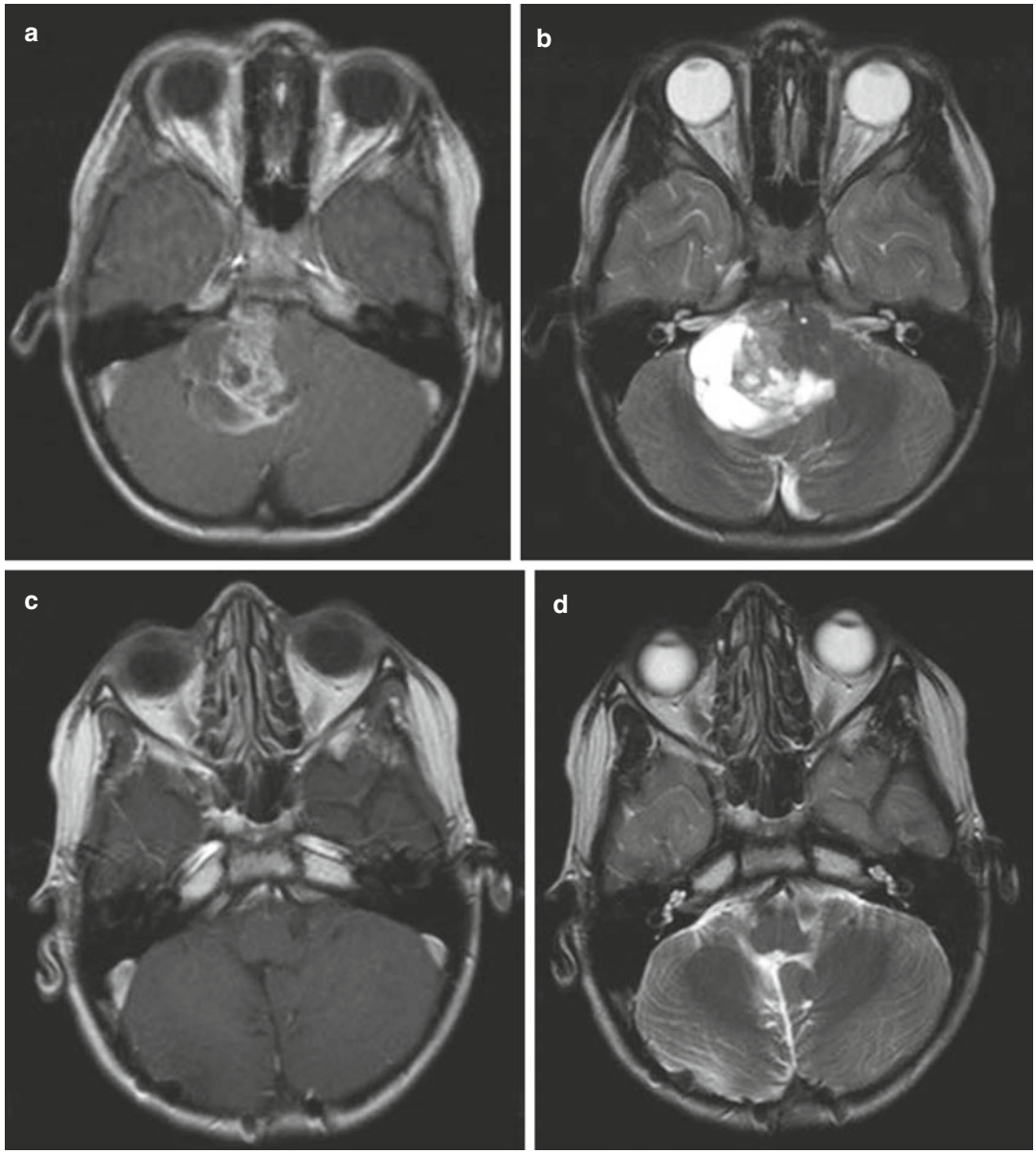

Fig. 4.6 A preoperative T1-weighted MR image with contrast (**a**) and T2-weighted image (**b**) from a 7-year-old boy with a right cerebellopontine angle grade 2 ependymoma. After resection and external beam radiation therapy, he remains progression-free for 5 years. The postoperative T1-weighted image with contrast (**c**) and T2-weighted image (**d**) show no evidence of tumor recurrence

survival after 3 years of follow-up, compared with 38 % for those without complete resection (Timmermann et al. 2000). In a similar study of 32 children with ependymoma between 2 and 18 years of age, 66 % of patients with complete resection had 5-year progression-free survival, compared with 11 % of those without complete resection (Robertson et al. 1998).

In patients where complete resection may be unobtainable, some groups have investigated the use of a "second-look surgery." An Italian group investigated this approach in a population of 38

patients who underwent repeat surgery for a variety of indications: complications impeding resection on first attempt, missed tumor tissue, or anatomic areas where initial resection was not possible. Out of the 38 investigated patients, 21 were able to achieve total resection after one or more repeat surgeries. Many of these patients also received adjuvant chemotherapy or radiation prior to repeat resection attempts. Overall, patients who were ultimately able to achieve complete resection even after multiple surgical attempts still went on to have higher rates of survival when compared to patients that continued to have evidence of disease (Massimino et al. 2011). This study highlights the significance of surgical resection in ependymoma treatment.

A recent review looked at 26 patients with intracranial ependymomas that underwent surgery alone and achieved GTR. This study also evaluated status of outcome in groups of patients with varying Ki-67 indices and status of EZH2 positivity. From this population of 12 posterior fossa and 14 supratentorial tumors, the 5-year overall survival was 70% in both populations. Patients with higher Ki-67 indices and positive EZH2 status were associated with poorer rates of progression-free survival, despite GTR. These studies outline the potential for risk stratification of ependymoma subtypes from a WHO grade, histological, and ultimately from a molecular standpoint.

Some investigators have used surgery alone to treat ependymoma. In one study of ten selected patients with intracranial ependymoma (eight supratentorial and two posterior fossa tumors), seven remained free of disease without any other interventions at a median follow-up of 48 months (Hukin et al. 1998). Investigators at St. Jude Children's Research Hospital reported 10/16 patients with residual disease after the first surgery achieved GTR after a "second-look" surgery (Osterdock et al. 2000).

Posterior fossa ependymomas frequently arise from the floor of the fourth ventricle or the region of the foramina of Luschka, extending out to the cerebellopontine angle (Fig. 4.6). Cranial nerves and vascular structures are frequently encased or displaced by the tumor, making surgical excision difficult. Sequelae of an aggressive surgical approach often include cranial neuropathy, bulbar dysfunction, and the risk of posterior circulation infarction. Surgical results have improved through technical advances, such as intraoperative electromyographic monitoring of cranial nerves, computer-assisted navigation, and the operating microscope. Due to the strong prognostic impact of the degree of surgical resection, all children with suspected ependymoma should be referred to a center that can provide the expertise required for optimal management of these tumors.

4.6.2 Radiation Therapy

Radiation therapy (RT) is considered the standard adjuvant treatment of intracranial ependymomas in older children, with different definitions of lower age limit in different studies. The approach to radiation therapy of ependymoma, in particular the radiation field, has changed over a period of decades. In the 1960s and 1970s, local field radiation was used, as improved outcomes were noted in irradiated patients, when compared to historical controls. In 1975, Salazar recommended extending the radiation field to include the whole brain in patients with low-grade ependymomas and the entire craniospinal axis in patients with high-grade ependymomas (Salazar et al. 1975). These recommendations were based on an overestimated risk of dissemination from autopsy findings and on poor distinction between ependymomas and ependymoblastomas. In the late 1980s and early 1990s, multiple studies questioned the role of craniospinal radiation (Shaw et al. 1987; Goldwein et al. 1991; Vanuytsel and Brada 1991), as there was no difference in failure rates between patients undergoing localized versus craniospinal radiation. Local relapse was confirmed to be the most significant component of failure, and a local radiation dose of more than 4,500 cGy was recommended (Goldwein et al. 1991).

In the late 1980s, cooperative pediatric cancer groups initiated studies of postoperative chemotherapy in infant brain tumors with the goal to

delay and possibly avoid radiation in young patients for whom large radiation fields would cause significant morbidity (Duffner et al. 1993; Geyer et al. 1994). Young children with ependymomas were treated in these studies together with patients with primitive neuroectodermal tumors. In the 1990s, attempts were made to replace radiation therapy with high-dose chemotherapy consolidation in children less than 6 years of age with malignant brain tumors (Mason et al. 1998) or to replace radiation with postoperative chemotherapy in children under 5 years of age (Grill et al. 2001). However, radiation was avoided in only 23 % of patients in the later study, and after progression of tumor, only those children who underwent a second complete resection remained in remission following radiation therapy.

Hyperfractionated radiation therapy was investigated by the Society for Pediatric Oncology. They reported on 24 children over the age of 5 years, treated with either 60 Gy (for patients with complete resection) or 66 Gy (for patients with incomplete resection), given in two daily fractions. Five-year overall survival was 74 % and progression-free survival was 54 %. The study concluded that although the treatment was well tolerated, the survival figures were comparable to those for more conventional treatment regimens, and hence hyperfractionated therapy did not warrant further investigation (Conter et al. 2009). Other investigators have focused on reducing the radiation field by using conformal radiotherapy. In one such study, 36 children with localized ependymoma underwent conformal radiotherapy with an anatomically defined clinical target volume margin of 10 mm surrounding the postoperative residual tumor and tumor bed. Two failures occurred after a median follow-up period of 15 months. It is of significance that 30/36 children in this preliminary report had complete surgical resection (Merchant et al. 2000). More recently, the authors have published a follow-up study of 153 pediatric patients with ependymoma (median age 2.9 years). Patients received conformal, focal radiation to a dose of 54–55.9 Gy following definitive surgery. Thirty-five subjects had prior chemotherapy. Seven-year local control, event-free survival, and overall survival were 87, 69, and 81 %. Survival was affected by tumor grade and extent of resection (Merchant et al. 2009). Radiosurgery has also been used in patients with ependymoma, usually at the time of recurrence, and it can be used safely without significant risk of radionecrosis (Hodgson et al. 2001). In another study, tumor control was achieved in three out of five patients undergoing radiosurgery for residual localized ependymoma (Aggarwal et al. 1997). It is possible that radiosurgery will have a significant role in local control of ependymoma in the future; however, more studies comparing radiosurgery to standard radiation are necessary.

Given the limited effectiveness of chemotherapy in avoiding radiation (see Sect. 4.6.3) and concerns about radiation-induced neurocognitive deficits, 88 patients at St. Jude's between the ages of 2.85 and 4.5 years were treated with conformal radiation therapy (54 or 59 Gy) to gross tumor volume plus a margin of 1 mm (Merchant et al. 2004). Median follow-up was more than 3 years. The 3-year progression-free survival rate in this study was nearly 75 %, with a cumulative incidence of local failure as a component of failure (distant + local) at 3 years being 14.8 %. Serial neurocognitive evaluations performed until patients were 24 months postcompletion of radiation therapy revealed stable IQs. In a follow-up study, the group at St. Jude's reported on outcome of 153 patients with age range of 0.9–22.9 years, median 2.9 years, with localized ependymoma treated with conformal radiation after definitive surgery. Seven-year local control, EFS, and OS were 83.7 %, 69.1 %, and 81.0 %, again supporting the use of conformal techniques in this setting, even for very young patients (Merchant et al 2009). This significant study has prompted continued evaluation of conformal radiotherapy in patients older than 12 months of age, an ongoing Children's Oncology Group clinical trial to use conformal radiation therapy in a subgroup of patients older than 1 year of age with higher-risk localized ependymomas.

There remain patients, however, that may not benefit from RT. In one retrospective analysis of 92 patients with supratentorial WHO grade I or II

ependymomas who underwent GTR with or without associated RT, those that underwent resection alone showed no worse overall survival (83.2 % vs. 84.1 %) when compared to the GTR + RT group (Ghia et al. 2013). In these instances, conservative approaches without radiation therapy may be indicated as long as GTR is achievable, but improved delineation of prognostic features is necessary.

Craniospinal radiation is still to be used alone or in combination with chemotherapy for older patients with disseminated ependymoma.

In summary, although the role of radiation therapy has not been confirmed in randomized studies, the high risk of relapse in younger children treated with chemotherapy only, even after GTR, warrants using this modality. Studies are underway to confirm the role of conformal field radiation in local control of ependymoma.

4.6.3 Chemotherapy

Ependymomas have variable sensitivity to chemotherapy. In multiple studies involving adults with relapsed ependymoma, cisplatin-containing regimens have yielded superior response rates to alternate approaches. Complete and partial responses have been observed at rates that range between 30 (Walker and Allen 1988; Brandes et al. 2005) and 60 % (Gornet et al. 1999). Despite these high rates of response, no chemotherapy regimens have yet been demonstrated to improve overall survival of adults with recurrent ependymoma.

In newly diagnosed patients with ependymoma, chemotherapy has been evaluated for the treatment of children with residual disease or to avoid radiotherapy in young children (<3 years old). In eight children under the age of four with residual ependymoma, an 86 % response rate to VETOPEC therapy (vincristine, etoposide, cyclophosphamide, cisplatin, carboplatin) was reported (White et al. 1998). The Children's Cancer Group protocol (CCG-9942) investigated the role of preirradiation chemotherapy with vincristine, etoposide, cisplatin, and cyclophosphamide in children older than 3 years of age with residual disease. In a preliminary report from this study, the event-free survival did not differ between patients without residual disease whose postoperative treatment consisted of radiation therapy alone (62 ± 8 %) and patients with residual disease who received chemotherapy and irradiation (55 ± 9 %). The chemotherapy objective response rate was 58 %, but 14 % of patients experienced tumor progression while receiving chemotherapy prior to irradiation (Garvin et al. 2004).

The role of chemotherapy in delaying or avoiding radiation in young children with ependymoma has been well studied (Table 4.2). The outcomes are difficult to compare due to differences in the use of radiation. In the earlier studies, although radiation was planned, it was not always given (Duffner et al. 1993; Geyer et al. 1994). In later studies, radiation was used only after tumor progression, and its use indicated chemotherapy failure (Mason et al. 1998; Grill et al. 2001; Grundy et al. 2007). These issues notwithstanding, several valuable observations regarding the effectiveness of chemotherapy can be made. Grundy et al. report the most favorable outcome data with chemotherapy (vincristine, carboplatin, cisplatin, cyclophosphamide, and methotrexate) in the treatment of 80 children less than 3 years old with non-metastatic intracranial ependymoma (Grundy et al. 2007). The 5-year cumulative incidence for freedom from radiotherapy was 42 % in this group of patients. Further, with a median follow-up of 6 years, this group achieved an overall survival rate of approximately 80 % at 3 years and 60 % at 5 years. While the study is limited by lack of radiographic data and neurocognitive follow-up (Bouffet et al. 2007), it suggests that intensive chemotherapy may have benefit in the treatment of young children with ependymoma. While response in this recent study is promising, there are no data to suggest that the neurocognitive outcome for these patients will be superior to that observed with conformal radiotherapy (Merchant et al. 2004). Thus, concerns about response and outcome have resulted in a reexamination of local radiation in all but the youngest patients in several ongoing clinical trials for ependymoma.

Table 4.2 Progression-free survival of young children with ependymoma treated with chemotherapy

Study	Duffner et al. (1993)[a]	Geyer et al. (1994)	Mason et al. (1998)	Grill et al. (2001)	Grundy et al. (2007)[b]
Age group	<36 months	<18 months	<6 years	<5 years	<3 years
Chemotherapy regimen	7 cycles VCR/CTX alternating with cisplatin/VP-16	8 courses of 8-drugs-in-1-day	5 cycles of induction VCR/CTX/cisplatin/VP-16; consolidation with high-dose carbo/thiotepa/VP-16 and stem-cell rescue	7 cycles alternating 3 regimens procarbazine/carboplatin VP-16/cisplatin VCR/CTX	7 cycles containing 4 courses of therapy VCR/carboplatin VCR/methotrexate VCR/cyclophosphamide Cisplatin
Complete resection	19	15 patients total, degree of resection not available	4	46	41
Incomplete resection	27		6	27	36
Progression-free survival	42 % at 2 years 27 % at 5 years	26 % at 3 years	30 % at 2 years	22 % PFS at 4 years	47 % at 3 years 42 % at 5 years

[a]Most patients in this study underwent irradiation following chemotherapy
[b]42/89 total patients, 36/80 nonmetastatic patients received radiation therapy upon relapse or progression. Table entries refer to the nonmetastatic group only

A study completed at the Children's Hospital Los Angeles looked at 19 children with newly diagnosed ependymoma treated with the radiation-sparing "Head Start III" chemotherapy regimen. This regimen involves five induction chemotherapy cycles with one myeloablative consolidation cycle immediately followed by autologous stem-cell rescue. Older children ranging 6–10 years old were then offered radiation therapy. GTR prior to chemotherapy initiation was achieved in 53 % of patients. This study found that children with residual disease localized to the supratentorium were still able to achieve complete response with a high-dose chemotherapy regimen versus only 1.7 % of those with residual disease in the infratentorium. These findings perhaps identify the role of aggressive chemotherapy in patients with residual supratentorial tumors, but not necessarily in patients with infratentorial tumors. Irradiation appears necessary in this population (Venkatramani et al. 2013).

High-dose chemotherapy followed by autologous bone marrow rescue has been used in the setting of recurrent or progressive disease with dismal results. In a study using a thiotepa-, etoposide-, and carboplatin-conditioning regimen in addition to autologous bone marrow rescue, 5/15 children with recurrent ependymoma died of treatment complications and all other patients sustained disease recurrence (Mason et al. 1998). In another study using busulfan and thiotepa as a conditioning regimen, 1/16 patients died from treatment-related toxicity, and only 3 were alive at follow-up times of 15–25 months. All three surviving patients received additional radiation (one patient) or surgery and radiation (two patients) after transplant (Grill et al. 1996). In two additional studies, involving similar conditioning regimens, only one of four patients with relapsed ependymoma responded and survived to 37 months (Thorarinsdottir et al. 2007; Shih et al. 2008). Because of the poor outcomes in these small studies, high-dose therapy is not recommended in patients with relapsed or progressive disease. Zacharoulis et al. reported on the Head Start protocol experience for young children with newly diagnosed ependymoma (Zacharoulis et al. 2007). Patients with metastatic disease underwent five cycles of chemotherapy with vincristine, cisplatin, cyclophosphamide, etoposide, and high-dose methotrexate. This was followed by a single myeloablative cycle of thiotepa, carboplatin, and etoposide, with autologous stem-cell rescue. Five-year event-free and overall

survival rates were 12 and 38 %, and the study concluded that the regimen showed no advantage over nonmyeloablative regimens.

Conventional chemotherapy for relapsed ependymoma typically has low response rates (Bouffet et al. 2009). Novel strategies such as small-molecule targeted therapy and anti-angiogenic chemotherapy are of great interest. Kieran et al. reported on the toxicity and progression-free survival rate following an anti-angiogenic, metronomic chemotherapy regimen (Kieran et al. 2005). Twelve patients with relapsed brain tumors were treated with a cocktail of oral anti-angiogenic agents including thalidomide, celecoxib, low-dose oral etoposide, and cyclophosphamide. Four of the twelve patients had relapsed ependymoma. While one patient progressed during the first 3-week treatment cycle, the remaining three patients continued to receive therapy for 58–83 weeks and had progression-free survival ranging from 58 weeks to longer than 157 weeks. Currently, fenofibrate in combination with oral thalidomide, celecoxib, low-dose oral etoposide, and cyclophosphamide and the combination of bevacizumab and irinotecan are being studied. Several biologically targeted therapies have been investigated in phase I settings in small groups of patients, but definitive response rates are not established (Bouffet et al. 2009). The CERN (Collaborative Ependymoma Research Network) conducted a phase 2 clinical trial of the Erb 1/2 inhibitor, lapatinib, in combination for relapsed ependymoma, but concluded that this combination was not active in this setting (DeWire et al. 2015).

Currently, chemotherapy is used as an adjuvant treatment in patients with postoperative residual disease, with a goal of achieving a response that would make a second-look surgery and conformal radiation therapy more feasible. Chemotherapy may also control microscopic disseminated disease, but it rarely results in complete response of macroscopic disease.

4.6.4 Spinal Cord Ependymomas

Spinal cord ependymoma has a more favorable prognosis than its intracranial counterpart. Surgery remains the primary mode of therapy for spinal cord ependymomas, and complete resection is usually curative. Current treatment recommendations are that another resection must be attempted, if residual tumor is unexpectedly found on the postoperative scan, or in the case of recurrence (Nadkarni and Rekate 1999). Radiation therapy is used when complete resection is not possible. In some studies, excellent control rates of residual tumor were achieved with radiation therapy (80 % progression-free survival at 5 years after diagnosis) (Garrett and Simpson 1983; Waldron et al. 1993), while others report higher postradiation relapse rates (37–89 %) (Whitaker et al. 1991; Cervoni et al. 1994). More information regarding spinal cord tumors is presented in Chap. 10.

Extent of surgical resection is an important prognostic feature in spinal cord ependymomal tumors. In a group of 183 patients with myxopapillary spinal tumors, the estimated overall survival was 92.4 %; however, those not achieving gross total resection (GTR) showed significantly higher proportion of both recurrence and progression (Weber et al. 2015). An additional 24 patients with ependymomal spinal cord tumors of varying grades illustrated that those undergoing GTR experienced recurrence rates of 20 % in comparison to 40 % of those who underwent subtotal resections (STR) (Safaee et al. 2014).

4.6.5 Recurrent Disease

Depending on the completeness of surgical resection and patient age, disease recurs in 25–80 % of patients. One multi-institutional, retrospective review among a group of 22 patients experiencing recurrence reflected a median time of 16 months before first recurrence. There is proportion of patients that exhibit late recurrence beyond 5 years from initial diagnosis. A substantial proportion of these patients (63 %) had disease noted on surveillance prior to exhibiting any clinical symptoms, and most of these patients (62 %) had infratentorial tumors (Antony et al. 2015). In another retrospective series of 52 relapsed pediatric patients, the majority of progressions occurred at the original tumor site (73 %), the original and a new site were involved

in 16 %, and a new site alone in 11 %. Thirteen percent of patients with previously localized disease recurred with disseminated disease (Horn et al. 1999). A similar distribution of site of relapse was observed in another retrospective study of 37 relapsed patients (Goldwein et al. 1990). Very similar results were obtained in a prospective study of young children. Eighty-seven percent of relapses in that study were local and 13 % were at a distant site (Grill et al. 2001). Merchant reported substantially improved local control rates following treatment with focal conformal radiation (cumulative incidence of local failure was 12 %) (Merchant et al. 2009). A variety of treatments were used after relapse including second surgery, radiation, radiosurgery, chemotherapy, and high-dose chemotherapy (Antony et al. 2015). Twenty to 28 % of patients achieved a second complete remission (Goldwein et al. 1990; Grill et al. 2001). Children under 5 years of age who did not receive irradiation upfront and who underwent a second complete resection followed by irradiation therapy had the best chance of second complete remission (28 %). However, there was no benefit of irradiation for recurrent disease if a second complete resection was not achieved (Grill et al. 2001). Despite a small population size, Antony described survivorship rates of 37 % at 5 years and 25 % at 10 years with median survival of 35 months even after recurrence (2015).

Although recurrent ependymoma carries a poorer prognosis, routine neuroimaging surveillance is recommended as patients with asymptomatic recurrences, discovered on routine imaging scans, had longer survival than patients who were symptomatic at the time of tumor recurrence (60 vs. 30 % at 2 years postrecurrence) (Good et al. 2001).

4.6.6 Novel Therapies

Recent advancements into the molecular biology of ependymoma offer new approaches to treatment stratification and potential targeted therapies. Specifically, the discovery of CpG methylation islands within the Group A type of posterior fossa ependymomas has led to investigation of histone deacetylase or CpG methylation inhibitors (see Sect. 4.2.2) (Gajjar et al. 2014). This approach may be especially applicable to the seemingly higher-risk population of ependymomas that overexpress EZH2 (Li et al. 2015). In vitro and in vivo studies using xenograft models have supported this potential target using the EZH2 inhibitor, 3-deazaneplanocin (DZNep). This compound has previously shown efficacy in a variety of tumors including lung cancer, AML, and colon cancer (Fiskus et al. 2009; Glazer et al. 1986; Kikuchi et al. 2012). Accordingly, in CpG island methylated ependymoma xenograft models, DZNep was trialed and resulted in both decreased tumor volume and prolonged survival (Gajjar et al. 2014).

A study from St. Jude implemented a high-throughput screening with mouse model ependymoma cells to identify potential targeted therapies. This study investigated one molecular subtype of ependymomas with upregulation of EphB-Ephrin signaling (prevalent in supratentorial ependymoma tumors) against a panel of 7,890 compounds. From the preliminary results in individual cell lines, investigators isolated two drugs, 5- fluorouracil and bortezomib, and then effectively applied them in vivo with mouse xenografts. This approach perhaps represents another novel method to identifying both targeted therapies and information regarding disease biology surrounding why certain drugs are more effective than others (Atkinson et al. 2011).

4.7 Outcome

4.7.1 Neurologic Function

With long-term remission rates of at least 50 % at 5 years after diagnosis, long-term effects of tumor and its treatment on neurologic functioning have become increasingly more important. Long-term sequelae most commonly include cranial nerve deficits, abnormal gait, and difficulties with fine motor functioning (Table 4.3). Of note, 30 % of children with supratentorial ependymomas and 50 % of those with infratentorial tumors required placement of a ventriculoperitoneal

Table 4.3 Results of neurologic exam in children with intracranial ependymoma (Horn et al. 1999)

Neurologic finding	Percentage of children with normal findings, 1 month after surgery ($n=84$)	Percentage of surviving children with normal findings, 6 years after diagnosis ($n=39$)
Consciousness	92	100
Speech	80	82
Memory	98	80
Visual acuity	86	90
Visual fields	80	90
Cranial nerves	49	67
Fine motor function	64	74
Sensory function	97	97
Gait	43	67
Swallowing	84	95
Posterior fossa mutism[a]	79	93

[a]Only patients with posterior fossa tumors included

shunt (Horn et al. 1999). Brannon Morris et al. described a cohort of 96 patients >1 year of age with posterior fossa ependymoma (Brannon Morris et al. 2009). They were treated with surgery and radiation in a phase 2 trial. Late neurologic effects included limb dysmetria, cranial nerve VI and VII deficits, limb paresis, dysphagia, truncal ataxia, and hypotonia. Oculomotor deficits, facial paresis, dysphagia, and gait disturbances improved with time.

Long-term cognitive impairment occurs in most of the patients with posterior fossa tumors, even after posterior fossa irradiation only. The impairment correlates well with the dose of craniospinal irradiation (Grill et al. 1999). The mean full-scale IQ score was found to be 85 in 12 patients with posterior fossa ependymoma who underwent posterior fossa irradiation as a part of their treatment. This was significantly better than in patients with medulloblastoma who underwent craniospinal irradiation, whose mean full-scale IQ score was 70. Ninety-two percent of children who underwent posterior fossa irradiation alone were able to pursue normal schooling (Grill et al. 1999).

4.7.2 Progression-Free Survival

In one retrospective series, a group of 84 children with ependymoma (all ages and treatment modalities) treated between 1987 and 1991 had close to 50% overall long-term survival and somewhat lower progression-free survival (Fig. 4.7) (Horn et al. 1999). These observations are consistent with those published from the Children's Hospital of Philadelphia (Shu et al. 2007), and the 5-year overall survival rates obtained from SEER registry, which indicate 56% survival for children with ependymoma treated between 1985 and 1994 (Linet et al. 1999; Ries et al. 1999). With current treatment approaches, low-risk patients (older patients with complete surgical resection) treated with observation or conformal field radiation can expect 75% progression-free survival.

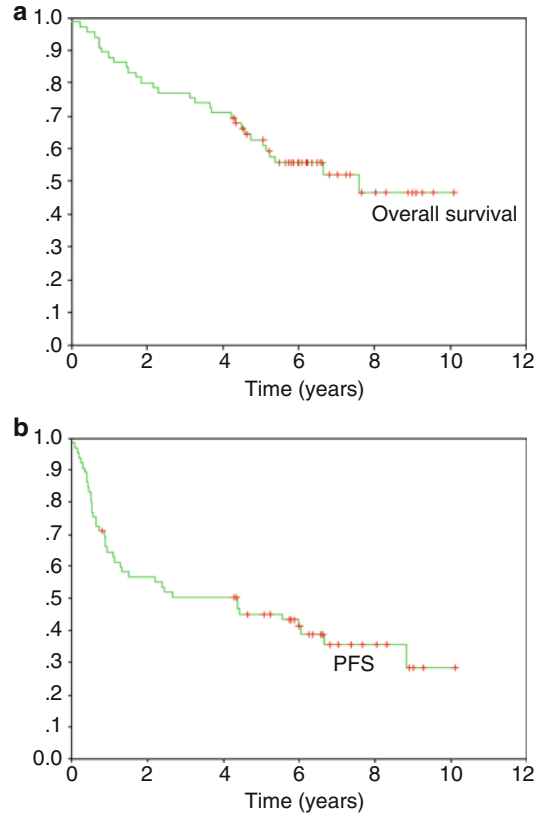

Fig. 4.7 Kaplan–Meier curves for 84 children with ependymoma treated between 1987 and 1991: (**a**) overall survival and (**b**) progression-free survival (PFS) (Horn et al. 1999)

Older patients with postoperative residual disease may achieve 30–50 % progression-free survival when treated with radiation with or without chemotherapy and second-look surgery. In addition, up to 20 % of patients whose disease progresses or recurs may achieve a prolonged second complete remission. Up to 50 % of young children treated with upfront surgery and chemotherapy and rescue surgery and irradiation are alive and in first or second complete remission at 4 years after diagnosis (Grill et al. 2001). Expectations are that current treatment of infants with chemotherapy and conformal field radiation can sustain similar results.

A recent SEER data review investigated outcomes in a group of 474 patients with ependymoma. This study identified that patients still alive at 5 years post-diagnosis had a 30-year overall survival and cancer-specific survival of 57.3 % and 68.8 %, respectively (Frandsen et al. 2015).

Conclusions

In summary, ependymoma affects 2.6 per million children annually. Children under 4 years of age have the highest incidence of this disease. Two-thirds of the patients with intracranial ependymomas present with posterior fossa tumors, and more than 85 % present with localized disease. Complete surgical resection is the most important predictor of good outcome. Conformal field radiation is recommended as adjuvant therapy in most patients, and chemotherapy is used in control of microscopic dissemination. Currently, overall survival of all children with ependymoma is in the range of 50–60 %. Most children undergoing posterior fossa irradiation for this tumor are able to pursue normal schooling.

References

Agarwal S, Stevenson ME, Sughrue ME, Wartchow EP, Mierau GW, Fung KM (2014) Features of intraventricular tanycytic ependymoma: report of a case and review of literature. Int J Clin Exp Pathol 7(6):3399–3407

Aggarwal R, Yeung D, Kumar P, Muhlbauer M, Kun LE (1997) Efficacy and feasibility of stereotactic radiosurgery in the primary management of unfavorable pediatric ependymoma. Radiother Oncol 43:269–273

Alfaro-Cervello C, Soriano-Navarro M, Ramirez M, Bernet L, Martinez Banaclocha M, Cano R, Reyes Santias RM, Forteza-Vila J, Garcia-Verdugo JM (2015) Ultrastructural pathology of anaplastic and grade II ependymomas reveals distinctive ciliary structures—electron microscopy redux. Ultrastruct Pathol 39(1):23–29

Antony R, Wong KE, Patel M, Olch AJ, McComb G, Krieger M, Gilles F, Sposto R, Erdreich-Epstein A, Dhall G, Gardner S, Finlay J (2015) A retrospective analysis of recurrent intracranial ependymoma. Pediatr Blood Cancer 61:1195–1201

Atkinson JM, Shelat AA, Carcaboso AM, Kranenburg TA, Arnold LA et al. (2011) An integrated in vitro and in vivo high-throughput screen identifies treatment leads for ependymoma. Cancer Cell 20(3):384–399

Awaad YM, Allen JC, Miller DC, Schneider SJ, Wisoff J, Epstein FJ (1996) Deferring adjuvant therapy for totally resected intracranial ependymoma. Pediatr Neurol 14:216–219

Balovannis SJ, Balovannis IS (2014) The fine structure of ependymomas. CNS Oncol 3(1):49–59

Bergsagel DJ, Finegold MJ, Butel JS, Kupsky WJ, Garcea RL (1992) DNA sequences similar to those of simian virus 40 in ependymomas and choroid plexus tumors of childhood. N Engl J Med 326:988–993

Bi Z, Ren X, Zhang J, Jia W (2015) Clinical, radiological, and pathological features in 43 case of intracranial subependymoma. J Neurosurg 122(1):49–60

Bijlsma EK, Voesten AMJ, Bijleveld EH, Troost D, Westerveld A, Mérel P et al (1995) Molecular analysis of genetic changes in ependymomas. Genes Chromosom Cancer 13(4):272–277

Birch BD, Johnson JP, Parsa A, Desai RD, Yoon JT, Lycette CA, Li YM, Bruce JN (1996) Frequent type 2 neurofibromatosis gene transcript mutations in sporadic intramedullary spinal cord ependymomas. Neurosurgery 39:135–140

Bird AP, Wolffe AP (1999) Methylation-induced repression—belts, braces, and chromatin. Cell 99(5): 451–454

Bouffet E, Tabori U, Bartels U (2007) Paediatric ependymomas: should we avoid radiotherapy? Lancet Oncol 8:665–666

Bouffet E, Capra M, Bartels U (2009) Salvage chemotherapy for metastatic and recurrent ependymoma of childhood. Childs Nerv Syst 25:1293–1301

Brandes AA, Cavallo G, Reni M, Tosoni A, Nicolardi L, Scopece L, Franceschi E, Sotti G, Talacchi A, Turazzi S, Ermani M (2005) A multicenter retrospective study of chemotherapy for recurrent intracranial ependymal tumors in adults by the Gruppo Italiano Cooperativo di Neuro-Oncologia. Cancer 104:143–148

Brannon Morris E, Li C, Khan RB, Sanford RA, Boop F, Pinlac R, Xiong X, Merchant TE (2009) Evolution

of neurological impairment in pediatric infratentorial ependymoma patients. J Neurooncol 94: 391–398
Carbone M, Rizzo P, Pass HI (1997) Simian virus 40, poliovaccines and human tumors: a review of recent developments. Oncogene 15:1877–1888
Carter M, Nicholson J, Ross F, Crolla J, Allibone R, Balaji V et al (2002) Genetic abnormalities detected in ependymomas by comparative genomic hybridisation. Br J Cancer 86(6):929–939
Cervoni L, Celli P, Fortuna A, Cantore G (1994) Recurrence of spinal ependymoma. Risk factors and long-term survival. Spine 19:2838–2841
Cimino PJ, Agarwal A, Dehner LP (2014) Myxopapillary ependymoma in children: a study of 11 cases and a comparison with the adult experience. Pediatr Blood Cancer 61(11):1969–1971
Ciraldo AV, Platt MS, Agamanolis DP, Boeckman CR (1986) Sacrococcygeal myxopapillary ependymomas and ependymal rests in infants and children. J Pediatr Surg 21:49–52
Conter C, Carrie C, Bernier V, Geoffray A, Pagnier A, Gentet JC, Lellouch-Tubiana A, Chabaud S, Frappaz D (2009) Intracranial ependymomas in children: society of pediatric oncology experience with postoperative hyperfractionated local radiotherapy. Int J Radiat Oncol Biol Phys 74(5):1536–1542
Coulon RA, Till K (1977) Intracranial ependymomas in children: a review of 43 cases. Childs Brain 3: 154–168
Debiec-Rychter M, Hagemeijer A, Sciot R (2000) Cytogenetic analysis in three cerebral subependymomas: further evidence for a hamartomatous nature? Cancer Genet Cytogenet 122:63–64
DeWire M, Fouladi M, Turner DC, Wetmore C, Hawkins C, Jacobs C, Yuan Y, Liu D, Goldman S, Fisher P, Rytting M, Bouffet E, Khakoo Y, Hwang EI, Foreman N, Stewart CF, Gilbert MR, Gilbertson R, Gajjar A (2015) An open-label, two stage, phase II study of bevacizumab and lapatinib in children with recurrent or refractory ependymoma: a collaborative ependymoma research network study (CERN). J Neuro-Oncol 123:85–91
Dohrmann GJ, Farwell JR, Flannery JT (1976) Ependymomas and ependymoblastomas in children. J Neurosurg 45:273–283
Duffner PK, Horowitz ME, Krischer JP, Friedman HS, Burger PC, Cohen ME, Sanford RA, Mulhern RK, James HE, Freeman CR et al (1993) Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med 328:1725–1731
Evans DGR, Sainio M, Baser ME (2000) Neurofibromatosis type 2. J Med Genet 37(12):897–904
Ellison DW, Kocak M, Figarella-Branger D, Felice G, Catherine G, Pietsch T, Frappaz D, Massimino M, Grill J, Boyett JM, Grundy RG (2011) Histopathological grading of pediatric ependymoma: reproducibility and clinical relevance in European trial cohorts. J Negat Results Biomed 31;10:7
Fassett DR, Pingree J, Kestle JR (2005) The high incidence of tumor dissemination in myxopapillary ependymoma in pediatric patients. Report of five cases and review of the literature. J Neurosurg 102;1 suppl:59–64
Feldman WB, Clark AJ, Safaee M, Ames CP, Parsa AT (2013) Tumor control after surgery for spinal myxopapillary ependymomas: distinct outcomes in adults versus children: a systematic review. J Neurosurg Spine 19(4):471–476
Fiskus W, Wang Y, Sreekumar A, Buckley K, Shi H, Jillella A, Ustun C, Rao R, Fernandez P, Chen J, Balusu R, Koul S, Atadja P, Marquez V, Bhalli K (2009) Combined epigenetic therapy with the histone methyltransferase EZH2 inhibitor 3-deazaneplanocin A and the histone deacetylase inhibitor panobinostat against human AML cells. Blood 114(13):2733–2743
Fouladi M, Helton K, Dalton J, Gilger E, Gajjar A, Merchant T, Kun L, Newsham I, Burger P, Fuller C (2003) Clear cell ependymoma: a clinicopathologic and radiographic analysis of 10 patients. Cancer 98(10):2232–2244
Frandsen JE, Wagner A, Bollo RJ, Shrieve DC, Poppe MM (2015) Long-term life expectancy for children with ependymoma and medulloblastoma. Pediatr Blood Cancer 62(11):1986–1991, epub
Furie DM, Provenzale JM (1995) Supratentorial ependymomas and subependymomas: CT and MR appearance. J Comput Assist Tomogr 19:518–526
Gajjar A, Pfister SM, Taylor MD, Gilbertson RJ (2014) Molecular insights into pediatric brain tumors have the potential to transform therapy. Clin Cancer Res 20(22):5630–5640
Garrett PG, Simpson WJ (1983) Ependymomas: results of radiation treatment. Int J Radiat Oncol Biol Phys 9:1121–1124
Garvin J, Sposto R, Stanley P, Rorke L, Packer P (2004) Childhood ependymoma: improved survival for patients with incompletely resected tumors with the use of preirradiation chemotherapy. In: 11th International Symposium on Pediatric Neuro-oncology, Boston
Geyer JR, Zeltzer PM, Boyett JM, Rorke LB, Stanley P, Albright AL, Wisoff JH, Milstein JM, Allen JC, Finlay JL et al (1994) Survival of infants with primitive neuroectodermal tumors or malignant ependymomas of the CNS treated with eight drugs in 1 day: a report from the Childrens Cancer Group. J Clin Oncol 12:1607–1615
Ghia AJ, Majaian A, Allen PK, Armstrong TS, Lang FF Jr, Gilbert MR, Brown PD (2013) Supratentorial grosstotally resected non-anaplastic ependymoma: population based patterns of care and outcomes analysis. J Neurooncol 115(3):513–520
Gilbertson RJ, Bentley L, Hernan R, Junttila TT, Frank AJ, Haapasalo H, Connelly M, Wetmore C, Curran T, Elenius K, Ellison DW (2002) ERBB receptor signaling promotes ependymoma cell proliferation and represents a potential novel therapeutic target for this disease. Clin Cancer Res 8:3054–3064
Glazer RI, Knode MC, Tseng CK, Haines DR, Marquez VE (1986) 3-Deazaneplanocin A: a new inhibitor of

S-adenosylhomocysteine synthesis and its effects in human colon carcinoma cells. Biochem Pharmacol 35(24):4523–4527

Godfraind C, Kaczmarska JM, Kocak M, Dalton J, Wright KD, Sanford RA et al (2012) Distinct disease-risk groups in pediatric supratentorial and posterior fossa ependymomas. Acta Neuropathol 124(2):247–257

Gold EB, Leviton A, Lopez R, Austin DF, Gilles FH, Hedley-Whyte ET, Kolonel LN, Lyon JL, Swanson GM, Weiss NS et al (1994) The role of family history in risk of childhood brain tumors. Cancer 73:1302–1311

Goldwein JW, Glauser TA, Packer RJ, Finlay JL, Sutton LN, Curran WJ, Laehy JM, Rorke LB, Schut L, D'Angio GJ (1990) Recurrent intracranial ependymomas in children. Survival, patterns of failure, and prognostic factors. Cancer 66:557–563

Goldwein JW, Corn BW, Finlay JL, Packer RJ, Rorke LB, Schut L (1991) Is craniospinal irradiation required to cure children with malignant (anaplastic) intracranial ependymomas? Cancer 67:2766–2771

Good CD, Wade AM, Hayward RD, Phipps KP, Michalski AJ, Harkness WF, Chong WK (2001) Surveillance neuroimaging in childhood intracranial ependymoma: how effective, how often, and for how long? J Neurosurg 94:27–32

Gornet MK, Buckner JC, Marks RS, Scheithauer BW, Erickson BJ (1999) Chemotherapy for advanced CNS ependymoma. J Neurooncol 45:61–67

Grill J, Kalifa C, Doz F, Schoepfer C, Sainte-Rose C, Couanet D, Terrier-Lacombe MJ, Valteau-Couanet D, Hartmann O (1996) A high-dose busulfan-thiotepa combination followed by autologous bone marrow transplantation in childhood recurrent ependymoma. A phase-II study. Pediatr Neurosurg 25:7–12

Grill J, Renaux VK, Bulteau C, Viguier D, Levy-Piebois C, Sainte-Rose C, Dellatolas G, Raquin MA, Jambaque I, Kalifa C (1999) Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes. Int J Radiat Oncol Biol Phys 45:137–145

Grill J, Le Deley MC, Gambarelli D, Raquin MA, Couanet D, Pierre-Kahn A, Habrand JL, Doz F, Frappaz D, Gentet JC, Edan C, Chastagner P, Kalifa C (2001) Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. J Clin Oncol 19:1288–1296

Grundy RG, Wilne SA, Weston CL, Robinson K, Lashford LS, Ironside J, Cox T, Chong WK, Campbell RH, Bailey CC, Gattamaneni R, Picton S, Thorpe N, Mallucci C, English MW, Punt JA, Walker DA, Ellison DW, Machin D (2007) Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study. Lancet Oncol 8:696–705

Hagel C, Treszl A, Fehlert J, Harder J, von Haxthausen F, Kern M, von Bueren AO, Kordes U (2013) Supra- and infratentorial pediatric ependymomas differ significantly in NeuN, p75, and GFAP expression. J Neurooncol 112(2):191–197

Hamilton RL, Pollack IF (1997) The molecular biology of ependymomas. Brain Pathol 7:807–822

Hayden Gephart MG, Lober RM, Arrigo RT, Zygourakis CC, Guzman R, Boakye M, Edwards MS, Fisher PG (2012) Trends in the diagnosis and treatment of pediatric primary spinal cord tumors. J Neurosurg Pediatr 10(6):555–559

Hemminki K, Li X, Vaittinen P, Dong C (2000) Cancers in the first-degree relatives of children with brain tumours. Br J Cancer 83:407–411

Hodgson DC, Goumnerova LC, Loeffler JS, Dutton S, Black PM, Alexander E 3rd, Xu R, Kooy H, Silver B, Tarbell NJ (2001) Radiosurgery in the management of pediatric brain tumors. Int J Radiat Oncol Biol Phys 50:929–935

Horn B, Heideman R, Geyer R, Pollack I, Packer R, Goldwein J, Tomita T, Schomberg P, Ater J, Luchtman-Jones L, Rivlin K, Lamborn K, Prados M, Bollen A, Berger M, Dahl G, McNeil E, Patterson K, Shaw D, Kubalik M, Russo C (1999) A multi-institutional retrospective study of intracranial ependymoma in children: identification of risk factors. J Pediatr Hematol Oncol 21:203–211

Hukin J, Epstein F, Lefton D, Allen J (1998) Treatment of intracranial ependymoma by surgery alone. Pediatr Neurosurg 29:40–45

Hulsebos TJ, Oskam NT, Bijleveld EH, Westerveld A, Hermsen MA, van den Ouweland AM, Hamel BC, Tijssen CC (1999) Evidence for an ependymoma tumour suppressor gene in chromosome region 22pter-22q11.2. Br J Cancer 81:1150–1154

Ilgren EB, Stiller CA, Hughes JT, Silberman D, Steckel N, Kaye A (1984) Ependymomas: a clinical and pathologic study. Part I. Biologic features. Clin Neuropathol 3:113–121

Ishizawa K, Komori T, Aihara Y, Maruyama T, Okada Y, Ikuta S, Muragaki Y, Hirose T, Homma T, Sasaki A (2012) Clear cells are associated with proliferative activity in ependymoma: a quantitative study. Clin Neuropathol 31(3):146–151

Kieran MW, Turner CD, Rubin JB, Chi SN, Zimmerman MA, Chordas C, Klement G, Laforme A, Gordon A, Thomas A, Neuberg D, Browder T, Folkman J (2005) A feasibility trial of antiangiogenic (metronomic) chemotherapy in pediatric patients with recurrent or progressive cancer. J Pediatr Hematol Oncol 27: 573–581

Kikuchi J, Takashina T, Kinoshita I, Kikuchi E, Shimizu Y, Sakakibar-Konishi J et al. (2012) Epigenetic therapy with 3-deazaneplanocin A, an inhibitor of the histone methyltransferase EZH2, inhibits growth of non-small cell lung cancer cells. Lung Cancer 78;2:138–143

Koperek O, Gelpi E, Birner P, Haberler C, Budka H, Hainfellner JA (2004) Value and limits of immunohistochemistry in differential diagnosis of clear cell primary brain tumors. Acta Neuropathol 108(1):24–30

Kukreia S, Ambekar S, Sin AH, Nanda A (2014) Cumulative survival analysis of patients with spinal myxopapillary ependymomas in the first 2 decades of life. J Neurosurg Pediatr 13(4):400–407

Lamszus K, Lachenmayer L, Heinemann U, Kluwe L, Finckh U, Hoppner W, Stavrou D, Fillbrandt R, Westphal M (2001) Molecular genetic alterations on chromosomes 11 and 22 in ependymomas. Int J Cancer 91:803–808

Lamzabi I, Arvanitis LD, Reddy VB, Bitterman P, Gattuso P (2013) Immunophenotype of myxopapillary ependymomas. Appl Immunohistochem Mol Morphol 21(6):485–489

Lee M, Rezai AR, Freed D, Epstein FJ (1996) Intramedullary spinal cord tumors in neurofibromatosis. Neurosurgery 38:32–37

Li AM, Dunham C, Tabori U, Carret AS, McNeely PD, Johnston D, Laray-Cousin L, Wilson B, Eisenstat DD, Jabado N, Zelcer S, Silva M, Scheinemann K, Fryer C, Hendson G, Fotovati A, Hawkins C, Yip S, Dunn SE, Hukin J (2015) EZH2 expression is a prognostic factor in childhood intracranial ependymoma: a Canadian pediatric brain tumor consortium study. Cancer 121(9):1499–1507

Linet MS, Gridley G, Cnattingius S, Nicholson HS, Martinsson U, Glimelius B, Adami HO, Zack M (1996) Maternal and perinatal risk factors for childhood brain tumors (Sweden). Cancer Causes Control 7(4):437–448

Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS (1999) Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. J Natl Cancer Inst 91:1051–1058

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) (2007) WHO classification of tumors of the central nervous system. International Agency for Research on Cancer, Lyon

Mack SC, Taylor MD (2009) The genetic and epigenetic basis of ependymoma. Childs Nerv Syst 25(10):1195–1201

Mack SC, Witt H, Piro RM, Gu L, Zuyderduyn S, Stütz AM et al (2014) Epigenomic alterations define lethal CIMP-positive ependymomas of infancy. Nature 506(7489):445–450

Martini F, Iaccheri L, Lazzarin L, Carinci P, Corallini A, Gerosa M, Iuzzolino P, Barbanti-Brodano G, Tognon M (1996) SV40 early region and large T antigen in human brain tumors, peripheral blood cells, and sperm fluids from healthy individuals. Cancer Res 56:4820–4825

Mason WP, Goldman S, Yates AJ, Boyett J, Li H, Finlay JL (1998) Survival following intensive chemotherapy with bone marrow reconstitution for children with recurrent intracranial ependymoma–a report of the Children's Cancer Group. J Neurooncol 37: 135–143

Massimino M, Solero CL, Garre ML, Biassoni V, Cama A, Genitori L et al. (2011) Second-look surgery for ependymoma: the Italian experience. J Neurosurg Pediatr 8;3:246–250

Mendrzyk F, Korshunov A, Benner A, Toedt G, Pfister S, Radlwimmer B, Lichter P (2006) Identification of gains on 1q and epidermal growth factor receptor overexpression as independent prognostic markers in intracranial ependymoma. Clin Cancer Res 12:2070–2079

Merchant TE, Thompson S, Williams T (2000) Preliminary results from a phase II trial of conformal radiation therapy for localized pediatric brain tumors. In: Annual Meeting of the American Society of Therapeutic Radiology and Oncology, Boston

Merchant TE, Mulhern RK, Krasin MJ, Kun LE, Williams T, Li C, Xiong X, Khan RB, Lustig RH, Boop FA, Sanford RA (2004) Preliminary results from a phase II trial of conformal radiation therapy and evaluation of radiation-related CNS effects for pediatric patients with localized ependymoma. J Clin Oncol 22:3156–3162

Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA (2009) Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. Lancet Oncol 10:258–266

Modena P, Lualdi E, Facchinetti F, Veltman J, Reid JF, Minardi S, Janssen I, Giangaspero F, Forni M, Finocchiaro G, Genitori L, Giordano F, Riccardi R, Schoenmakers EF, Massimino M, Sozzi G (2006) Identification of tumor-specific molecular signatures in intracranial ependymoma and association with clinical characteristics. J Clin Oncol 24:5223–5233

Mork SJ, Loken AC (1977) Ependymoma: a follow-up study of 101 cases. Cancer 40:907–915

Nadkarni TD, Rekate HL (1999) Pediatric intramedullary spinal cord tumors. Critical review of the literature. Childs Nerv Syst 15:17–28

Nazar GB, Hoffman HJ, Becker LE, Jenkin D, Humphreys RP, Hendrick EB (1990) Infratentorial ependymomas in childhood: prognostic factors and treatment. J Neurosurg 72:408–417

Newton HB, Henson J, Walker RW (1992) Extraneural metastases in ependymoma. J Neurooncol 14:135–142

Ohgaki H, Eibl RH, Wiestler OD, Yasargil MG, Newcomb EW, Kleihues P (1991) p53 mutations in nonastrocytic human brain tumors. Cancer Res 51(22):6202–6205

Osterdock R, Sanford RA, Merchant TE (2000) Pediatric ependymoma. AANS/CNS Section on Pediatric Neurological Surgery, Coronado

Pachella LA, Kamiya-Matsuoka C, Lee EL, Olar A, Yung WK (2015) Supratentorial extraventricular anaplastic ependymoma with extracranial metastasis. J Clin Neurosci 22(3):605–607

Perez-Bovet J, Rimbau-Munoz J, Martin-Ferrer S (2013) Anaplastic ependymoma with holocordal and intracranial meningeal carcinomatosis and holospinal bone metastases. Neurosurgery 72(3):E497–E503

Perilongo G, Massimino M, Sotti G, Belfontali T, Masiero L, Rigobello L, Garre L, Carli M, Lombardi F, Solero C, Sainati L, Canale V, del Prever AB, Giangaspero F, Andreussi L, Mazza C, Madon E (1997) Analyses of prognostic factors in a retrospective review of 92 children with ependymoma: Italian Pediatric Neuro-oncology Group. Med Pediatr Oncol 29:79–85

Pezzolo A, Capra V, Raso A, Morandi F, Parodi F, Gambini C et al (2008) Identification of novel chromosomal abnormalities and prognostic cytogenetics markers in

intracranial pediatric ependymoma. Cancer Lett 261(2):235–243
Prayson RA, Suh JH (1999) Subependymomas: clinicopathologic study of 14 tumors, including comparative MIB-1 immunohistochemical analysis with other ependymal neoplasms. Arch Pathol Lab Med/Arch Pathol Lab Med 123:306–309
Ries LA, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds) (1999) Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995, National Cancer Institute, SEER Program (NIH Pub. No. 99-4649). NIH, Bethesda
Robertson PL, Zeltzer PM, Boyett JM, Rorke LB, Allen JC, Geyer JR, Stanley P, Li H, Albright AL, McGuire-Cullen P, Finlay JL, Stevens KR Jr, Milstein JM, Packer RJ, Wisoff J (1998) Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer Group. J Neurosurg 88:695–703
Rogers HA, Kilday JP, Mayne C, Ward J, Adamowicz-Brice M, Schwalbe EC et al (2011) Supratentorial and spinal pediatric ependymomas display a hypermethylated phenotype which includes the loss of tumor suppressor genes involved in the control of cell growth and death. Acta Neuropathol 123(5):711–725
Ross GW, Rubinstein LJ (1989) Lack of histopathological correlation of malignant ependymomas with postoperative survival. J Neurosurg 70:31–36
Rousseau P, Habrand JL, Sarrazin D, Kalifa C, Terrier-Lacombe MJ, Rekacewicz C, Rey A (1994) Treatment of intracranial ependymomas of children: review of a 15-year experience. Int J Radiat Oncol Biol Phys 28:381–386
Safaee M, Oh MC, Mummaneni PV, Weinstein PR, Ames CP, Chou D, Berger MS, Parsa AT, Gupta N (2014) Surgical outcomes in spinal cord ependymomas and the importance of extent of resection in children and young adults. J Neurosurg Pediatr 13(4):393–399
Salazar OM, Rubin P, Bassano D, Marcial VA (1975) Improved survival of patients with intracranial ependymomas by irradiation: dose selection and field extension. Cancer 35:1563–1573
Sara A, Bruner JM, Mackay B (1994) Ultrastructure of ependymoma. Ultrastruct Pathol 18:33–42
Sato K, Schäuble B, Kleihues P, Ohgaki H (1996) Infrequent alterations of the p15, p16, CDK4 and CYCLIN D1 genes in non-astrocytic human brain tumors. Int J Cancer 66(3):305–308
Schiffer D, Chio A, Giordana MT, Migheli A, Palma L, Pollo B, Soffietti R, Tribolo A (1991) Histologic prognostic factors in ependymoma. Childs Nerv Syst 7:177–182
Shaw EG, Evans RG, Scheithauer BW, Ilstrup DM, Earle JD (1987) Postoperative radiotherapy of intracranial ependymoma in pediatric and adult patients. Int J Radiat Oncol Biol Phys 13:1457–1462
Shih CS, Hale GA, Gronewold L, Tong X, Laningham FH, Gilger EA, Srivastava DK, Kun LE, Gajjar A, Fouladi M (2008) High-dose chemotherapy with autologous stem cell rescue for children with recurrent malignant brain tumors. Cancer 112:1345–1353
Shu HK, Sall WF, Maity A, Tochner ZA, Janss AJ, Belasco JB, Rorke-Adams LB, Phillips PC, Sutton LN, Fisher MJ (2007) Childhood intracranial ependymoma: twenty-year experience from a single institution. Cancer 110:432–441
Slasky BS, Bydder GM, Niendorf HP, Young IR (1987) MR imaging with gadolinium-DTPA in the differentiation of tumor, syrinx, and cyst of the spinal cord. J Comput Assist Tomogr 11:845–850
Smyth MD, Pitts L, Jackler RK, Aldape KD (2000) Metastatic spinal ependymoma presenting as a vestibular schwannoma. Case illustration. J Neurosurg 92:247
Strickler HD, Rosenberg PS, Devesa SS, Hertel J, Fraumeni JF Jr, Goedert JJ (1998) Contamination of poliovirus vaccines with simian virus 40 (1955–1963) and subsequent cancer rates. JAMA 279:292–295
Tarapore PE, Modera P, Naujokas A, Oh MC, Amin B, Tihan T, Parsa AT, Ames CP, Chou D, Mummaneni PV, Weinstein PR (2013) Pathology of spinal ependymomas: an institutional experience over 25 years in 134 patients. Neurosurgery 73(2):247–255
Taylor MD, Poppleton H, Fuller C, Su X, Liu Y, Jensen P, Magdaleno S, Dalton J, Calabrese C, Board J, Macdonald T, Rutka J, Guha A, Gajjar A, Curran T, Gilbertson RJ (2005) Radial glial cells are candidate stem cells of ependymoma. Cancer Cell 8:323–335
Thorarinsdottir HK, Rood B, Kamani N, Lafond D, Perez-Albuerne E, Loechelt B, Packer RJ, MacDonald TJ (2007) Outcome for children <4 years of age with malignant central nervous system tumors treated with high-dose chemotherapy and autologous stem cell rescue. Pediatr Blood Cancer 48:278–284
Tihan T, Zhou T, Holmes E, Burger PC, Ozuysal S, Rushing EJ (2008) The prognostic value of histological grading of posterior fossa ependymomas in children: a Children's Oncology Group study and a review of prognostic factors. Mod Pathol 21:165–177
Timmermann B, Kortmann RD, Kuhl J, Meisner C, Slavc I, Pietsch T, Bamberg M (2000) Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: results of the German prospective trials HIT 88/89 and HIT 91. Int J Radiat Oncol Biol Phys 46:287–295
Tortori-Donati P, Fondelli MP, Cama A, Garre ML, Rossi A, Andreussi L (1995) Ependymomas of the posterior cranial fossa: CT and MRI findings. Neuroradiology 37:238–243
Tsai CJ, Wang Y, Allen PK, Mahajan A, McCutcheon IE, Rao G, Rhines LD, Tatsui CE, Armstrong TS, Maor MH, Chang EL, Brown PD, Li J (2014) Outcomes after surgery and radiotherapy for spinal myxopapillary ependymoma: update of the MD Anderson Cancer Center experience. Neurosurgery 75(3):204–214
Vanuytsel L, Brada M (1991) The role of prophylactic spinal irradiation in localized intracranial ependymoma. Int J Radiat Oncol Biol Phys 21:825–830

Vege KD, Giannini C, Scheithauer BW (2000) The immunophenotype of ependymomas. Appl Immunohistochem Mol Morphol 8(1):25–31

Venkatramani R, Ji L, Lasky J, Haley K, Judkins A, Zhou S, Sposto R, Olshefski R, Garvin J, Tekautz T, Kennedy G, Rassekh SR, Moore T, Gardner S, Allen J, Shore R, Moertel C, Atlas M, Dhall G, Finlay J (2013) Outcome of infants and young children with newly diagnosed ependymoma treated on the "Head Start" III prospective clinical trial. J Neurooncol 113(2): 285–291

Villano JL, Parker CK, Dolecek TA (2013) Descriptive epidemiology of ependymal tumours in the United States. Br J Cancer 108(11):2367–2371

Wager M, Lapierre F, Blanc JL, Listrat A, Bataille B (2000) Cauda equina tumors: a French multicenter retrospective review of 231 adult cases and review of the literature. Neurosurg Rev 23:119–129; discussion 130–131

Waha A, Koch A, Hartmann W, Mack H, Schramm J, Sörensen N et al (2004) Analysis of HIC-1 methylation and transcription in human ependymomas. Int J Cancer 110(4):542–549

Waldron JN, Laperriere NJ, Jaakkimainen L, Simpson WJ, Payne D, Milosevic M, Wong CS (1993) Spinal cord ependymomas: a retrospective analysis of 59 cases. Int J Radiat Oncol Biol Phys 27:223–229

Walker RW, Allen JC (1988) Cisplatin in the treatment of recurrent childhood primary brain tumors. J Clin Oncol 6:62–66

Weber DC, Wang Y, Miller R, Villa S, Zaucha R, Pica A, Poortmans P, Anacak Y, Ozygit G, Baumert B, Haller G, Preusser M, Li J (2015) Long-term outcome of patients with spinal myxopapillary ependymoma: treatment results from the MD Anderson Cancer Centre and institutions from the Rare Cancer Network. Neuro Oncol 17(4):588–595

Whitaker SJ, Bessell EM, Ashley SE, Bloom HJ, Bell BA, Brada M (1991) Postoperative radiotherapy in the management of spinal cord ependymoma. J Neurosurg 74:720–728

White L, Kellie S, Gray E, Toogood I, Waters K, Lockwood L, Macfarlane S, Johnston H (1998) Postoperative chemotherapy in children less than 4 years of age with malignant brain tumors: promising initial response to a VETOPEC-based regimen. A study of the Australian and New Zealand Children's Cancer Study Group (ANZCCSG). J Pediatr Hematol Oncol 20:125–130

Witt H, Mack SC, Ryzhova M, Bender S, Sill M, Isserlin R et al (2011) Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. Cancer Cell 20(2):143–157

Woesler B, Moskopp D, Kuchelmeister K, Schul C, Wassmann H (1998) Intracranial metastasis of a spinal myxopapillary ependymoma. A case report. Neurosurg Rev 21:62–65

Zacharoulis S, Levy A, Chi SN, Gardner S, Rosenblum M, Miller DC, Dunkel I, Diez B, Sposto R, Ji L, Asgharzadeh S, Hukin J, Belasco J, Dubowy R, Kellie S, Termuhlen A, Finlay J (2007) Outcome for young children newly diagnosed with ependymoma, treated with intensive induction chemotherapy followed by myeloablative chemotherapy and autologous stem cell rescue. Pediatr Blood Cancer 49:34–40

Zemmoura I, Vourch P, Paubel A, Parfait B, Cohen J, Bilan F, Kitzis J, Rousselot C, Parker J, Andres CR (2014) A deletion causing exon NF2 exon 9 skipping is associated with familial autosomal dominant intramedullary ependymoma. Neuro-Oncol 16:250–255

Embryonal Tumors

5

David Raleigh, Corey Raffel,
and Daphne A. Haas-Kogan

Contents

D. Raleigh, MD, PhD (✉)
Department of Radiation Oncology, University of California San Francisco, 1600 Divisadero Street, Suite H1031, San Francisco, CA 94115, USA
e-mail: david.raleigh@ucsf.edu

C. Raffel, MD, PhD
Department of Neurological Surgery, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th St, 4th Floor, San Francisco, CA 94143-0137, USA
e-mail: corey.raffel@ucsf.edu

D.A. Haas-Kogan, MD
Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, & Boston Children's Hospital, 450 Brookline Ave. D1622, Boston, MA 02215-5418, USA
e-mail: dhaas-kogan@lroc.harvard.edu

5.1 Introduction

Embryonal tumors comprise a large fraction of pediatric brain tumors (Ostrom et al. 2014), but their cell(s) of origin, histopathologic classification, and treatment remain controversial. For others, such as medulloblastoma, recent molecular studies have identified both oncogenic "driver" mutations and promising therapeutic targets. The prognosis of these tumors was at one time exceedingly poor, but therapeutic advances have led to substantial improvement in survival. Despite these gains, current treatment protocols, which rely on surgery, adjuvant radiation and cytotoxic chemotherapy, often lead to debilitating and severe late effects.

Embryonal tumors were previously grouped as *primitive neuroectodermal tumors* (PNET), regardless of their site of origin in the central

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_5

nervous system (CNS) (Rorke 1983). For instance, medulloblastoma was sometimes referred to as infratentorial PNET, although the distinct biologic nature of medulloblastoma has become apparent. Unified by relatively homogeneous histopathological characteristics, these tumors are typified by poorly cohesive, undifferentiated neuroepithelial, small monomorphic, round cells, often with a high mitotic rate and neuroblastic differentiation. All embryonal tumors were conjectured to arise from a common precursor cell of the subependymal matrix in the CNS. Moreover, each of these tumors had an innate tendency for dissemination through the cerebrospinal fluid (CSF).

Contemporary evidence indicates that rather than a single uniform group of tumors, PNETs are a heterogeneous group of neoplasms. Early gene-expression profiling studies favored the concept of distinct and site-specific cells of origin for individual embryonal tumors (Gilbertson 2002; Pomeroy et al. 2002b). Since that time, lineage-tracing experiments in mouse models and next-generation sequencing of human tumors have further enhanced our understanding of the genesis of some embryonal tumors, but many questions remain. Clinically, embryonal tumors are best identified by tumor location, divergent histopathological characteristics, and patterns of differentiation. The embryonal neoplasms include medulloblastoma, atypical teratoid/rhabdoid tumor (ATRT), pineoblastoma, ependymoblastoma, cerebral neuroblastoma, ganglioneuroblastoma, medulloepithelioma, and supratentorial PNET. In this chapter, we consider and discuss separately the entities of medulloblastoma, ATRT, pineoblastoma, and other embryonal tumors, as recognized by the current World Health Organization (WHO) classification of tumors (Louis et al. 2007).

5.2 Medulloblastoma

5.2.1 Epidemiology

The incidence of pediatric CNS neoplasms is approximately 3.5 per 100,000 children per year, and medulloblastoma accounts for about 20 % of cases (Gurney et al. 1999). In the period from 1973 to 2003, the 5-year overall survival from medulloblastoma increased from approximately 43 % to 63 % with the introduction and refinement of multimodal therapies (Gurney et al. 1999; McNeil et al. 2002; Patel et al. 2014). Although some data suggest that the incidence of medulloblastoma has slightly decreased over time, other studies postulate a relatively stable rate of 1.5 cases per million people over the last 40 years (Morland and Parkes 1995; Smoll and Drummond 2012; Thorne et al. 1994). Peak occurrence is around the age of 4 years, although 30 % or more of cases occur in patients over 15 years of age (Gurney et al. 1999; Peterson and Walker 1995; Prados et al. 1995; Roberts et al. 1991; Thorne et al. 1994). Males are affected 1.5 times more frequently than females, except among infants, where incidence by gender is nearly equal. Girls fare marginally better than male patients beyond the age of 3, but outcomes are equivalent in infants (Curran et al. 2009; Gurney et al. 1999; McNeil et al. 2002; Weil et al. 1998).

The vast majority of medulloblastomas arise in a sporadic manner and cannot be linked to an inciting event. Some studies suggest that medulloblastoma is linked to environmental and in utero exposures, such as JC virus, SV40 virus, maternal consumption of cured meats, and *N*-nitroso compounds, but the majority of these data depict weak, inconsistent associations (Fine 2002; Gurney et al. 1999). A small fraction of patients harbor germline mutations in one or more tumor-suppressor genes, as is the case in Gorlin syndrome, Turcot syndrome, Li-Fraumeni syndrome, ataxia telangiectasia, and Coffin-Siris syndrome (Hamilton et al. 1995; Pearson et al. 1982; Rogers et al. 1988; Shuster et al. 1966). Gorlin syndrome, for instance, is identified by nevoid basal-cell carcinoma, jaw cysts, palmar and plantar pits, rib anomalies, hyporesponsiveness to parathyroid hormone, and medulloblastoma (Gorlin and Goltz 1960; Gorlin et al. 1965). Indeed, it was through the investigation of inherited cancer predisposition syndromes that the underlying molecular etiology of medulloblastoma began

to emerge (Raffel et al. 1997; Zurawel et al. 1998). Next-generation sequencing techniques have revealed that medulloblastoma segregates into distinct molecular subtypes that are thought to drive inherited and sporadic cases alike.

5.2.2 Pathology

5.2.2.1 Grading and Histopathology

Medulloblastoma is a malignant, WHO grade IV, invasive embryonal neoplasm of the cerebellum with predominantly neuronal differentiation and a tendency to metastasize through the CSF pathways (Louis et al. 2007). Beyond the demographic factors already discussed, and the molecular and clinical characteristics that will be described in subsequent sections, numerous histopathologic features have prognostic value for medulloblastoma. Among other morphologic features, lesser differentiation and increasing anaplasia are both associated with a significantly worse outcome (Eberhart et al. 2002; McManamy et al. 2003). Moreover, severe anaplasia appears to be indicative of high relapse risk and poor survival, especially in the presence of a high apoptotic rate (Giangaspero et al. 2006).

The so-called "classic" medulloblastoma is composed of tightly packed, small, round blue cells with scant cytoplasm, dense basophilic nuclei, abundant mitotic figures, and poor differentiation (Fig. 5.1). Glial or neuronal differentiation may also be present, as well as perivascular pseudorosettes or Homer-Wright rosettes, both of which appear as a circle of neuroblastic nuclei around tangled cytoplasmic processes (Fig. 5.2). Vascular proliferation and hemorrhage are seldom noted. Grossly, medulloblastoma appears as a several-centimeter, circumscribed, friable, tan-to-pink mass within the cerebellar vermis, or cerebellar hemispheres, adjacent to the fourth ventricle (Fig. 5.3).

Microscopically, desmoplastic medulloblastoma is characterized by reticulin-rich stroma surrounding nodular foci of tumor in a so-called pale island configuration (Fig. 5.4). Tumors with these characteristics often arise at the superficial edge of a cerebellar hemisphere in adolescent or young adult patients where they cause a brisk inflammatory reaction of the meninges (Fig. 5.5) (Levy et al. 1997). In general, desmoplastic medulloblastoma has a more favorable outcome than other histopathologic variants, especially in infants, but this may be due in large part to co-occurrence with favorable molecular pathways (Kool et al. 2012; McManamy et al. 2007).

Large-cell medulloblastoma is identified histologically by pleomorphic, large round-to-irregular nuclei with prominent nucleoli, abundant cytoplasm, numerous mitoses, and a high apoptotic rate (Fig. 5.6) (Giangaspero et al. 1992). Synaptophysin and chromogranin expression are common, as are bulky spinal metastases (Fig. 5.7) and an aggressive disease course with 5-year overall survival as low as 10% (Brown et al. 2000).

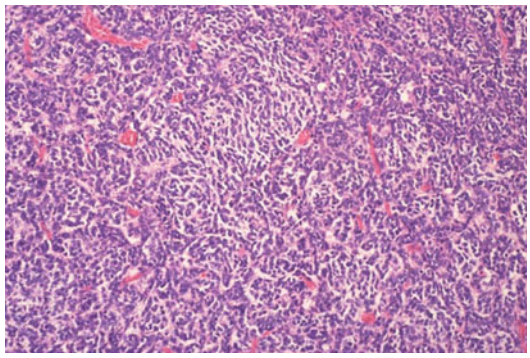

Fig. 5.1 Hematoxylin and eosin micrograph of classic medulloblastoma. There are dense sheets of small round blue cells with scant cytoplasm

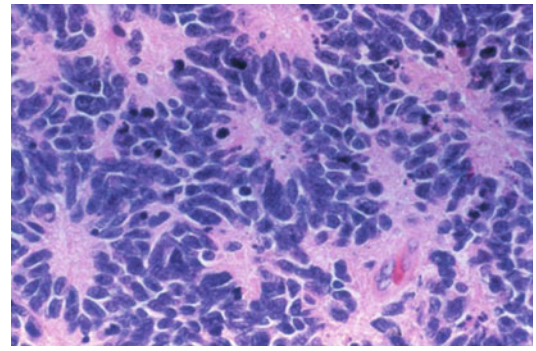

Fig. 5.2 Hematoxylin and eosin micrograph of Homer-Wright rosettes in medulloblastoma

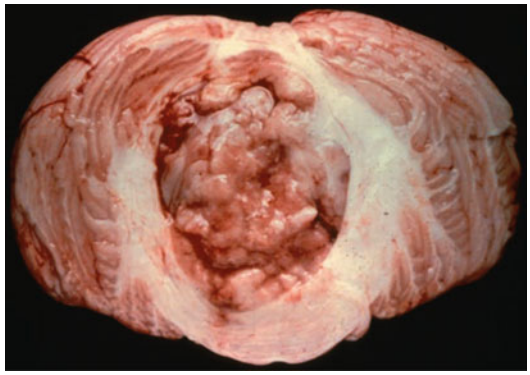

Fig. 5.3 Gross specimen of circumscribed medulloblastoma at the level of the cerebellar vermis and fourth ventricle

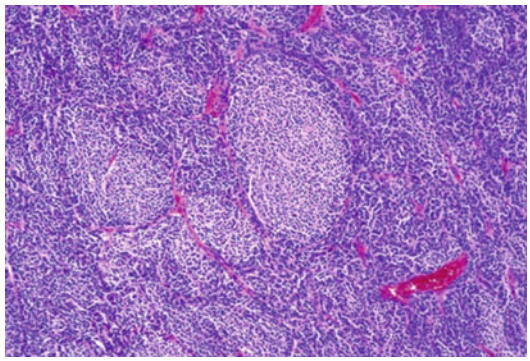

Fig. 5.4 Hematoxylin and eosin micrograph of desmoplastic medulloblastoma with pale islands of tumor cells and intervening dense reticulin

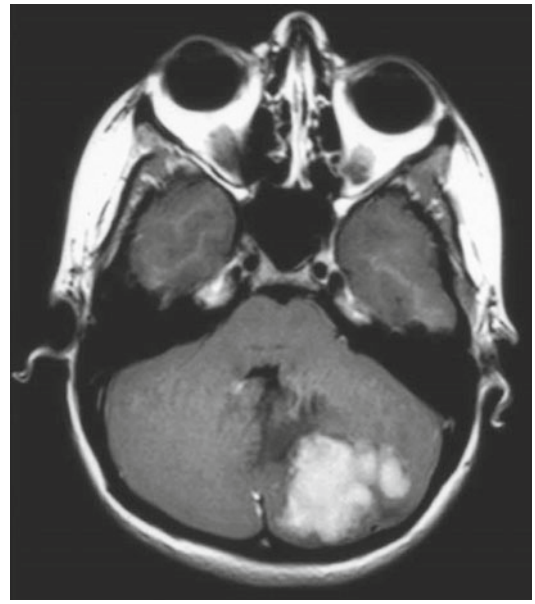

Fig. 5.5 Transverse T1-weighted axial magnetic resonance image following contrast administration demonstrating a superficial left cerebellar desmoplastic medulloblastoma in a 16-year-old girl

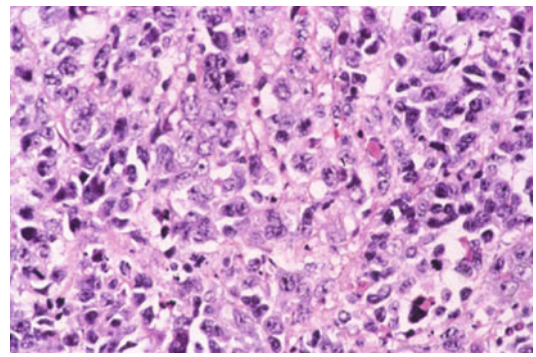

Fig. 5.6 Hematoxylin and eosin micrograph of large-cell medulloblastoma with cells having abundant cytoplasm, irregular nuclei, and prominent nucleoli

Similar to large-cell tumors, anaplastic medulloblastoma is characterized by nuclear pleomorphism and molding, a high mitotic rate, and prominent apoptosis. Though these changes can be seen focally in all histopathologic subtypes of medulloblastoma, these histological findings are widespread throughout large-cell tumors. Since anaplastic regions are also common in large-cell tumors, many providers advocate for adoption of a unified large-cell/anaplastic category (McManamy et al. 2003).

Desmoplastic and nodular medulloblastomas, which are similarly sometimes unified under a joint desmoplastic/nodular designation, have significantly better outcomes than large-cell/anaplastic tumors. Other histopathologic variants are exceedingly rare, including medullomyoblastoma, characterized by striated muscle or muscle antigen expression, and melanotic medulloblastoma which is identified by melanin-forming neuroepithelial cells (Fowler and Simpson 1962; Marinesco and Goldstein 1933). Both these subtypes may carry a worse prognosis than classic medulloblastoma, but their respective incidences are too low to accurately calculate outcomes.

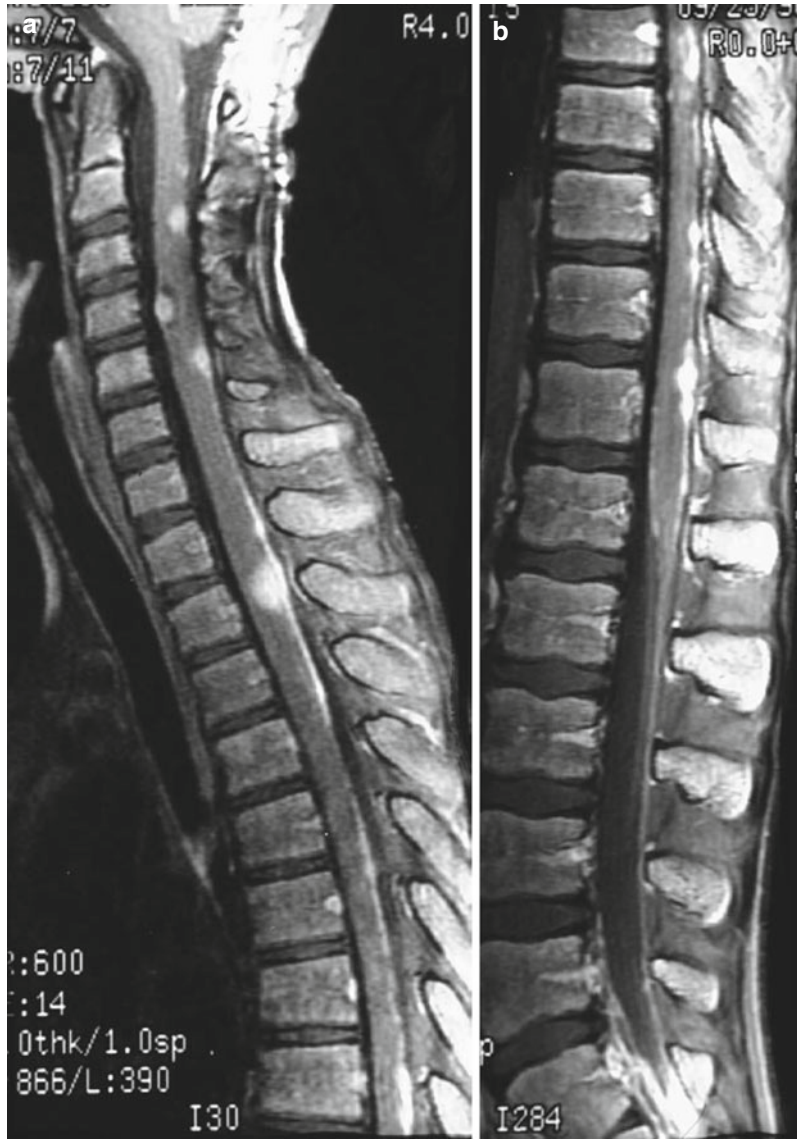

Fig. 5.7 T1-weighted sagittal post-gadolinium images of the thoracic (**a**) and lumbar spine (**b**) of a 10-year-old with widely metastatic large-cell medulloblastoma just after resection of a vermian primary mass. Widespread tumor dissemination is visualized on the surface of the cerebellum and spinal cord

5.2.2.2 Molecular Features and Cytogenetics

Improved characterization of the histologic variants of medulloblastoma has also led to an improved understanding of the underlying biologic features. Early studies of cytogenetic and molecular features identified a variety of prognostic factors (Table 5.1). Proliferative index, as determined by Ki-67 antigen/MIB-1 staining, and the rate of apoptosis have both been found to influence outcome as well (Grotzer et al. 2001; Haslam et al. 1998).

Cytogenetic studies have demonstrated that isochromosome 17q is present in approximately 50 % of cases, almost always in conjunction with loss of heterozygosity at 17p and most commonly in large-cell medulloblastoma (Bigner et al. 1988; Brown et al. 2000). Chromosome 1

Table 5.1 Cytogenetic and molecular features associated with medulloblastoma outcome

Good prognosis
Hyperdiploidy (Gajjar et al. 1993)
High *trkC* expression (Kim et al. 1999; Grotzer et al. 2000)
β-expression nuclear immunoreactivity (Ellison et al. 2005)
Poor prognosis
Isolated 17p loss of heterozygosity (Gilbertson et al. 2001)
Elevated *erbB2* expression (Gilbertson et al. 2001; Gajjar et al. 2004)
Elevated c-*myc* expression (Scheurlen et al. 1998; Eberhart et al. 2004)
Overexpression of calbindin-D_{28k} (Pelc et al. 2002)

rearrangements and 1q loss have been also variably noted in medulloblastoma (Bigner et al. 1988). In general, hyperdiploidy is associated with a better outcome than diploidy, but all cytogenetic features are prognostic only insofar as they affect molecular signaling pathways (Gajjar et al. 1993). In that regard, early investigations of molecular markers in medulloblastoma demonstrated associations with the loci containing c-*myc*, *erbB2*, *β-catenin*, *and trkC* (Ellison et al. 2005; Gajjar et al. 2004; Gilbertson et al. 2001; Grotzer et al. 2000; Kim et al. 1999). Whereas elevated expression of c-Myc and mutation of ErbB2 are both associated with unfavorable outcomes, high expression of the neurotrophic receptor gene *trkC* and *β-catenin* confers a more favorable prognosis. Amplification of the c-*myc* proto-oncogene is particularly associated with poor prognosis and perhaps unsurprisingly is frequently found in large-cell medulloblastomas associated with tumor anaplasia (Brown et al. 2000; Eberhart et al. 2002; Scheurlen et al. 1998).

Although genetic syndromes account for less than 5% of all medulloblastoma diagnoses, molecular profiling of tumors from these patients provided an early understanding of the distinct molecular features that dominate sporadic and germline cases alike. For instance, germline mutations of the human homolog of the Drosophila gene *Patched* (*PTCH*), which has an inhibitory effect on the Sonic Hedgehog (Shh) pathway, are responsible for both medulloblastoma and basal-cell carcinoma in Gorlin syndrome patients, which is also known as nevoid basal-cell carcinoma syndrome (Raffel et al. 1997). Follow-up studies identified mutations in *PTCH* and other Shh pathway members such as *GLI1* and *SUFU* in sporadic medulloblastoma cases as well (Pietsch et al. 1997; Raffel et al. 1997; Taylor et al. 2002; Wolter et al. 1997; Xie et al. 1997). Overexpression of *PTCH* and downstream Shh target genes, including *GLI* and *N-myc*, is highly correlated with desmoplastic medulloblastoma, and consistently, patients with these genomic aberrations are thought to have a relatively favorable clinical course (Pomeroy et al. 2002a). Transgenic mouse models of medulloblastoma further demonstrate that inactivation of the *PTCH* allele leads to medulloblastoma formation in a minority of animals, an incidence that is increased by concurrent *TP53* mutation (Wetmore et al. 2000, 2001). Notably, patients with Li-Fraumeni syndrome, which is caused by loss of p53 function, are also at risk for medulloblastoma.

Turcot syndrome, which includes familial adenomatous polyposis (FAP), is defined by the simultaneous presence of brain tumors and inherited colonic polyposis. Medulloblastoma is found in association with mutation of the *APC* gene in FAP, which normally functions downstream of Wnt to assemble a protein complex that constitutively degrades β-catenin. In the absence of APC, β-catenin is trafficked to the nucleus to promote expression of diverse pro-growth genes. Somatic driver mutations are found in a subset of sporadic medulloblastoma patients and, much like cytogenetic abnormalities of the *β-catenin* locus, are generally associated with a more favorable outcome (Hamilton et al. 1995; Vasen et al. 2008; Zurawel et al. 1998).

5.2.2.3 Molecular Subgroups

Since 2006, high-throughput bioinformatic techniques such as genome-wide DNA copy number analysis, mRNA expression profiling, somatic copy number aberrations, whole-genome sequencing, and whole-exome sequencing have greatly enhanced our understanding of the molecular determinants of medulloblastoma in two

ways (Cho et al. 2011; Hovestadt et al. 2014; Kool et al. 2012, 2008; Northcott et al. 2014, 2011a, b, 2012b; Pugh et al. 2012; Rausch et al. 2012; Robinson et al. 2012; Thompson et al. 2006). First, using unbiased sequencing techniques, these studies corroborate the prognostic significance of cytogenetic and molecular markers, many of which have a long history of clinical application. Second, the body of genomic evidence supports the existence of distinct molecular subgroups that dictate clinical outcomes. Although a variety of molecular subgroups have been proposed, the most widely accepted system separates medulloblastoma into Wnt, Shh, group 3 and group 4 tumors (Table 5.2) (Taylor et al. 2012). Among the various schema for clinical prognostication and stratification of patients with medulloblastoma – which include age, presence or absence of metastases, extent of resection, and histologic subtype – transcriptional profiling studies have demonstrated that molecular subgroup is the most important factor for risk assessment.

Among the four principal molecular subgroups, Wnt and Shh tumors are named for the developmental signaling pathways that are thought to drive medulloblastoma formation. The molecular cornerstones of group 3 and group 4 tumors are less well characterized, although mutations in the Shh transcription factor *GLI1* are common in both (Northcott et al. 2014). Indeed, the data suggest that subsets exist within each molecular subgroup, especially group 3 and group 4 neoplasms, and several high-quality review articles are available that thoroughly review these complexities (Batora et al. 2014; Kool et al. 2012; Northcott et al. 2012a).

Wnt subgroup tumors have a very low rate of metastatic spread and are associated with an excellent prognosis (Gajjar et al. 1993; Kool et al. 2012). Long-term survival for these patients exceeds 90 %, and as such, many individuals may live long enough to experience complications of therapy, rather than succumbing to recurrent disease. Wnt tumors account for approximately 10 % of sporadic cases, are equally distributed between males and females, and typically occur in adolescents and young adults (Ellison et al. 2005; Gajjar et al. 2004; Gilbertson et al. 2001; Grotzer et al. 2000; Kim et al. 1999; Northcott et al. 2012a, b).

Table 5.2 Molecular subgroups of sporadic medulloblastoma

	Wnt	Shh	Group 3	Group 4
Pediatric prevalence	~10 %	~30 %	~25 %	~35 %
Peak incidence	Adolescents and young adults	Infants and young adults	Between infancy and adolescents	Adolescents
5-year survival	~95 %	~60–80 %	~40–50 %	~75 %
Cell of origin	Lower rhombic lip progenitors	GNPs from EGL and cochlear nuclei; SVZ stem cells	GNPs from EGL	Unknown
Histology[a]	Classic	Nodular/desmoplastic	Classic and LC/A	Classic
Genetic correlate	Turcot syndrome (FAP)	Gorlin syndrome (NBCCS)	Unknown	Unknown
TP53 status	~15 % rate of co-mutation, equivalent prognosis	~20 % rate of co-mutation, worse overall survival (~40 %)	Uncommon	Rare in conjunction with isochromosome 17, but common with *MYCN* amplification; prognostic significance unclear
Adult tumor characteristics	~10–20 % incidence, worse prognosis	~50–70 % incidence, comparable outcome	Extremely rare, worse prognosis	~20–30 %, prognostic significance unclear

EGL external granule layer, *FAP* familial adenomatous polyposis, *GNP* granule neuron precursor, *LC/A* large-cell/anaplastic, *NBCCS* nevoid basal-cell carcinoma syndrome, *Shh* sonic hedgehog, *SVZ* subventricular zone, *Wnt* int/wingless

[a]Most common histological association(s)

Although they may occur in the setting of any histopathologic variant, Wnt tumors generally exhibit classic histology (Brown et al. 2000; Eberhart et al. 2002; Gibson et al. 2010; Scheurlen et al. 1998).

Wnt peptides are a collection of highly conserved, lipid-modified glycoproteins which bind to the Frizzled family of transmembrane receptors to transduce intercellular signals upstream of APC and β-catenin. Although first identified as a proto-oncogene in a mouse model of breast cancer, autocrine and paracrine Wnt signaling are critical for embryonic development through regulation of cell migration and proliferation, body axis patterning, and cell fate determination (Nusse and Varmus 2012; Raffel et al. 1997). Deregulation of the canonical Wnt pathway is associated with numerous malignancies, including skin, breast, lung, esophageal, colorectal, prostate, ovarian, and brain cancer (Anastas and Moon 2013; Pietsch et al. 1997; Raffel et al. 1997; Taylor et al. 2002; Wolter et al. 1997; Xie et al. 1997). With respect to the pathogenesis of medulloblastoma, alterations in Wnt signaling that promote stabilization and nuclear localization of β-catenin are common to both syndromic and sporadic tumors. In particular, somatic mutations of *CTNNB1*, the gene that encodes β-catenin, and loss of chromosome 6 are present in the majority of sporadic Wnt medulloblastomas. As such, β-catenin immunohistochemistry has become a routine component of pathological analysis following resection of medulloblastoma.

Hedgehog proteins, such as Shh, are secreted glycolipoproteins that control cell fate and proliferation by binding to the transmembrane protein Ptch. In the presence of Shh, Ptch-mediated repression of Smoothened (Smo) is released. In turn, Smo triggers a signal transduction pathway that culminates in activation of Gli transcription factors (Corbit et al. 2005; Pomeroy et al. 2002; Stone et al. 1999). Shh pathway-associated medulloblastoma accounts for approximately 30 % of all sporadic cases, is slightly more common in males, and occurs primarily in infants and adults (Al-Halabi et al. 2011; Archer et al. 2012; Kool et al. 2012; Wetmore et al. 2000; 2001). These tumors are rarely metastatic upon diagnosis, are frequently associated with nodular/desmoplastic histology, and are considered to have an intermediate prognosis with approximate overall survival ranging from 60 % to 80 % (Archer et al. 2012; Hamilton et al. 1995; Vasen et al. 2008; Zurawel et al. 1998). Given the prevalence of this molecular signature, immunohistochemistry for GAB1, a transmembrane mediator of Shh signaling, is routinely performed on all medulloblastoma resection specimens.

Large-cell anaplastic medulloblastoma, which has an aggressive clinical course, is most commonly associated with the molecular subtype known as group 3 (Kool et al. 2008; Leonard et al. 2001; Northcott et al. 2011; Thompson et al. 2006). Rarely found in adults or infants, and associated with a mere 40–50 % overall survival, nearly half of these tumors present with metastatic spread at the time of diagnosis (Kool et al. 2012). Males are approximately twofold more likely than females to be effected with group 3 medulloblastoma, which accounts for approximately 25 % of all cases.

In general, group 3 medulloblastoma is characterized by high levels of *Myc* amplification and genomic instability including gain of chromosomes 1q, 7, and isochromosome 17q, as well as loss of chromosomes 10q, 11, 16q, and 17p (Cho et al. 2011; Northcott et al. 2011). Group 4 medulloblastomas, which comprise 35 % of all cases, are also characterized by cytogenetic abnormalities, including isochromosome 17q and heterozygous loss of the X chromosome, in addition to amplification of *CDK6* and *N-Myc* (Kool et al. 2012). Usually found in adolescent males and associated with classic histology, approximately 40 % of group 4 medulloblastomas are associated with metastases at diagnosis. Less is known about the biology of group 3 and group 4 tumors, although both are unified by specific collections of epigenetic and structural DNA variations, as opposed to misregulation of a canonical developmental pathway such as Wnt or Shh. Mechanistic investigations of group 3 and group 4 medulloblastomas are therefore required to better understand the pathophysiology of these tumors and to identify targets for molecular therapies. In that regard, the Shh antagonist

vismodegib has been trialed for medulloblastoma, but responses are near-universally transient. Indeed, subsequent mechanistic and genomic studies have shown that medulloblastoma cells are capable of rapid evolution to develop resistance to single-agent molecular therapy (He et al. 2014; Rudin et al. 2009; Kool et al. 2014; Yauch et al. 2009). As such, combination therapy may be necessary if molecular agents are to be successfully incorporated into the treatment regimen for medulloblastoma.

5.2.3 Clinical Features

Children with medulloblastoma frequently present with signs and symptoms of obstructive hydrocephalus and cerebellar dysfunction over the course of 2–6 months due to obstruction of the fourth ventricle. Early symptoms may include irritability, behavioral changes, and declining school performance. Infants are frequently found to display macrocephaly, splitting of the cranial sutures, or a bulging anterior fontanel. Many patients progress to develop emesis, particularly upon awakening, horizontal diplopia, head tilt, clumsiness, ataxia, and headaches. Seizures may occur, as can symptoms associated with leptomeningeal dissemination, including cranial nerve dysfunction, pituitary abnormalities such as precocious puberty, and distal neurologic deficits from spinal metastases. Late neurologic signs include strabismus, ataxia, or weakness (Honig and Charney 1982). Untreated, the symptoms from mass effect and obstructive hydrocephalus invariably lead to progressive neurologic deterioration and death. Every effort should therefore be made for expedient relief of CSF pressure and an oncologic resection of tumor, as discussed below.

5.2.4 Natural History

At diagnosis, 14–43 % of medulloblastoma patients are found to have microscopic or nodular seeding in the subarachnoid space of the spine or brain (Deutsch and Reigel 1980; Tarbell et al. 2000). Indeed, medulloblastoma has the greatest tendency for subarachnoid space seeding and extraneural spread among all pediatric brain tumors. In less than 5 % of cases, tumors spread outside the CNS (Kleinman et al. 1981).

Medulloblastoma relapse most often occurs at the primary tumor site or elsewhere within the cerebellum, with or without neuraxis spread (Halberg et al. 1991). Median time to recurrence is 14 months from diagnosis, although for infants, the time to progression is just 6 months (Duffner et al. 1993; Minn et al. 2001). Subclinical subarachnoid tumor spread is not uncommon at autopsy, although these data are derived from children treated with 36 Gy of craniospinal irradiation (CSI), or infants treated without radiotherapy. In total, approximately 75 % of patients present with neuraxial dissemination at the time of recurrence, but it is not known how the pattern and timing of relapse will change with variation of prophylactic neuraxial radiation dose, different systemic and intrathecal chemotherapy regimens, or molecular targeted agents.

Children diagnosed before 3 years of age have significantly worse survival than older patients, but there do not appear to be significant differences among age groups of 4–9 years, 10–14 years, and 15–19 years (McNeil et al. 2002). Outcome is independent of race (McNeil et al. 2002). It is debated whether the generally adverse effect of very young age on outcome may be confounded by the frequent absence of irradiation during treatment of these patients. However, emerging evidence suggests a high incidence of molecular mutations with a particularly aggressive natural history that may explain the trend toward impaired survival in this patient population (Kool et al. 2012).

5.2.5 Diagnostic Imaging

Although imaging has not historically played a role in the definitive diagnosis of medulloblastoma, central nervous system imaging is universally employed for children presenting with the clinical features described above. Most often for

the sake of expediency, as well as due to the frequent need for pediatric anesthesia during magnetic resonance imaging (MRI), patients will initially undergo a computed tomography (CT) scan of the head. A high-quality CT scan will almost always detect a posterior fossa mass. Classically, medulloblastoma appears as a cerebellar mass that is hyperattenuated due to its high cellular density (Fig. 5.8). These lesions homogeneously enhance following contrast injection, and approximately 20 % of lesions contain intratumoral calcifications (Bourgouin et al. 1992; Poretti et al. 2012). Nonetheless, anatomic definition and preoperative planning require a high-quality MRI scan. Children with large posterior fossa masses detected on CT or MRI are at high risk for neurologic deterioration from transient increases in intracranial pressure (ICP) while supine or sedated during a prolonged MRI screening. However, there is risk of shunt failure due to retained blood products in the ventricles after resection of tumor, and placement of a shunt increases the risks of intratumoral hemorrhage and upward herniation. For these reasons, shunting is not advocated before resection, and most patients are managed with steroids. External ventriculostomy may be considered in emergency scenarios, and in general, shunt placement does not appear to increase the risk of neuraxial or systemic tumor spread (Berger et al. 1991).

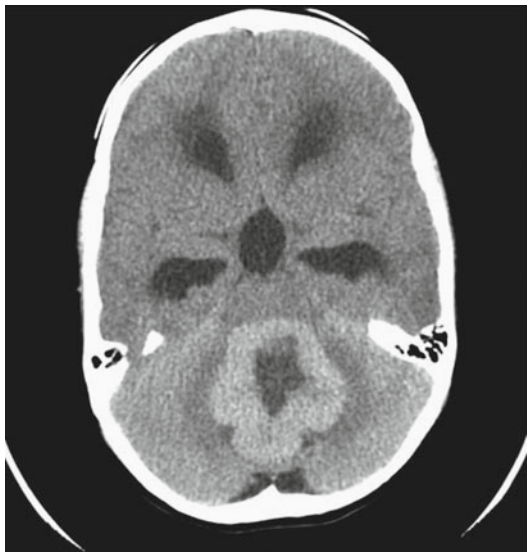

Fig. 5.8 Axial noncontrast CT scan of a patient with a hyperdense medulloblastoma

The appearance of medulloblastoma on MRI can be varied. On T1-weighted images, the mass can be either homogenous or heterogeneous in consistency, is generally iso- or hypointense, and avidly enhances with contrast administration (Fig. 5.9). Large-cell/anaplastic tumors in particular may demonstrate ring enhancement as a result of tumor necrosis. T2-weighted images have similarly been reported to vary with histologic subtype: classic tumors may display T2 signal

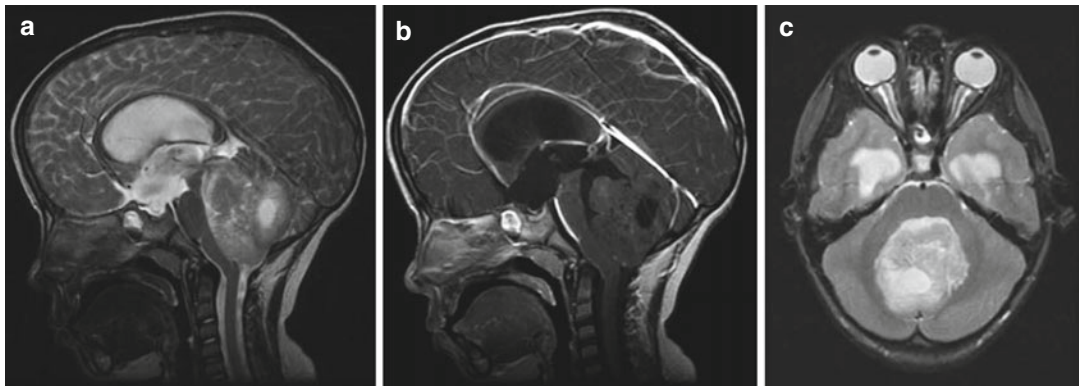

Fig. 5.9 (**a**–**c**) Magnetic resonance images of a 5-year-old boy with a typical posterior fossa medulloblastoma. (**a**) T2-weighted sagittal image showing a large heterogeneous partially cystic mass arising within the cerebellar vermis, displacing the brainstem anteriorly and with associated ventricular enlargement. (**b**) T1-weighted image with contrast demonstrates minimal enhancement, which is a common finding. (**c**) T2-weighted axial image showing that the tumor extends to the floor of the fourth ventricle but does not invade the brainstem

hyperintensity from cysts and calcifications, and desmoplastic/nodular lesions may be isointense with internal heterogeneity on T2 sequences. If possible, a full spine MRI should be obtained preoperatively to determine if there is leptomeningeal dissemination, the presence of which markedly affects long-term outcome. At the most extreme end of this spectrum, a minority of patients present with diffuse leptomeningeal dissemination which is described as "sugar coating" of the brain and spine on post-contrast T1-weighted MR images (Fig. 5.10). If an MRI of the spine cannot be obtain preoperatively, it is recommended that 10–14 days be allowed to pass after surgery to allow for reabsorption of blood products that collect within the thecal sack following craniotomy and may obscure evaluation for tumor nodules. In contrast, it is imperative that the postoperative restaging scans of the posterior fossa are completed within 24–72 h of resection before granulation tissue, gliosis, and blood products obscure residual tumor.

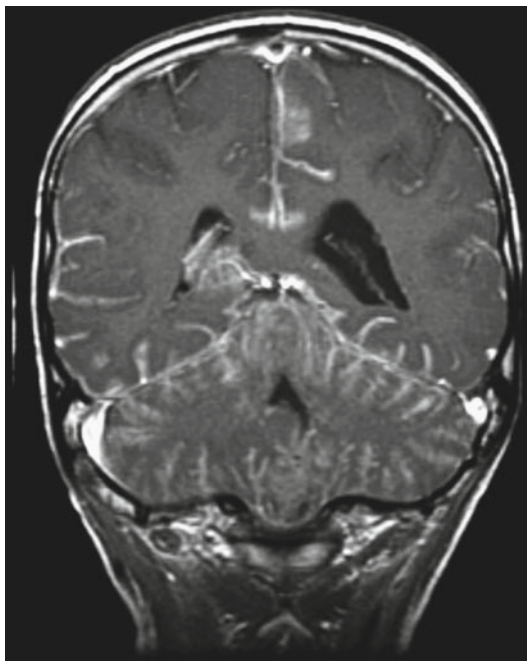

Fig. 5.10 A coronal T1-weighted magnetic resonance image following contrast administration. Disseminated leptomeningeal tumor is clearly seen as a bright layer of tissue "sugar coating" the brain

5.2.6 Treatment

5.2.6.1 Surgery

Virtually all children with a posterior fossa mass undergo craniotomy, the goals of which are to relieve mass effect, obtain a tissue diagnosis, reestablish CSF circulation, and cytoreduction to facilitate adjuvant therapy. In general, there is no indication for stereotactic or open biopsy, unless the cerebellar tumor is diffuse or there is extensive leptomeningeal seeding. Even in such instances, symptomatic relief following primary tumor debulking is more durable than after CSF diversion alone and certainly lessens the risk of death from mass effect and brainstem compression. In cases without evidence of metastases, every effort should be made for maximal safe resection. Although children with less than 1.5 cm^2 of residual disease on postoperative imaging have an improved prognosis for long-term, relapse-free survival, these data were largely obtained during the CT era, and it is unclear how well they generalize to MRI studies (Zeltzer et al. 1999a). As brainstem infiltration does not affect overall prognosis, removal of tiny tumor foci in this region or lying at the floor or exit of the fourth ventricle is not warranted due to the significant risk of morbidity and mortality associated with these surgical procedures (Duffner et al. 1993; Zeltzer et al. 1999b).

Following primary tumor resection, external ventriculostomies are usually weaned in an intensive care setting over the first week or 10 days by either gradually elevating or clamping the external drain. If ICP rises with weaning of the ventriculostomy, the presence of hydrocephalus must be presumed and a permanent ventriculoperitoneal shunt should be placed. Similarly, if the ventriculostomy can be removed successfully, ventricular size and clinical symptoms must continue to be observed carefully as delayed hydrocephalus can still occur in approximately 30 % of patients.

5.2.6.2 Staging

Following resection and histopathological diagnosis of medulloblastoma, a lumbar puncture for CSF cytology should be obtained 10–14 days

Table 5.3 Chang metastasis staging system for medulloblastoma (Chang et al. 1969)

M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells within the cerebrospinal fluid
M2	Gross nodular seeding in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Extraneural metastasis

Table 5.4 Risk stratification for medulloblastoma

Average risk
<1.5 cm^2 postoperative residual tumor, stage M0, and age >3 years
High risk
>1.5 cm^2 postoperative residual tumor, stage M1-4, or age ≤3 years

postoperatively to assess for microscopic tumor spread. Ventricular sampling of CSF for cytology has inferior sensitivity and should not be used, unless a lumbar sample absolutely cannot be obtained (Gajjar et al. 1999). Although bone-marrow biopsy is not recommended, a bone or positron emission tomography scan may be obtained if there is evidence of disseminated disease.

The classic system of medulloblastoma staging separates patients into two risk groups based upon patient age, extent of resection, and presence or absence of metastases (Tables 5.3 and 5.4) (Chang et al. 1969b). Notably, primary tumor size is not prognostic and does not factor into this system. Average risk includes children greater than 3 years old, less than 1.5 cm^2 residual tumor, and no evidence of either gross or microscopic metastases. High risk is defined by more than 1.5 cm^2 residual, patient age less than 3 years, and M+ disease. Notably, the prognostic significance of micrometastatic disease has been debated, as two trials have demonstrated no difference in the overall survival of patients with M1 and M0 medulloblastoma. Moreover, these staging criteria have been challenged due to the omission of histopathologic data and tumor molecular subtype. Indeed, ongoing clinical trials are beginning to incorporate these features to stratify patients, and it is likely that the formal staging system for medulloblastoma will be amended to incorporate biologic features in the future.

5.2.6.3 Radiotherapy

Adjuvant treatment for medulloblastoma most often commences with radiotherapy beginning approximately 3–4 weeks after surgery because of time required for wound healing, neurologic recovery, and staging. Since most patients requiring CSI are children, special considerations are often necessary, such as proper stabilization during treatment and assistive anesthesia. In addition, many children have neurologic deficits impairing their ability to lie motionless for any length of time.

Baseline assessments of endocrine and cognitive function should be performed during the postoperative period as CSI may adversely affect the pituitary and thyroid glands along with the cerebrum. Numerous studies have quantified the long-term sequelae of CSI in pediatric patients, which also include skeletal deformity from stunted vertebral body growth. Along with endocrine and neurocognitive dysfunction, these toxicities are intrinsically related to patient age at the time of treatment, as well as the dose of radiation administered (Mabbott et al. 2005; Merchant et al. 2009; Palmer et al. 2013). Processing speed and memory seem to be most affected, although the combined effects of craniotomy and chemotherapy certainly contribute to all of these findings.

At present, a radiation dose of 23.4 Gy to the craniospinal axis plus a boost to 54 Gy to the posterior fossa followed by chemotherapy is the standard of care for average-risk disease (Packer et al. 2006). This approach has resulted in 5-year overall survival of approximately 85 %, but given the aforementioned treatment-associated toxicities, reduced-dose craniospinal irradiation of 18 Gy and conformal radiotherapy boost to the tumor bed are active areas on ongoing clinical investigation. Given their

uniquely favorable prognosis, WNT-driven average-risk medulloblastoma patients constitute a particularly appealing cohort for which to diminish therapy intensification, including reduced CSI dose to 18 Gy to limited target volume boost to a total of 54 Gy. Intensification of chemotherapy with autologous peripheral blood stem-cell support has also been reported and may offer one potential avenue for reducing the dose of ionizing radiation to the craniospinal axis (Gajjar et al. 2006a). In high-risk disease, 36 Gy to the craniospinal axis plus a boost at the posterior fossa to 55.8 Gy, followed by chemotherapy, is the standard therapy and results in 5-year survival rates of 50–70 %.

The CSI field arrangement for medulloblastoma radiotherapy classically consists of opposed lateral brain portals and a posterior spinal axis field, all of which are matched in the region of the cervical spine with the patient in the prone position. The posterior fossa is typically treated with at least 1 cm margin, and the inferior border is set at C2. However, treatment of the entire posterior fossa also delivers a significant dose to the parietal, occipital, and temporal lobes, as well as the parotid glands, cochlea, pharynx, and other associated structures. Therefore, ongoing cooperative studies are evaluating whether the target volume reduction to the primary site tumor bed alone in average-risk medulloblastoma can be performed without compromising disease control. Indeed, many pediatric oncologists have already incorporated this approach into practice.

Beyond reducing the total dose of CSI and the boost target volume, alternative radiation modalities such as proton-beam and helical intensity-modulated radiotherapy (IMRT) (e.g., TomoTherapy®) are increasingly in use in an effort to mitigate potential long-term side effects of radiation. Outcome data for each are limited, and benefits are largely theoretical. However, comparisons of proton beam, conventional 3D radiation, and IMRT for treatment of the posterior fossa and spinal column suggest superior sparing of normal structures by protons, likely with mitigation of long-term toxicities (St Clair et al. 2004).

5.2.6.4 Chemotherapy

Attempts to omit CSI in children less than 3 years or exclusion of the entire neuraxis from the radiation field have resulted in reduced survival (Bouffet et al. 1992). However, the morbid sequela of CSI, along with the poor survival of children with high-risk medulloblastoma, has led to sustained efforts by cooperative groups to introduce chemotherapy and reduce or delay radiation. Indeed, these efforts have at least allowed for radiation to be reserved for salvage in select infants (Ashley et al. 2008; Duffner et al. 1993; Geyer et al. 2005; Grill et al. 2005; Rutkowski et al. 2005).

Chemotherapy was formally introduced for medulloblastoma in the late 1970s, when the International Society of Pediatric Oncology (SIOP I), the Children's Cancer Study Group (CCG 942), and the Pediatric Oncology Group (POG 7909) each performed prospective randomized trials of CSI alone versus postradiation chemotherapy. These studies investigated different systemic cytotoxic regimens, but were alike in the heavy application of DNA alkylating agents such as lomustine and procarbazine, as well as the microtubule poison vincristine (Evans et al. 1990; Krischer et al. 1991; Tait et al. 1990). Although chemotherapy did not improve overall survival for all children, a benefit was apparent in patients with bulky residual or metastatic disease. In sum, these findings and a series of subsequent trials demonstrated that medulloblastoma is one of the most chemotherapy-sensitive of all brain tumors. Alkylators and platinum compounds are the foundation of adjuvant chemotherapy, particularly lomustine and cisplatin, and sometimes procarbazine, cyclophosphamide, ifosfamide, or carboplatin. Vincristine is often administered weekly during radiation and then again during adjuvant chemotherapy. In addition, the topoisomerase II inhibitor etoposide is active in disseminated and infant forms of the disease (Ashley et al. 1996; Duffner et al. 1993). Finally, methotrexate, an antimetabolite, has been used in European trials, but is uncommon in the United States due to an association with radiation-induced leukoencephalopathy.

In average-risk medulloblastoma, a series of trials from SIOP, the French Society of Pediatric Oncology (SFOP), the Children's Oncology Group (COG, the result of a merger between POG and CCG), and the German Society of Pediatric Oncology (GPO and HIT) have attempted to reduce CSI by adding either preradiation neoadjuvant chemotherapy or, more commonly, postradiation chemotherapy (Table 5.5) (Bailey et al. 1995; Gajjar et al. 2006a; Gentet et al. 1995; Kortmann et al. 2000; Kuhl et al. 1998; Packer et al. 2006, 1999; Taylor et al. 2001; Thomas et al. 2000). POG 8631/CCG 923 treated patients without chemotherapy and either 23.4 Gy or 36 Gy CSI, but was suspended in 1990 when an interim statistical analysis revealed an elevated rate of relapse in the reduced-dosage radiotherapy group (Thomas et al. 2000). Follow-up over time demonstrated that patients treated with 36 Gy experienced an event-free survival of 67 % at 5 years. Event-free survival was marginally inferior in the 23.4 Gy group, at 52 % after 5 years ($p = 0.077$), but there was also an increased rate of early relapse and isolated exoprimary recurrence, contrary to earlier limited institutional experiences (Deutsch et al. 1996; Halberg et al. 1991). Subsequently, CCG 9892 employed 23.4 Gy CSI plus a boost to the posterior fossa to a total of 55.8 Gy with concurrent weekly vincristine, followed by eight cycles of lomustine, cisplatin, and vincristine. By this approach, 5-year event-free survival from average-risk disease reached 78 % and was statistically no different than the POG 8631/CCG 923 benchmark using 36 Gy. While CCG 9892 accrued just 65 eligible patients, the results suggested that chemotherapy could be substituted for at least a portion of CSI. In support of this hypothesis, COG A9961 randomized average-risk medulloblastoma patients to receive either lomustine or cyclophosphamide in combination with cisplatin and vincristine following 23.4 Gy CSI and a whole posterior fossa boost to 54 Gy. Both arms achieved >80 % event-free survival at 5 years (Packer et al. 2006).

Since these early trials, subsequent studies have explored various regimens in an effort to improve outcomes, reduce toxicity, and shorten the overall length of treatment. SJMB-96 effectively treated both average- and high-risk patients with risk-adapted radiotherapy followed by four cycles of cisplatin, vincristine, cyclophosphamide, and stem-cell rescue. Event-free survival from this trial was 85 % in the average-risk group and 70 % in the high-risk group. In a recently closed COG study, the results of which are eagerly awaited, patients with average-risk medulloblastoma from ages 3–7 were randomized to either 18 or 23.4 Gy to further reduce the potential side effects of radiation without compromising outcome.

Following surgery, there has been a consistent effort to deliver neoadjuvant and postirradiation chemotherapy in high-risk medulloblastoma studies (Table 5.6) (Bailey et al. 1995; Chang et al. 1969a; Gajjar et al. 2006b; Gentet et al. 1995; Kuhl et al. 1998; Mosijczuk et al. 1993; Tarbell et al. 2000; Taylor et al. 2000; Zeltzer et al. 1999b). The rationale for neoadjuvant chemotherapy is unencumbered treatment before radiation, when tolerance may be better and toxicity is less, but there are minimal data to support such hypothetical advantages. In fact, myelosuppression from neoadjuvant systemic treatment sometimes delays initiation of radiotherapy even further (Kortmann et al. 2000; Mosijczuk et al. 1993). Moreover, this approach appears to increase the risk of distant neuraxis relapse (Hartsell et al. 1997). For these reasons, preradiation chemotherapy for high-risk medulloblastoma is not a standard in the United States. In contrast, the available data indicate that postradiation chemotherapy improves survival for high-risk medulloblastoma to approximately 50 % and should therefore be offered to all appropriate candidates (Packer et al. 1994).

5.2.7 Outcome

Data from multiple, international prospective studies in the chemotherapy era demonstrate that overall survival for all children with medulloblastoma is approximately 60 % at 5 years and at least 40–50 % at 10 years (Evans et al. 1990; Tait et al. 1990). Relapse is most common within the

Table 5.5 Cooperative group studies for average-risk medulloblastoma, age ≥3 years

Study	Years of accrual	Number of eligible patients	Preirradiation chemotherapy × cycles	Craniospinal radiotherapy[a]	Postirradiation chemotherapy × cycles	Percent event-free survival at 5 years	Comments
SIOP II[b,c] (Bailey et al. 1995)	1984–1989	40	None	35 Gy	None	60 ± 8	No significant benefit from "sandwich" chemotherapy, but negative interaction between "sandwich" chemotherapy and reduced irradiation
		36	None	25 Gy	None	69 ± 8	
		38	PCZ/VCR/MTX × 1	35 Gy	None	75 ± 7	
		36	PCZ/VCR/MTX × 1	25 Gy	None	42 ± 8	
SFOP M7[b,d] (Gentet et al. 1995)	1985–1988	31	″1-ln-11[e] × 2,HD	30–37.5 Gy[f]	None	74	
			MTX × 2				
POG 8631/ CCG 923[b] (Thomas et al. 2000)	1986–1990	44	None	36 Gy	None	67 ± 7	Increased incidence of early, exoprimary neuraxis relapse
		44	None	23.4 Gy	None	52 ± 11	
HIT ′88/′89 (Kuhl et al. 1998)	1987–1991	55	PCZ/IFOS/VP16/MTX/CDDP/ ARAC × 2	35.2 Gy (n=34)	None	61 ± 7	Results compiled for all patients together
				<30 Gy (n=21)			
CCG 9892[g] (packer et al. 1999)	1990–1994	65	None	23.4 Gy + weekly VCR	CCNU/CDDP/VCR × 8	78 ± 5	23 % completed CDDP only with dose reduction and 36 % did not complete CDDP because of ototoxicity
HIT ′91[h] (Kortmann et al. 2000)	1991–1997	64	None	35.2 Gy + weekly VCR	CCNU/CDDP/VCR × 8		78 ± 6 % 3-year PFS
		94	IFOS/CDDP/HDMTX/VP16/ ARAC × 2	35.2 Gy	CCNU/CBDCA/VCR × 8 *if incomplete remission or progressive disease*		65 ± 5 % 3-year PFS
							Nonrandomized patients included

(continued)

Table 5.5 (continued)

Study	Years of accrual	Number of eligible patients	Preirradiation chemotherapy × cycles	Craniospinal radiotherapy[a]	Postirradiation chemotherapy × cycles	Percent event-free survival at 5 years	Comments
PNET-3[i] (Taylor et al. 2001)	1992–2000	89	None	35 Gy	None	72	EFS statistically significant, $p = 0.05$
		90	VP16/VCR/CBDCA/CPM × 3	35 Gy	None	59	
COG A9961[f] (Packer et al. 2006)	1996–2000	193	None	23.4 Gy CSI	CCNU/CDDP/VCR × 8, or	81 ± 2	EFS and OS not significant in two arms
		186		23.4 Gy CSI	CPM/CDDP/VCR × 8	86 ± 9	Electrolyte disturbance more common in CCNU arm and infections more frequent in CPM arm
SJMB-96[j] (Gajjar et al. 2006)	1996–2003	86	None	23.4 Gy CSI	CPM/CDDP/VCR followed by stem-cell rescue × 4	83 ± 0	Classic histology had better EFS than desmoplastic and large-cell anaplastic tumors

PCZ procarbazine, *VCR* vincristine, *MTX* methotrexate, *HD* high dose, *IFOS* ifosfamide, *VP16* etoposide, *CDDP* cisplatin, *ARAC* cytarabine, *CCNU* lomustine, *VCR* vincristine, *PFS* progression-free survival, *CBDCA* carboplatin, *CPM* cyclophosphamide

[a]Posterior fossa boost totaling 50–55.2 Gy

[b]Patients classified as low risk

[c]Children 0–3 years included

[d]Children 24–35 months included and received 20 Gy to cranium

[e]Children 24–35 months included/VCR/CCNU/PCZ/hydroxyurea/CDDP/ARAC/CPM

[f]23–35 Gy to cranium

[g]Children 3–10 years only

[h]Patients with and without residual disease, M1 patients included, and not all patients were randomized to therapy

[i]M0 and M1 patients only

[j]M0 only patients

Table 5.6 Cooperative group studies for high-risk medulloblastoma, age >3 years

Study	Years of accrual	Number of eligible patients	Preirradiation chemotherapy × cycles	Craniospinal radiotherapy[a]	Postirradiation chemotherapy × cycles	Percent event-free survival	Comments
SFOP M7[b,c] (Gentet et al. 1995)	1985–1988	37	″8-in-T″[d] ×2, HD	30–37.500A0Gy[e]	″8-in-1″ ×4	57 at 5 years	
			MTXx2				
POG 8695[f] (Mosijczuk et al. 1993)	1986–1990	36	CDDP/VCR × 3;	36 Gy	None		PFS 40 % at 2 years
			CPM × 2				Only 22 of 36 completed therapy, secondary to toxicity; start of radiotherapy delayed in most patients because of myelosuppression
SIOPII[g] (Bailey et al. 1995)	1984–1989	62	PCZ/VCR/MTX × 1	35 Gy	CCNU/VCR ×6	56 ± 7 at 5 years	
		71	None	35 Gy	CCNU/VCR ×6	53 ± 6 at 5 years	
CCG 921[h] (Zeltzer et al. 1999)	1986–1992	101	None	36 Gy + weekly VCR	CCNU/VCR/PCZ × 8		63 ± 5 % PFS at 5 years
		102	″8-in-1 × 2	36 Gy	″8-in-1″ × 8		45 ± 5 % PFS at 5 years
HIT ′88/′89 (Kuhl et al. 1998)	1987–1991	39	PCZ/IFOS/VP16/MTX/CDDP/ARAC × 2	352 Gy	CCNU/PCZ	33 ± 8 at 5 years	
POG 9031[c] (Tarbell et al. 2000)	1990–1996	114	CDDP/VP16 × 3	35.2 M0-1;40 Gy M2-3	CPM/VCR × 8	78 ± 4at 2 years	Response to chemotherapy correlated with outcome
		112	None	35.2 M0-1;40 Gy M2-3	CDDP/VP16 × 3, then		80 ± 4 at 2 years
					CPM/VCR × 8		
HIT ‘91 (Kortmann et al. 2000)	1991–1997	40[i]	None	35.2 Gy + weekly	CCNU/CDDP/VCR × 8		For all patients 65 ± 12 % PFS for M1, and 30 ± 15 % for M2-3
			IFOS/CDDP/HD MTX/VP16/ARAC × 2	VCR	CCNU/CBDCA/VCR X 8 *if incomplete remission or progressive disease*		
				35.2 Gy			

(continued)

Table 5.6 (continued)

Study	Years of accrual	Number of eligible patients	Preirradiation chemotherapy × cycles	Craniospinal radiotherapy[a]	Postirradiation chemotherapy × cycles	Percent event-free survival	Comments
PNET-3[j] (Taylor et al. 2005)	1992–2000	68	VCR/VP 16/CBDCA × 4 alternating with VIN/VP16/CPM × 4	35 Gy	None	35 ± 11.5 at 5 years	Seven patients treated with chemotherapy did not receive RT; 24 patients given boost to metastatic areas
SJMB-96[k] (Gajjar et al. 2006)	1996–2003	48	None	36–39.6 Gy	TPT/CPM/CDDP/VCR followed by stem-cell rescue × 4	70 ± 15 at 5 years ±	No significant difference in those who received TPT. 54 % had classic histology

HDMTX high-dose methotrexate, *CDDP* cisplatin, *VCR* vincristine, *CRM* cyclophosphamide, *PFS* progression-free survival, *PCZ* procarbazine, *CCNU* lomustine, *IFOS* ifosfamide, *VP16* etoposide, *ARAC* cytarabine, *CBDCA* carboplatin, *TPT* topotecan

[a]Posterior fossa boost to 54–55.8 Gy

[b]Children >10–35 months included and received 20 Gy to cranium

[c]Brainstem invasion used as a criterion for high risk

[d]″8-in-1″ = methylprednisolone/VCR/CCNU/PCZ/hydroxyurea/CDDP/ARAC/CPM

[e]22–35 Gy to cranium

[f]Children ≥4 years and brainstem invasion used as additional criterion for high risk

[g]Children 0–3 years included and brainstem invasion but not M1 used as criteria for high risk

[h]Children ≥1.5 years included and brainstem invasion used as additional criterion for high risk

[i]21 M1 non-randomized patients and 19 M2-3 randomized patients

[j]M1 randomized, M2-M3 treated on experimental arm only

[k]M1-M3 patients and M0 patients with assessable disease on MRI after radiation. M0-1 treated with 36 Gy and M2-3 with 39.6 Gy

[l]31 out of 48 received TPT prior to radiotherapy

first 2 years after completion of definitive therapy, and although tumor recurrence is unlikely after 8 years, many average-risk patients can recur on long-term follow-up (Belza et al. 1991; Packer et al. 2008). The growing number of medulloblastoma survivors has led to a sobering recognition of the aforementioned late effects, namely, cognitive decline, growth failure, endocrinopathies, hearing loss, CNS vascular disease, and secondary malignancies. Survivors of childhood cancers, even once cured of their malignancies, remain 13-fold more likely to die than age-matched cohorts (Perkins et al. 2013). Although cardiovascular and cerebrovascular events account for a portion of this finding, the largest contributors are secondary malignancies. For instance, the 8-year cumulative incidence of secondary malignancies in the average-risk protocol COG A9961 was 3.5 % (Packer et al. 2008). Children with Gorlin syndrome and other cancer predisposition conditions are at a particularly high risk for secondary cancers, and all patients should therefore be surveyed for the rest of their lives.

5.2.8 Future Directions

Future investigation in medulloblastoma will focus on both the optimal doses and delivery methods for radiotherapy. As far as delivery is concerned, technological improvements can limit radiation scatter from the posterior fossa boost or even reduce the target volume of the boost to the tumor bed, rather than the entire posterior fossa without compromising outcome in preliminary studies (Freeman et al. 2002). The overall radiation dose to the temporal lobes, cochleae, and hypothalamus is significantly reduced by this approach, which could reduce long-term toxicities (Merchant et al. 2008). Rapidly evolving understanding of the biologic pathways that promote and perpetuate medulloblastoma will clearly influence clinical staging. Indeed, the current scientific data strongly suggest that molecular subtype is the most important prognostic factor in medulloblastoma. Patients with Wnt pathway tumors have comparatively favorable outcomes that stand in contrast to the poor outcomes of those with group 3 tumors and the mixed results for medulloblastomas with aberrations in the Hh pathway. Although early experience with molecular targeted agents for Hh medulloblastoma has led to transient and often disappointment results, greater mechanistic knowledge will certainly reveal new therapeutic targets in the future.

5.3 Atypical Teratoid/Rhabdoid Tumor

5.3.1 Epidemiology

Although precise calculations are difficult due to the scarcity of ATRT, some estimates suggest that this rare neoplasm accounts for 1 % of all pediatric brain tumors and up to 10 % of brain tumors in infants (Biegel 2006; Louis et al. 2007). With a striking predilection for infants and twofold more likely to occur in males, the mean age of patients with ATRT is 1–7 months, and 94 % of patients are less than 5 years of age at diagnosis (Hilden et al. 2004; Louis et al. 2007; Packer et al. 2002; Tekautz et al. 2005).

5.3.2 Pathology

ATRT is a malignant (WHO grade IV) embryonal tumor containing rhabdoid cells, but in 90 % of cases also exhibit additional disparate components of small embryonal, mesenchymal, and epithelial cells (Packer et al. 2002) (Fig. 5.11). Rhabdoid cells are ovoid and are often found in sheets with eccentric and reniform nuclei, prominent nucleoli, and fine granular homogeneous cytoplasm. These cells almost always express epithelial membrane antigen and vimentin and frequently display abundant mitotic activity with MIB-1 indices in excess of 75 % (Burger et al. 1998; Louis et al. 2007). The epithelial components of these tumors may have adenomatous or squamous morphology and can misleadingly suggest a teratoma. However, unlike teratoma, ATRT is negative for germ-cell markers

(Packer et al. 2002). Similarly, small-cell components of ATRT may be suggestive of medulloblastoma or other embryonal tumors (Louis et al. 2007). Given these morphologic ambiguities, cytogenetic and molecular findings are required to establish the diagnosis of ATRT, and every effort should be made to obtain a formal consultation with a neuropathology specialist in suspected cases of ATRT.

Intraoperatively, ATRT is a soft, pinkish, bulky, circumscribed tumor, often with evidence of necrosis. Calcification, cysts, and hemorrhage are comparatively less common findings. Although ATRT can occur in either the supra- or infratentorial space, it appears similar to medulloblastoma on MRI with heterogeneous enhancement after gadolinium, hypointensity on T1-weighted images, and isointensity on T2-weighted sequences (Fig. 5.12).

Ninety percent of ATRT demonstrate chromosomal aberrations, most commonly monosomy or a deletion of chromosome 22 (Biegel et al. 1999; Burger et al. 1998). While chromosome 22 abnormalities are seen in many other tumors, it is believed that ATRTs are unified by homozygous deletions or mutations of the *hSNF5/INI1* gene that maps to chromosome 22q11.2 (Biegel et al. 1999). While its role in malignant transformation is unknown, *INI1* does appear to be a tumor-suppressor gene involved in rhabdoid tumors of the brain, as well as certain variants of Wilms' tumor of the kidney, and in neoplasms within other extraneural sites. A fraction of children have germline mutations of *INI1*, and in rare cases, these deleterious alleles are transmitted to progeny in an autosomal dominant fashion with incomplete penetrance (Biegel et al. 1999; Taylor et al. 2000). Recent mechanistic studies demonstrate that *SNF5* functions as a tumor suppressor through interaction with Gli1 and modulation of the Hh pathway (Jagani et al. 2010). While further preclinical and translational investigations are still required, these data reveal promising molecular targets for the treatment of ATRT.

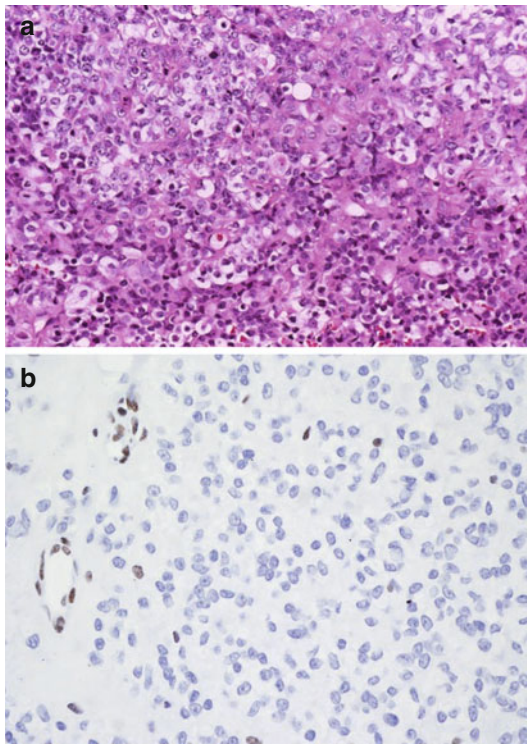

Fig. 5.11 Atypical teratoid/rhabdoid tumor. (**a**) Hematoxylin and eosin micrograph, with its disparate small embryonal cell and epithelial and mesenchymal cell components. (**b**) BAF47 immunostain showing lack of reactivity for the vast majority of tumor cells. There is some scattered positive reactivity adjacent to blood vessels which is not significant

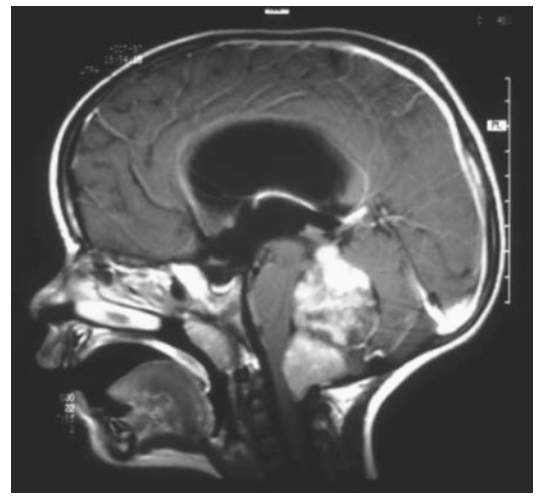

Fig. 5.12 T1-weighted post-contrast sagittal magnetic resonance image of a large posterior fossa ATRT in a 3-month-old boy presenting with a facial palsy

5.3.3 Treatment

Optimal therapy for ATRT is unknown, and median survival is less than 10 months (Biegel et al. 1999; Burger et al. 1998; Hilden et al. 2004; Olson et al. 1995). Staging studies similar to those in medulloblastoma are reasonable, although ATRT has not been reported to metastasize to bone. The incidence of neuraxis dissemination is uncertain, and reports range from 15 % to 40 % at diagnosis (Burger et al. 1998; Hilden et al. 1998; (Packer et al. 2002). There have been case reports of prolonged survival using high-dose chemotherapy with hematopoietic stem-cell rescue or multimodality treatment with CSI, multiagent chemotherapy, and triple intrathecal chemotherapy, similar to Intergroup Rhabdomyosarcoma Study III guidelines (Hilden et al. 1998; Olson et al. 1995). Other attempts using infant brain tumor chemotherapy regimens with cyclophosphamide, vincristine, cisplatin, and etoposide have led to tumor reduction, but responses do not appear to be sustained (Packer et al. 2002). Early incorporation of radiation therapy with intensive combination chemotherapy may be of benefit, when feasible (Chi et al. 2009).

5.4 Other Embryonal Tumors

5.4.1 Pineoblastoma

Pineoblastomas are WHO grade IV malignant tumors which account for approximately 45 % of pineal parenchymal tumors (Hirato and Nakazato 2001). Significantly more aggressive than either indolent pineocytomas, or recently described pineal parenchymal tumors of intermediately differentiation, pineoblastomas are characterized by retinoblastic differentiation in the form of Homer-Wright and Flexner-Wintersteiner rosettes. These tumors typically occur in the first two decades of life, are slightly more common in males, and like other embryonal tumors, have a tendency for neuraxial metastasis (Louis et al. 2007; Schild et al. 1996). In rare cases, pineoblastomas can occur with bilateral retinoblastoma, a condition termed "trilateral retinoblastoma" given the preponderance of melanocytes reminiscent of retinal architecture in the pineal gland (De Potter et al. 1994).

The mainstay of treatment for pineoblastomas is maximal safe surgical resection, followed by CSI and often chemotherapy, each of which correlates with improved survival in small patient series (Gilheeney et al. 2008). This approach leads to 1-, 3-, and 5-year overall survival rates of 88 %, 78 %, and 58 %, respectively, although some investigators have reported 5-year overall survival as low as 10 % (Fauchon et al. 2000; Schild et al. 1993). Limited prospective data suggest that CSI plus chemotherapy, such as vincristine, lomustine, and prednisone as in CCG 921, may improve long-term overall and progression-free survival in children older than 3 years to 73 % and 61 %, respectively (Jakacki et al. 1995). However, as is true for other embryonal tumors, chemotherapy alone is insufficient for managing these tumors, especially among infants, although high-dose systemic therapy with autologous stem-cell rescue may play a role (Duffner et al. 1995; Gururangan et al. 2003; Jakacki 1999; Jakacki et al. 1995). Notably, a residual enhancing mass may persist for as long as 5 years following definitive adjuvant treatment in some patients with pineoblastoma and is not indicative of treatment failure (Jakacki et al. 1995).

5.4.2 Other Non-pineal Embryonal Tumors

Outcomes in children with non-pineal supratentorial embryonal tumors have historically been worse than those for either pineoblastoma or medulloblastoma patients, with 3-year PFS of approximately 30 % (Cohen et al. 1995). The prospective study PNET-3 randomized 68 patients, 54 of which had non-pineal region tumors, to induction chemotherapy followed by radiation versus radiation alone, with both groups receiving chemotherapy after completion of radiation. In patients with non-pineal region tumors, 3- and 5-year EFS were both 41 %, whereas those with pineal region tumors had EFS of 93 % and 71 % after 3- and 5-years, respectively (Pizer et al. 2006).

Despite these disparities, non-pineal supratentorial embryonal tumors share several common prognostic features with other embryonal tumors. For instance, incomplete resection, tumor dissemination, and younger age are all associated with worse outcomes (Albright et al. 1995; Reddy et al. 2000). Following maximal safe surgical resection, radiotherapy for non-pineal supratentorial embryonal tumors is similar to that for other high-risk embryonal malignancies and consists of CSI to 36 Gy followed by an additional boost to the tumor bed of at least 54 Gy (Timmermann et al. 2002).

The extraordinarily small numbers of non-pineal embryonal tumors limit execution of trials aimed specifically at these entities. Additionally, their biologic characterization is incomplete. Analysis by comparative genomic hybridization shows that supratentorial PNET and medulloblastoma have distinctly different patterns of chromosomal gains and losses, suggesting different biologic entities (Russo et al. 1999). Nevertheless, the distinct natural history and comparably poorer prognosis of PNET merit experimental, innovative treatments different from those for medulloblastoma.

Conclusions

Pediatric embryonal malignancies are a heterogeneous group of tumors with distinct molecular characteristics that clinicians and scientists alike are beginning to understand. Although therapeutic advances in surgical technique, radiation dosimetry, and systemic chemotherapy have improved survival from medulloblastoma, each of these is associated with significant treatment-related toxicity and, in the case of adjuvant chemotherapy and radiation, secondary malignancies. In the recent past, improved understanding of pathologic and molecular features has allowed for identification of ATRT as a distinct tumor type and has facilitated better stratification of medulloblastoma. Ongoing investigation is required to determine if conventional adjuvant treatments for medulloblastoma can be modified according to molecular subtype and whether emerging biologic targets will lead to improved strategies. Similarly, further studies of oncogenic drivers in ATRT, pineoblastoma, and other embryonal tumors are necessary to better characterize these neoplasms and identify targets for molecular agents.

References

Albright AL, Wisoff JH, Zeltzer P, Boyett J, Rorke LB, Stanley P, Geyer JR, Milstein JM (1995) Prognostic factors in children with supratentorial (nonpineal) primitive neuroectodermal tumors. A neurosurgical perspective from the Children's Cancer Group. Pediatr Neurosurg 22:1–7

Al-Halabi H, Nantel A, Klekner A, Guiot M-C, Albrecht S, Hauser P, Garami M, Bognar L, Kavan P, Gerges N et al (2011) Preponderance of sonic hedgehog pathway activation characterizes adult medulloblastoma. Acta Neuropathol 121:229–239

Anastas JN, Moon RT (2013) WNT signalling pathways as therapeutic targets in cancer. Nat Rev Cancer 13:11–26

Archer TC, Weeraratne SD, Pomeroy SL (2012) Hedgehog-GLI pathway in medulloblastoma. J Clin Oncol 30:2154–2156

Ashley DM, Meier L, Kerby T, Zalduondo FM, Friedman HS, Gajjar A, Kun L, Duffner PK, Smith S, Longee D (1996) Response of recurrent medulloblastoma to low-dose oral etoposide. J Clin Oncol 14:1922–1927

Ashley D, Merchant T, Zhou T, Coleman L, Pollack I, Duffner P, Burger P, Miller D, Buxton A, Douglas S (2008) P9934: systemic chemotherapy, second-look surgery and conformal radiation therapy limited to the posterior fossa and primary site for children >8 months and. Neuro Oncol 10:436–437

Bailey CC, Gnekow A, Wellek S, Jones M, Round C, Brown J, Phillips A, Neidhardt MK (1995) Prospective randomised trial of chemotherapy given before radiotherapy in childhood medulloblastoma. International Society of Paediatric Oncology (SIOP) and the (German) Society of Paediatric Oncology (GPO): SIOP II. Med Pediatr Oncol 25:166–178

Batora NV, Sturm D, Jones DTW, Kool M, Pfister SM, Northcott PA (2014) Transitioning from genotypes to epigenotypes: why the time has come for medulloblastoma epigenomics. Neuroscience 264:171–185

Belza MG, Donaldson SS, Steinberg GK, Cox RS, Cogen PH (1991) Medulloblastoma: freedom from relapse longer than 8 years – a therapeutic cure? J Neurosurg 75:575–582

Berger MS, Baumeister B, Geyer JR, Milstein J, Kanev PM, LeRoux PD (1991) The risks of metastases from shunting in children with primary central nervous system tumors. J Neurosurg 74:872–877

Biegel JA (2006) Molecular genetics of atypical teratoid/rhabdoid tumor. Neurosurg Focus 20, E11

Biegel JA, Zhou JY, Rorke LB, Stenstrom C, Wainwright LM, Fogelgren B (1999) Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. Cancer Res 59:74–79

Bigner SH, Mark J, Friedman HS, Biegel JA, Bigner DD (1988) Structural chromosomal abnormalities in human medulloblastoma. Cancer Genet Cytogenet 30:91–101

Bouffet E, Bernard JL, Frappaz D, Gentet JC, Roche H, Tron P, Carrie C, Raybaud C, Joannard A, Lapras C et al (1992) M4 protocol for cerebellar medulloblastoma: supratentorial radiotherapy may not be avoided. Radiat Oncol Biol 24:79–85

Bourgouin PM, Tampieri D, Grahovac SZ, Léger C, Del Carpio R, Melançon D (1992) CT and MR imaging findings in adults with cerebellar medulloblastoma: comparison with findings in children. AJR Am J Roentgenol 159:609–612

Brown HG, Kepner JL, Perlman EJ, Friedman HS, Strother DR, Duffner PK, Kun LE, Goldthwaite PT, Burger PC (2000) "Large cell/anaplastic" medulloblastomas: a Pediatric Oncology Group Study. J Neuropathol Exp Neurol 59:857–865

Burger PC, Yu IT, Tihan T, Friedman HS, Strother DR, Kepner JL, Duffner PK, Kun LE, Perlman EJ (1998) Atypical teratoid/rhabdoid tumor of the central nervous system: a highly malignant tumor of infancy and childhood frequently mistaken for medulloblastoma: a Pediatric Oncology Group study. Am J Surg Pathol 22:1083–1092

Chang CH, Housepian EM, Herbert C (1969) An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. Radiology 93:1351–1359

Chi SN, Zimmerman MA, Yao X, Cohen KJ, Burger P, Biegel JA, Rorke-Adams LB, Fisher MJ, Janss A, Mazewski C et al (2009) Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. J Clin Oncol 27:385–389

Cho Y-J, Tsherniak A, Tamayo P, Santagata S, Ligon A, Greulich H, Berhoukim R, Amani V, Goumnerova L, Eberhart CG et al (2011) Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. J Clin Oncol 29:1424–1430

Cohen BH, Zeltzer PM, Boyett JM, Geyer JR, Allen JC, Finlay JL, McGuire-Cullen P, Milstein JM, Rorke LB, Stanley P et al (1995) Prognostic factors and treatment results for supratentorial primitive neuroectodermal tumors in children using radiation and chemotherapy: a Childrens Cancer Group randomized trial. J Clin Oncol 13:1687–1696

Corbit KC, Aanstad P, Singla V, Norman AR, Stainier DYR, Reiter JF (2005) Vertebrate smoothened functions at the primary cilium. Nature 437:1018–1021

Curran EK, Sainani KL, Le GM, Propp JM, Fisher PG (2009) Gender affects survival for medulloblastoma only in older children and adults: a study from the Surveillance Epidemiology and End Results Registry. Pediatr Blood Cancer 52:60–64

De Potter P, Shields CL, Shields JA (1994) Clinical variations of trilateral retinoblastoma: a report of 13 cases. J Pediatr Ophthalmol Strabismus 31:26–31

Deutsch M, Reigel DH (1980) The value of myelography in the management of childhood medulloblastoma. Cancer 45:2194–2197

Deutsch M, Thomas PR, Krischer J, Boyett JM, Albright L, Aronin P, Langston J, Allen JC, Packer RJ, Linggood R et al (1996) Results of a prospective randomized trial comparing standard dose neuraxis irradiation (3,600 cGy/20) with reduced neuraxis irradiation (2,340 cGy/13) in patients with low-stage medulloblastoma. A Combined Children's Cancer Group-Pediatric Oncology Group Study. Pediatr Neurosurg 24:167–176; discussion 176–7

Duffner PK, Horowitz ME, Krischer JP, Friedman HS, Burger PC, Cohen ME, Sanford RA, Mulhern RK, James HE, Freeman CR et al (1993) Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med 328:1725–1731

Duffner PK, Cohen ME, Sanford RA, Horowitz ME, Krischer JP, Burger PC, Friedman HS, Kun LE (1995) Lack of efficacy of postoperative chemotherapy and delayed radiation in very young children with pineoblastoma. Pediatric Oncology Group. Med Pediatr Oncol 25:38–44

Eberhart CG, Kepner JL, Goldthwaite PT, Kun LE, Duffner PK, Friedman HS, Strother DR, Burger PC (2002) Histopathologic grading of medulloblastomas: a Pediatric Oncology Group study. Cancer 94: 552–560

Eberhart CG, Kratz J, Wang Y, Summers K, Stearns D, Cohen K, Dang CV, Burger PC (2004) Histopathological and molecular prognostic markers in medulloblastoma: c-myc, N-myc, TrkC, and anaplasia. J Neuropathol Exp Neurol 63:441–449

Ellison DW, Onilude OE, Lindsey JC, Lusher ME, Weston CL, Taylor RE, Pearson AD, Clifford SC (2005) Beta-catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour Committee. J Clin Oncol 23:7951–7957

Evans AE, Jenkin RD, Sposto R, Ortega JA, Wilson CB, Wara W, Ertel IJ, Kramer S, Chang CH, Leikin SL et al (1990) The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. J Neurosurg 72:572–582

Fauchon F, Jouvet A, Paquis P, Saint-Pierre G, Mottolese C, Ben Hassel M, Chauveinc L, Sichez JP, Philippon J, Schlienger M et al (2000) Parenchymal pineal tumors: a clinicopathological study of 76 cases. Radiat Oncol Biol 46:959–968

Fine HA (2002) Polyomavirus and medulloblastoma: a smoking gun or guilt by association? J Natl Cancer Inst 94:240–241

Fowler M, Simpson DA (1962) A malignant melanin-forming tumour of the cerebellum. J Pathol Bacteriol 84:307–311

Freeman CR, Taylor RE, Kortmann RD, Carrie C (2002) Radiotherapy for medulloblastoma in children: a perspective on current international clinical research efforts. Med Pediatr Oncol 39:99–108

Gajjar AJ, Heideman RL, Douglass EC, Kun LE, Kovnar EH, Sanford RA, Fairclough DL, Ayers D, Look AT (1993) Relation of tumor-cell ploidy to survival in children with medulloblastoma. J Clin Oncol 11:2211–2217

Gajjar A, Fouladi M, Walter AW, Thompson SJ, Reardon DA, Merchant TE, Jenkins JJ, Liu A, Boyett JM, Kun LE et al (1999) Comparison of lumbar and shunt cerebrospinal fluid specimens for cytologic detection of leptomeningeal disease in pediatric patients with brain tumors. J Clin Oncol 17:1825–1828

Gajjar A, Hernan R, Kocak M, Fuller C, Lee Y, McKinnon PJ, Wallace D, Lau C, Chintagumpala M, Ashley DM et al (2004) Clinical, histopathologic, and molecular markers of prognosis: toward a new disease risk stratification system for medulloblastoma. J Clin Oncol 22:984–993

Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, Woo S, Wheeler G, Ahern V, Krasin MJ et al (2006) Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. Lancet Oncol 7:813–820

Gentet JC, Bouffet E, Doz F, Tron P, Roche H, Thyss A, Plantaz D, Stephan JL, Mottolese C, Ponvert D et al (1995) Preirradiation chemotherapy including "eight drugs in 1 day" regimen and high-dose methotrexate in childhood medulloblastoma: results of the M7 French Cooperative Study. J Neurosurg 82:608–614

Geyer JR, Sposto R, Jennings M, Boyett JM, Axtell RA, Breiger D, Broxson E, Donahue B, Finlay JL, Goldwein JW et al (2005) Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. J Clin Oncol 23:7621–7631

Giangaspero F, Rigobello L, Badiali M, Loda M, Andreini L, Basso G, Zorzi F, Montaldi A (1992) Large-cell medulloblastomas. A distinct variant with highly aggressive behavior. Am J Surg Pathol 16:687–693

Giangaspero F, Wellek S, Masuoka J, Gessi M, Kleihues P, Ohgaki H (2006) Stratification of medulloblastoma on the basis of histopathological grading. Acta Neuropathol 112:5–12

Gibson P, Tong Y, Robinson G, Thompson MC, Currle DS, Eden C, Kranenburg TA, Hogg T, Poppleton H, Martin J et al (2010) Subtypes of medulloblastoma have distinct developmental origins. Nature 468:1095–1099

Gilbertson R (2002) Paediatric embryonic brain tumours. Biological and clinical relevance of molecular genetic abnormalities. Eur J Cancer 38:675–685

Gilbertson R, Wickramasinghe C, Hernan R, Balaji V, Hunt D, Jones-Wallace D, Crolla J, Perry R, Lunec J, Pearson A et al (2001) Clinical and molecular stratification of disease risk in medulloblastoma. Br J Cancer 85:705–712

Gilheeney SW, Saad A, Chi S, Turner C, Ullrich NJ, Goumnerova L, Scott RM, Marcus K, Lehman L, De Girolami U et al (2008) Outcome of pediatric pineoblastoma after surgery, radiation and chemotherapy. J Neurooncol 89:89–95

Gorlin RJ, Goltz RW (1960) Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. N Engl J Med 262:908–912

Gorlin RJ, Vickers RA, Kellen E, Williamson JJ (1965) Multiple basal-cell nevi syndrome. An analysis of a syndrome consisting of multiple nevoid basal-cell carcinoma, Jaw cysts, skeletal anomalies, medulloblastoma, and hyporesponsiveness to parathormone. Cancer 18:89–104

Grill J, Sainte-Rose C, Jouvet A, Gentet JC, Lejars O, Frappaz D, Doz F, Rialland X, Pichon F, Bertozzi AI et al (2005) Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. Lancet Oncol 6:573–580

Grotzer MA, Janss AJ, Fung K, Biegel JA, Sutton LN, Rorke LB, Zhao H, Cnaan A, Phillips PC, Lee VM et al (2000) TrkC expression predicts good clinical outcome in primitive neuroectodermal brain tumors. J Clin Oncol 18:1027–1035

Grotzer MA, Geoerger B, Janss AJ, Zhao H, Rorke LB, Phillips PC (2001) Prognostic significance of Ki-67 (MIB-1) proliferation index in childhood primitive neuroectodermal tumors of the central nervous system. Med Pediatr Oncol 36:268–273

Gurney JG, Smith MA, Bunin GR (1999) CNS and miscellaneous intracranial and intraspinal neoplasms. In: Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds) Cancer incidence and survival among children and adolescents: United States SEER program 1975–1995. National Cancer Institute, SEER Program, Bethesda

Gururangan S, McLaughlin C, Quinn J, Rich J, Reardon D, Halperin EC, Herndon J, Fuchs H, George T, Provenzale J et al (2003) High-dose chemotherapy with autologous stem-cell rescue in children and adults with newly diagnosed pineoblastomas. J Clin Oncol 21:2187–2191

Halberg FE, Wara WM, Fippin LF, Edwards MS, Levin VA, Davis RL, Prados MB, Wilson CB (1991) Low-dose craniospinal radiation therapy for medulloblastoma. Radiat Oncol Biol 20:651–654

Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, Krush AJ, Berk T, Cohen Z, Tetu B et al (1995) The molecular basis of Turcot's syndrome. N Engl J Med 332:839–847

Hartsell WF, Gajjar A, Heideman RL, Langston JA, Sanford RA, Walter A, Jones D, Chen G, Kun LE (1997) Patterns of failure in children with medulloblastoma: effects of preirradiation chemotherapy. Radiat Oncol Biol 39:15–24

Haslam RH, Lamborn KR, Becker LE, Israel MA (1998) Tumor cell apoptosis present at diagnosis may predict treatment outcome for patients with medulloblastoma. J Pediatr Hematol Oncol 20:520–527

He X, Zhang L, Chen Y, Remke M, Shih D, Lu F, Wang H, Deng Y, Yu Y, Xia Y, et al (2014) The G protein L.,

Chen, Y., Remke, M., Shih, D., Lu, F., Wang, H., Deng, Y., Yu, Y., Xia, Y., et al. http://www.ncbi.nlm.nih.gov/pubmed/25150496

Hilden JM, Watterson J, Longee DC, Moertel CL, Dunn ME, Kurtzberg J, Scheithauer BW (1998) Central nervous system atypical teratoid tumor/rhabdoid tumor: response to intensive therapy and review of the literature. J Neurooncol 40:265–275

Hilden JM, Meerbaum S, Burger P, Finlay J, Janss A, Scheithauer BW, Walter AW, Rorke LB, Biegel JA (2004) Central nervous system atypical teratoid/rhabdoid tumor: results of therapy in children enrolled in a registry. J Clin Oncol 22:2877–2884

Hirato J, Nakazato Y (2001) Pathology of pineal region tumors. J Neurooncol 54:239–249

Honig PJ, Charney EB (1982) Children with brain tumor headaches. Distinguishing features. Am J Dis Child 136:121–124

Hovestadt V, Jones DTW, Picelli S, Wang W, Kool M, Northcott PA, Sultan M, Stachurski K, Ryzhova M, Warnatz H-J et al (2014) Decoding the regulatory landscape of medulloblastoma using DNA methylation sequencing. Nature 510:537–541

Jagani Z, Mora-Blanco EL, Sansam CG, McKenna ES, Wilson B, Chen D, Klekota J, Tamayo P, Nguyen PTL, Tolstorukov M et al (2010) Loss of the tumor suppressor Snf5 leads to aberrant activation of the Hedgehog-Gli pathway. Nat Med 16:1429–1433

Jakacki RI (1999) Pineal and nonpineal supratentorial primitive neuroectodermal tumors. Childs Nerv Syst 15:586–591

Jakacki RI, Zeltzer PM, Boyett JM, Albright AL, Allen JC, Geyer JR, Rorke LB, Stanley P, Stevens KR, Wisoff J et al (1995) Survival and prognostic factors following radiation and/or chemotherapy for primitive neuroectodermal tumors of the pineal region in infants and children: a report of the Childrens Cancer Group. J Clin Oncol 13:1377–1383

Kim JY, Sutton ME, Lu DJ, Cho TA, Goumnerova LC, Goritchenko L, Kaufman JR, Lam KK, Billet al, Tarbell NJ et al (1999) Activation of neurotrophin-3 receptor TrkC induces apoptosis in medulloblastomas. Cancer Res 59:711–719

Kleinman GM, Hochberg FH, Richardson EPJ (1981) Systemic metastases from medulloblastoma: report of two cases and review of the literature. Cancer 48:2296–2309

Kool M, Koster J, Bunt J, Hasselt NE, Lakeman A, van Sluis P, Troost D, Meeteren NS-V, Caron HN, Cloos J et al (2008) Integrated genomics identifies five medulloblastoma subtypes with distinct genetic profiles, pathway signatures and clinicopathological features. PLoS ONE 3:e3088

Kool M, Korshunov A, Remke M, Jones DTW, Schlanstein M, Northcott PA, Cho Y-J, Koster J, Schouten-van Meeteren A, van Vuurden D et al (2012) Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathol 123:473–484

Kool M, Jones DTW, Jäger N, Northcott PA, Pugh TJ, Hovestadt V, Piro RM, Esparza LA, Markant SL, Remke M et al (2014) Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. Cancer Cell 25:393–405

Kortmann RD, Kuhl J, Timmermann B, Mittler U, Urban C, Budach V, Richter E, Willich N, Flentje M, Berthold F et al (2000) Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91. Radiat Oncol Biol 46:269–279

Krischer JP, Ragab AH, Kun L, Kim TH, Laurent JP, Boyett JM, Cornell CJ, Link M, Luthy AR, Camitta B (1991) Nitrogen mustard, vincristine, procarbazine, and prednisone as adjuvant chemotherapy in the treatment of medulloblastoma. A Pediatric Oncology Group study. J Neurosurg 74:905–909

Kuhl J, Muller HL, Berthold F, Kortmann RD, Deinlein F, Maass E, Graf N, Gnekow A, Scheurlen W, Gobel U et al (1998) Preradiation chemotherapy of children and young adults with malignant brain tumors: results of the German pilot trial HIT"88/"89. Klin Padiatr 210:227–233

Leonard JR, Cai DX, Rivet DJ, Kaufman BA, Park TS, Levy BK, Perry A (2001) Large cell/anaplastic medulloblastomas and medullomyoblastomas: clinicopathological and genetic features. J Neurosurg 95:82–88

Levy RA, Blaivas M, Muraszko K, Robertson PL (1997) Desmoplastic medulloblastoma: MR findings. AJNR Am J Neuroradiol 18:1364–1366

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109

Mabbott DJ, Spiegler BJ, Greenberg ML, Rutka JT, Hyder DJ, Bouffet E (2005) Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. J Clin Oncol 23:2256–2263

Marinesco G, Goldstein M (1933) Sur une forme anatomique, non encore decrite, de medulloblastoma: medullomyoblastoma. Ann Anat Pathol 10:513–525

McManamy CS, Lamont JM, Taylor RE, Cole M, Pearson AD, Clifford SC, Ellison DW (2003) Morphophenotypic variation predicts clinical behavior in childhood non-desmoplastic medulloblastomas. J Neuropathol Exp Neurol 62:627–632

McManamy CS, Pears J, Weston CL, Hanzely Z, Ironside JW, Taylor RE, Grundy RG, Clifford SC, Ellison DW (2007) Nodule formation and desmoplasia in medulloblastomas-defining the nodular/desmoplastic variant and its biological behavior. Brain Pathol 17:151–164

McNeil DE, Coté TR, Clegg L, Rorke LB (2002) Incidence and trends in pediatric malignancies medulloblastoma/primitive neuroectodermal tumor: a SEER update. Surveillance epidemiology and end results. Med Pediatr Oncol 39:190–194

Merchant TE, Kun LE, Krasin MJ, Wallace D, Chintagumpala MM, Woo SY, Ashley DM, Sexton M, Kellie SJ, Ahern V et al (2008) Multi-institution prospective trial of reduced-dose craniospinal irradiation (23.4 Gy) followed by conformal posterior fossa (36 Gy) and primary site irradiation (55.8 Gy) and dose-intensive chemotherapy for average-risk medulloblastoma. Radiat Oncol Biol 70:782–787

Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X (2009) Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol 27:3691–3697

Minn AY, Pollock BH, Garzarella L, Dahl GV, Kun LE, Ducore JM, Shibata A, Kepner J, Fisher PG (2001) Surveillance neuroimaging to detect relapse in childhood brain tumors: a Pediatric Oncology Group study. J Clin Oncol 19:4135–4140

Morland BJ, Parkes SE (1995) Decline in incidence of medulloblastoma in children. Cancer 76:155–156

Mosijczuk AD, Nigro MA, Thomas PR, Burger PC, Krischer JP, Morantz RA, Kurdunowicz B, Mulne AF, Towbin RB, Freeman AI et al (1993) Preradiation chemotherapy in advanced medulloblastoma. A Pediatric Oncology Group pilot study. Cancer 72:2755–2762

Northcott PA, Hielscher T, Dubuc A, Mack S, Shih D, Remke M, Al-Halabi H, Albrecht S, Jabado N, Eberhart CG et al (2011a) Pediatric and adult sonic hedgehog medulloblastomas are clinically and molecularly distinct. Acta Neuropathol 122:231–240

Northcott PA, Korshunov A, Witt H, Hielscher T, Eberhart CG, Mack S, Bouffet E, Clifford SC, Hawkins CE, French P et al (2011b) Medulloblastoma comprises four distinct molecular variants. J Clin Oncol 29:1408–1414

Northcott PA, Jones DTW, Kool M, Robinson GW, Gilbertson RJ, Cho Y-J, Pomeroy SL, Korshunov A, Lichter P, Taylor MD et al (2012a) Medulloblastomics: the end of the beginning. Nat Rev Cancer 12:818–834

Northcott PA, Shih DJH, Peacock J, Garzia L, Morrissy AS, Zichner T, Stütz AM, Korshunov A, Reimand J, Schumacher SE et al (2012b) Subgroup-specific structural variation across 1,000 medulloblastoma genomes. Nature 488:49–56

Northcott PA, Lee C, Zichner T, Stütz AM, Erkek S, Kawauchi D, Shih DJH, Hovestadt V, Zapatka M, Sturm D et al (2014) Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. Nature 511:428–434

Nusse R, Varmus H (2012) Three decades of Wnts: a personal perspective on how a scientific field developed. Embo J 31:2670–2684

Olson TA, Bayar E, Kosnik E, Hamoudi AB, Klopfenstein KJ, Pieters RS, Ruymann FB (1995) Successful treatment of disseminated central nervous system malignant rhabdoid tumor. J Pediatr Hematol Oncol 17:71–75

Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y, Dowling J, Wolinsky Y, Kruchko C, Barnholtz-Sloan J (2014) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro-Oncology 16(Suppl 4):iv1–iv63

Packer RJ, Sutton LN, Elterman R, Lange B, Goldwein J, Nicholson HS, Mulne L, Boyett J, D'Angio G, Wechsler-Jentzsch K et al (1994) Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. J Neurosurg 81:690–698

Packer RJ, Goldwein J, Nicholson HS, Vezina LG, Allen JC, Ris MD, Muraszko K, Rorke LB, Wara WM, Cohen BH et al (1999) Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group Study. J Clin Oncol 17:2127–2136

Packer RJ, Biegel JA, Blaney S, Finlay J, Geyer JR, Heideman R, Hilden J, Janss AJ, Kun L, Vezina G et al (2002) Atypical teratoid/rhabdoid tumor of the central nervous system: report on workshop. J Pediatr Hematol Oncol 24:337–342

Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL, Bayer L, LaFond D, Donahue BR, Marymont MH et al (2006) Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 24:4202–4208

Packer R, Zhou T, Vezina G, Holmes E, Gajjar A (2008) Long-term event-free, overall survival, and second malignant neoplasms in children with medulloblastoma treated with radiotherapy and adjuvant chemotherapy: results of COG-A9961. Neuro Oncol 10:482

Palmer SL, Armstrong C, Onar-Thomas A, Wu S, Wallace D, Bonner MJ, Schreiber J, Swain M, Chapieski L, Mabbott D et al (2013) Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. J Clin Oncol 31:3494–3500

Patel S, Bhatnagar A, Wear C, Osiro S, Gabriel A, Kimball D, John A, Fields PJ, Tubbs RS, Loukas M (2014) Are pediatric brain tumors on the rise in the USA? Significant incidence and survival findings from the SEER database analysis. Childs Nerv Syst 30:147–154

Pearson AD, Craft AW, Ratcliffe JM, Birch JM, Morris-Jones P, Roberts DF (1982) Two families with the Li-Fraumeni cancer family syndrome. J Med Genet 19:362–365

Pelc K, Vincent S, Ruchoux MM, Kiss R, Pochet R, Sariban E, Decaestecker C, Heizmann CW (2002) Calbindin-d(28k): a marker of recurrence for medulloblastomas. Cancer 95:410–419

Perkins SM, Fei W, Mitra N, Shinohara ET (2013) Late causes of death in children treated for CNS malignancies. J Neurooncol 115:79–85

Peterson K, Walker RW (1995) Medulloblastoma/primitive neuroectodermal tumor in 45 adults. Neurology 45:440–442

Pietsch T, Waha A, Koch A, Kraus J, Albrecht S, Tonn J, Sorensen N, Berthold F, Henk B, Schmandt N et al (1997) Medulloblastomas of the desmoplastic variant

carry mutations of the human homologue of drosophila patched. Cancer Res 57:2085–2088
Pizer BL, Weston CL, Robinson KJ, Ellison DW, Ironside J, Saran F, Lashford LS, Tait D, Lucraft H, Walker DA et al (2006) Analysis of patients with supratentorial primitive neuro-ectodermal tumours entered into the SIOP/UKCCSG PNET 3 study. Eur J Cancer 42:1120–1128
Pomeroy SL, Tamayo P, Gaasenbeek M, Sturla LM, Angelo M, McLaughlin ME, Kim JY, Goumnerova LC, Black PM, Lau C et al (2002) Prediction of central nervous system embryonal tumour outcome based on gene expression. Nature 415:436–442
Poretti A, Meoded A, Huisman TAGM (2012) Neuroimaging of pediatric posterior fossa tumors including review of the literature. J Magn Reson Imaging 35:32–47
Prados MD, Warnick RE, Wara WM, Larson DA, Lamborn K, Wilson CB (1995) Medulloblastoma in adults. Radiat Oncol Biol 32:1145–1152
Pugh TJ, Weeraratne SD, Archer TC, Pomeranz Krummel DA, Auclair D, Bochicchio J, Carneiro MO, Carter SL, Cibulskis K, Erlich RL et al (2012) Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. Nature 488:106–110
Raffel C, Jenkins RB, Frederick L, Hebrink D, Alderete B, Fults DW, James CD (1997) Sporadic medulloblastomas contain PTCH mutations. Cancer Res 57:842–845
Rausch T, Jones DTW, Zapatka M, Stütz AM, Zichner T, Weischenfeldt J, Jäger N, Remke M, Shih D, Northcott PA et al (2012) Genome sequencing of pediatric medulloblastoma links catastrophic DNA rearrangements with TP53 mutations. Cell 148:59–71
Reddy AT, Janss AJ, Phillips PC, Weiss HL, Packer RJ (2000) Outcome for children with supratentorial primitive neuroectodermal tumors treated with surgery, radiation, and chemotherapy. Cancer 88:2189–2193
Roberts RO, Lynch CF, Jones MP, Hart MN (1991) Medulloblastoma: a population-based study of 532 cases. J Neuropathol Exp Neurol 50:134–144
Robinson G, Parker M, Kranenburg TA, Lu C, Chen X, Ding L, Phoenix TN, Hedlund E, Wei L, Zhu X et al (2012) Novel mutations target distinct subgroups of medulloblastoma. Nature 488:43–48
Rogers L, Pattisapu J, Smith RR, Parker P (1988) Medulloblastoma in association with the Coffin-Siris syndrome. Childs Nerv Syst 4:41–44
Rorke LB (1983) The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumors. J Neuropathol Exp Neurol 42:1–15
Rudin CM, Hann CL, Laterra J, Yauch RL, Callahan CA, Fu L, Holcomb T, Stinson J, Gould SE, Coleman B et al (2009) Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. N Engl J Med 361:1173–1178
Russo C, Pellarin M, Tingby O, Bollen AW, Lamborn KR, Mohapatra G, Collins VP, Feuerstein BG (1999) Comparative genomic hybridization in patients with supratentorial and infratentorial primitive neuroectodermal tumors. Cancer 86:331–339
Rutkowski S, Bode U, Deinlein F, Ottensmeier H, Warmuth-Metz M, Soerensen N, Graf N, Emser A, Pietsch T, Wolff JE et al (2005) Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med 352:978–986
Scheurlen WG, Schwabe GC, Joos S, Mollenhauer J, Sorensen N, Kuhl J (1998) Molecular analysis of childhood primitive neuroectodermal tumors defines markers associated with poor outcome. J Clin Oncol 16:2478–2485
Schild SE, Scheithauer BW, Schomberg PJ, Hook CC, Kelly PJ, Frick L, Robinow JS, Buskirk SJ (1993) Pineal parenchymal tumors. Clinical, pathologic, and therapeutic aspects. Cancer 72:870–880
Schild SE, Scheithauer BW, Haddock MG, Wong WW, Lyons MK, Marks LB, Norman MG, Burger PC (1996) Histologically confirmed pineal tumors and other germ cell tumors of the brain. Cancer 78:2564–2571
Shuster J, Hart Z, Stimson CW, Brough AJ, Poulik MD (1966) Ataxia telangiectasia with cerebellar tumor. Pediatrics 37:776–786
Smoll NR, Drummond KJ (2012) The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children. J Clin Neurosci 19:1541–1544
St Clair WH, Adams JA, Bues M, Fullerton BC, La Shell S, Kooy HM, Loeffler JS, Tarbell NJ (2004) Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys 58:727–734
Stone DM, Murone M, Luoh S, Ye W, Armanini MP, Gurney A, Phillips H, Brush J, Goddard A, de Sauvage FJ et al (1999) Characterization of the human suppressor of fused, a negative regulator of the zinc-finger transcription factor Gli. J Cell Sci 112(Pt 23):4437–4448
Tait DM, Thornton-Jones H, Bloom HJ, Lemerle J, Morris-Jones P (1990) Adjuvant chemotherapy for medulloblastoma: the first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). Eur J Cancer 26:464–469
Tarbell NJ, Friedman H, Kepner J, Barnes P, Burger P, Kun LE (2000) Outcome for children with high stage medulloblastoma: results of the pediatric oncology group 9031. Int J Radiat Oncol Biol Phys 48(Suppl 1):179
Taylor MD, Gokgoz N, Andrulis IL, Mainprize TG, Drake JM, Rutka JT (2000) Familial posterior fossa brain tumors of infancy secondary to germline mutation of the hSNF5 gene. Am J Hum Genet 66:1403–1406
Taylor RE, Bailey CC, Lucraft H, Robinson K, Weston C, Gilbertson R, Lashford LS (2001) Results of a randomised study of pre-radiation chemotherapy (carboplatin, vincristine, cyclophosphamide, etoposide) with radiotherapy alone in Chang stage M0/M1 medulloblastoma (SIOP/UKCCSG PNET-3) [abstract]. Med Pediatr Oncol 37:191
Taylor MD, Liu L, Raffel C, Hui C-C, Mainprize TG, Zhang X, Agatep R, Chiappa S, Gao L, Lowrance A et al (2002) Mutations in SUFU predispose to medulloblastoma. Nat Genet 31:306–310

Taylor RE, Bailey CC, Robinson KJ, Weston CL, Walker DA, Ellison D, Ironside J, Pizer BL, Lashford LS (2005) Outcome for patients with metastatic (M2-3) medulloblastoma treated with SIOP/UKCCSG PNET-3 chemotherapy. Eur J Cancer 41:727–734

Taylor MD, Northcott PA, Korshunov A, Remke M, Cho Y-J, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A et al (2012) Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 123:465–472

Tekautz TM, Fuller CE, Blaney S, Fouladi M, Broniscer A, Merchant TE, Krasin M, Dalton J, Hale G, Kun LE et al (2005) Atypical teratoid/rhabdoid tumors (ATRT): improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. J Clin Oncol 23:1491–1499

Thomas PR, Deutsch M, Kepner JL, Boyett JM, Krischer J, Aronin P, Albright L, Allen JC, Packer RJ, Linggood R et al (2000) Low-stage medulloblastoma: final analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. J Clin Oncol 18:3004–3011

Thompson MC, Fuller C, Hogg TL, Dalton J, Finkelstein D, Lau CC, Chintagumpala M, Adesina A, Ashley DM, Kellie SJ et al (2006) Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. J Clin Oncol 24:1924–1931

Thorne RN, Pearson AD, Nicoll JA, Coakham HB, Oakhill A, Mott MG, Foreman NK (1994) Decline in incidence of medulloblastoma in children. Cancer 74:3240–3244

Timmermann B, Kortmann RD, Kuhl J, Meisner C, Dieckmann K, Pietsch T, Bamberg M (2002) Role of radiotherapy in the treatment of supratentorial primitive neuroectodermal tumors in childhood: results of the prospective German brain tumor trials HIT 88/89 and 91. J Clin Oncol 20:842–849

Vasen HFA, Möslein G, Alonso A, Aretz S, Bernstein I, Bertario L, Blanco I, Bülow S, Burn J, Capella G et al (2008) Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 57:704–713

Weil MD, Lamborn K, Edwards MS, Wara WM (1998) Influence of a child's sex on medulloblastoma outcome. JAMA 279:1474–1476

Wetmore C, Eberhart DE, Curran T (2000) The normal patched allele is expressed in medulloblastomas from mice with heterozygous germ-line mutation of patched. Cancer Res 60:2239–2246

Wetmore C, Eberhart DE, Curran T (2001) Loss of p53 but not ARF accelerates medulloblastoma in mice heterozygous for patched. Cancer Res 61:513–516

Wolter M, Reifenberger J, Sommer C, Ruzicka T, Reifenberger G (1997) Mutations in the human homologue of the drosophila segment polarity gene patched (PTCH) in sporadic basal cell carcinomas of the skin and primitive neuroectodermal tumors of the central nervous system. Cancer Res 57:2581–2585

Xie J, Johnson RL, Zhang X, Bare JW, Waldman FM, Cogen PH, Menon AG, Warren RS, Chen LC, Scott MP et al (1997) Mutations of the PATCHED gene in several types of sporadic extracutaneous tumors. Cancer Res 57:2369–2372

Yauch RL, Dijkgraaf GJP, Alicke B, Januario T, Ahn CP, Holcomb T, Pujara K, Stinson J, Callahan CA, Tang T et al (2009) Smoothened mutation confers resistance to a hedgehog pathway inhibitor in medulloblastoma. Science 326:572–574

Zeltzer PM, Boyett JM, Finlay JL, Albright AL, Rorke LB, Milstein JM, Allen JC, Stevens KR, Stanley P, Li H et al (1999) Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. J Clin Oncol 17:832–845

Zurawel RH, Chiappa SA, Allen C, Raffel C (1998) Sporadic medulloblastomas contain oncogenic beta-catenin mutations. Cancer Res 58:896–899

Intracranial Germ Cell Tumors

6

Steve Braunstein, Sean M. McBride,
and Daphne A. Haas-Kogan

Contents

S. Braunstein, MD, PhD (✉)
Department of Radiation Oncology, University of California San Francisco, 1825 4th St, Suite M2267, San Francisco, CA 94143, USA
e-mail: steve.braunstein@ucsf.edu

S.M. McBride, MD, MDH
Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA
e-mail: mcbrides@mskcc.org

D.A. Haas-Kogan, MD
Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, & Boston Children's Hospital, 450 Brookline Ave, Boston, MA D1622, USA
e-mail: dhaas-kogan@lroc.harvard.edu

6.1 Introduction

Intracranial germ cell tumors (GCTs) are a group of relatively uncommon tumors, comprising less than 1 % of all central nervous system (CNS) tumors, that have histological, genetic, biochemical, diagnostic, and therapeutic similarities to GCTs that occur outside the CNS (Ostrom et al. 2014). They share extraembryonic origins in the fetal yolk sac that account for their numerous similarities, while subsequent migratory paths in early fetal development are responsible for differences in location. There are two distinct histological groups within the larger group of intracranial GCTs: germinomas and nongerminomatous GCTs (NGGCTs). Germinomas are more common, accounting for 50–75 % of the total number of intracranial GCT (Al-Hussaini et al. 2009; Jooma and Kendall 1983; Oi and Matsumoto 1992). NGGCTs represent one third

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_6

Table 6.1 Classification of GCTs according to benign vs malignant tumors

Benign germ cell tumors	Malignant germ cell tumors
Immature teratoma[a]	Germinoma
Mature teratoma	Embryonal carcinoma
	Endodermal sinus tumor (yolk sac tumor)
	Choriocarcinoma
	Mixed germ cell tumor
	Teratoma with malignant transformation

[a]May indicate rare malignant germ cell elements

of intracranial GCTs and consist of embryonal carcinoma, endodermal sinus (yolk sac) tumor, choriocarcinoma, teratoma, and GCTs of mixed cellular origin. Jennings et al. found that germinomas accounted for 65% of intracranial GCTs, followed by teratomas (18%), endodermal sinus tumors (7%), embryonal carcinomas (5%), and choriocarcinomas (5%) (Jennings et al. 1985b). Other studies show a higher incidence of mixed tumors ranging from 21% to 32% (Matsutani et al. 1997; Salzman et al. 1997). As classified by the WHO, although most of these tumors are malignant, some are defined as benign (Table 6.1) (Louis et al. 2007).

Intracranial GCTs most commonly arise from the pineal or suprasellar region – deep locations that have reduced the likelihood of gross total resection. For this reason, radiation alone, frequently encompassing a large treatment volume, was considered the preferred treatment standard. Over the last several decades, effective chemotherapy in combination with improved neurosurgical procedures and radiation techniques has resulted in dramatic improvements in survival. However, in children, the morbidity caused by radiation therapy, particularly with craniospinal irradiation (CSI), has led to de-escalation in volume and dose of radiotherapy while preserving high cure rates for patients with only focal disease (Shirato et al. 1997; Choi et al. 1998; Matsutani et al. 1998; Aoyama et al. 2002; Jensen et al. 2010).

In this chapter, we review the epidemiology of intracranial GCTs, the pathologic features of both benign and malignant GCTs, and their molecular and cytogenetic characteristics. We discuss the clinical features of intracranial GCTs and the role of imaging and laboratory investigations in diagnosis. In broaching the controversy surrounding diagnostic biopsy, we delineate the arguments for and against mandatory biopsy prior to treatment. We review recent changes in practice with de-escalation in radiotherapy and chemotherapy treatment approaches. Lastly, we discuss risk stratification to intensify treatment in patients with intracranial GCTs that have a poor prognosis.

6.2 Epidemiology

6.2.1 Location

Intracranial GCTs account for less than 4% of pediatric brain tumors in North America, although slightly more common in Japan with an incidence of greater than 10% among pediatric brain tumors. Most intracranial GCTs originate near the third ventricle, extending from the suprasellar cistern to the pineal gland. Pineal region GCTs outnumber those in the suprasellar region by a ratio of 2:1, but in 5–10% of cases, the tumor is found in both regions (Jennings et al. 1985b). Whether this is due to synchronous bifocal disease or metastatic tumor, the spread remains unknown. Intracranial GCTs occur less commonly in other midline locations such as basal ganglia, thalamus, and ventricles, particularly the fourth ventricle. Intracranial GCTs have also been reported in the cerebellum (Nakase et al. 1994), brainstem (Nakajima et al. 2000; Madden et al. 2009; Hao et al. 2013), and optic nerves (Iizuka et al. 1996). By GCT subtype, germinomas are more frequent in the suprasellar region and in females, while NGGCTs are more common in the pineal region and in males.

6.2.2 Age, Sex, and Geographic Variation

In Western countries, intracranial GCTs account for 0.4–3.4% of all intracranial tumors, whereas in Japan and Taiwan, intracranial GCTs are more

common and account for 2.1–11.1 % of brain tumors (Jellinger 1973; Jennings et al. 1985b; Hoffman et al. 1991; Lin et al. 1997). This phenomenon is also seen in testicular GCTs for which the incidence in Japan is far greater than that seen in the United States (Packer et al. 2000). Most intracranial GCTs occur in adolescents and young adults (80–90 %), with peak incidence occurring at 10–14 years of age. However, these lesions can be seen in newborns as well as in older adults. In particular, NGGCTs preferentially arise in younger children, whereas germinomas are most common in teenagers (Jennings et al. 1985b; Rosenblum et al. 2007).

Intracranial GCTs are not distributed equally by gender. In the United States, between 1986 and 1995, incidence rates were 2.3 per million for males and 0.9 per million for females, representing a male predominance of 2.5:1. When examined by histology, NGGCTs demonstrate a male/female ratio of 3.2:1, while germinomas reveal a male:female ratio of only 1.8:1 (Jennings et al. 1985b). In females, 75 % of intracranial GCTs develop in the suprasellar region, whereas in males 70 % are found in the pineal area. The reason for these gender differences is unclear. Between the 1970s and the 1990s, the incidence of intracranial GCTs increased in the United States from 0.6 per million between 1975 and 1979 to 1.9 per million between 1990 and 1995 (Bernstein et al. 1999).

6.3 Pathology

6.3.1 Etiology

GCTs can be divided into extragonadal tumors and gonadal tumors, the latter encompassing half of all such tumors. Among extragonadal sites, half are sacrococcygeal and 40 % arise intracranially. Rare sites of extragonadal GCTs include midline regions such as the retroperitoneal and nasopharynx. Their sites of origin notwithstanding the features of GCTs, whether by light microscopy, electron microscopy, or enzyme or immunohistochemical assays, are identical (Jennings et al. 1985b; Felix and Becker 1990).

The pathogenesis of intracranial GCTs remains elusive. Although gonadotropins have been implicated in the pathogenesis of gonadal GCTs, such evidence for intracranial GCTs is lacking. One hypothesis is that GCTs arise most commonly near centers of gonadotropin regulation because such regions serve as sanctuary sites for undifferentiated germ cells (Jennings et al. 1985b). An additional role for the pineal gland in the neuroendocrine regulation of neoplastic growth has also been suggested (Lapin and Ebels 1981).

The etiology of intracranial GCTs is thought to be mismigration of primordial germ cells during embryonic development, followed by malignant transformation. According to the "germ cell theory," primordial germ cells normally develop from the extraembryonic yolk sac endoderm and migrate to the gonadal folds. Germinomas as well as embryonal carcinomas can develop by further differentiation and malignant transformation of the original primordial germ cells. Embryonal carcinomas are composed of pluripotent cells that develop into endodermal sinus tumors, choriocarcinomas, or teratomas depending on the developmental pathway the cells undertake (Teilum 1976). Others have suggested that primordial germ cells can differentiate to yield either embryonal carcinomas or teratomas by differentiation through embryonic pathways or endodermal sinus tumors or choriocarcinomas by extraembryonic pathways (Takei and Pearl 1981).

The "germ cell theory" is supported by the fact that interaction of the c-kit receptor with its ligand, steel factor (SLF), mediates the migration of primordial germ cells. Lack of c-kit in animal models prevents germ cell migration. The gradient of SLF found from the yolk sac to the gonadal ridge is thought to guide the migration of primordial germ cells, and extragonadal GCTs are thought to arise from such mismigration. The proto-oncogene *c-kit* encodes a cell-surface receptor that carries an intrinsic tyrosine kinase activity in its cytoplasmic portion. The interaction of Kit with SLF leads to receptor dimerization, kinase activation, and tyrosine phosphorylation of specific cytoplasmic proteins. Mutations in

Kit and SLF that result in a defective signaling pathway leading to infertility have been identified (Loveland and Schlatt 1997; Cushing et al. 2002).

An alternative theory, the "embryonic cell theory," suggests that a pluripotent embryonic cell escapes normal developmental signals and gives rise to GCTs. This theory may be supported by the finding of altered Wnt pathway signaling components including distinct expression levels of E-cadherin and beta-catenin in various GCTs (Honecker et al. 2004; Snow et al. 2009). A third hypothesis contends that germinoma is the only neoplasm arising from germ cells, and other GCTs arise from misfolding and misplacement of embryonic cells into the lateral mesoderm early in embryogenesis, leading to the entrapment of these cells into a variety of different brain regions (Sano et al. 1989). And finally, a more recent hypothesis argues that neural stem cells, because of their pluripotent potential in vitro, may be the initiating cell for intracranial germ cell lesions (Hoei-Hansen et al. 2006; Tan and Scotting 2013).

6.3.2 Classification

The current World Health Organization (WHO) classification of GCTs is based on histology and tumor markers such as alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-HCG) that have become important in diagnosis as well as prognosis (Louis et al. 2007). As mentioned above, different GCTs may represent the malignant forms of distinct stages of normal embryonic development. For example, primordial germ cells result in germinomas, embryonic differentiation gives rise to teratomas and embryonal carcinomas, and extraembryonic derivatives of the yolk sac and trophoblast give rise to endodermal sinus tumors and choriocarcinomas, respectively. Intracranial GCTs can also be classified based on tumor markers found in serum or cerebrospinal fluid (CSF), which can influence diagnoses and prognoses of patients with intracranial GCTs. Typically, germinomas are nonsecreting tumors, whereas NGGCTs usually secrete AFP and/or β-HCG. Germinomas are associated with better prognoses than NGGCTs.

6.3.3 Histopathology

Intracranial germinomas are histologically identical to dysgerminomas of the ovary and seminomas of the testis (Beeley et al. 1973). Microscopically, they are large monomorphic cells with abundant clear cytoplasm, arranged in nests separated by bands of connective tissue. The differential diagnosis includes lymphoma and endodermal sinus tumor. Germinomas can be identified by either positive placental alkaline phosphatase (PLAP) staining or positive OCT4 staining, with the latter being increasingly adopted as superior, whereas endodermal sinus tumors stain positive for AFP (Hattab et al. 2005).

Among NGGCTs, teratomas are designated as mature or immature, based on the absence or presence of differentiated tissues. Mature teratomas contain mature tissues from all three embryonic layers (ectoderm, mesoderm, and endoderm). Immature teratomas are distinguished from mature teratomas by the presence of immature tissues, usually neuroepithelium. Embryonal carcinomas arise from pluripotent embryonic cells and are characterized by large cells with large nuclei and nucleoli with varying amounts of central necrosis. Embryonal carcinomas can produce both AFP and β-HCG. Unlike other GCTs, CD30 (Ki-1 antigen) immunohistochemical staining is positive in embryonal carcinomas. Endodermal sinus tumors arise from differentiated extraembryonic tissue, which usually occur as part of mixed GCTs, and produce AFP. Choriocarcinomas arise from placental trophoblastic tissue, which also generally occur as part of mixed GCTs, and are characterized by the presence of syncytiotrophoblasts that secrete β-HCG (Felix and Becker 1990; Hawkins 1990; Cushing et al. 2002).

6.3.4 Molecular Biology and Cytogenetics

Multiple complex karyotypes have been reported for intracranial GCTs including loss of chromosomes 4, 9p, 11, 13, and 17p as well as gain of chromosomes 8q, 21, and 1q. In addition, whereas isochromosome 12p seems to be important in the

development of testicular tumors, its role in intracranial germ cell tumors is unclear. Multiple early studies observed low incidence in extragonadal tumors (de Bruin et al. 1994; Yu et al. 1995; Lemos et al. 1998), but isochromosome 12p has been found at more modest levels of 25% in a more recent series (Sukov et al. 2010 A study of comparative genomic hybridization to analyze pineal region GCTs reported various abnormalities including gains on 12p (40%), 8q (27%), and 1q (20%), as well as losses on 13q (47%), 18q (33%), 9q, and 11q (20% each). The authors also noted different cytogenetic abnormalities based on histology. For example, the most common chromosomal changes in germinomas were −13q and −18q (38% each), whereas in mixed teratomas, germinomas frequent abnormalities included +8q (100%), +12p (75%), −13q (75%), and −9q (50%) (Rickert et al. 2000). A recent series confirmed high-frequency (46%) 12p polysomy (Sukov et al. 2010). Okada et al. examined 25 intracranial GCTs and found an increased number of X chromosomes in 23/25 cases and noted hypomethylation of the additional X chromosome in 81% of the tumors. Only 20% of cases had increased copy number of 12p and 12% had loss of 13q. They concluded that along with the increased incidence of intracranial GCTs in males as well as predisposition in patients with Klinefelter syndrome, sex chromosome aberrations might have an important role in the development of GCTs (Okada et al. 2002).

In addition to cytogenetic changes, some of the genes that may be important in the development of GCTs have been defined. Alterations in the *mdm-2* gene, often amplified in sarcomas, have been implicated in tumorigenesis of some testicular and intracranial GCTs. The *mdm-2* is a negative regulator of the p53 tumor suppressor gene product and is, in turn, induced by p53. Iwato et al. searched for p53 mutations and *mdm-2* amplifications in intracranial GCTs and found *mdm-2* amplifications in 19% of intracranial GCTs. Theoretically, increases in *mdm-2* protein level would antagonize p53 function (Iwato et al. 2000b).

Iwato et al. examined the *INK4a/ARF* locus for alterations in intracranial GCTs and found alterations in 71% of 21 tumors. The *INK4a/ARF* genes are tumor suppressor genes, and the INK4a protein inhibits cyclin-dependent kinases and decreases phosphorylation of the retinoblastoma protein, resulting in cell cycle arrest. The ARF protein interacts with *mdm-2* and stimulates the latter's degradation. Interestingly, alterations in *INK4a/ARF* were more common in germinomas (90%) than in NGGCTs (55%) (Iwato et al. 2000a).

A recent next-generation sequencing analysis of 62 intracranial GCT demonstrated frequent (53%) novel somatic mutations in the KIT/RAS signaling pathway including KIT, KRAS, NRAS, CBL, and AKT1 (Wang et al. 2014). KIT mutations and overexpression were principally observed in germinomas, predominantly clustered in exons 17 and 11. Copy number gains were noted in AKT1 at 14q32.33 in 19% of patients, the majority of which had wild-type KIT, KRAS, and NRAS. Loss-of-function mutations and loss of heterozygosity were noted in the tumor suppressors BCORL1 and CBL, respectively.

6.4 Clinical Features: Signs and Symptoms

Presenting symptoms of pineal region tumors are directly related to tumor location. Pineal region tumors usually present with symptoms of eye-movement disorders or symptoms caused by increased intracranial pressure due to obstructive hydrocephalus. Headache, nausea, and vomiting are the most common symptoms, seen in 56–93% of patients. Blurred vision and somnolence are seen in 20–54% of patients, while ataxia, seizures, and behavioral disturbances are seen in 10–28% of patients (Saitoh et al. 1991; Drummond and Rosenfeld 1999; Steinbok and Cochrane 2001). Involvement of adjacent midbrain structures can result in visual disturbances, such as Parinaud's syndrome, which are seen in 25–50% of pineal region GCTs. Parinaud's syndrome is an impairment of upward gaze in combination with dilated pupils that are nonreactive to light (pseudo-Argyll Robertson pupils), but responsive to accommodation. Upward gaze may in addition elicit rhythmic convergence of the eyes followed by retraction

nystagmus of the eyes into the orbits. Eyelid retraction and conjugate downward gaze in the primary position (sun-setting sign) may be observed (Jennings et al. 1985b).

On examination, papilledema is present in about half of the patients. In patients with pineal region GCTs, approximately 80% present with symptoms of increased intracranial pressure, whereas less than 10% of patients with suprasellar GCTs present with increased intracranial pressure. Endocrinopathies such as diabetes insipidus or precocious puberty occur in patients with intracranial GCTs and account for approximately 6–12% of presenting symptoms. In fact, patients with suprasellar GCTs most commonly present with endocrinopathies such as diabetes insipidus and manifestations of anterior pituitary dysfunction such as growth failure. These symptoms were seen in 87% of patients versus only 8% of patients with pineal region GCT (Jooma and Kendall 1983; Edwards et al. 1988; Hoffman et al. 1991; Saitoh et al. 1991; Kang et al. 1998; Steinbok and Cochrane 2001). Intracranial GCTs may infiltrate adjacent structures such as the hypothalamus (11%) and third ventricle (22%) or disseminate throughout the CSF (10%). For endodermal sinus tumors and choriocarcinomas, dissemination is more common, and third ventricular involvement is present in over 40% of cases. Extracranial spread to the lungs and bones has also been reported in approximately 3% of patients (Gay et al. 1985; Jennings et al. 1985a, b).

6.5 Diagnosis and Staging

Operative morbidity and mortality prior to the 1980s were high and impeded histological diagnoses of many intracranial GCTs. Therefore, radiodiagnostic trials of 20 Gy historically functioned as surrogates for a histological diagnosis of germinoma, since these tumors were characteristically radioresponsive. Poor response to 20 Gy indicated an alternate diagnosis such as NGGCT or glioma. A robust response to 20 Gy suggested a diagnosis of germinoma, and treatment was continued to 50 Gy for definitive treatment. In light of the advances in neurosurgical techniques as well as the ability to differentially treat with chemotherapy, surgical biopsy in the modern era is generally much safer and usually recommended prior to treatment. However, some controversy remains whether biopsy is indicated for these tumors, and this decision determines the management plan.

Regardless of the ultimate histology, all GCTs are staged in a similar manner using magnetic resonance imaging (MRI) scans of the brain and spine in addition to CSF examination. Local lesions are categorized as M0. M1 disease is defined by microscopic dissemination in the CSF, while M2/M3 disease shows disseminated macroscopic lesions in the spinal region or cranial subarachnoid space visible on imaging.

6.5.1 Laboratory Investigations

AFP is normally expressed during embryonic development. It is the earliest serum-binding protein in the fetus, which reaches peak concentration at 12–14 weeks of gestation and then gradually falls to reach adult levels of 10 ng/dL at 1–2 years of age. As AFP levels decline during fetal development, albumin becomes the predominant binding protein. The presence of AFP (>25 ng/mL) indicates that there are malignant components in the tumor consisting of yolk sac elements or embryonal carcinoma. The half-life of AFP is 5–7 days and is a useful marker to follow, with one caveat: due to the variable rates of AFP levels in infants, AFP levels are less informative in this very young age group. Of note is the phenomenon of increasing AFP levels due to chemotherapy-induced tumor lysis and not necessarily due to disease progression. β-HCG is produced by syncytiotrophoblasts during pregnancy to maintain the corpus luteum, and minute amounts are found in normal adults. Pathologic elevations of β-HCG (>50 IU/L) are found when there is a clonal disorder of syncytiotrophoblasts, such as in choriocarcinoma, or when syncytiotrophoblastic giant cells are found in germinomas or embryonal carcinomas. Therefore, when an elevation of one of these tumor markers is present, it is highly suggestive of GCT.

Table 6.2 GCTs according to tumor markers

Tumor type	AFP	β-HCG	PLAP	OCT4	SALL4
Mature teratoma	–	–	–	±	±
Immature teratoma	±	±	–	±	±
Pure germinoma	–	–	+	+	+
Endodermal sinus tumor	+	–	–	–	+
Choriocarcinoma	–	+	–	–	±
Embryonal carcinoma	+	+	–	±	+
Mixed germ cell tumor	±	±	±	±	+

Embryonal carcinomas secrete both AFP and β-HCG, while endodermal sinus tumors secrete only AFP, and choriocarcinomas secrete only β-HCG. However, in as many as 30 % of GCTs, more than one histological subtype is found (Matsutani et al. 1997). The most useful laboratory values for the diagnosis of GCTs are elevations of AFP and/or β-HCG in serum or CSF. It is important to sample both serum and CSF, as serum levels can be normal in the presence of elevated CSF levels and vice versa. If present, the protein levels can serve as useful tumor markers since they decrease as tumor burden decreases. GCTs that have elevations of these tumor markers show worse prognosis when matched with patients with identical histological diagnoses, but normal marker levels (Itoyama et al. 1995; Nishizaki et al. 2001). AFP can be used as a tumor marker in endodermal sinus tumors, and β-HCG is useful in choriocarcinoma.

Another helpful tumor marker is PLAP, which is a fetal isoenzyme of alkaline phosphatase, and is almost always elevated in germinomas (Cushing et al. 2002). Therefore, one controversial option in patients with elevated PLAP, but normal β-HCG and AFP, would be to assume the diagnosis is germinoma and treat accordingly (Steinbok 2001) (Table 6.2). However, PLAP is not readily available as a test in many institutions, and such empiric diagnoses are extraordinarily rare. Another marker for germinoma that has been employed is c-kit (CD117), and its soluble isoform, s-kit. Elevations of s-kit were found in the CSF of patients with germinoma and mixed GCT and may correlate with patients' clinical courses. Moreover, the level of s-kit was remarkably higher in patients with tumor dissemination, such that s-kit has been a useful tumor marker (Miyanohara et al. 2002; Kamakura et al. 2006). In addition, immunohistochemical staining for OCT4, an 18-kDa POU-domain transcription factor encoded by the POU5F1 gene, has been shown to be a highly specific and sensitive test for germinomas, preferred over PLAP (Hattab et al. 2005). Recently, the novel stem-cell marker SALL4, a zinc-finger transcription factor upstream of OCT4, has been shown a highly sensitive and specific diagnostic marker for intracranial GCT expressed in germinomas, yolk sac tumors, and embryonal carcinomas (Mei et al. 2009). Glypican 3 (GPC3) immunostaining may also have diagnostic utility for detection of yolk sac tumors (Zynger et al. 2008).

6.5.2 Diagnostic Imaging

Like other brain tumors, computed tomography (CT) and MRI are the most common modalities used to diagnose intracranial GCTs. Of historic interest only, pineal region tumors can be detected on plain skull films by the presence of calcifications. MRI is the study of choice, although CT has an advantage over MRI in identifying calcifications. The identification of calcification in the pineal gland in a child younger than 6 years old is an indication for an MRI, even when no mass is apparent on CT (Zimmerman and Bilaniuk 1982; Steinbok 2001).

Findings on CT or MRI are almost never sufficient for the diagnosis of GCTs (Awa et al. 2014). Germinomas are usually diffusely enhancing on CT and MRI, whereas NGGCTs are more likely to be heterogeneous in part due

to hemorrhage. A tumor in the suprasellar region in association with a pineal tumor is usually a GCT, most likely a germinoma (Fig. 6.1). Larger germinomas can have a heterogeneous appearance and fill the third ventricle (Fig. 6.2). A bifocal location is not guaranteed to be a germinoma as GCTs with mixed elements can also appear in two locations (Fig. 6.3). A recent or old hemorrhage seen in the tumor suggests an NGGCT, particularly common with choriocarcinoma (Fig. 6.4). Intracranial teratomas tend to be well circumscribed and have large cysts and calcifications within the tumor, which can be helpful in distinguishing them from germinomas (Fig. 6.5). Immature teratomas tend to have fewer cysts and calcifications and may secrete tumor markers (Fujimaki et al. 1994).

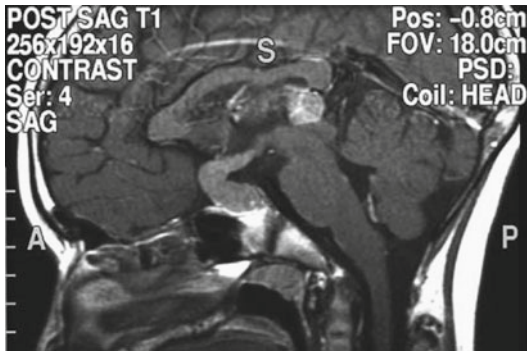

Fig. 6.1 A sagittal T1-weighted MR image following contrast administration shows an anterior third ventricle mass and a pineal region mass that both enhance relative to the normal brain. After biopsy, this tumor was diagnosed as a germinoma

Molecular imaging approaches including positron emission tomography (PET) have been evaluated with initial reports of (11)C-methionine demonstrating greater diagnostic and treatment planning utility over (18)F-fluorodeoxyglucose (Okochi et al. 2014); however, PET approaches are not currently widely employed in diagnosis of intracranial GCT.

In addition to GCT, the differential diagnosis of a pineal lesion includes pineoblastoma, trilateral retinoblastoma in a patient with bilateral retinoblastoma, pineocytoma, glioma, meningioma, lymphoma, or a benign lesion such as a cyst. Benign cysts can generally be distinguished from malignant cystic neoplasms by the lack of enhancement or a very thin rim of enhancement surrounding a hypointense center (Steinbok 2001).

6.5.3 Obtaining Tissue Diagnosis

There is geographic variation in management strategies. In 1992, Oi and Matsumoto noted that the majority (84 %) of Japanese neurosurgeons were comfortable using a radiodiagnostic trial of 20 Gy in lieu of histological confirmation of a

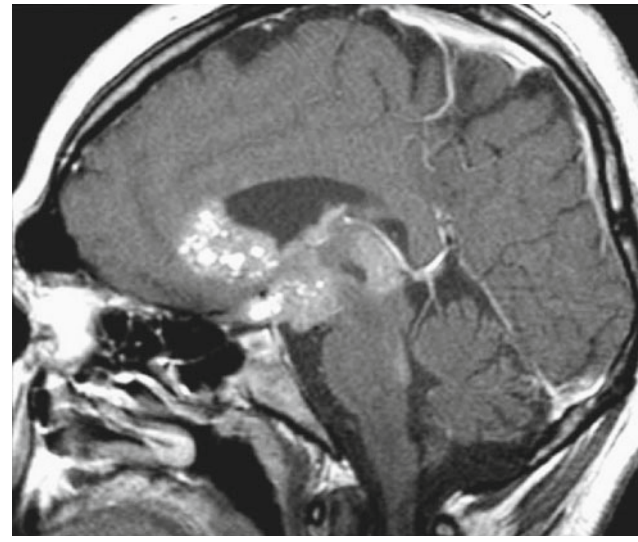

Fig. 6.2 A sagittal T2-weighted image shows an extensive heterogeneous suprasellar germinoma with multiple cysts. The tumor fills the anterior portion of the third ventricle and extends posteriorly into the pineal region

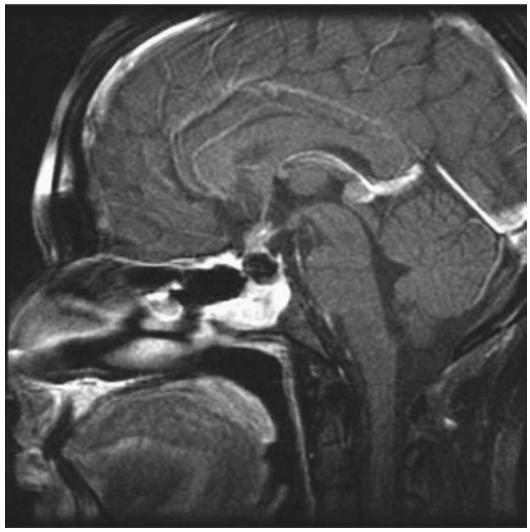

Fig. 6.3 A sagittal T1-weighted image following contrast shows an unusual case of a mixed germ cell tumor containing both germinoma and teratoma located in the suprasellar, sellar, and pineal regions. The sellar component was biopsied through a transsphenoidal approach. The area of low signal intensity within the sella represents a fat patch to prevent postoperative CSF leak

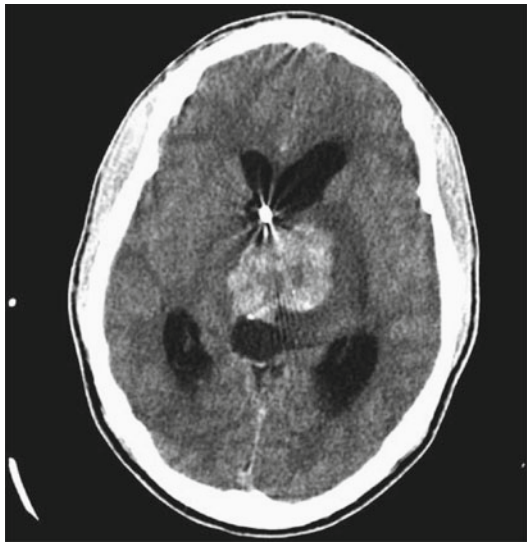

Fig. 6.4 An axial CT image from a teenage boy who presented with headaches and a change in his mental status. A large partially hemorrhagic tumor is seen extending into the lateral ventricles. An endoscopic biopsy was consistent with choriocarcinoma. β-HCG as measured in the CSF was 88,767 IU/L (normal: <1.5). Hydrocephalus is present, and an external ventricular catheter has been inserted into the anterior portion of the ventricle

germinoma. In contrast, the majority (78 %) in Western countries recommended histological diagnosis as the initial management of pineal region tumors. This discrepancy may be due to the fact that pineal region tumors are much more common in Japan, and the incidence of germinomas in particular is higher (Oi and Matsumoto 1992). A follow-up study showed that by 1998, radical resection of the tumor was recommended as the initial procedure by only 22 % of Japanese neurosurgeons, while 39 % recommended biopsy, and 39 % recommended radiation therapy. The authors suggested tissue diagnosis by ventriculoscopic or stereotactic approach as the most appropriate initial step for the treatment planning of pineal region tumors (Oi et al. 1998).

Because histology influences the choice of treatment and is coincident with improved surgical techniques, the need for obtaining tumor histology is now recognized (Aydin et al. 1992; Sawamura et al. 1997). Although a definitive conclusion cannot be reached, a prudent strategy would be to utilize a safe and minimally invasive technique to obtain tissue for histological analysis. Such techniques would include endoscopic biopsy at the time of third ventriculostomy or aqueductoplasty or stereotactic biopsy. A review of 370 cases of stereotactic biopsies in France reported only 1.3 % mortality and 1 % major morbidity rates (Regis et al. 1996). Despite these relatively low rates, most surgeons are more comfortable with open biopsy in this region due to the close proximity of deep cerebral veins. One of the advantages of open biopsy is that sampling error can be minimized by taking several biopsies. This is particularly important since mixed GCTs are commonly encountered. Advances in surgical techniques allow open procedures to access the pineal region without major morbidity.

As results from intracranial GCT studies have emerged, stratification into "intermediate"- and "high"-risk prognostic groups has refined the role of biopsy. Specifically, serum and/or CSF β-HCG levels greater than 1000 IU/L and AFP levels greater than 1000 ng/mL nearly uniformly indicate the diagnosis of pure or predominant choriocarcinoma and yolk sac tumor, respectively

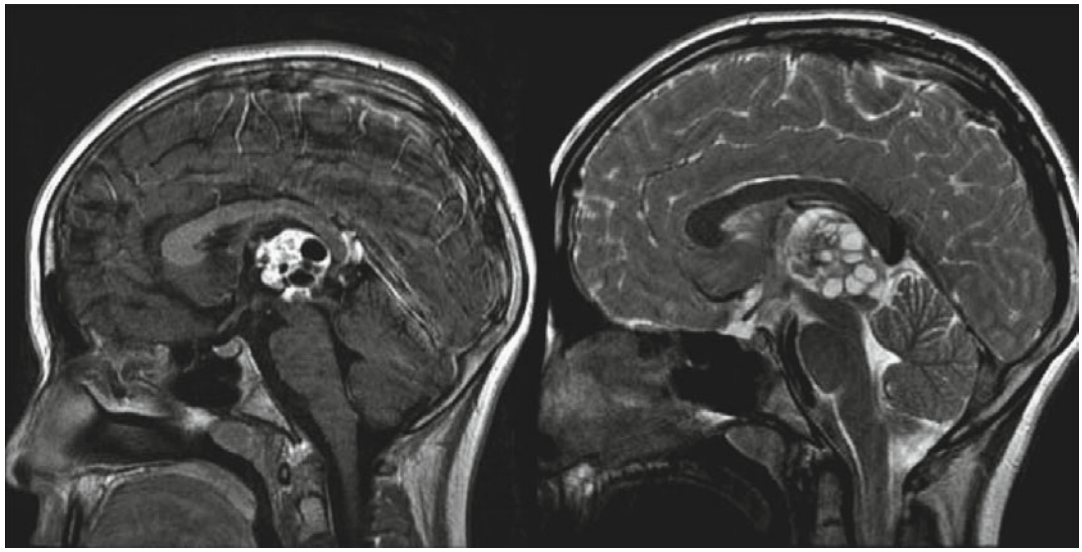

Fig. 6.5 A sagittal T1-weighted image following contrast (*left*) and a T2-weighted image (*right*) demonstrate the typical appearance of a mixed GCT, in this case a teratoma with germinoma. The tumor is heterogeneous with robust enhancement of the solid component although there are also multiple cysts within the tumor

(Matsutani et al. 1997; Kretschmar et al. 2007). Such conspicuous marker elevations may obviate the need for biopsy since they denote pure and/or predominant malignant elements and thus should be treated within the highest risk group. Current studies have further relaxed the need for biopsy in the presence of even lower serum or CSF levels of β-HCG or AFP >50 IU/L.

6.6 Treatment

6.6.1 Role of Surgery

Prior to 1970, surgery resulted in 25–70 % morbidity and mortality rates and led to radiotherapy becoming the treatment of choice with a modern 10-year overall survival, at least for germinomas, in the order of 80–100 %. In Japan, the standard of care was administration of a radiodiagnostic trial of 20 Gy followed by definitive doses of radiation if 20 Gy induced a tumor response (Handa and Yamashita 1981). Conventional radiotherapy for CNS germinomas involved 30 Gy of CSI followed by a boost to the primary disease site to a total dose of 50 Gy. The main role of surgery at that time was for treatment of hydrocephalus by placement of ventriculoperitoneal shunts, which resulted in peritoneal metastases at times (Brandes et al. 2000). Currently, other than as a diagnostic tool, surgery has no proven role in the treatment of intracranial germinomas due to the high operative morbidity and excellent outcomes with chemoradiotherapy (Pollack 2012). Several studies have shown no benefit to radical surgical resection in overall survival for germinoma patients (Sawamura et al. 1997).

For NGGCTs, surgery plays an important role along with other treatment modalities. In a study by Weiner et al., radical resection in addition to chemotherapy improved prognosis for patients with intracranial NGGCT. They recommended delayed surgical resection for patients who have normalized tumor markers with persistent radiographic abnormalities after three cycles of initial chemotherapy in order to avoid unnecessary radiation or further chemotherapy (Balmaceda et al. 1996; Weiner et al. 2002). For mature teratomas, it is generally accepted that gross total surgical resection is sufficient for cure. For immature teratomas, adjuvant chemoradiotherapy should be used if tumor markers are present because it is

assumed that malignant germ cell elements are present. Even following gross total resection of nonsecreting immature teratomas, there is still a risk of relapse without additional adjuvant therapy (Sawamura et al. 1998b). Endoscopic approaches may more effectively access these midline suprasellar lesions (Somma et al. 2014; Tseng et al. 2012).

Second-look surgery, in particular, was proposed by some authors (Friedman et al. 2001; Weiner et al. 2002). A retrospective review of 126 patients enrolled on the First and Second International Central Nervous System Germ Cell Tumor Studies for patients with newly diagnosed CNS GCTs sought to establish the role of delayed surgical resection in patients who exhibit less than complete radiographic response despite declining tumor markers after initial chemotherapy. Indeed, after at least three cycles of chemotherapy, ten patients underwent delayed surgical resection due to residual radiographic abnormalities in the setting of declining or completely normalized serum and CSF levels of β-HCG and AFP. Second-look surgery revealed three mature teratomas, two immature teratomas, and five cases of necrosis or scar tissue alone. At an average follow-up time of 36.9 months (range 3–96 months), only three of the ten patients had experienced tumor recurrence. Three of the four patients with NGGCTs whose tumor markers had not completely normalized ultimately developed tumor dissemination/progression and required radiation therapy even though pathology at second-look surgery showed only teratoma or necrosis/scar tissue. In contrast, three of four patients with NGGCTs whose tumor marker levels had completely normalized did not progress and did not require radiation therapy. The authors concluded that delayed surgical resection was indicated in patients with GCTs who have residual radiographic abnormalities and normalized tumor markers following chemotherapy (Weiner et al. 2002). The current experimental schema for localized GCT, ACNS1123, recommends second-look surgery following induction chemotherapy for less than complete response with normalization of markers (COG ACNS 1123 2012).

6.6.2 Chemotherapy

Chemotherapy was incorporated into the treatment of intracranial GCTs after agents known to have activity against testicular GCTs were shown to cross the blood–brain barrier (Ginsberg et al. 1981; Brandes et al. 2000). As single agents, actinomycin D, vinblastine, bleomycin, doxorubicin, cisplatin, carboplatin, etoposide, ifosfamide, and cyclophosphamide are active against GCTs, and combinations of these agents are the basis for treatment regimens. The most common combinations are PEB (cisplatin, etoposide, and bleomycin), PVB (cisplatin, vinblastine, and bleomycin), and JEB (carboplatin with etoposide and bleomycin) (Hawkins et al. 1986; Pinkerton et al. 1990; Cushing et al. 2002; Einhorn and Donohue 2002). In addition, ifosfamide has been found to be the third most active agent against GCTs, following cisplatin and etoposide, and was investigated as salvage therapy in patients with refractory disease (Nichols 1996). The recent Children's Oncology Group NGGCT study, ACNS0122, utilized a regimen of carboplatin and etoposide alternating with ifosfamide and etoposide that demonstrated safety and efficacy.

However, efforts to omit radiation and treat intracranial GCTs with chemotherapy alone have been less promising. Yoshida et al. saw a response rate of 80–85 % in patients treated with a combination regimen of cisplatin and etoposide, but survival rates at 2 years were disappointing at 88 % in patients with germinomas and 48 % in patients with NGGCTs. Baranzelli et al. reported that of 13 AFP- and β-HCG-secreting GCTs treated by chemotherapy and surgery alone, 12 recurred. Approximately 50 % of the patients with tumor recurrence experienced remission following salvage radiation therapy. Because of the need for salvage radiation therapy, the authors concluded that focal radiation therapy should be part of the treatment of these tumors.

Finally, Balmaceda et al. enrolled 45 patients with germinomas and 26 with NGGCTs in a clinical study and treated them with four cycles of carboplatin, etoposide, and bleomycin. Those with a complete response defined by imaging studies received two additional cycles, and those

with less than a complete response received two additional cycles intensified by cyclophosphamide. Overall, 78 % of patients achieved a complete response with chemotherapy only. However, of the 54 patients surviving at 2 years, 32 (59 %) received irradiation. The 2-year survival was 84 % for patients with germinoma and 62 % for those with NGGCT. Thus, it appears that chemotherapy alone does not provide comparable cure rates when compared to combined modality treatment (Yoshida et al. 1993; Balmaceda et al. 1996; Baranzelli et al. 1998). Of particular pertinence to NGGCTs, results from the First International CNS GCT Study Group indicated that approximately one third of NGGCT patients who initially had a complete response to chemotherapy had recurrent disease. And most importantly, unlike recurrent germinoma patients, these NGGCT patients were not amenable to salvage with radiation therapy (Balmaceda et al. 1996).

Due to their differing prognoses, more recent studies have made an effort to exclusively enroll and evaluate specific GCT subtypes in order to assess the efficacy of chemotherapy-only regimens. Kellie et al., looking exclusively at germinomas, confirmed the aforementioned generally disappointing results with chemotherapy (Kellie et al. 2004a). Here 19 patients were enrolled and treated with two courses of cisplatin, etoposide, cyclophosphamide, and bleomycin. If a complete response was achieved, patients then completed two courses of carboplatin, etoposide, and bleomycin. If complete response was not achieved, patients still received the above second regimen and, following a complete response, an additional cycle of both regimens. However, if, even after this intensive treatment, residual disease was still present, patients underwent second-look surgery and/or irradiation. Five-year event-free survival (EFS) was 47 % and 5-year overall survival was 68 %. Thus, because of the higher cure rates achieved with radiation therapy, there is no currently established role for chemotherapy-only regimens in the treatment of germinomas.

For NGGCTs, radiation alone produces 5-year survival rates of only 30–40 %. Excellent response rates to chemotherapy have shifted the standard treatment of NGGCT to combined modality therapy consisting of chemotherapy and radiation. However, a recent study by Kellie et al. suggested promising results for chemotherapy-only regimens in the treatment of NGGCT. In this study, 20 NGGCT patients were enrolled and received two courses of cisplatin, etoposide, cyclophosphamide, and bleomycin (Regimen A). Patients who had a complete response subsequently received two cycles of carboplatin, etoposide, and bleomycin (Regimen B). Those with less than a complete response to the initial regimen still received two cycles of Regimen B. If a complete response was then achieved, they received two additional cycles – one of Regimen A and one of Regimen B. If a complete response was absent, patients who did not respond to either Regimen A or B were taken off protocol for surgery and/or irradiation. These results improved upon historical controls, with a 5-year overall survival of 75 % and a reduction in deaths from chemotherapy-related toxicities (Kellie et al. 2004b).

6.6.3 Radiation Therapy

Published reports corroborate poorer prognoses for patients with NGGCT compared to those with germinoma. For NGGCTs, radiation alone produces 5-year survival rates of only 30–40 % with high rates of early relapse (Fuller et al. 1994; Matsutani et al. J Neurosurg 1997). These dismal results for radiation-only therapies, coupled with the success of chemotherapy in improving overall survival, have shifted the standard of care for NGGCTs toward multimodality approaches. However, open questions still remain, regarding radiation dose and volume.

There is little literature addressing the appropriate radiation field for localized NGGCT, with only small patient numbers. In a study by the French Society of Pediatric Oncology, chemotherapy and focal radiation resulted in five relapses among 24 patients with localized NGGCTs (Bouffet et al. 1999). A similar regimen in a separate study resulted in 3 of 18 patients experiencing disease recurrence, 2 with isolated spinal relapses (Robertson et al. 1997).

Additional studies support the opinion that "intermediate"-risk NGGCT patients (see Sect. 6.5.3 earlier for delineation of "intermediate"- and "high"-risk groups), particularly those with complete responses, do not require CSI. The Japanese cooperative group reported an excellent 5-year survival rate of 89% for "intermediate"-risk patients who were treated with five cycles of chemotherapy, 30 Gy to whole ventricular fields, and 54 Gy total dose to the primary tumor volume (Matsutani 2008). The International Society of Pediatric Oncology treated patients with localized NGGCTs with four cycles of cisplatin, etoposide, and ifosfamide, followed by focal radiation to a total dose of 54 Gy. Progression-free survival was 67%, although nearly half of the 34 patients with residual disease faced a recurrence even after chemotherapy (Calaminus and Patte 2005).

Because of their relative radioresistance, recommendations for the multimodality approach to NGGCT have emerged from recent studies. Within that context, for patients with NGGCT and complete responses to chemotherapy, Buckner recommended 54 Gy limited-field irradiation and 30 Gy CSI, if the spinal axis is involved; in patients with partial response, 59.4 Gy limited field was recommended with 36 Gy CSI, if spinal involvement is evident (Buckner et al. 1999).

Our recommendation for NGGCTs again depends on the stage at diagnosis. For disseminated disease (M1-M3), we recommend CSI to a dose of 24–36 Gy depending on variables that include patient age, tumor response, and disease bulk, with focal boosts to macroscopic disease to a dose of 54 Gy. For M0 lesions, because adjuvant or neoadjuvant chemotherapy is now often included in the treatment regimen, we frequently limit radiation volumes. For those with "intermediate"-risk disease and a complete response to induction chemotherapy, we recommend 30 Gy to a whole ventricular field and 54 Gy total dose to a focal radiation field. A consensus atlas is available for definition of whole ventricular field that includes the third, fourth, and lateral ventricles, along with the prepontine cistern (Mailhot et al. *ASTRO* 2013). For those with "intermediate"-risk with less than a complete response and for "high"-risk patients, we recommend 36 Gy to the craniospinal axis and 54 Gy to the primary tumor volume.

Among intracranial GCTs, germinoma represents the most common and prognostically favorable subgroup. The roles of surgery, chemotherapy, and radiation are constantly evolving. Unlike surgery, radiation remains a critical component of the treatment of intracranial germinomas. In fact, the gold standard against which all new approaches must be measured remains radiotherapy alone. ANCS0232 attempted to compare neoadjuvant chemotherapy followed by radiotherapy to radiotherapy alone, but failed to accrue. A series from Mayo Clinic with long-term follow-up demonstrated freedom from progression of 80% at 10 years for patients receiving neoadjuvant platinum-based chemotherapy with complete response followed by reduced-field radiotherapy, although cautioned against local field only RT due to a freedom from progression rate of 44% in this subgroup vs 100% for those treated with extended fields (Jensen et al. 2010). A historical series from UCSF likewise demonstrated improved outcomes with whole ventricular radiotherapy over focal radiation irrespective of chemotherapy (Schoenfeld et al. 2014). For M1–M3 disease, volumes involving the entirety of the craniospinal axis with focal boosts to macroscopic disease remain standard of care. Current evidence substantiates omitting CSI from the treatment of localized germinoma. Spinal failure rates of <10% in the absence of CSI, reported in most contemporary series, do not justify routine incorporation of CSI into treatment strategies for localized germinoma. Indeed, a recent review of the data regarding volumes and doses for M0 germinoma concluded that, because the rate of spinal relapse is similar, regardless of whether CSI or whole brain irradiation is used, prophylactic whole brain and CSI are contraindicated (Rogers et al. 2005). The late effects of CSI are increasingly recognized as particularly debilitating in the pediatric population and may include neurocognitive, endocrine, visual, and auditory pathway impairments, as well as secondary malignant

neoplasms, such that reduced volume radiotherapy is largely recommended for localized disease (Broniscer et al. 2004; Fossati et al. 2009). The current standard "involved field" volume includes the whole ventricle to 24 Gy followed by a boost to a total dose of 45 Gy to the tumor bed and any gross residual tumor that may be present, at a dose of 1.5 Gy per fraction. Dose de-escalation is noted on current combined chemoradiation protocols below. Some have gone still further in questioning the value of whole ventricular radiation, although whole ventricular fields are employed in current protocols.

Modern radiation techniques have demonstrated greater dose sparing of nontarget cerebral hemispheric tissue. As compared to whole ventricular irradiation with 3-D conventional radiotherapy techniques, IMRT has the ability to reduce uninvolved tissue treatment volumes at both high- and low-dose levels, with a small absolute increase in dose to peripheral body volumes (Chen 2010). Moreover, further dose sparing may be afforded by proton radiation. A series of 22 patients receiving proton radiotherapy for localized CNS germinomas demonstrated excellent survival outcomes (LC 100 % with median follow-up of 28 months) and increased normal tissue sparing as compared with IMRT plans generated in parallel (MacDonald et al. 2011). Other dosimetric studies comparing proton and photon-based approaches have shown excellent target coverage with improved dose sparing of temporal and hippocampal regions for both scattered and spot scanning proton delivery techniques as compared to IMRT in treatment of intracranial germ cell tumors (Park 2015). Other highly conformal radiotherapy techniques such as stereotactic radiosurgery have been effectively employed as a limited-field tumor boost following whole ventricular radiation (Endo et al. 2005).

Although most investigators now omit whole brain radiation, several studies have reported higher recurrence rates when only the tumor volume is treated (Uematsu et al. 1992; Shibamoto et al. 1994b; Wolden et al. 1995; Brandes et al. 2000; Rogers et al. 2005). Specifically, tumor recurrences following radiation fields confined to the primary tumor volume usually occur within the adjacent brain parenchyma and ventricles. Therefore, investigators have recommended initial inclusion of the entire ventricular field followed by a boost to the primary tumor to a total dose of 45 Gy for tumors less than 4 cm in size and 20 Gy for spinal prophylaxis in case of positive cytology (Uematsu et al. 1992; Shibamoto et al. 1994a). Shibamoto et al. suggested modulating the radiotherapy dose according to tumor diameter with 40 Gy for tumors up to 2.5 cm, 45 Gy for tumors between 2.5cm and 4 cm, and 50 Gy for tumors over 4 cm (Shibamoto et al. 1994b). Dissemination to the hypothalamus, third ventricle, or spinal cord identifies a high-risk group that warrants consideration of CSI with systemic chemotherapy (Jennings et al. 1985b).

We recommend whole ventricular irradiation, followed by a boost to the primary tumor for localized germinoma, when using radiation alone. Some question the rationale of whole ventricular irradiation, given the continuity of CSF space throughout the entire CNS. We argue that the natural history of germinomas is characterized by multifocality and intracranial relapses at foci separate from the primary tumor with lesser propensity for diffuse CNS involvement (Eom et al. 2008). These features distinguish germinomas from other CNS malignancies, such as medulloblastoma, that require CSI for cure. Whether more generous local radiation fields sterilize occult multifocal disease or target direct ventricular invasion, there appears to be a role for whole ventricular irradiation in the treatment of localized germinoma. In addition, the literature supports a dose of ≥45 Gy to the primary tumor for germinomas treated with radiation alone.

6.6.4 Combined Modality Treatment

In an effort to increase cure rates and limit toxicities associated with radiation, investigators have formulated multimodal regimens for the treatment of these lesions (Allen et al. 1987). Calaminus et al. reported promising results for patients with secreting intracranial GCTs given

four courses PEI, cisplatin (20 mg/m^2 day 1–5), VP-16 (100 mg/m^2 day 1–3), and ifosfamide (1.5 g/m^2 day 1–5) and resection, if feasible, of the residual tumor, followed by radiation consisting of 30 Gy CSI and an additional 24 Gy boost to the primary site. EFS was 81 % with 11 months follow-up, representing a significant improvement from previous studies (Calaminus et al. 1997). Robertson et al. reported improved outcome for intracranial NGGCTs after a treatment plan of initial radical surgical resection followed by three to four cycles of adjuvant chemotherapy with cisplatin (100 mg/m^2/cycle) and VP-16 (500 mg/m^2/cycle), followed by radiotherapy and finally four additional cycles of postradiation chemotherapy. Four-year actuarial EFS and overall survival rates were 67 % and 74 %, respectively (Robertson et al. 1997). It remains to be seen whether further intensification using myeloablative chemotherapy with autologous stem-cell rescue has a role in patients with poor-prognosis GCTs or relapsed GCTs.

A retrospective analysis of 41 patients concluded that treatment for NGGCTs should be tailored to histological subtype. For patients in the intermediate-risk group, which included those with germinoma with syncytiotrophoblastic giant cells, immature teratoma, teratoma with malignant transformation, and mixed tumors composed of germinoma or teratoma, there was a significant difference in overall survival for patients who had combined chemotherapy, radiation, and surgery (84 %) compared to those who had only radiation and surgery (44 %) (Ogawa et al. 2003). In this instance, chemotherapy consisted of various carboplatin or cisplatin combinations. However, in the poor-prognosis group (choriocarcinoma, yolk sac tumor, embryonal carcinoma, and mixed tumors), those who had incomplete resection, chemotherapy, and radiation had an abysmal 5-year survival rate of 8 %. For those with complete macroscopic resection, survival was more favorable, arguing for a possible role for surgery in NGGCT patients with these particular subtypes.

In the SIOP CNS GCT-96 trial (Calaminus et al. 2013), 135 patients with localized disease received four cycles of neoadjuvant chemotherapy consisting of cisplatin, ifosfamide, and etoposide followed by involved field radiotherapy to 54 Gy. At a median follow-up of 39 months, the progression free survival (PFS) for the patients was 69 ± 5 %. Relapses were predominantly local.

The recent Children's Oncology Group NGGCT study, ACNS0122, demonstrated 2-year PFS and OS of 84 ± 4 % and 93 ± 3 %, respectively, with a regimen of 6 cycles of induction chemotherapy followed by 36 Gy CSI and involved field boost to 54 Gy (Goldman et al. 2015). Seventy-nine of the 104 patients enrolled on ACNS0122 were noted to have localized tumors. CR and PR rates following induction chemotherapy were 31.65 % and 21.5 %, respectively. Of the 18 patients who underwent second-look surgery after induction therapy, 8 were found to have had only mature teratomas, residual scar, or fibrosis on pathology. Three-year EFS rates were 92 %, 94.1 %, and 85.7 % for these three groups, respectively (p=ns).

Sawamura et al. have also recommended further risk stratification of patients into three categories. They have categorized pure germinoma and mature teratoma as the good-prognosis group, with the poor-prognosis group including embryonal carcinoma, yolk sac tumor, choriocarcinoma, and mixed GCT containing any embryonal carcinoma, yolk sac, or choriocarcinoma elements. The intermediate-prognosis group includes germinoma with elevated (β-HCG, immature teratoma, extensive/multifocal germinoma, and mixed GCT containing only germinoma with teratoma elements (Sawamura et al. 1998a). Further therapeutic studies incorporating this type of risk stratification are warranted to determine if prognosis can be improved in the poor-prognosis group while minimizing therapy-induced physical or cognitive sequelae.

Historically, intracranial germinomas have been treated with radiation alone, producing excellent cure rates. The significant long-term toxicity of radiation, particularly in children, has prompted investigations into alternative treatments that minimize the dose and volume of irradiation. However, these alternative approaches must preserve the high cure rates established with radiation alone. Combined modality approaches

in which chemotherapy precedes radiation have gained credence and are now considered a standard alternative to radiation alone. The current GCT protocol, ACNS1123, indicates dose de-escalation to 18 Gy whole ventricular irradiation followed by 12 Gy boost to the primary disease site for patients evidencing a complete response with normalization of markers following four cycles of induction cisplatin/etoposide. For patients with partial response, 24 Gy whole ventricular irradiation followed by 12 Gy boost is indicated.

Several series have reported excellent clinical outcome with preirradiation chemotherapy followed by focal irradiation. Buckner et al. and Sawamura et al. reported 100% survival with median follow-up times of 51 months and 24 months, respectively (Sawamura et al. 1998c; Buckner et al. 1999). Buckner et al. treated nine patients with germinomas and eight with mixed GCTs. Treatment consisted of etoposide (100 mg/m^2/day) plus cisplatin (20 mg/m^2/day) daily for 5 days every 3 weeks for four cycles, followed by radiation therapy. They recommend that germinoma patients with complete responses after standard chemotherapy receive 30 Gy to a limited field with the addition of 20 Gy CSI for disseminated disease. For patients with partial responses, doses of 54 Gy to a limited field were recommended with 30 Gy CSI for disseminated disease.

Another study reported excellent results for patients treated with chemoradiation. Patients with pure germinomas were treated with EP (etoposide, 100 mg/m^2, and cisplatin, 20 mg/m^2) given for 5 days every 4 weeks for four cycles, and patients with other pathologic types were treated with ICE (ifosfamide, 900 mg/m^2; cisplatin, 20 mg/m^2; and etoposide, 60 mg/m^2) for five consecutive days every 4 weeks for up to six cycles depending on chemoresponsiveness, extent of surgical resection, and tumor marker levels. At 5 years, the overall survival rate was 100%, and relapse-free survival rates were 90% for germinoma patients and 44% for patients with β-HCG-secreting germinomas, which represent a mixed GCT with β-HCG-secreting syncytiotrophoblastic giant cells. This is strong evidence that treatment should be directed at the most malignant element. The 5-year overall survival rates were 93% for non-β-HCG-secreting germinomas and 75% for β-HCG-secreting germinomas (Aoyama et al. 2002). The authors recommend that following EP chemotherapy, dose and volume be reduced to 24 Gy in 12 fractions for non-β-HCG-secreting germinomas, but higher radiation doses should be maintained for β-HCG-secreting germinomas (Aoyama et al. 2002). Most recently, the volume of radiation in the setting of chemoradiation for germinomas has been addressed by Eom et al. They reviewed 81 patients treated for histologically confirmed intracranial germinomas with either radiation alone or chemoradiation. Of 42 patients who received chemotherapy followed by focal radiation, 4 relapsed, 1 in the primary tumor bed, 2 in the ventricles outside the radiation fields, and 1 in the spinal epidural space. This contrasts with no relapses among 39 patients who were treated with radiation alone consisting of craniospinal fields followed by a focal boost. Thus, recurrence-free survival at 5 years was 100% in the radiation alone arm and 88.1% in the chemoradiation arm, a difference that was statistically significant. The authors concluded that chemotherapy cannot prevent subependymal spread that is very effectively controlled by radiation, and they argued that whole ventricular radiation fields are appropriate following induction chemotherapy (Eom et al. 2008).

In the most current NGGCT protocol, patients who demonstrate complete or partial response with normalization of markers following six cycles of induction chemotherapy with alternating carboplatin/etoposide and ifosfamide/etoposide receive 30.6 Gy whole ventricular radiotherapy followed by 23.4 Gy boost to the primary site (COG ACNS1123 2012).

6.6.5 Treatment of Recurrent Disease

As with most malignancies, relapse poses a formidable problem. Imber et al. reported high rates of effective salvage treatment in a series of 24 patients with NGGCT reflected in a 10-year OS of 88% despite a 5-year progression-free survival of <50% after initial multimodal therapy (Imber et al. 2015). For patients who relapse with intracranial GCTs,

salvage therapy using the same chemotherapy regimen followed by radiotherapy has been effective (Sawamura et al. 1998a). Kobayashi et al. used combinations of cisplatin and etoposide in four cases of recurrent intracranial GCT (three malignant teratomas and one germinoma) and saw a response rate of 100 % (Kobayashi et al. 1989). Aoyama et al. successfully treated recurrent germinomas with further chemotherapy and reirradiation (Aoyama et al. 2002). However, improving prognosis for NGGCTs remains a concern. Encouraging results from a study using high-dose chemotherapy (200 mg/m^2 cisplatin, 1250 mg/m^2 etoposide, and 150 mg/m^2 ACNU) with autologous stem-cell rescue in six patients with high-risk, intracranial NGGCT showed 100 % survival at 1–7-year follow-up (Tada et al. 1999). Although trials using high-dose chemotherapy with stem-cell rescue show promise in relapsed extracranial GCTs, it remains to be seen whether myeloablative consolidation therapy has a role in the treatment of intracranial GCTs.

6.6.6 Future Trials

The Children's Oncology Group has been actively investigating treatment approaches for intracranial GCTs. The first trial has focused exclusively on NGGCTs, attempting to improve overall and progression-free survival by using a neoadjuvant 3-drug combination consisting of carboplatin, VP-16, and ifosfamide, followed by CSI with involved field boost. For those patients that have persistently positive markers, residual tumor, or unresectable disease, even after induction chemotherapy, myeloablative chemotherapy followed by stem-cell rescue is to be attempted before CSI.

For germinomas, a Phase III trial has stratified patients according to extent of disease (M0 for local, M+ for multifocal, and modified M+ for assumed occult multifocal) and then randomized them into one of two treatment arms: Regimen A consists exclusively of radiotherapy; M0 and modified M+ patients receive ventricular radiation with a focal boost, while those with disseminated disease receive CSI. In Regimen B, patients with focal disease that experience a favorable response to induction chemotherapy receive reduced-dose and volume-involved field radiotherapy. Those with disseminated disease who respond well to induction chemotherapy receive a reduction in CSI and boost doses. Those with modified M+ disease who respond well receive reductions in ventricular and boost doses. Final results of these two studies are pending. Such response-directed fields and doses of radiation have gained favor.

Future trials for intracranial NGGCTs will likely further stratify patients into "intermediate"- and "high"-risk groups in an effort to identify those patients who do not require as aggressive a regimen as is currently administered. Such a group of "intermediate"-risk tumors will include those with immature teratoma, mixed GCT with predominantly germinoma or teratoma components, and histologically confirmed NGGCTs with β-HCG <1,000 IU/L or AFP <1,000 ng/mL. Although the current NGGCT Children's Oncology Group protocol dictates CSI for all such patients, emerging evidence indicates that less toxic approaches will not compromise clinical outcome in this group of patients. Thus, in future trials, M0 "intermediate"-risk NGGCT patients will likely receive chemotherapy followed by response-based radiation consisting of a whole ventricular field and a boost to the primary tumor region.

6.7 Outcome

The outcome for patients with pure intracranial germinoma is significantly better than the outcome for those with NGGCT. Cure rates above 90 % with radiation alone establish radiation as the benchmark against which combined modality therapy must be compared. Comparable outcomes are achieved in patients with intracranial teratoma. Prognosis for NGGCTs other than teratoma is worse than that for germinomas, and historically the 5-year survival rates for these tumors have been between 20 % and 49 % (Jennings et al. 1985b; Schild et al. 1996; Matsutani et al. 1997; Drummond and Rosenfeld 1999; Jaing

et al. 2002). However, it is clear that combined modality therapy has improved dramatically on the poor historic survival rates of patients with NGGCTs. The roles of surgical resection and high-dose chemotherapy with stem-cell rescue for patients with NGGCTs are currently under investigation.

Early studies identified "intermediate"- and "high"-risk groups among NGGCT patients. More than a decade ago, Matsutani et al. found 27 % survival rates at 3 years for those with pure malignant GCTs (choriocarcinoma, endodermal sinus tumor, and embryonal carcinoma), compared with 70 % or greater survival rates for patients with mixed germinoma and teratoma, and mixed teratoma or germinoma with some pure malignant elements (Matsutani et al. 1997). In contrast, mixed tumors with predominantly pure malignant elements had less than 10 % survival at 3 years.

In addition to histology, a key prognostic factor for NGGCTs is tumor marker elevation. In particular, serum and/or CSF β-HCG or AFP levels greater than 1,000 IU/L or 1,000 ng/mL, respectively, portent significantly worse outcome (Matsutani et al. 1997; Kellie et al. 2004b; Kretschmar et al. 2007). For example, the Second International CNS Germ Cell Study Group reported that from 20 patients with NGGCTs treated with chemotherapy alone, 4 of 9 patients with serum and/or CSF β-HCG or AFP levels greater than 1,000 IU/L or ng/mL, respectively, died of disease progression, whereas only 1 death occurred among 11 patients without such marker elevations (Kellie et al. 2004b). Lesion size greater than 4 cm may also be associated with poorer outcome (Huo et al. 2015).

Given higher cure rates for patients with intracranial GCTs, long-term toxicities are clearly evident. Sawamura et al. reported a variety of late adverse effects of therapy including stroke, secondary malignancy, and cognitive, endocrinologic, auditory, and visual dysfunctions. Of 85 patients, 58 required hormone replacement therapy and 26 showed poor performance status (Sawamura et al. 1998a). Young patients are at an increased risk of physical as well as neuropsychologic deficits. As expected, patients who received less than 55 Gy showed higher Karnofsky performance scores (Ono et al. 1994).

Sands et al. reported on quality of life and neuropsychologic functioning in patients enrolled in the First International CNS Germ Cell Tumor Study. Patients who received CNS radiation therapy had worse physical health, but similar psychosocial health. Patients with germinomas significantly outperformed those with NGGCTs on all neuropsychologic measures, and younger patients were at increased risk for psychosocial and physical problems as well as neuropsychologic deficits (Sands et al. 2001). In the study by Aoyama et al., using chemotherapy followed by low-dose, involved field radiotherapy, the authors noted no remarkable deterioration in quality of life or neurocognitive function (Aoyama et al. 2002).

Combination chemoradiotherapy regimens with risk stratification and dose adjustments will likely decrease the long-term side effects of therapy while improving the prognosis for those with the high-risk intracranial GCTs. A study of nine children with germinomas, all of whom received radiotherapy and five of whom received neoadjuvant chemotherapy, confirmed the relative safety of limited-field and reduced-dose radiotherapy when supplemented with chemotherapy (Strojan et al. 2006). Another retrospective study examined data from 19 patients, 14 of whom received various chemotherapies in addition to radiation, and the authors found adverse effects to be relatively limited (Osuka et al. 2007).

While chemoradiation is the reigning paradigm for the treatment of both germinoma and NGGCT, new approaches hold promise as well. Osada et al. provide a case report of dendritic cell-based immunotherapy in a patient with relapsed, intracranial GCT who had significant tumor shrinkage as well as decrease in tumor markers after four infusions of peripheral blood dendritic cells followed by monocyte-derived dendritic cells (Osada et al. 2001).

Conclusions

In this chapter, we have reviewed the epidemiology, pathology, clinical features, diagnosis, and treatment of intracranial GCTs. The use of tumor markers, improved imaging technologies,

and safer biopsy techniques has made the diagnosis of intracranial GCTs relatively straightforward. Mixed GCTs remain a diagnostic challenge. The outcomes of patients with GCTs have paralleled the success that has been achieved with other types of pediatric cancers, with the advances in combinatorial regimens and intensification of treatments. As with other pediatric malignancies, the challenge is to distinguish the patients who require more intensive therapy from those needing standard treatment. Risk-stratified treatment protocols individualized to a patient's tumor profile are ongoing with promising initial results. Technological advances in the field of diagnostic radiology, neurosurgery, and radiation oncology have improved efficacy of diagnosis and treatment while decreasing the long-term sequelae of therapies. As the molecular profiles of these rare tumors are further revealed, it is hoped that novel, targeted, and less toxic therapeutics will be increasingly available.

References

Al-Hussaini M, Sultan I, Abuirmileh N, Jaradat I, Qaddoumi I (2009) Pineal gland tumors: experience from the SEER database. J Neurooncol 94(3):351–358. doi:10.1007/s11060-009-9881-9

Allen JC, Kim JH, Packer RJ (1987) Neoadjuvant chemotherapy for newly diagnosed germ-cell tumors of the central nervous system. J Neurosurg 67:65–70

Aoyama H, Shirato H, Ikeda J, Fujieda K, Miyasaka K, Sawamura Y (2002) Induction chemotherapy followed by low dose involved-field radiotherapy for intracranial germ cell tumors. J Clin Oncol 20:857–865

Awa R, Campos F, Arita K, Sugiyama K, Tominaga A, Kurisu K et al (2014) Neuroimaging diagnosis of pineal region tumors-quest for pathognomonic finding of germinoma. Neuroradiology 56(7):525–534. doi:10.1007/s00234-014-1369-4

Aydin F, Ghatak NR, Radie-Keane K, Kinard J, Land SD (1992) The short-term effect of low-dose radiation on intracranial germinoma. A pathologic study. Cancer 69:2322–2326

Balmaceda C, Heller G, Rosenblum M, Diez B, Villablanca JG, Kellie S, Maher P, Vlamis V, Walker RW, Leibel S, Finlay JL (1996) Chemotherapy without irradiation–a novel approach for newly diagnosed CNS germ cell tumors: results of an international cooperative trial. The First International Central Nervous System Germ Cell Tumor Study. J Clin Oncol 14:2908–2915

Baranzelli MC, Patte C, Bouffet E, Portas M, Mechinaud-Lacroix F, Sariban E, Roche H, Kalifa C (1998) An attempt to treat pediatric intracranial alphaFP and betaHCG secreting germ cell tumors with chemotherapy alone. SFOP experience with 18 cases. Societe Francaise d'Oncologie Pediatrique. J Neurooncol 37:229–239

Beeley JM, Daly JJ, Timperley WR, Warner J (1973) Ectopic pinealoma: an unusual clinical presentation and a histochemical comparison with a seminoma of the testis. J Neurol Neurosurg Psychiatry 36:864–873

Bernstein L, Smith MA, Liu L, Deapen D, Friedman DL (1999) Germ cell, trophoblastic and other gonadal neoplasms. In: Ries LAG, Smith MA, Gurney JG, Linet M, Tamara T, Young JL, Bunin GR (eds) Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. National Cancer Institute SEER Program, Bethesda

Bouffet E, Baranzelli MC, Patte C, Portas M, Edan C, Chastagner P, Mechinaud-Lacroix F, Kalifa C (1999) Combined treatment modality for intracranial germinomas: results of a multicentre SFOP experience. Societe Francaise d'Oncologie Pediatrique. Br J Cancer 79:1199–1204

Brandes AA, Pasetto LM, Monfardini S (2000) The treatment of cranial germ cell tumours. Cancer Treat Rev 26:233–242

Broniscer A, Ke W, Fuller CE, Wu J, Gajjar A, Kun LE (2004) Second neoplasms in pediatric patients with primary central nervous system tumors. Cancer, 100:2246–2252

Buckner JC, Peethambaram PP, Smithson WA, Groover RV, Schomberg PJ, Kimmel DW, Raffel C, O'Fallon JR, Neglia J, Shaw EG (1999) Phase II trial of primary chemotherapy followed by reduced-dose radiation for CNS germ cell tumors. J Clin Oncol 17:933–940

Calaminus G, Patte C (2005) Germ cell tumors in children and adolescents. In: Agarwal BR, Perilongo G, Rogers P, Strahl Endorf C, Eden OB (eds) International society of paediatric oncology (SIOP) education book. International Society of Paediatric Oncology, Vancouver, pp 109–116

Calaminus G, Andreussi L, Garre ML, Kortmann RD, Schober R, Gobel U (1997) Secreting germ cell tumors of the central nervous system (CNS). First results of the cooperative German/Italian pilot study (CNS sGCT). Klin Padiatr 209:222–227

Calaminus G, Kortmann R, Worch J, Nicholson JC, Alapetite C, Garrè ML, Patte C, Ricardi U, Saran F, Frappaz D (2013) SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma,comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. Neuro Oncol 15(6):788–796

Chen MJ, Santos Ada S, Sakuraba RK, Lopes CP, Gonçalves VD, Weltman E, Ferrigno R, Cruz JC (2010) Intensity-modulated and 3D-conformal radiotherapy for whole-ventricular rradiation as compared

with conventional whole-brain irradiation in the management of localized central nervous system germ cell tumors. Int J Radiat Oncol Biol Phys 76(2):608–614
Choi JU, Kim DS, Chung SS, Kim TS (1998) Treatment of germ cell tumors in the pineal region. Childs Nerv Syst 14:41–48
Cushing B, Perlman EJ, Marina NM, Castleberry RP (2002) Germ cell tumors. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology. Lippincott Williams & Wilkins, Philadelphia, pp 1091–1113
de Bruin TW, Slater RM, Defferrari R, Geurts van Kessel A, Suijkerbuijk RF, Jansen G, de Jong B, Oosterhuis JW (1994) Isochromosome 12p-positive pineal germ cell tumor. Cancer Res 54:1542–1544
Drummond KJ, Rosenfeld JV (1999) Pineal region tumours in childhood. A 30-year experience. Childs Nerv Syst 15:119–126, discussion 127
Edwards MS, Hudgins RJ, Wilson CB, Levin VA, Wara WM (1988) Pineal region tumors in children. J Neurosurg 68:689–697
Einhorn LH, Donohue J (2002) *Cis*-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. J Urol 167:928–932, discussion 933
Endo H, Kumabe T, Jokura H, Tominaga T (2005) Stereotactic radiosurgery followed by whole ventricular irradiation for primary intracranial germinoma of the pineal region. Minim Invasive Neurosurg 48(3):186–190
Eom KY, Kim IH, Park CI, Kim HJ, Kim JH, Kim K, Kim SK, Wang KC, Cho BG, Jung HW, Heo DS, Kang HJ, Shin HY, Ahn HS (2008) Upfront chemotherapy and involved-field radiotherapy results in more relapses than extended radiotherapy for intracranial germinomas: modification in radiotherapy volume might be needed. Int J Radiat Oncol Biol Phys 71:667–671
Felix I, Becker LE (1990) Intracranial germ cell tumors in children: an immunohistochemical and electron microscopic study. Pediatr Neurosurg 16:156–162
Fossati P, Ricardi U, Orecchia R (2009) Pediatric medulloblastoma: toxicity of current treatment and potential role of proton therapy. Cancer Treat Rev 35(1):79–96
Friedman JA, Lynch JJ, Buckner JC, Scheithauer BW, Raffel C (2001) Management of malignant pineal germ cell tumors with residual mature teratoma. Neurosurgery 48:518–522, discussion 522–513
Fujimaki T, Matsutani M, Funada N, Kirino T, Takakura K, Nakamura O, Tamura A, Sano K (1994) CT and MRI features of intracranial germ cell tumors. J Neurooncol 19:217–226
Fuller BG, Kapp DS, Cox R (1994) Radiation therapy of pineal region tumors: 25 new cases and a review of 208 previously reported cases. Int J Radiat Oncol Biol Phys 28:229–245
Gay JC, Janco RL, Lukens JN (1985) Systemic metastases in primary intracranial germinoma. Case report and literature review. Cancer 55:2688–2690
Ginsberg S, Kirshner J, Reich S, Panasci L, Finkelstein T, Fandrich S, Fitzpatrick A, Shechtman L, Comis R (1981) Systemic chemotherapy for a primary germ cell tumor of the brain: a pharmacokinetic study. Cancer Treat Rep 65:477–483
Goldman S, Bouffet E, Fisher PG, Allen JC, Robertson PL, Chuba PJ, Donahue B, Kretschmar CS, Zhou T, Buxton AB, Pollack IF (2015) Phase II Trial Assessing the Ability of Neoadjuvant Chemotherapy With or Without Second-Look Surgery to Eliminate Measurable Disease for Nongerminomatous Germ Cell Tumors: A Children's Oncology Group Study. J Clin Oncol 1;33(22):2464–2471
Handa H, Yamashita J (1981) Current treatment of pineal tumors (author's transl). Neurol Med Chir 21:147–154
Hao S, Li D, Feng J, Wang L, Wu Z, Zhang J, Zhang L (2013) Primary medulla oblongata germinomas: two case reports and review of the literature. World J Surg Oncol 11(1):274. doi:10.1186/1477-7819-11-274
Hattab EM, Tu PH, Wilson JD, Cheng L (2005) OCT4 immunohistochemistry is superior to placental alkaline phosphatase (PLAP) in the diagnosis of central nervous system germinoma. Am J Surg Pathol 29:368–371
Hawkins EP (1990) Pathology of germ cell tumors in children. Crit Rev Oncol Hematol 10:165–179
Hawkins EP, Finegold MJ, Hawkins HK, Krischer JP, Starling KA, Weinberg A (1986) Nongerminomatous malignant germ cell tumors in children. A review of 89 cases from the Pediatric Oncology Group, 1971–1984. Cancer 58:2579–2584
Hoei-Hansen CE, Sehested A, Juhler M, Lau Y-FC, Skakkebaek NE, Laursen H, Rajpert-de Meyts E (2006) New evidence for the origin of intracranial germ cell tumours from primordial germ cells: expression of pluripotency and cell differentiation markers. J Pathol 209(1):25–33. doi:10.1002/path.1948
Hoffman HJ, Otsubo H, Hendrick EB, Humphreys RP, Drake JM, Becker LE, Greenberg M, Jenkin D (1991) Intracranial germ-cell tumors in children. J Neurosurg 74:545–551
Honecker F, Kersemaekers A-MF, Molier M, Van Weeren PC, Stoop H, De Krijger RR et al (2004) Involvement of E-cadherin and beta-catenin in germ cell tumours and in normal male fetal germ cell development. J Pathol 204(2):167–174. doi:10.1002/path.1614
Huo L, Wang X, Allen PK, Wang L, Liao Y, Han Z, Shen L, Tu Q, Zhong M, Zhuang Y, Li J, Hong J (2015) Predictors of long-term survival following postoperative radiochemotherapy for pathologically confirmed suprasellar germ cell tumors. Mol Clin Oncol 3(2):430–434
Iizuka H, Nojima T, Kadoya S (1996) Germinoma of the optic nerve: case report. Noshuyo Byori 13:95–98
Imber B, Braunstein S, Banerjee A, Tihan T, Bollen A, Haas-Kogan D, Mueller S (2015) Intracranial nongerminomatous germ cell tumors: treatment strategies and outcomes. Neuro Oncol 17(supp 3)
Itoyama Y, Kochi M, Kuratsu J, Takamura S, Kitano I, Marubayashi T, Uemura S, Ushio Y (1995) Treatment of intracranial nongerminomatous malignant germ cell tumors producing alpha-fetoprotein. Neurosurgery 36:459–464, discussion 464–456

Iwato M, Tachibana O, Tohma Y, Arakawa Y, Nitta H, Hasegawa M, Yamashita J, Hayashi Y (2000a) Alterations of the INK4a/ARF locus in human intracranial germ cell tumors. Cancer Res 60: 2113–2115

Iwato M, Tachibana O, Tohma Y, Nitta H, Hayashi Y, Yamashita J (2000b) Molecular analysis for p53 and mdm2 in intracranial germ cell tumors. Acta Neuropathol 99:21–25

Jaing TH, Wang HS, Hung IJ, Tseng CK, Yang CP, Hung PC, Lui TN (2002) Intracranial germ cell tumors: a retrospective study of 44 children. Pediatr Neurol 26: 369–373

Jellinger K (1973) Primary intracranial germ cell tumours. Acta Neuropathol 25:291–306

Jennings CD, Powell DE, Walsh JW, Mortara RH (1985a) Suprasellar germ cell tumor with extracranial metastases. Neurosurgery 16:9–12

Jennings MT, Gelman R, Hochberg F (1985b) Intracranial germ-cell tumors: natural history and pathogenesis. J Neurosurg 63:155–167

Jensen AW, Laack NN, Buckner JC, Schomberg PJ, Wetmore CJ, Brown PD (2010) Long-term follow-up of dose-adapted and reduced-field radiotherapy with or without chemotherapy for central nervous system germinoma. Int J Radiat Oncol Biol Phys 77(5):1449–1456. doi:10.1016/j.ijrobp.2009.06.077

Jooma R, Kendall BE (1983) Diagnosis and management of pineal tumors. J Neurosurg 58:654–665

Kamakura Y, Hasegawa M, Minamoto T, Yamashita J, Fujisawa H (2006) C-kit gene mutation: common and widely distributed in intracranial germinomas. J Neurosurg 104(3 Suppl):173–180. doi:10.3171/ped.2006.104.3.173

Kang JK, Jeun SS, Hong YK, Park CK, Son BC, Lee IW, Kim MC (1998) Experience with pineal region tumors. Childs Nerv Syst 14:63–68

Kellie SJ, Boyce H, Dunkel IJ, Diez B, Rosenblum M, Brualdi L, Finlay JL (2004a) Intensive cisplatin and cyclophosphamide-based chemotherapy without radiotherapy for intracranial germinomas: failure of a primary chemotherapy approach. Pediatr Blood Cancer 43:126–133

Kellie SJ, Boyce H, Dunkel IJ, Diez B, Rosenblum M, Brualdi L, Finlay JL (2004b) Primary chemotherapy for intracranial nongerminomatous germ cell tumors: results of the second international CNS germ cell study group protocol. J Clin Oncol 22: 846–853

Kobayashi T, Yoshida J, Ishiyama J, Noda S, Kito A, Kida Y (1989) Combination chemotherapy with cisplatin and etoposide for malignant intracranial germ-cell tumors. An experimental and clinical study. J Neurosurg 70:676–681

Kretschmar C, Kleinberg L, Greenberg M, Burger P, Holmes E, Wharam M (2007) Pre-radiation chemotherapy with response-based radiation therapy in children with central nervous system germ cell tumors: a report from the Children's Oncology Group. Pediatr Blood Cancer 48:285–291

Lapin V, Ebels I (1981) The role of the pineal gland in neuroendocrine control mechanisms of neoplastic growth. J Neural Transm 50:275–282

Lemos JA, Barbieri-Neto J, Casartelli C (1998) Primary intracranial germ cell tumors without an isochromosome 12p. Cancer Genet Cytogenet 100: 124–128

Lin IJ, Shu SG, Chu HY, Chi CS (1997) Primary intracranial germ-cell tumor in children. Zhonghua Yi Xue Za Zhi 60:259–264

Loveland KL, Schlatt S (1997) Stem cell factor and c-kit in the mammalian testis: lessons originating from Mother Nature's gene knockouts. J Endocrinol 153:337–344

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114(2): 97–109

MacDonald SM, Trofimov A, Safai S, Adams J, Fullerton B, Ebb D, Tarbell NJ, Yock TI (2011) Proton radiotherapy for pediatric central nervous system germ cell tumors: early clinical outcomes. Int J Radiat Oncol Biol Phys 79(1):121–129

Madden J, Foreman NK, Liu AK (2009) Germ cell tumors of the brainstem: report on two cases with pulmonary complications and a review of the literature. J Neurooncol 93(3):405–408. doi:10.1007/s11060-008-9780-5

Mailhot Vega RB, Kim J, Bussiere M, Hattangadi J, Hollander A, Michalski J, Tarbell NJ, Yock T, MacDonald SM (2013) Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. Cancer 119:4299–4307

Matsutani M (2008) Treatment of intracranial germ cell tumors: the second phase II study of Japanese GCT Study Group. In: 13th International Symposium on Pediatric Neuro-Oncology. Chicago. p 420

Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O, Funata N, Seto T (1997) Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. J Neurosurg 86:446–455

Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O (1998) Combined treatment with chemotherapy and radiation therapy for intracranial germ cell tumors. Childs Nerv Syst 14:59–62

Mei K(1), Liu A, Allan RW, Wang P, Lane Z, Abel TW, Wei L, Cheng H, Guo S, Peng Y, Rakheja D, Wang M, Ma J, Rodriguez MM, Li J, Cao D (2009) Diagnostic utility of SALL4 in primary germ cell tumors of the central nervous system: a study of 77 cases. Mod Pathol 22(12):1628–1636

Miyanohara O, Takeshima H, Kaji M, Hirano H, Sawamura Y, Kochi M, Kuratsu J (2002) Diagnostic significance of soluble c-kit in the cerebrospinal fluid of patients with germ cell tumors. J Neurosurg 97:177–183

Nakajima H, Iwai Y, Yamanaka K, Yasui T, Kishi H (2000) Primary intracranial germinoma in the medulla oblongata. Surg Neurol 53:448–451

Nakase H, Ohnishi H, Touho H, Karasawa J, Tsunoda S (1994) Cerebellar primary germ-cell tumor in a young boy. Brain Dev 16:396–398

Nichols CR (1996) Ifosfamide in the treatment of germ cell tumors. Semin Oncol 23:65–73

Nishizaki T, Kajiwara K, Adachi N, Tsuha M, Nakayama H, Ohshita N, Ikeda N, Ito H, Suzuki M (2001) Detection of craniospinal dissemination of intracranial germ cell tumours based on serum and cerebrospinal fluid levels of tumour markers. J Clin Neurosci 8:27–30

Ogawa K, Toita T, Nakamura K, Uno T, Onishi H, Itami J, Shikama N, Saeki N, Yoshii Y, Murayama S (2003) Treatment and prognosis of patients with intracranial nongerminomatous malignant germ cell tumors: a multiinstitutional retrospective analysis of 41 patients. Cancer 98:369–376

Oi S, Matsumoto S (1992) Controversy pertaining to therapeutic modalities for tumors of the pineal region: a worldwide survey of different patient populations. Childs Nerv Syst 8:332–336

Oi S, Matsuzawa K, Choi JU, Kim DS, Kang JK, Cho BK (1998) Identical characteristics of the patient populations with pineal region tumors in Japan and in Korea and therapeutic modalities. Childs Nerv Syst 14:36–40

Okada Y, Nishikawa R, Matsutani M, Louis DN (2002) Hypomethylated X chromosome gain and rare isochromosome 12p in diverse intracranial germ cell tumors. J Neuropathol Exp Neurol 61:531–538

Okochi Y, Nihashi T, Fujii M, Kato K, Okada Y, Ando Y, Maesawa S, Takebayashi S, Wakabayashi T, Naganawa S (2014) Clinical use of (11)C-methionine and (18)F-FDG-PET for germinoma in central nervous system. Ann Nucl Med 28(2):94–102. doi:10.1007/s12149-013-0787-4

Ono N, Kakegawa T, Zama A, Nakamura M, Inoue HK, Tamura M, Wakao T, Uki J, Takeda F, Kurihara H et al (1994) Factors affecting functional prognosis in survivors of primary central nervous system germinal tumors. Surg Neurol 41:9–15

Osada T, Fujimaki T, Takamizawa M, Tsuno NH, Kirino T, Shibata Y (2001) Dendritic cells activate antitumor immunity for malignant intracranial germ cell tumor: a case report. Jpn J Clin Oncol 31:403–406

Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y, Dowling J et al (2014) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro Oncol 16(Suppl 4):iv1–iv63. doi:10.1093/neuonc/nou223

Osuka S, Tsuboi K, Takano S, Ishikawa E, Matsushita A, Tokuuye K, Akine Y, Matsumura A (2007) Long-term outcome of patients with intracranial germinoma. J Neurooncol 83:71–79

Packer RJ, Cohen BH, Cooney K (2000) Intracranial germ cell tumors. Oncologist 5:312–320

Park J, Park Y, Lee SU, Kim T, Choi Y-K, Kim J-Y (2015) Differential dosimetric benefit of proton beam therapy over intensity modulated radiotherapy for a variety of targets in patients with intracranial germ cell tumors Radiation Oncology 10:135

Pinkerton CR, Broadbent V, Horwich A, Levitt J, McElwain TJ, Meller ST, Mott M, Oakhill A, Pritchard J (1990) 'JEB'–a carboplatin based regimen for malignant germ cell tumours in children. Br J Cancer 62:257–262

Pollack IF (2012) Surgical options for pineal region tumors. World Neurosurg 77(2):302–303. doi:10.1016/j.wneu.2011.06.020

Regis J, Bouillot P, Rouby-Volot F, Figarella-Branger D, Dufour H, Peragut JC (1996) Pineal region tumors and the role of stereotactic biopsy: review of the mortality, morbidity, and diagnostic rates in 370 cases. Neurosurgery 39:907–912, discussion 912–904

Rickert CH, Simon R, Bergmann M, Dockhorn-Dworniczak B, Paulus W (2000) Comparative genomic hybridization in pineal germ cell tumors. J Neuropathol Exp Neurol 59:815–821

Robertson PL, DaRosso RC, Allen JC (1997) Improved prognosis of intracranial non-germinoma germ cell tumors with multimodality therapy. J Neurooncol 32:71–80

Rogers SJ, Mosleh-Shirazi MA, Saran FH (2005) Radiotherapy of localised intracranial germinoma: time to sever historical ties? Lancet Oncol 6:509–519

Rosenblum MK, Nakazato Y, Matsutani M (2007) Germ cell tumors. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) World Health Organization classification of tumours. Pathology and genetics of tumours of the central nervous system. IARC Press, Lyon, pp 197–204

Saitoh M, Tamaki N, Kokunai T, Matsumoto S (1991) Clinico-biological behavior of germ-cell tumors. Childs Nerv Syst 7:246–250

Salzman KL, Rojiani AM, Buatti J, Quisling RG, Marcus RB Jr, Maria BL, Mickle JP, Kedar A (1997) Primary intracranial germ cell tumors: clinicopathologic review of 32 cases. Pediatr Pathol Lab Med 17:713–727

Sands SA, Kellie SJ, Davidow AL, Diez B, Villablanca J, Weiner HL, Pietanza MC, Balmaceda C, Finlay JL (2001) Long-term quality of life and neuropsychologic functioning for patients with CNS germ-cell tumors: from the First International CNS Germ-Cell Tumor Study. Neuro Oncol 3:174–183

Sano K, Matsutani M, Seto T (1989) So-called intracranial germ cell tumours: personal experiences and a theory of their pathogenesis. Neurol Res 11:118–126

Sawamura Y, de Tribolet N, Ishii N, Abe H (1997) Management of primary intracranial germinomas: diagnostic surgery or radical resection? J Neurosurg 87:262–266

Sawamura Y, Ikeda J, Shirato H, Tada M, Abe H (1998a) Germ cell tumours of the central nervous system: treatment consideration based on 111 cases and their long-term clinical outcomes. Eur J Cancer 34:104–110

Sawamura Y, Kato T, Ikeda J, Murata J, Tada M, Shirato H (1998b) Teratomas of the central nervous system: treatment considerations based on 34 cases. J Neurosurg 89:728–737

Sawamura Y, Shirato H, Ikeda J, Tada M, Ishii N, Kato T, Abe H, Fujieda K (1998c) Induction chemotherapy followed by reduced-volume radiation therapy for

newly diagnosed central nervous system germinoma. J Neurosurg 88:66–72
Schild SE, Haddock MG, Scheithauer BW, Marks LB, Norman MG, Burger PC, Wong WW, Lyons MK, Schomberg PJ (1996) Nongerminomatous germ cell tumors of the brain. Int J Radiat Oncol Biol Phys 36:557–563
Schoenfeld A, Haas-Kogan DA, Molinaro A, Banerjee A, Nicolaides T, Tihan T,Bollen AW, Gupta N, Mueller S (2014) Pure germinomas of the central nervous system: treatment strategies and outcomes. J Neurooncol 120(3):643–649
Shibamoto Y, Oda Y, Yamashita J, Takahashi M, Kikuchi H, Abe M (1994a) The role of cerebrospinal fluid cytology in radiotherapy planning for intracranial germinoma. Int J Radiat Oncol Biol Phys 29:1089–1094
Shibamoto Y, Takahashi M, Abe M (1994b) Reduction of the radiation dose for intracranial germinoma: a prospective study. Br J Cancer 70:984–989
Shirato H, Nishio M, Sawamura Y, Myohjin M, Kitahara T, Nishioka T, Mizutani Y, Abe H, Miyasaka K (1997) Analysis of long-term treatment of intracranial germinoma. Int J Radiat Oncol Biol Phys 37:511–515
Snow GE, Kasper AC, Busch AM, Schwarz E, Ewings KE, Bee T, Spinella MJ, Dmitrovsky E, Freemantle SJ (2009) Wnt pathway reprogramming during human embryonal carcinoma differentiation and potential for therapeutic targeting. BMC Cancer 9:383. doi:10.1186/1471-2407-9-383
Somma AD, Bronzoni C, Guadagno E, Solari D, Dell'aversana GO, De Caro BS, Cappabianca P (2014) The "extended" endoscopic endonasal approach for the removal of a mixed intrasuprasellar germinoma: technical case report. Surg Neurol Int 5:14. doi:10.4103/2152-7806.126043
Steinbok P (2001) Management of malignant pineal germ cell tumors with residual mature teratoma. Neurosurgery 49:1271
Steinbok P, Cochrane DD (2001) Pineal region and intracranial germ cell tumors. In: McLone DG (ed) Pediatric neurosurgery: surgery of the developing nervous system. W.B. Saunders, Philadelphia, pp 711–724
Strojan P, Zadravec LZ, Anzic J, Korenjak R, Jereb B (2006) The role of radiotherapy in the treatment of childhood intracranial germinoma: long-term survival and late effects. Pediatr Blood Cancer 47: 77–82
Sukov WR, Cheville JC, Giannini C, Carlson AW, Shearer BM, Sinnwell JP, Ketterling RP (2010) Isochromosome 12p and polysomy 12 in primary central nervous system germ cell tumors: frequency and association with clinicopathologic features. Hum Pathol 41(2):232–238. doi:10.1016/j.humpath.2009.07.017
Tada T, Takizawa T, Nakazato F, Kobayashi S, Koike K, Oguchi M, Ishii E, Amano Y (1999) Treatment of intracranial nongerminomatous germ-cell tumor by high-dose chemotherapy and autologous stem-cell rescue. J Neurooncol 44:71–76
Takei Y, Pearl GS (1981) Ultrastructural study of intracranial yolk sac tumor: with special reference to the oncologic phylogeny of germ cell tumors. Cancer 48:2038–2046
Tan C, Scotting PJ (2013) Stem cell research points the way to the cell of origin for intracranial germ cell tumours. J Pathol 229(1):4–11. doi:10.1002/path.4098
Teilum G (1976) Special tumors of ovary and testis and related extragonadal lesions: comparative pathology and histological identification. J.B. Lippincott, Philadelphia
Tseng KY, Ma HI, Liu WH, Tang CT (2012) Endoscopic supracerebellar infratentorial retropineal approach for tumor resection. World Neurosurg 77(2):399.E1–E4. doi:10.1016/j.wneu.2011.05.035
Uematsu Y, Tsuura Y, Miyamoto K, Itakura T, Hayashi S, Komai N (1992) The recurrence of primary intracranial germinomas. Special reference to germinoma with STGC (syncytiotrophoblastic giant cell). J Neurooncol 13:247–256
Wang L, Yamaguchi S, Burstein MD, Terashima K, Chang K, Ng H-K et al (2014) Novel somatic and germ line mutations in intracranial germ cell tumours. Nature 511(7508):241–245. doi:10.1038/nature13296
Weiner HL, Lichtenbaum RA, Wisoff JH, Snow RB, Souweidane MM, Bruce JN, Finlay JL (2002) Delayed surgical resection of central nervous system germ cell tumors. Neurosurgery 50:727–733, discussion 733–724
Wolden SL, Wara WM, Larson DA, Prados MD, Edwards MS, Sneed PK (1995) Radiation therapy for primary intracranial germ-cell tumors. Int J Radiat Oncol Biol Phys 32:943–949
Yoshida J, Sugita K, Kobayashi T, Takakura K, Shitara N, Matsutani M, Tanaka R, Nagai H, Yamada H, Yamashita J et al (1993) Prognosis of intracranial germ cell tumours: effectiveness of chemotherapy with cisplatin and etoposide (CDDP and VP-16). Acta Neurochir 120:111–117
Yu IT, Griffin CA, Phillips PC, Strauss LC, Perlman EJ (1995) Numerical sex chromosomal abnormalities in pineal teratomas by cytogenetic analysis and fluorescence in situ hybridization. Lab Invest 72:419–423
Zimmerman RA, Bilaniuk LT (1982) Age-related incidence of pineal calcification detected by computed tomography. Radiology 142:659–662
Zynger DL, Everton MJ, Dimov ND, Chou PM, Yang XJ (2008) Expression of glypican 3 in ovarian and extragonadal germ cell tumors. Am J Clin Pathol 130(2):224–230. doi:10.1309/8DN7DQRDFB4QNH3N

Craniopharyngioma

7

Lauren Ostling, Daphne A. Haas-Kogan,
Robert H. Lustig, and Nalin Gupta

Contents

L. Ostling, MD
Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

Department of Neurological Surgery, UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA
e-mail: lauren.ostling@ucsf.edu

D.A. Haas-Kogan, MD
Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute and Boston Children's Hospital, Boston, MA, USA

R.H. Lustig, MD, MSL
Department of Pediatrics & Institute for Health Policy Studies, University of California, San Francisco, CA, USA

UCSF Benioff Children's Hospital San Francisco, San Francisco, CA, USA

N. Gupta, MD, PhD (✉)
Division of Pediatric Neurosurgery, Departments of Neurological Surgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA
e-mail: nalin.gupta@ucsf.edu

7.1 Introduction

Harvey Cushing, who coined the term craniopharyngioma, stated that these tumors "offer the most baffling problem which confronts the neurosurgeon," which still holds true today (Cushing 1932). Craniopharyngiomas are histologically benign neuroepithelial tumors that arise from rests of squamous cell epithelium that remain along the path of the primitive craniopharyngeal duct and adenohypophysis. Although considered benign (WHO grade I) tumors of the sellar

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_7

region, they have a propensity to adhere to adjacent structures such as the hypothalamus and optic chiasm. This feature can prevent a complete resection from being achieved. Furthermore, even if a complete resection is achieved, there is the possibility of significant postoperative morbidity. Currently, there are reports in the literature favoring a variety of approaches such as gross total resection (GTR), subtotal resection (STR) with radiation, or intracystic therapy, including ^{32}phosphorous, bleomycin, and interferon-alpha. In the pediatric population, the short-term and long-term adverse effects of radiation therapy must be carefully weighed against the potential surgical morbidity. More recently, based upon the discovery of mutations in the beta-catenin gene *CTNNB1*, and corresponding abnormal signaling in the Wnt pathway in a subset of adamantinomatous craniopharyngiomas, new chemotherapeutic agents are also being proposed (Kato et al. 2004; Buslei et al. 2005; Cao et al. 2010; Hussain et al. 2013).

7.2 Epidemiology

For children and adolescents, the incidence of craniopharyngioma is estimated to be 0.19 per 100,000 person years according to data obtained from the Central Brain Tumor Registry of the United States (CBTRUS; Ostrem et al. 2015). There is a distinct bimodal distribution with peaks at 5–14 years of age and then in later adulthood (65–74 years of age). There is no definitive data that indicates a gender or racial predilection. Three to 6 % of all primary brain tumors in children are craniopharyngiomas, and they are the most common non-glial tumor in the pediatric population (Hoffman et al. 1977; May et al. 2006; Wisoff and Donahue 2015; Ostrom et al. 2015).

7.3 Pathology

7.3.1 Etiology

There are two main histologic subtypes of craniopharyngiomas: adamantinomatous and papillary. The vast majority in children (>90 %) are of the adamantinomatous subtype. Two theories exist regarding the origin of these tumors. The "embryogenetic theory" suggests that adamantinomatous subtype arises from remnants of Rathke's pouch (Donovan and Nesbit 1996). In the middle of the fourth week of gestation, Rathke's pouch projects upward from the roof of the stomodeum (oral cavity) and grows toward the infundibulum, which is a downward growth from the diencephalon (Fig. 7.1). During the sixth week of gestation, the connection between Rathke's pouch and the oral cavity (the pharyngohypophyseal stalk) disappears. Rathke's pouch then develops into the pars distalis, pars intermedia, and pars tuberalis which comprise the adenohypophysis (Samii and Tatagiba 1997). The "metaplastic theory" suggests that tumors from the papillary subtype arise from metaplasia of squamous cell rests that contributed to developing buccal mucosa (Miller 1994).

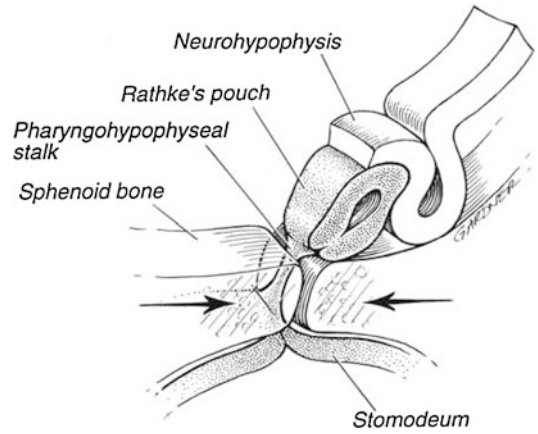

Fig. 7.1 Rathke's pouch projects from the roof of the stomodeum and grows toward the infundibulum during the fourth week of gestation. During the sixth week of gestation, the connection between Rathke's pouch and the pharyngohypophyseal stalk disappears. Rathke's pouch then develops into the adenohypophysis. Craniopharyngiomas are generally believed to develop from squamous cell rests along the path of the primitive craniopharyngeal duct and adenohypophysis

7.3.2 Classification

Although the adamantinomatous type is common in all age groups, the squamous papillary type is rare in children. In pediatric studies, 92–96 % were

adamantinomatous, 0 % were squamous papillary, 0–4 % were mixed, and 4 % were not classified (Miller 1994; Weiner et al. 1994). In adults, 63–66 % were adamantinomatous, 27–28 % were squamous papillary, 6–7 % were mixed, and 3 % were not classified. The squamous papillary tumors are seen almost exclusively in adults and make up 11–14 % of all craniopharyngiomas and approximately 28 % of adult tumors (Weiner et al. 1994; Miller 1994; Pekmezci et al. 2010).

Aside from the pathologic subgroups, craniopharyngiomas can be divided into four groups based upon their relationship to the optic chiasm. These include sellar or infrachiasmatic, prechiasmatic, retrochiasmatic, and giant or laterally expansile tumors. This classification is important in understanding how tumors in each of these locations present and, as will later be discussed, the different operative approaches and considerations that must be taken into account for each anatomic location. Sellar or subchiasmatic tumors do not typically involve the optic chiasm and, therefore, do not present with visual disturbances. They can, however, present with pituitary dysfunction as invasion into the pituitary gland can occur when the diaphragma is not preserved. Prechiasmatic tumors grow between the optic nerves and tend to expand anteriorly. Thus, they typically avoid the development of hydrocephalus but can lead to visual deficits from compression of the optic nerve(s) or the chiasm. Retrochiasmatic lesions tend to push the chiasm anteriorly and can thin the chiasm. These tumors often grow into and fill the third ventricle, which leads to the development of hydrocephalus and patients may present with signs and/or symptoms of increased intracranial pressure. Giant tumors can present with any of the above findings including visual or endocrine disturbance, signs of elevated intracranial pressure, or even posterior fossa signs (Hoffman 1994).

7.3.3 Histopathology

The adamantinomatous subtype is characterized by cysts, which contain a cholesterol rich, brownish color fluid, along with clusters of columnar cells and loose stellate zones (Sidawy and Jannotta 1997). Pale eosinophilic masses, known as "wet keratin" or "keratin nodules," can be seen from desquamated epithelium, and areas of calcification are common. The tissue is very similar to tumors of tooth-forming tissues seen in the oropharynx and long bones which are called adamantinomas, hence the term adamantinomatous craniopharyngiomas. Microscopically, the epithelium consists of a basal layer of small basophilic cells, followed by an intermediate layer of variable thickness composed of a loose collection of stellate cells whose processes traverse the intercellular spaces (Fig. 7.2). The top layer consists of keratinized squamous cells, which desquamate as stacks of flat keratin plates within the cyst cavity. Therefore, the cyst fluid is rich in membrane lipids such as cholesterol and keratin and can cause chronic inflammation within the cyst walls. The desquamated cells often calcify and can rarely progress to metaplastic bone formation (Miller 1994). Areas of gliosis with Rosenthal fibers are also frequently seen at the interface between tumor and surrounding normal tissue. The papillary subtype consists of well-differentiated stratified, squamous epithelium organized into cords that extend into the surrounding tissues. Typically, calcifications and desquamated cells are absent (Muller 2014). The cyst fluid is typically lighter in color, and the cells are more tightly arranged in comparison (Miller 1994; Prabhu and Brown 2005). Mixed craniopharyngiomas do exist and have features of both adamantinomatous and papillary types (Prieto and Pascual 2013).

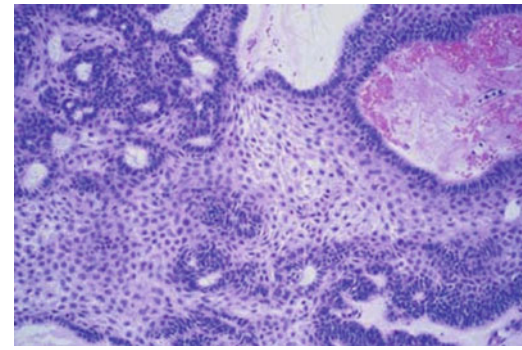

Fig. 7.2 Adamantinomatous craniopharyngioma showing palisading basal squamous epithelium surrounding loosely arranged epithelial cells (stellate reticulum) and nodules of eosinophilic keratinized cells

7.3.4 Tumor Biology

The oncogenesis of craniopharyngioma remains unclear. Although a number of previously identified markers used in the characterization of other tumors have been used, their value for these tumors is limited. For example, although the proliferative activity of craniopharyngiomas based on their MIB-1 immunostaining for the Ki-67 nuclear antigen is known, no correlation was identified with morphological features or clinical outcomes (Raghavan et al. 2000). The estrogen receptor gene is expressed in the proliferative epithelial component of adamantinomatous and papillary craniopharyngiomas, suggesting hormonal involvement in the genesis and/or progression of craniopharyngiomas, but no correlation was identified with clinical outcome (Thapar et al. 1994). Strong cytoplasmic immunoreactivity for vascular endothelial growth factor (VEGF) in the epithelial cells of both adamantinomatous and papillary craniopharyngiomas was identified and microvessel density, a measure of angiogenesis, correlated with an increased risk of recurrence (Vidal et al. 2002). However, not every recurrent tumor had a high microvessel density, indicating that other factors are involved.

The genetic alterations involved in the pathogenesis of craniopharyngiomas are not well known. Sarubi et al. studied three genes associated with odontogenic tumors, *Gsα*, *Gi2α*, and *patched* (*PTCH*), in a group of 22 adamantinomatous craniopharyngiomas but did not identify any mutations (Sarubi et al. 2001). Matsuo et al. demonstrated the expression of prostaglandin H synthetase-2 (PHS-2) in a variety of brain tumors, including two out of four craniopharyngiomas, but the significance of this isolated finding remains unclear (Matsuo et al. 2001). Nozaki et al. found no evidence of *TP53* mutations in four craniopharyngiomas (Nozaki et al. 1998).

Buslei et al. examined the role of the Wnt signaling pathway in the pathogenesis of craniopharyngioma. Nuclear localization of beta-catenin, a transcriptional regulator involved in tumorigenesis and inhibited by the Wnt signaling cascade (Takamaru et al. 2008), is seen in adamantinomatous craniopharyngioma, but not in the more benign Rathke's cleft cyst (Hoffman et al. 2006). This group also found mutations within exon 3 of the *CTNNB1* gene, which codes for beta-catenin and translates into aberrant target gene expression within the adamantinomatous craniopharyngioma (Hölsken et al. 2008). Although intriguing, it is not clear if new therapeutic agents can be developed to take advantage of these targets.

7.4 Clinical Features

7.4.1 Neurologic Signs and Symptoms

The anatomic location of craniopharyngiomas in the sellar and suprasellar region results in predictable clinical patterns. Symptoms and signs develop due to compression or destruction of the optic chiasm, nerves and/or tracts, hypothalamus, pituitary stalk, or adjacent vascular structures. Children typically present with headache (50–70 %), visual disturbance (23–58 %), or endocrine abnormalities (10–33 %) (de Vries et al. 2003; Merchant et al. 2002; Stripp et al. 2004). Mental status changes are unusual in children, but occur in 25 % of adults.

The exact location of the tumor can result in varying clinical pictures. For example, retrochiasmatic tumors will displace the chiasm in an anterior direction and grow into the third ventricle leading to hydrocephalus; thus, roughly 60 % of patients present with headache, 50 % with nausea, 35 % with vomiting, and 10–20 % with lethargy (Sanford 1994; Hoffman et al. 1999; Merchant et al. 2002; de Vries et al. 2003; Stripp et al. 2004). A midline suprasellar mass typically causes a superior temporal quadrantanopia by compression of the overlying optic chiasm, but eccentric growth of a craniopharyngioma can lead to patterns of visual loss that vary in type and severity. Eighty percent of adults experience visual disturbance, while only 20–63 % of children have this sign (Merchant et al. 2002; de Vries et al. 2003; Stripp et al. 2004); this discrepancy may be due to the lack of awareness among children of a progressive narrowing of the peripheral fields. Toddlers, in particular, can become virtually blind before the extent of visual loss becomes apparent. Visual acuity and field testing should be performed in all patients,

although accurate field testing is difficult to perform in young children.

7.4.2 Endocrine Signs and Symptoms

Craniopharyngiomas can compress or destroy the hypothalamus, anterior pituitary, or the pituitary stalk, leading to varying types of endocrinopathy. Virtually all of the pituitary hormones can be affected, including GH (75 %), luteinizing hormone (LH) or follicle-stimulating hormone (FSH) (40–44 %), adrenocorticotropic hormone (ACTH) (25–56 %), and thyroid-stimulating hormone (TSH) (25–64 %). Hyperprolactinemia occurs in 1–20 % of cases from impingement on the pituitary stalk (also known as the "stalk effect"), due to reduced amounts of prolactin inhibitory factor (mainly dopamine) reaching the lactotrophs of the anterior pituitary. Diabetes insipidus occurs only in approximately 16 % of patients prior to surgery (Sanford and Muhlbauer 1991; Honegger et al. 1999; Moore and Couldwell 2000; de Vries et al. 2003), although it is extremely common in the postoperative setting (see Sect. 7.9.1).

GH deficiency, hypothyroidism, and gonadotropin deficiency are the three most common endocrine abnormalities at presentation in children (Sanford and Muhlbauer 1991; Merchant et al. 2002; de Vries et al. 2003; Stripp et al. 2004). Short stature is the most common endocrinologic aberration on presentation occurring in about 33 % of pediatric cases (Merchant et al. 2002). However, review of the German Kraniopharyngiom database reveals that virtually all children exhibit a reduction in growth prior to diagnosis (Muller et al. 2004).

Hypothyroidism leads to poor growth, weight gain, cold intolerance, and fatigability (Rose et al. 1999b; Zhou and Shi 2004). Gonadotropin deficiency may only be evident in adolescents, but interferes with the pubertal growth spurt. Growth failure can be a result of GH deficiency, central hypothyroidism, gonadotropin deficiency, or a combination of all three. ACTH deficiency is less common at presentation (Honegger et al. 1999), but is potentially life-threatening (see Sect. 7.9.4). Lastly, many of these children have increased body mass index (BMI) at presentation, due to continued weight gain in the absence of normal growth (Muller et al. 2004). However, the obesity is likely to worsen, due to post-therapy damage of the ventromedial hypothalamus, with resultant dysregulation of energy balance, termed "hypothalamic obesity" (see Sect. 7.9.4) (Hoffman et al. 1999; Lustig 2002, 2008; Lustig et al. 2003).

7.5 Natural History

Craniopharyngiomas are histologically and cytologically benign, but locally aggressive and tend to recur. Untreated craniopharyngiomas demonstrate progressive growth causing mass effect or hydrocephalus. The rate of recurrence with any form of treatment is 8–26 % at 5 years and 9–100 % at 10 years (Fahlbusch et al. 1999; Stripp et al. 2004). If recurrence cannot be controlled, local invasion and growth can result in death. Malignant change, however, is extremely rare. There is one report of an adamantinomatous craniopharyngioma in a patient who underwent surgical resections and three courses of radiotherapy, which underwent subsequent transition into a moderately differentiated squamous cell carcinoma (Kristopaitis et al. 2000). Other cases of malignant transformation reported in literature were presumably from transplantation of tumor fragments during surgery or from meningeal seeding (Barloon et al. 1988; Ragoowansi and Piepgras 1991; Malik et al. 1992; Israel and Pomeranz 1995; Gupta et al. 1999; Lee et al. 1999; Ito et al. 2001).

7.6 Diagnosis and Imaging

7.6.1 Computed Tomography and Magnetic Resonance Imaging

While plain films of the skull are rarely used today, they can provide useful diagnostic information that may suggest a craniopharyngioma. Up to 65 % of adults and 90 % of children will have abnormal findings on plain films such as erosion of the sella, enlargement of the sella, or

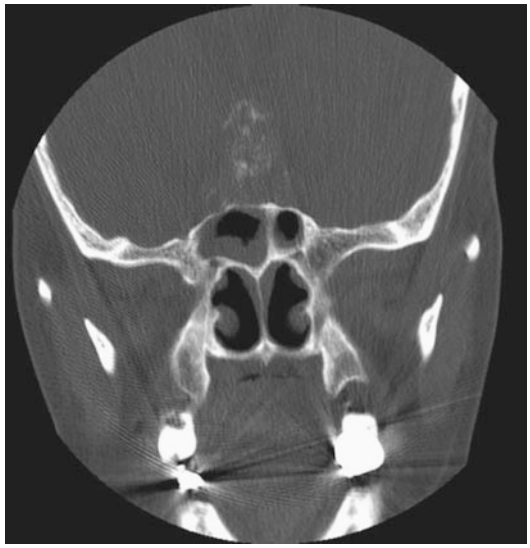

Fig. 7.3 CT scan (coronal view) showing punctate calcifications within a tumor

calcification in the location of the tumor (Harwood Nash 1994). Adult tumors have associated calcification approximately 40 % of the time, compared to 85 % of pediatric cases (Moore and Couldwell 2000). Sellar enlargement is seen in 65 % of patients, while sellar erosion is seen in 44 % (Donovan and Nesbit 1996).

CT and MRI are much more commonly used today as initial diagnostic imaging tools. Typically, CT will reveal a mixed density, often lobulated, lesion consisting of solid and cystic portions, with hyperdense calcifications frequently present (Fig. 7.3). Any associated hydrocephalus or erosion of the sella can also be clearly evaluated by CT. The cystic component will appear iso- or hypodense. Most frequently, tumors will have both an intrasellar and suprasellar component (75 %), while a smaller proportion will be purely suprasellar (20 %) and very rarely can be located purely within the third ventricle.

An MRI with and without contrast administration is the study of choice for craniopharyngioma. While calcification can be more difficult to appreciate, an MRI defines the critical relationships between the tumor and the surrounding vessels, optic chiasm, hypothalamus, and sella. Similar to CT, the tumor will have a heterogeneous appearance with the cystic portion of adamantinomatous lesions appearing iso- or even hyperintense on T1-weighted images due to the high protein content within the cyst. If a papillary tumor has a cystic component, the cyst more frequently resembles CSF density. The solid component, of either histologic subtype, will avidly enhance after the administration of contrast (Figs. 7.4 and 7.5).

The differential diagnosis of cystic suprasellar masses in children includes Rathke's cleft cysts (which usually do not have a solid component, are not lobulated, are nonenhancing, and are more homogeneous), pituitary adenomas (which enlarge the sella, are more homogeneous, and are usually less cystic), meningiomas (which are rarely cystic and are isointense on T1- and T2-weighted images), optic pathway gliomas (which are usually not calcified), and giant aneurysms (which usually contain a laminated thrombus) (Donovan and Nesbit 1996; Fischbein et al. 2000).

7.6.2 Clinical Evaluation

The evaluation and management of patients with craniopharyngiomas requires a multidisciplinary team approach, with the active participation of subspecialties such as neurosurgery, radiation and medical oncology, neuroophthalmology, endocrinology, and psychology.

If the patient does not require immediate neurosurgical intervention, then they should have a complete assessment of visual acuity and a visual field examination prior to treatment. Endocrine function should be evaluated both clinically and by laboratory measurements. A complete endocrine assessment is necessary prior to surgery and is invaluable when varying degrees of endocrine dysfunction may develop (Table 7.1). Where possible, based on the projected time to surgery, hormonal deficiencies should be treated (Wilson et al. 1998). All patients should get stress-dose steroids prior to surgery on the assumption that normal ACTH regulation is blunted (Samii and Tatagiba 1997); however, the use of dexamethasone to reduce brain swelling provides more than adequate glucocorticoid coverage. Hypothyroidism can take several days to correct and should be begun preoperatively; however, thyroxine supplementation can induce hepatic P450 enzymes responsible for metabolizing

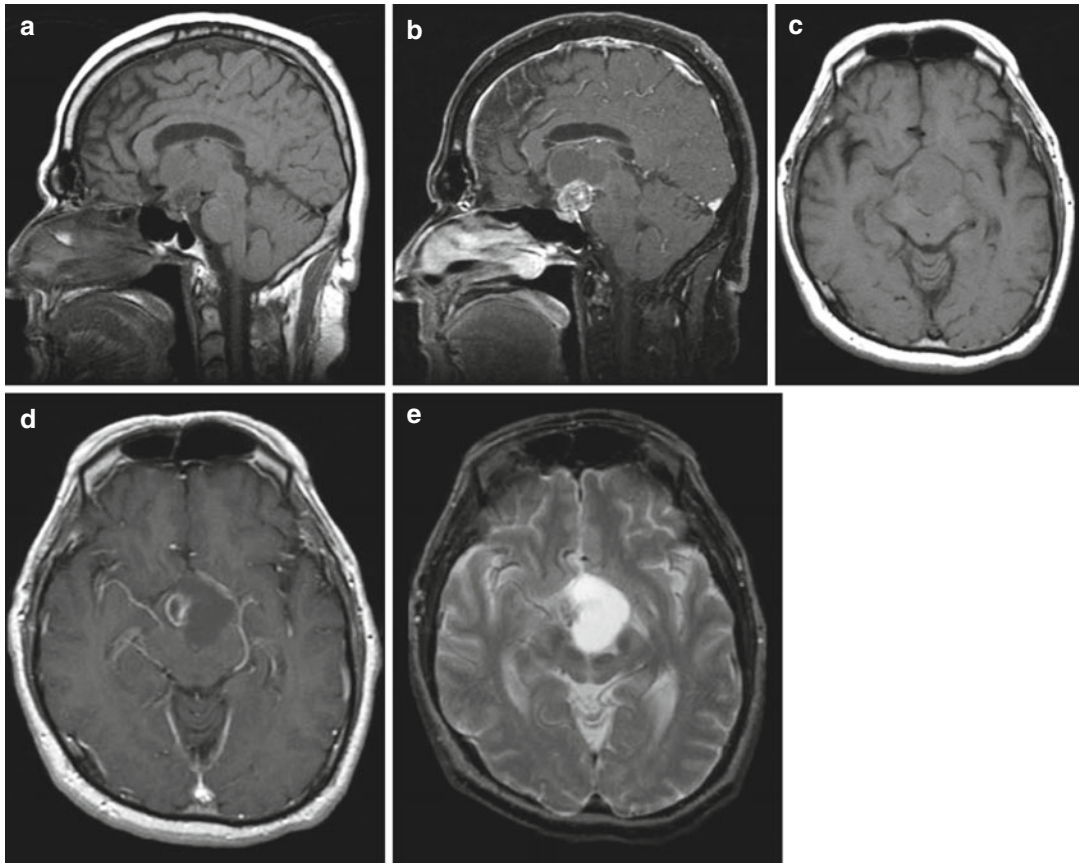

Fig. 7.4 Multiple MRI sequences of a typical mixed solid and cystic craniopharyngioma: (**a**) Sagittal T1-weighted image without contrast. A multilobulated mass is seen in the suprasellar region. (**b**) Sagittal T1-weighted image following gadolinium. The suprasellar solid component enhances, while the cystic area above it does not. (**c**) Axial T1-weighted image without contrast. (**d**) Axial T1-weighted image with gadolinium, (**e**) axial T2-weighted image

glucocorticoid, thereby unmasking glucocorticoid insufficiency and leading to hypotension and shock. Thus, glucocorticoid must be replaced prior to thyroxine supplementation (Moore and Couldwell 2000). Finally, any fluid and electrolyte abnormalities, including diabetes insipidus, should be identified and treated prior to surgery.

7.7 Treatment

7.7.1 Surgery

7.7.1.1 Surgical Indications

There are three goals in the surgical treatment of craniopharyngiomas: diagnosis, decompression, and prevention of recurrence (Van Effenterre and Boch 2002). For the most part, current imaging studies provide a high degree of confidence in terms of diagnosis. Hydrocephalus can be treated acutely with either an external ventricular drain or a ventriculoperitoneal shunt prior to definitive surgery. Patients with craniopharyngiomas who present with acute visual deterioration or symptoms of elevated intracranial pressure from tumor-associated mass effect also require urgent surgical decompression. Since endocrine abnormalities such as hypothyroidism or diabetes insipidus may take several days to correct, a patient who is neurologically stable should have surgery performed electively after all endocrine abnormalities are controlled. Patients with large tumors will benefit from dexamethasone to reduce cerebral edema.

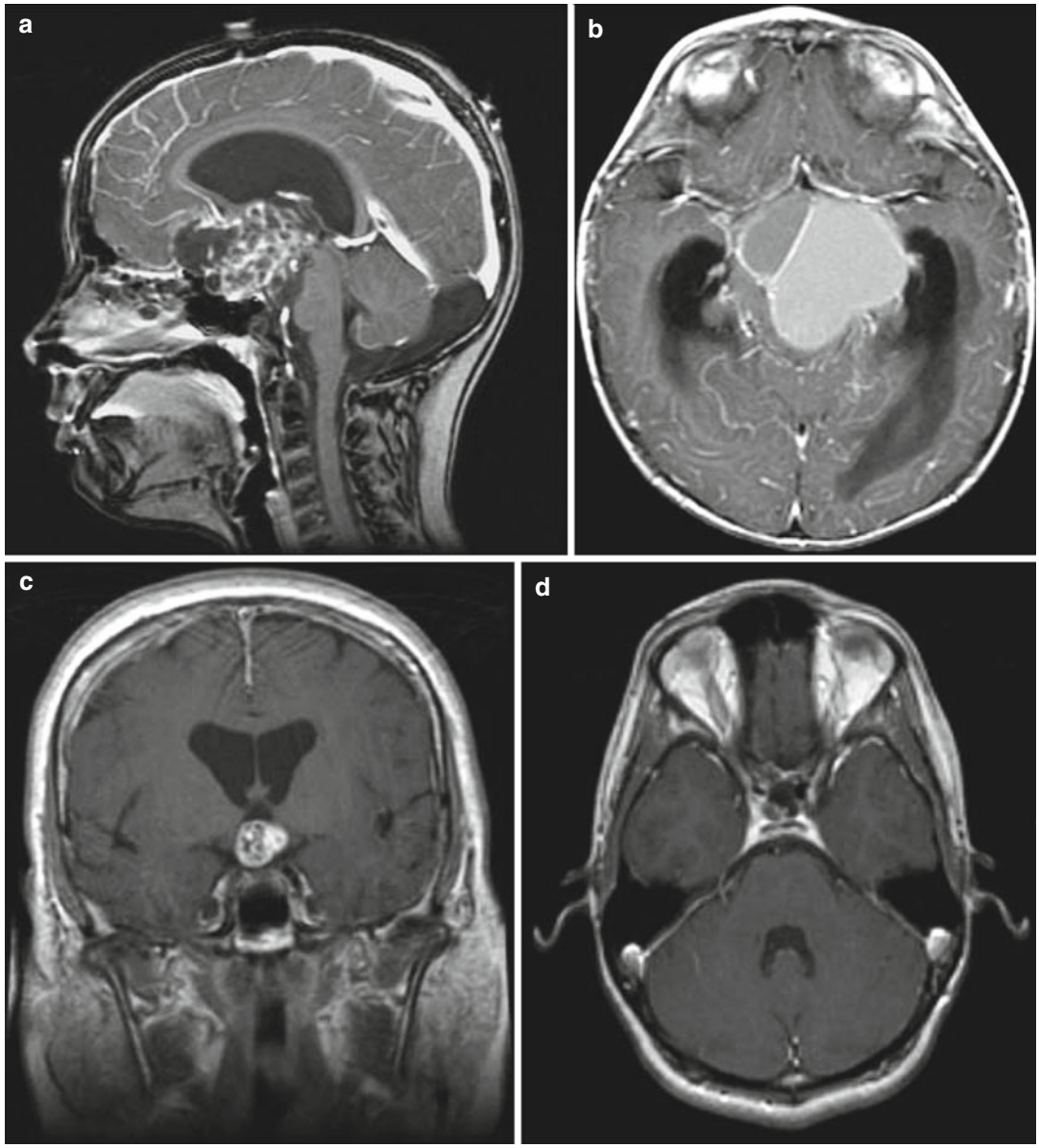

Fig. 7.5 Other examples of craniopharyngiomas: (**a**) Sagittal T1-weighted image with contrast showing a large mixed solid and cystic craniopharyngioma. (**b**) Axial T1-weighted image with contrast showing a large cystic craniopharyngioma with two major compartments. (**c**) Coronal T1-weighted image with contrast showing a small, solid suprasellar craniopharyngioma. (**d**) Axial T1-weighted image with contrast showing a small, recurrent craniopharyngioma within the sella

The goals of the surgical procedure should be clearly defined, as well as a recognition of potential risks associated with the size, location, and nature of the tumor. A small purely sellar tumor can be removed completely with postoperative morbidity restricted to endocrine dysfunction. A larger tumor that extends into the third ventricle with attachment to the hypothalamus may be associated with substantial morbidity if complete resection is planned. The consequences of complete anterior and posterior pituitary dysfunction also vary depending on the patient's age and

Table 7.1 Endocrine evaluation

Endocrine function	Tests
Adrenal axis	8 a.m. cortisol level
	24-h urine free cortisol level
	ACTH stimulation test
	Metyrapone test (difficult to get metyrapone currently)
Thyroid axis	Free T4 level
	Thyroid-stimulating hormone level
	Thyarotropin-releasing hormone stimulation test in questionable cases
Gonadal axis	Follicle-stimulating hormone level
	Luteinizing hormone level
	Sex steroids: estradiol in women, testosterone in men
Growth hormone (GH)	IGF-I level
	IGFBP-3 level
	GH stimulation test (GH is pulsatile and low during the day, so a single random level is useless)
Prolactin	Prolactin level
	Serum sodium or osmolality
Antidiuretic hormone (ADH)	Urine specific gravity or osmolality
	Fluid intake vs. urine output
	Water deprivation test in difficult cases
Hypothalamic obesity	Oral glucose tolerance test with simultaneous insulin levels

whether he/she has already completed puberty. The expectations of the postoperative complications should be clearly explained to the patient's family prior to surgery.

7.7.1.2 Surgical Approaches

The surgical approach for craniopharyngiomas is largely dictated by tumor location, size, consistency, and anatomical relationships, as well as comfort of the surgeon with the particular approach. Techniques include both open and endoscopic approaches, or a combination of both may be utilized. Open microsurgical procedures include pterional, subfrontal, bifrontal interhemispheric, interhemispheric transcallosal, and transcortical transventricular approaches. Modifications to the pterional approach, such as the orbitofrontal and orbitozygomatic approach, may also be employed. Typically, the interhemispheric transcallosal and transcortical transventricular approaches are reserved for purely intraventricular tumors. As with all operative approaches, there are advantages and disadvantages to each route, but a detailed description of each operative approach will not be covered here.

The pterional route allows for access to both prechiasmatic and retrochiasmatic lesions and provides a lateral view. However, a significant amount of retraction may be necessary for larger tumors after dissection of the Sylvian fissure. Furthermore, lesions which extend superiorly far into the third ventricle may require a combined orbitozygomatic approach to allow for optimal visualization. Subfrontal approaches are best for prechiasmatic lesions and allow for early visualization of the optic nerves, internal carotid arteries, and lamina terminalis. Disadvantages include difficult access to the sella without the use of an angled endoscope, possible olfactory nerve injury, and potential entry into the frontal sinus requiring cranialization. In the bifrontal interhemispheric approach, a wider view is obtained, and one can gain access to large, retrochiasmatic lesions, but with the added potential cost of bilateral frontal lobe injury. Again, interhemispheric transcallosal and transcortical transventricular approaches are most often used when approaching purely intraventricular tumors or when a combined approach is needed.

Historically, the transsphenoidal route was used purely for tumors which were confined to the sella and below the diaphragm. More recently, the extended endoscopic-endonasal approach allows access to tumors in the suprasellar compartment. The advantages of this approach include direct access to the inferior portion of the tumor and visualization of important structures such as the chiasm and hypothalamus, avoidance of brain retraction associated with open approaches, and cosmesis/avoidance of craniotomy (Fernandez-Miranda et al. 2012). One series from Pittsburgh included 17 children with a mean follow-up time of 35.3 months. All patients were treated by an endoscopic-endonasal approach unless they had a purely intraventricular tumor.

GTR was achieved in 52.9% of patients. Postoperatively, no patients developed new visual deficits, but over 75% had worsened or new pituitary dysfunction, 78% developed DI, and 33% had new onset obesity. CSF leak occurred in 11%, and more significantly, 41.2% of the pediatric cohort experienced tumor recurrence during follow-up, with an average of 19.6 months of progression-free survival (Koutourousiou et al. 2013). In another smaller series of seven patients treated by an endoscopic-endonasal approach for suprasellar craniopharyngiomas, GTR was achieved in all patients (Ali et al. 2013). Visual deficits improved in all patients, CSF leak occurred in 15%, DI occurred in 100%, and five of the seven had worsening or new anterior pituitary dysfunction. The endoscopic-endonasal approach appears to result in comparable outcomes as open procedures, but there are limitations to its use.

For intrasellar and monocystic craniopharyngiomas, the transsphenoidal approach is ideal in allowing drainage of the cyst and decompression of the optic chiasm. In a small group of cases at our institution, intracystic treatment with alcohol at the time of surgery resulted in excellent tumor control with minimal endocrine dysfunction (Fig. 7.6).

7.7.2 Radiation Therapy

7.7.2.1 Conventional Radiotherapy

Radiation has been a mainstay of craniopharyngioma treatment for decades and is utilized for both initial and salvage therapies for recurrences. While the benefit of radiation therapy is clear in terms of tumor control, it must be carefully balanced with the negative long-term consequences of radiation, particularly in very young children. Long-term side effects including secondary malignancies, neurocognitive decline, vasculopathy, endocrinologic disturbances, and visual disturbances have all been well described.

Conventional fractionated radiation therapy consists of the delivery of a high dose of radiation to a target by dividing the treatment into multiple doses, with a single dose, or fraction, given each day, allowing for normal tissue repair between fractions. Total doses have typically ranged from 50 to 65 Gy, divided into 1.8–2 Gy daily fractions (Merchant et al. 2002). Typically, the maximum dose delivered to the optic apparatus is 50–54 Gy. Current dosing is typically 50–54 Gy divided into daily fractions of 1.8–2 Gy. Cyst growth during or after radiation therapy has been well documented and requires frequent imaging to ensure appropriate volume modifications and interventions if indicated (Bishop et al. 2014; Merchant et al. 2013; Winkfield et al. 2009; Boehling).

7.7.2.2 Intensity-Modulated Radiotherapy

Intensity-modulated radiation therapy (IMRT), a form of photon therapy, utilizes "beamlets" of varying intensities in attempts to conform to the tumor boundaries with rapid falloff of dosage to surrounding tissues. This results in a lower dose to a larger area of surrounding tissue (integral dose) compared to conventional radiotherapy which results in a higher dose to smaller amount of surrounding tissue (Wisoff and Donahue 2015).

7.7.2.3 Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) typically consists of one to five treatments, using either a Gamma Knife unit or a linear accelerator, of focused radiation to the target (tumor) and allows for a greater decrement in dosage to the surrounding normal tissues. No more than 8–10 Gy can be delivered in a single dose to the optic apparatus. Higher doses have been shown to result in optic neuropathy (Leber et al. 1998; Stafford et al. 2003). Therefore, multisession or fractionated treatment has become attractive for most craniopharyngioma patients given the tumor's relationship to critical structures.

7.7.2.4 Fractionated Stereotactic Radiosurgery

Fractionated SRS is typically done in more than five, and usually 25–28, treatment sessions. This technique has the advantages of both fractionated external beam radiation therapy (normal tissue

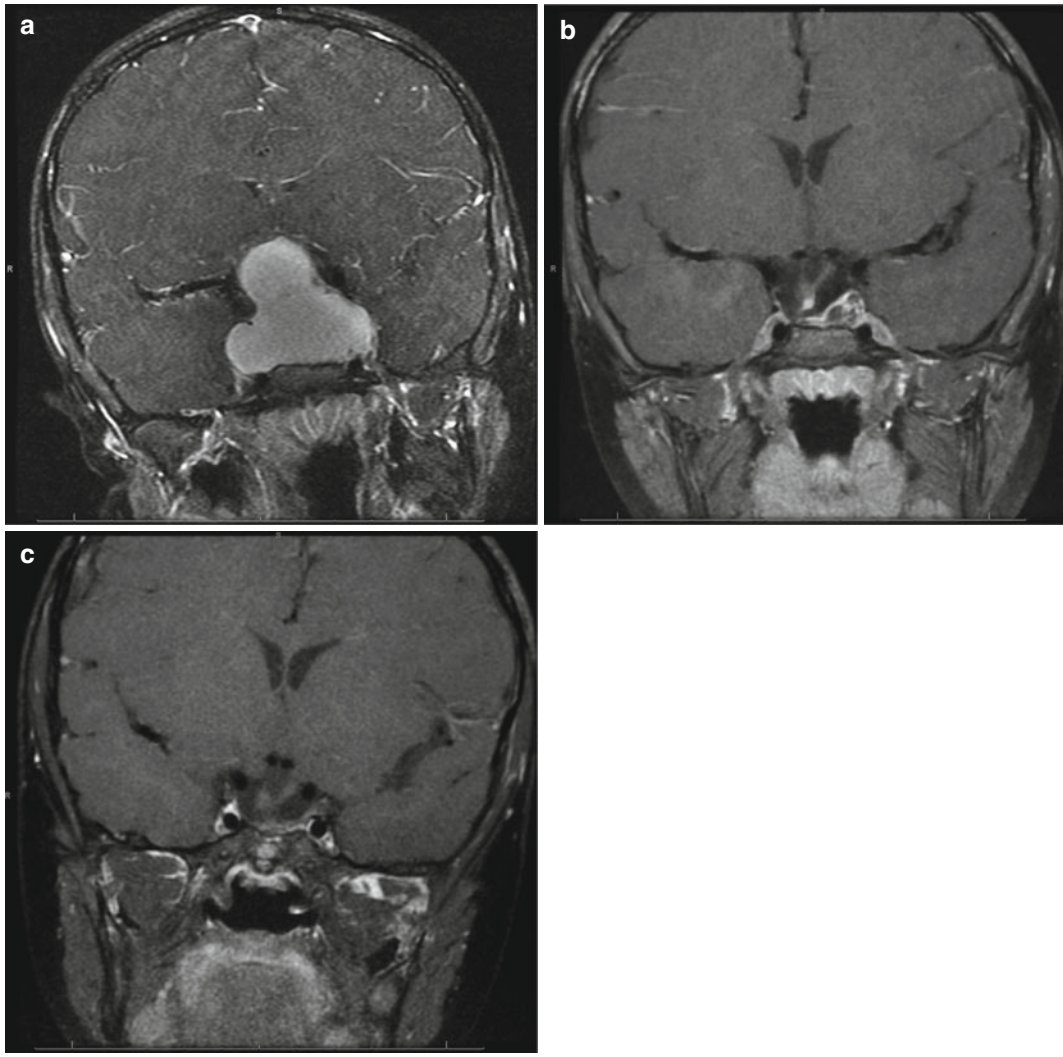

Fig. 7.6 (**a**) Coronal T1-weighted image with contrast showing a large cystic suprasellar craniopharyngioma in a 4-year-old girl. (**b**) Six months following a transsphenoidal procedure, the cyst is completely decompressed with a small residual lesion along the left side of the sella. This showed growth several years later and was removed by another transsphenoidal procedure. (**c**) Seven years after presentation, there is no residual tumor; the patient requires GH and thyroid supplementation but does not have DI

repair between fractions) and radiosurgery (minimal dose to structures away from the targeted region) and can be used to treat tumors that are greater than 3 cm, as well as those that abut the optic apparatus.

A large series from the University of Heidelberg (Combs et al. 2007) reported 100 % local control at both 5 and 10 years following treatment. Overall survival rates were 97 % and 89 %, respectively. The median target dose was 52.2 Gy, given with conventional fractionation of 1.8 Gy per fraction. A complete response was observed in 4 patients, partial response in 25 patients, and stable disease in 11 patients. There were no visual impairments or second malignancies reported at a median follow-up time of 98 months. These results were corroborated by a similar series using stereotactic techniques with conventional fractionation from the Royal Marsden Hospital (Minniti et al. 2007).

7.7.2.5 Proton Beam Therapy

Proton therapy is also being used for the treatment of craniopharyngioma patients. The benefit of proton therapy is the inverse dosing profile, which results in less radiation to normal tissues proximal to the target and nearly no radiation to normal tissues distal to the target as a product of the distal Bragg peak (Suit et al. 1975; Luu et al. 2006). This reduction in integral dosage to normal tissues has been quantified by Boehling et al. for a number of structures in comparison to IMRT including the hippocampus, brainstem, and vascular structures (Boehling et al. 2012). Theoretically, this may result in a decrease in radiation-induced vasculopathy and neurocognitive decline seen with other forms of radiotherapy. Future studies with long-term neurocognitive outcomes will help answer this question.

Recent publications have highlighted potential higher toxicities with protons as compared to photons. Using protons, the tumor volume and adjacent normal tissues receive high doses equivalent to those using photons, but dose-effect models were derived chiefly using photons, without incorporating uncertainties that still exist regarding proton-dose deposition and biological effects. A study examining imaging changes following proton- and photon-based (IMRT) radiotherapy demonstrated increased changes following proton-based radiation compared to photon-based IMRT. Furthermore, only proton-treated patients experienced grade 3 or 4 changes and had persistent symptoms, including one grade 5 toxicity related to radiation necrosis documented on autopsy (Gunther et al. 2015). A similar study assessing brainstem toxicity following proton radiotherapy for pediatric brain or skull-base tumors reported a 2-year cumulative incidence of grade 3 or higher brainstem toxicity of 2.1 ± 0.9 %, with one grade 5 toxicity (Indelicato et al. 2014).

The largest pediatric series using proton therapy includes a total of 16 patients aged 7–34 years (Luu et al. 2006). Patients were treated for both initial treatment following resection and for recurrences. Twelve patients survived, three of which developed treatment-related toxicity including panhypopituitarism at 36 months, cerebrovascular accident at 34 months, and meningioma in a patient who had previously received photon therapy. With a mean follow-up of 60 months, the overall tumor control rate was 93 %, which is comparable to other forms of radiation. A recent review comparing outcomes for proton therapy vs. conformal photon therapy found equivalent tumor control and a trend toward early cyst growth in the conformal photon therapy group that did not reach statistical significance (Bishop et al. 2014).

7.7.2.6 Intracavitary Radiation Therapy

Over 90 % of craniopharyngiomas have a cystic component. Frequently, the cyst is large and can comprise the majority of the tumor. Direct intracystic treatment has the goals of reducing cyst volume and achieving long-term tumor control. Leksell and Liden first described intracavitary therapy with the use of beta-emitting radionuclides such as ^{90}yttrium, ^{32}phosphorus, or ^{186}rhenium into the cyst (Leksell 1952). From a review by Blackburn et al., 121 of 149 cysts treated in 127 patients reduced in size or were obliterated in the follow-up period of 0.2–13 years. However, the distinction between recurrence of a cyst and recollection of the initial lesion varied among the different studies (Blackburn et al. 1999). In a study of 30 patients treated with ^{32}phosphorus, which cyst regression was defined as more than 50 % reduction in volume, 88 % of patients were found to have cyst regression, with response occurring within 3 months of surgery and continued decrease in cyst size up to 2 years after surgery (Pollock et al. 1995). Overall survival was 55 % at 5 years and 45 % at 10 years, with a mean survival of 9 years (Voges et al. 1997). The impact of intracavitary irradiation on vision varied widely among studies ranging from 100 % deterioration to 100 % improvement, with improvement in 53 % of patients, over all the studies considered (Voges et al. 1997; Blackburn et al. 1999). The major risks of intracavitary radiotherapy include visual loss and radiation necrosis of the hypothalamus. There are situations in which intracystic therapy is the only option, but its broad adoption has been limited by the difficulty in obtaining of these compounds and the process for handling/injecting.

7.7.3 Chemotherapy

7.7.3.1 Systemic Chemotherapy

There are no effective systemic chemotherapeutic agents for craniopharyngioma. The strongest evidence to date is for the use of interferon-alpha (IFN-α). Its use was based on its activity in squamous cell carcinoma and the observation that craniopharyngioma shares a similar epithelial cell origin. A phase II trial of IFN-α for progressive, recurrent, or unresectable craniopharyngiomas in children under 21 years of age was reported a number of years ago (Jakacki et al. 2000). Treatment consisted of an induction phase of 8,000,000 U/m^2 daily for 16 weeks. Patients without progressive disease at 16 weeks then continued at the same dose three times a week for 32 weeks. Time to progression after discontinuation of IFN-α was 6–23 months. IFN-α toxicity occurred in 60 % of cases during the first 8 weeks of treatment, but resolved with discontinuation or dose reduction. Toxicities include hypoadrenal crisis with fever, neutropenia, transaminitis, fatigue, rash, insomnia, and seizures. A follow-up study of pegylated interferon-alpha 2b in a small group of children demonstrated activity of the agent with five out of five patients achieving radiographic responses (Yeung et al. 2012).

Insights into the genetics and molecular biology of craniopharyngioma may lead to new therapeutic opportunities. A subset of adamantinomatous craniopharyngiomas is of monoclonal origin (Rienstein et al. 2003; Sarubi et al. 2001). This suggests that an acquired somatic mutation may be an initiating event. Early studies also indicate very low levels of O-6 methylguanine DNA methyltransferase (MGMT) suggesting temozolomide may have a role in future treatment paradigms (Zuhur et al. 2011). Finally, in vitro testing of EGFR inhibitors has been successful in inhibiting tumor cell migration. Prior work has shown that EGFR is preferentially overexpressed at the border zone between tumor and normal brain tissue (Holsken et al. 2011).

Adamantinomatous craniopharyngiomas have also been shown to exhibit mutations in the beta-catenin gene *CTNNB1* on chromosome 3 (Buslei et al. 2005; Cao et al. 2010; Kato et al. 2004). This mutation then leads changes in gene transcription that control angiogenesis, cell proliferation, and mobility. Of note, some craniopharyngioma cells have demonstrated increased levels of beta-catenin without mutations in *CTNNB1* suggesting an alternative pathway for tumorigenesis. Future therapies directed at downregulating beta-catenin or inhibiting its interactions with certain transcription factors could prove to be quite beneficial in treating patients with adamantinomatous craniopharyngiomas.

A recently published mRNA microarray gene expression analysis of 15 patients with adamantinomatous craniopharyngioma identified a number of potentially actionable therapeutic targets in the transcriptome of these tumors. Of interest included frequent high expression of *LCK*, *EPHA1*, and *SRC*, which can all be targeted with the therapeutic agent dasatinib, as well as other targets of interest including *SHH*, *MMP9*, and *MMP12* (Gump et al. 2015).

7.7.3.2 Intracavitary Chemotherapy

In 1985, Takahashi et al. reported their experience with intracystic bleomycin in seven pediatric patients as adjuvant therapy immediately following STR (Takahashi et al. 1985). Since that time, numerous reports have been published using intracystic bleomycin for both initial treatment and for tumor recurrences. The immediate side effects resulting from bleomycin treatment are generally mild and self-limited and include nausea, vomiting, and headache. In approximately 3 % of patients, more serious side effects occurred in a delayed fashion (Linnert and Gehl 2009). These include hearing loss, visual loss, hypothalamic dysfunction, cerebral ischemia, panhypopituitarism, and even death.

There are a number of limitations associated with the use of intracystic bleomycin. It has direct toxicity to CNS structures, and a number of steps must be taken to avoid any leakage into the subarachnoid space (Steinbok and Hukin 2010). The appropriate dose and frequency of injection have not been clearly defined. While initial tumor responses are promising, there are some results that suggest that all tumors will eventually grow

despite treatment (Steinbok and Hukin 2010). In young children, this may be an acceptable option, since one goal may be to delay external radiation.

More recently IFN-α has also been used as an intracystic agent. In contrast to bleomycin, IFN-α is not toxic when placed in the subarachnoid space. Ierardi et al. suggested that IFN-α may reduce cyst volume by inducing apoptosis through activation of the Fas apoptotic pathway (Ierardi et al. 2007). In a series of 21 patients, all pediatric patients with adamantinomatous craniopharyngiomas, greater than 50 % of patients, had a complete response following treatment with intracystic IFN-α (Cavalheiro et al. 2010). An additional 30 % of patients had a partial response to treatment. Minor complications such as fatigue, weight loss, and behavioral changes were observed. The use of IFN-α in combination with other therapies may increase given its relatively benign side effect profile and lack of toxicity in comparison to bleomycin.

Table 7.2 Outcomes of primary surgery, gross total resection, for craniopharyngioma

References	Number of patients	Recurrence-free survival (%)	Percent survival
Lin (2008)	14	54 at 6 years	100 at 6 years
Shi (2008)	276	86 at 6 years	98 at 6 years
Puget (2007)	33	64 at 6 years	94 at 6 years
Bojanowski (2006)	12	91 at 2–14 years	91 at 2–14 years
Stripp et al. (2004)	44	47 at 10 years	86 at 10 years
Duff et al. (2000)	121	77 at 5 years	88 at 10 years
			74 at 15 years
Kalapurakal et al. (2000)	14	92 at 5 years	100 at 5 years
		60 at 10 years	86 at 10 years
Fahlbusch et al. (1999)	73	87 at 5 years	93 at 10 years
		81 at 10 years	
Villani et al. (1997)	17	82 at 7 years	94 at 7 years
Hetelekidis et al. (1993)	5	0 at 10 years	100 at 10 years

7.8 Outcome

On the basis of postoperative imaging, GTR varies widely in various series ranging from 29 % to 77 % of cases (Sanford 1994; Villani et al. 1997; Einhaus and Sanford 1999; Fahlbusch et al. 1999; Duff et al. 2000; Van Effenterre and Boch 2002; Stripp et al. 2004; Caldarelli et al. 2005; Shi et al. 2008). Reflecting the heterogeneity of patient groups, recurrence has been reported to occur in 8–100 % of patients after initial GTR. The mean duration of follow-up in these studies ranges from 5 to 10 years (Table 7.2) (Hetelekidis et al. 1993; Villani et al. 1997; Fahlbusch et al. 1999; Duff et al. 2000; Kalapurakal et al. 2000; Poretti et al. 2004; Stripp et al. 2004; Shi et al. 2008). Recurrence following GTR can be assumed to occur because of unrecognized deposits of tumor capsule. Even high-quality imaging will miss small amounts of epithelium that have the potential to develop into recurrent tumors. The use of adjunctive radiation therapy following GTR is controversial.

In many cases, only a portion of the tumor can be removed. The main reasons for incomplete tumor removal are adhesions to vessels and structures such as the optic nerve and chiasm and major calcifications (Samii and Tatagiba 1997; Fahlbusch et al. 1999). In patients undergoing STR without radiation therapy, the recurrence rate is 43–75 % with mean follow-up periods of 5–7 years (Villani et al. 1997; Fahlbusch et al. 1999; Khoo et al. 2001). For partial resection followed by radiotherapy, the recurrence rate was 43–54 % during a mean follow-up period of 65–84 months, which is comparable with the rate for GTR (Villani et al. 1997; Fahlbusch et al. 1999; Stripp et al. 2004). In a systematic review, Clark et al. compared tumor control rates for aggressive surgical resection to STR followed by radiation. They found comparable rates of progression-free survival at 1 and 5 years between the two treatment groups (Clark et al. 2013). Cohen et al. also found similar results when comparing their prior data, which reflected mainly complete surgical resections when possible, to their most recent data (2001–2011) which was comprised of mostly biopsies or partial resections followed by adjuvant therapy. The reported rates of recurrence were not statistically different, and they found a lower rate of endocrinopathies in children treated by their current protocol (Cohen 2013).

Table 7.3 Outcomes for subtotal resection combined with radiotherapy for patients treated for primary and recurrent disease

References	Primary disease vs. recurrence	Number of patients	Recurrence-free survival (%)	Percent survival
Stripp et al. (2004)	Primary	18	84 at 10 years	83 at 10 years
	Recurrence	36	91 at 5 years	87 at 5 years
			82 at 10 years	82 at 10 years
Habrand et al. (1999)	Primary and recurrence	37	78 at 5 years	91 at 5 years
			57 at 10 years	65 at 10 years
Gurkaynak (1994)	Primary	23	74 at 5 years	N/A
			62 at 10 years	
Hetelekidis et al. (1993)	Primary	37	86 at 10 years	86 at 10 years

N/A not available, not reported

The management of recurrent tumors is often fraught with difficulties. If a focal recurrence is present on imaging studies, repeat surgical exploration may be warranted. Not surprisingly, recurrent tumors are more difficult to resect and have a resection rate of 13–50 % through the transcranial approach (Villani et al. 1997; Fahlbusch et al. 1999; Duff et al. 2000) and 53 % through the transsphenoidal route (Fahlbusch et al. 1999). Tumors that are purely in an intrasellar location are contained by the bony margins of the sella and are more amenable for repeat surgery. Overall, 81 % percent of patients who underwent surgery (intracranial or transsphenoidal) were disease-free on follow-up at 65 months (Fahlbusch et al. 1999).

Survival of patients with craniopharyngioma treated with radiation therapy for initial or recurrent disease is comparable to those treated with different modalities (Table 7.3). Overall survival for two series of patients treated in a variety of ways at 5, 10, and 15 years was 100 %, 68–86 %, and 59–86 %, respectively (Bulow et al. 1998; Kalapurakal et al. 2000).

Radiation therapy has been shown to be an effective adjuvant treatment following surgical STR for initial disease as well as for recurrent disease compared with treatment with surgery alone. In the review by Clark et al., they showed a 5-year progression-free survival of 43 % with subtotal resection alone compared to 73 % when radiation was used in combination with subtotal resection. For recurrent tumors, surgery combined with radiotherapy can achieve a much better result than surgery alone (Clark 2013). However, Bulow et al. found that when patients who died within 6 months of therapy were excluded, the advantage of radiation therapy was no longer statistically significant. There was also no difference in rate of recurrence with respect to age or extent of surgery (Bulow et al. 1998).

The outcome did not differ between adults and pediatric patients, between papillary and adamantinomatous tumors, or between transsphenoidal and transcranial approaches. Recurrence rates also did not correlate with preoperative radiologic findings (Duff et al. 2000).

7.9 Complications Associated with Treatment

7.9.1 Complications of Surgery

Aside from the mass effect of the tumor, surgical resection itself is associated with significant risks to endocrine function and vision (Table 7.4). The most common postoperative complication is diabetes insipidus, caused by death of the vasopressingeric neurons of the supraoptic and paraventricular nuclei, or by pituitary stalk transection close to the hypothalamic perikarya, such that axonal regeneration within the posterior pituitary cannot occur. Diabetes insipidus occurs in 50–93 % of patients following surgery (Yasargil et al. 1990; Hoffman et al. 1992; Tomita and McLone 1993; Sanford 1994; Fahlbusch et al.

Table 7.4 Complications for patients treated with surgery

References	Number of patients	Diabetes insipidus (%)	Panhypopituitarism (%)	Visual loss
Elliott et al. (2010)	86	78 % (35 % at presentation)	N/A	13 % decreased acuity; 25 % decreased visual field
Zuccaro (2005)	153	50	N/A	8.5 % worsening
Tomita and Bowman (2005)	54	47	93	7 % worsening
Zhou and Shi (2004)	40	58	95	N/A
Stripp et al. (2004)	44	88	84	N/A
Merchant et al. (2002)	15	73	N/A	33 % decreased visual acuity 40 % decreased visual field
Kalapurakal et al. (2000)	14	100	100	N/A
Duff et al. (2000)	31	21	N/A	N/A
Honegger et al. (1998)	92	66 (16 % at presentation)	N/A	N/A
Rilliet et al. (1999)	31	74	74	22 %
Fahlbusch et al. (1999)	89	N/A	N/A	13 %
Villani et al. (1997)	24	81	N/A	19 %
Hetelekidis et al. (1993)	13	79 (14 % at presentation)	77 %	N/A
Yasargil et al. (1990)	141	79 (23 % at presentation)	N/A	13 %

N/A not available, not reported

1999; Hoffman et al. 1999; Rilliet et al. 1999; Zuccaro 2005; Elliott et al. 2010).

Anterior pituitary lobe function is also frequently compromised. Although Fahlbusch et al. reported that normal postoperative anterior pituitary function was maintained in over 50 % of patients after surgery, and the incidence of hypogonadism increased only from 77 % to 80 % (Fahlbusch et al. 1999), other series report that panhypopituitarism occurs in 75–100 % of patients who underwent surgical resection (DeVile et al. 1996a, b; Kalapurakal et al. 2000).

Visual deterioration occurred in 2–66 % of patients who underwent surgical resection (Pierre-Kahn et al. 1994; Fahlbusch et al. 1999; Poretti et al. 2004). Minor surgical trauma to the hypothalamus can also cause sleep disorders, memory problems, apathy, and appetite changes (Samii and Tatagiba 1997).

In addition to neurologic and endocrinologic complications, intellectual, psychological, and social morbidities must also be considered. Neuropsychological and behavioral disturbances were found in 36–60 % of children who underwent radical resection (Anderson et al. 1997; Villani et al. 1997; Riva et al. 1998; Kalapurakal et al. 2000). Many of these children are affected by their body images as a result of the obesity, which occurred in 36 % of children (see Sect. 7.9.3) (Kalapurakal et al. 2000). There were no changes in long-term or short-term memory (Riva et al. 1998; Kalapurakal et al. 2000). A decrease in school performance and learning disability occurred in 0–50 % of children (Zuccaro et al. 1996; Villani et al. 1997; Riva et al. 1998; Poretti et al. 2004). Merchant et al. found a drop in IQ scores by 9.8 points in 15 pediatric patients treated with GTR alone (Merchant et al. 2002). However, Zuccaro found that all children who underwent GTR were no more than one grade level behind in school compared to only 62 % of children who had STR followed by radiation (Zuccaro 2005). While neuropsychological outcome is most often studied in children, adults can have neuropsychological sequelae as well. Donnet et al. found in a study of 22 adults that 9 % had severe memory and intellectual defects

and 14 % had moderate learning defects (Donnet et al. 1999). Van Efferenterre et al. found in a study of 122 patients that the rate of normal neuropsychological function was 91 % as assessed by patients and their families (Van Effenterre and Boch 2002). Honneger et al. found that cognitive function in adults remained the same or improved postoperatively (Honegger et al. 1998).

Complications from the transsphenoidal approach are similar to other surgical approaches except for a lower incidence of behavioral and visual disturbances. Behavioral disturbance occurred in 9 % of children, and only 0–1 % of adults and children had visual deterioration (Laws 1994; Norris et al. 1998; Fahlbusch et al. 1999; Rilliet et al. 1999). This low complication rate can be attributed to the types of tumors for which the transsphenoidal approach is best suited, namely, intrasellar and cystic tumors, which do not extend into the hypothalamus.

7.9.2 Complications of Radiotherapy

Radiation therapy results in endocrine dysfunction and visual defects similar to that observed following surgery, but the severity of these complications, particularly with respect to diabetes insipidus, appears to be reduced (Table 7.5). Duff et al. found an overall good outcome rate of 60 % in a retrospective study of 121 patients with a mean follow-up of 10 years (Duff et al. 2000). In a review of 72 patients treated for initial disease at UCSF from 1972 to 1999, 32 % had visual deficits after subtotal resection followed by radiation, although 81 % of these had visual deficits prior to treatment and 72 % retained their pretreatment functional status (unpublished data). In the same series, of the 36 patients treated for recurrent disease, only 53 % retained the same functional status. No difference was associated with extent of surgical resection, with 78 % having permanent deficits. A majority of patients had impaired endocrine function. Sixty-four percent required thyroid hormone replacement, 56 % required cortisol, 44 % required sex hormones, 17 % had diabetes insipidus, and 1 % had elevated prolactin levels. The endocrinologic sequelae of radiotherapy compare with other series which report 6–38 % incidence of diabetes insipidus after radiation therapy, much lower than that of patients who have undergone GTR (Einhaus and Sanford 1999). In a series by Regine et al., the incidence of endocrinologic sequelae was correlated with both age and maximum dose of radiation, being 80 % in children and 26 % in adults for doses greater than 61 Gy and 36 % in children and 13 % in adults for doses less than 61 Gy (Regine et al. 1993).

The effects of partial- or whole-brain radiation on the intellectual function of children with various brain tumors have been extensively studied and have shown much greater effects on younger children (Weiss et al. 1989). In children less than 3 years of age treated with either partial- or whole-brain radiation for various brain tumors, excluding craniopharyngiomas, 60 % were mentally retarded with IQ less than 69. The incidence of mental retardation/dementia and vascular complications of radiation therapy for craniopharyngioma is highly correlated with the maximum dose, being 40 % in children and 45 % in adults for doses greater than 61 Gy vs. 0 % in children

Table 7.5 Complications in patients treated with surgery and radiotherapy

Reference	Number of patients	Diabetes insipidus (%)	Panhypopituitarism	Visual loss (%)
Merchant et al. (2002)	14	33	N/A	33 % decreased visual acuity; 60 % with decreased visual field
Habrand et al. (1999)	37	66 (22 % at presentation)	97 % (22 % at presentation)	0
Hetelekidis et al. (1993)	34	38 (25 % at presentation)	53 %	N/A

N/A not available, not reported

and adults at doses less than 61 Gy (Regine et al. 1993). In children who had received radiotherapy, 32–33 % had poor school performance or required special schooling due to moderate to severe learning disability after treatment (Zuccaro et al. 1996; Habrand et al. 1999). Merchant et al. found a median drop in IQ scores of 1.25 points in 15 children treated with limited surgery and radiation compared with 9.8 points in the surgery-only group (Merchant et al. 2002). Although the results of the damaging effects of radiation on the intellectual function of children less than 3 years of age were not studied in patients with craniopharyngiomas, we do not recommend adjuvant radiation therapy in children under 3 years of age who have undergone a STR, unless they become symptomatic.

Other complications of radiation therapy include radiation-induced neoplasms (glioblastoma, sarcoma, meningioma), radiation necrosis, vascular occlusion, radiation vasculitis, optic neuritis, dementia, calcification of basal ganglia, hypothalamic-pituitary dysfunction, hypothalamic obesity, and decreased intellect in children (Einhaus and Sanford 1999; Moore and Couldwell 2000; Lustig et al. 2003).

7.9.3 Complications of Radiosurgery

A majority of patients retained good function after treatment with SRS. Diabetes insipidus, panhypopituitarism, and visual loss occur in 0–4 %, 0–2 %, and 0–4 % of patients who have undergone radiosurgery, respectively (Mokry 1999; Chung et al. 2000; Yu et al. 2000). Chung et al. reported good to excellent outcomes (independent living) in all patients with mainly solid or cystic tumors and in 50 % of those with mixed solid and cystic tumors (Chung et al. 2000). Visual deterioration occurred in 10–66 % of patients (Kobayashi et al. 1994; Einhaus and Sanford 1999). Given its potential effects on vision, SRS should be applied only to small tumors less than 2 cm in size and more than 4–5 mm away from the optic apparatus (Lunsford et al. 1994).

Most patients treated with fractionated SRS also have good outcomes following treatment. In the Royal Marsden series, vision remained stable following treatment in 88 % of patients and improved in 8 % of patients. Only one patient, with severely compromised pretreatment vision, showed visual deterioration that was possibly attributable to radiation (Minniti et al. 2007). This is similar to the University of Heidelberg series, where no patient developed a new visual deficit following radiation therapy (Combs et al. 2007). With regard to endocrine function, results of fractionated SRS remain similar to those of conventional external beam radiation therapy, with 30–50 % of patients developing deficits. Most patients with intact pituitary function following surgery maintain function following radiosurgery (Combs et al. 2007; Minniti et al. 2007). None of the available studies have done formal prospective neuropsychological testing. Thus, it is not possible to conclude that stereotactic treatment is safer in this regard. Likewise, these techniques have not been in use long enough to draw conclusions regarding rates of secondary malignancies.

7.9.4 Endocrinopathy and Hypothalamic Injury

Damage to the hypothalamus, either from the craniopharyngioma itself or subsequent surgery or radiation, can result in numerous functional morbidities and endocrinopathies, which predict reduction in long-term survival (Sterkenberg et al. 2015). A recent analysis suggests that gross total resection significantly increases risk for endocrinopathies vs. more conservative management (Clark et al. 2012). Indeed, preservation of the pituitary stalk improves morbidity but does not alter recurrence rates (Li et al. 2015). ACTH deficiency is the least common endocrinopathy after hypothalamic damage, perhaps because cortisol is essential for survival and because the pituitary corticotrophs are the most radioresistant of pituicytes (Rose et al. 2005). Approximately 25 % percent of patients with craniopharyngioma manifest ACTH

deficiency after treatment (Honegger et al. 1999; Rose et al. 2005). Patients experience fatigue, chronic headache, hypotension, and tachycardia with illness or other severe stress, which can lead to shock and death. Diagnosis is made by suboptimal cortisol response to an ACTH stimulation test or a suboptimal 11-deoxycortisol response to a metyrapone test (Rose et al. 1999). Such patients require lifelong hydrocortisone replacement. Growth hormone deficiency is extremely common, although usually due to the craniopharyngioma itself; however, each therapeutic modality can diminish pituitary GH release, either individually or in combination. Growth hormone therapy appears to be as efficacious in improving the metabolic status of these patients as it is in other forms of childhood hypopituitarism (Yuen et al. 2013).

Diabetes insipidus is rare on presentation (16 %) (Honegger et al. 1999; de Vries et al. 2003), but can reach an incidence of 60–95 % after surgical treatment (Honegger et al. 1999; Zhou and Shi 2004). Treatment is lifelong desmopressin acetate (DDAVP) therapy (either oral, intranasal, or subcutaneous). Usually, the patient will be able to drink enough water to maintain eunatremia and adequate hydration, but this can be a problem in infants and toddlers or in the aged. Diabetes insipidus is particularly worrisome when it is complicated by adipsia (Smith et al. 2004), thus requiring a water prescription and frequent monitoring of serum sodium levels; such patients have a high risk for mortality.

Damage to the ventromedial hypothalamus often results in defective energy balance, termed "hypothalamic obesity" (Bray and Gallagher 1975; Lustig 2002; Daousi et al. 2005). An extremely high frequency of hypothalamic obesity (30–77 %) has been documented after craniopharyngioma treatment (Harz et al. 2003); indeed the presence of diabetes insipidus (inferring hypothalamic damage) is associated with a higher risk for hypothalamic obesity (Yuen et al. 2014). Although slightly increased BMI is common at initial presentation, either surgery or hypothalamic radiation (greater than 51 Gy) can precipitate this syndrome (Lustig et al. 2003). Rates of weight gain range from 12 to 20 kg/year persist without plateau, and obesity often becomes the most debilitating aspect of the postoperative course. Metabolic complications of the obesity are frequent and manifest early (Srinivasan et al. 2004). Children with hypothalamic obesity exhibit weight gain, even in response to forced caloric restriction (Bray and Gallagher 1975). This phenomenon occurs due to ventromedial hypothalamus damage, preventing normal hypothalamic leptin signal transduction, which leads to (1) defective activation of the sympathetic nervous system (Schofl et al. 2002; Coutant et al. 2003), which retards lipolysis and reduces energy expenditure (Shaikh et al. 2008), and (2) overactivation of the vagus nerve (Lee et al. 1989), which promotes an obligate insulin hypersecretion and energy storage (Lustig et al. 2003; Preeyasombat et al. 2005; Lustig 2007). Diagnosis can be made on an oral glucose tolerance test, where the insulin hypersecretion is evident (Preeyasombat et al. 2005; Lustig 2007). Many treatments have been proposed, which include adrenergics to increase energy expenditure (Mason et al. 2002), suppression of insulin secretion using octreotide (Lustig et al. 1999, 2003), and bariatric surgery (Inge et al. 2007). A recent pooling of surgical cases has suggested that roux-en-Y gastric bypass may yield the greatest degree of weight loss over 1 year, although still not adequate with respect to long obesity management or resolution (Bretault et al. 2013). Therefore, it is imperative to diagnose this complication early in the postoperative course, so that preventative and pharmacologic measures can be implemented.

Conclusions

Despite recent advances in treatment options, and a wide variety of approaches, craniopharyngiomas remain a challenging disease for the neuro-oncology team. There are a limited number of medical options and the long-term consequences of treatment can be significant. There is an ongoing debate regarding the ideal initial strategy for the treatment of craniopharyngioma in children. At a simplistic level, this is a choice between aggressive surgical

resection and subtotal resection followed by radiation.

The data and experience reported in the literature do not allow one to make a definitive recommendation. It is clear, however, that there are specific points that must be considered when selecting the ideal treatment option for an individual child. First, the likelihood of hypothalamic injury should be reduced as much as possible; its presence will have a major impact on a child's ability to function independently and resultant long-term risk for chronic disease. Second, complete loss of pituitary function (anterior and posterior lobe) in a young, prepubertal child should be avoided if at all possible. Although hormone replacement therapy is an option, panhypopituitarism, especially diabetes insipidus, is a source of substantial morbidity. The impact of this problem should be explained clearly to the parents or caregivers if it is to occur. Finally, an institution's experience with these relatively rare and complex tumors should be evaluated carefully. The results reported by centers that see large number of these patients cannot be extrapolated easily, and the ability to offer a broad set of treatment options increases the eventual likelihood that tumor control will be achieved with acceptable long-term morbidity.

Other therapies such as intracavitary irradiation, radiosurgery, intracavitary chemotherapy with bleomycin, or systemic chemotherapy with agents such as IFN-α either remain restricted to specific tumor subtypes or are still experimental in nature. More data is needed to understand the long-term endocrine, psychological, and social consequences of treatment, especially in children.

References

Ali ZS, Lang SS, Kamat AR, Adappa ND, Palmer JN, Storm PB, Lee JY (2013) Suprasellar pediatric craniopharyngioma resection via endonasal endoscopic approach. Childs Nerv Syst 29(11):2065–2070

Anderson CA, Wilkening GN, Filley CM, Reardon MS, Kleinschmidt-DeMasters BK (1997) Neurobehavioral outcome in pediatric craniopharyngioma. Pediatr Neurosurg 26(5):255–260

Barloon TJ, Yuh WT, Sato Y, Sickels WJ (1988) Frontal lobe implantation of craniopharyngioma by repeated needle aspirations. AJNR Am J Neuroradiol 9(2):406–407

Bishop AJ, Greenfield B, Mahajan A, Paulino AC, Okcu MF, Allen PK, Chintagumpala M, Kahalley LS, McAleer MF, McGovern SL, Whitehead WE, Grosshans DR (2014) Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. Int J Radiat Oncol Biol Phys 90(2):354–361

Blackburn TP, Doughty D, Plowman PN (1999) Stereotactic intracavitary therapy of recurrent cystic craniopharyngioma by instillation of 90yttrium. British Journal of Neurosurgery 13:359–365

Boehling NS, Grosshans DR, Bluett JB, Palmer MT, Song X, Amos RA, Sahoo N, Meyer JJ, Mahajan A, Woo SY (2012) Dosimetric comparison of three-dimensional conformal proton radiotherapy, intensity-modulated proton therapy, and intensity-modulated radiotherapy for treatment of pediatric craniopharyngiomas. Int J Radiat Oncol Biol Phys 82(2):643–652

Bojanowski K, Marchel A (2006) Long-term result of the surgical treatment of craniopharyngioma. Polish Journal of Neurology and Neurosurgery 40:478-482

Bray GA, Gallagher TF (1975) Manifestations of hypothalamic obesity in man: a comprehensiveinvestigation of eight patients and a review of the literature. Medicine 54:301– 333

Bretault M, Boillot A, Muzard L, Poitou C, Oppert JM, Barsamian C, Gatta B, Müller H, Weismann D, Rottembourg D, Inge T, Veyrie N, Carette C, Czernichow S (2013) Clinical review: bariatric surgery following treatment for craniopharyngioma: a systematic review and individual-level data meta-analysis. J Clin Endocrinol Metab 98(6):2239–2246

Bulow B, Attewell R, Hagmar L, Malmstrom P, Nordstrom CH, Erfurth EM (1998) Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence. J Clin Endocrinol Metab 83(11):3897–3904

Buslei R, Nolde M, Hofmann B, Meissner S, Eyupoglu IY, Siebzehnrübl F, Hahnen E, Kreutzer J, Fahlbusch R (2005) Common mutations of beta-catenin in adamantinomatous craniopharyngiomas but not in other tumours originating from the sellar region. Acta Neuropathol 109(6):589–597

Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C (2005) Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. Childs Nerv Syst 21(8–9):747–757

Cao J, Lin JP, Yang LX, Chen K, Huang ZS (2010) Expression of aberrant beta-catenin and impaired p63 in craniopharyngiomas. Br J Neurosurg 24(3):249–256

Cavalheiro S, Di Rocco C, Valenzuela S, Dastoli PA, Tamburrini G, Massimi L, Nicacio JM, Faquini IV,

Ierardi DF, Silva NS, Pettorini BL, Toledo SR (2010) Craniopharyngiomas: intratumoral chemotherapy with interferon-alpha: a multicenter preliminary study with 60 cases. Neurosurg Focus 28(4):E12

Chung WY, Pan DH, Shiau CY, Guo WY, Wang LW (2000) Gamma knife radiosurgery for craniopharyngiomas. J Neurosurg 93(Suppl 3):47–56

Clark AJ, Cage TA, Aranda D, Parsa AT, Auguste KI, Gupta N (2012) Treatment related morbidity and the management of pediatric craniopharyngioma: a systematic review. J Neurosurg Pediatr 10(4):293–301

Clark AJ, Cage TA, Aranda D, Parsa AT, Sun PP, Auguste KI, Gupta N (2013) A systematic review of the results of surgery and radiotherapy on tumor control for pediatric craniopharyngioma. Childs Nerv Syst 29(2):231–238

Cohen M, Bartels U, Branson H, Kulkarni AV, Hamilton J (2013) Trends in treatment and outcomes of pediatric craniopharyngioma, 1975–2011. Neuro Oncol 15(6):767–774

Combs SE, Thilmann C, Huber PE, Hoess A, Debus J, Schulz-Ertner D (2007) Achievement of long-term local control in patients with craniopharyngiomas using high precision stereotactic radiotherapy. Cancer 109(11):2308–2314

Coutant R, Maurey H, Rouleau S, Mathieu E, Mercier P, Limal JM, Le Bouil A (2003) Defect in epinephrine production in children with craniopharyngioma: functional or organic origin? Journal of Clincal Endocrinology and Metabolism 88:5969–5975

Cushing H (1932) The craniopharyngiomas. In: Intracranial tumors- notes upon a series of two thousand verified cases with surgical mortality percentages thereto. Charles C Thomas, Springfield

Daousi C, Dunn AJ, Foy PM, MacFarlane IA, Pinkney JH (2005) Endocrine and neuroanatomic features associated with weight gain and obesity in adult patients with hypothalamic damage. American Journal of Medicine 118:45–50

de Vries L, Lazar L, Phillip M (2003) Craniopharyngioma: presentation and endocrine sequelae in 36 children. J Pediatr Endocrinol Metab 16(5):703–710

DeVile CJ, Grant DB, Hayward RD, Stanhope R (1996a) Growth and endocrine sequelae of craniopharyngioma. Arch Dis Child 75(2):108–114

De Vile CJ, Grant DB, Kendall BE, Neville BG, Stanhope R, Watkins KE, Hayward RD (1996b) Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? Journal of Neurosurgery 85:73–81

Donnet A, Schmitt A, Dufour H, Grisoli F (1999) Neuropsychological follow-up of twenty two adult patients after surgery for craniopharyngioma. Acta Neurochir (Wien) 141(10):1049–1054

Donovan JL, Nesbit GM (1996) Distinction of masses involving the sella and suprasellar space: specificity of imaging features. AJR Am J Roentgenol 167:597–603

Duff J, Meyer FB, Ilstrup DM, Laws ER Jr, Schleck CD, Scheithauer BW (2000) Long-term outcomes for surgically resected craniopharyngiomas. Neurosurgery 46(2):291–302

Einhaus SL, Sanford RA (1999) Craniopharyngiomas. In: Albright L, Pollack I, Adelson D (eds) Principles and practice of pediatric neurosurgery. Thieme, New York

Elliott RE, Hsieh K, Hochm T, Belitskaya-Levy I, Wisoff J, Wisoff JH (2010) Efficacy and safety of radical resection of primary and recurrent craniopharyngiomas in 86 children. J Neurosurg Pediatr 5(1):30–48

Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M (1999) Surgical treatment of craniopharyngiomas: experience with 168 patients. J Neurosurg 90(2): 237–250

Fernandez-Miranda JC, Gardner PA, Snyderman CH, Devaney KO, Strojan P, Suárez C, Genden EM, Rinaldo A, Ferlito A (2012) Craniopharyngioma: a pathologic, clinical, and surgical review. Head Neck 34(7):1036–1044

Fischbein NJ, Dillon WP, Barkovich AJ (2000) Teaching atlas of brain imaging. Thieme, New York

Gump JM, Donson AM, Birks DK, Amani VM, Rao KK, Griesinger AM, Kleinschmidt-De-Masters BK, Johnston JM, Anderson RCE, Rosenfeld A, Handler M, Gore L, Foreman N, Hankinson T (2015) Identification of targets for rational pharmacological therapy in childhood craniopharyngioma. Acta Neuropathol Commun 3:30

Gunther JR, Sato M, Chintagumpala M, Ketonen L, Jones JY, Allen PK, Paulino AC, Okcu MF, Su JM, Weinberg J, Boehling NS, Khatua S, Adesina A, Dauser R, Whitehead WE, Mahajan A (2015) Imaging changes in pediatric intracranial ependymoma patients treated with proton beam radiation therapy compared to intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 93(1):54–63

Gupta K, Kuhn MJ, Shevlin DW, Wacaser LE (1999) Metastatic craniopharyngioma. AJNR Am J Neuroradiol 20(6):1059–1060

Gurkaynak M, Ozyar E, Zorlu F, Akyol FH, Atahan IL (1994) Results of radiotherapy in craniopharyngiomas analyzed by the linear quadratic model. Acta Oncologica 33:941–943

Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C, Pierre-Kahn A, Kalifa C (1999) The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. Int J Radiat Oncol Biol Phys 44(2):255–263

Harwood-Nash DC (1994) Neuroimaging of childhood craniopharyngioma. Pediatric Neurosurgery 21(Suppl 1): 2–10

Hetelekidis S, Barnes PD, Tao ML, Fischer EG, Schneider L, Scott RM, Tarbell NJ (1993) 20-year experience in childhood craniopharyngioma. Int J Radiat Oncol Biol Phys 27(2):189–195

Hoffman HJ (1994) Surgical management of craniopharyngioma. Pediatr Neurosurg 21(Suppl 1):44–49

Hoffman HJ, Hendrick EB, Humphreys RP, Buncic JR, Armstrong DL, Jenkin RD (1977) Management of craniopharyngioma in children. J Neurosurg 47(2): 218–227

Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI (1992) Aggressive surgical

management of craniopharyngiomas in children. J Neurosurg 76(1):47–52

Hoffman HJ, Drake JM, Stapleton SR (1999) Craniopharyngiomas and pituitary tumors. In: Choux M, Di Rocco C, Hockley AD, Walker ML (eds) Pediatric neurosurgery. Churchill Livingstone, New York

Hoffman BM, Kreutzer J, Saeger W, Buchfelder M, Blümcke I, Fahlbusch R, Buslei R (2006) Nuclear beta-catenin accumulation as reliable marker for the differentiation between cystic craniopharyngiomas and Rathke cleft cysts: a clinico-pathologic approach. American Journal of Surgical Pathology 30: 1595–1603

Holsken A, Gebhardt M, Buchfelder M, Fahlbusch R, Blumcke I, Buslei R (2011) EGFR signaling regulates tumor cell migration in craniopharyngiomas. Clin Cancer Res 17(13):4367–4377

Hölsken A, Kreutzer J, Hofmann BM, Hans V, Oppel F, Buchfelder M, Fahlbusch R, Blümcke I, Buslei R (2008) Target gene activation of the Wnt signaling pathway in nuclear beta-catenin accumulating cells of adamantinomatous craniopharyngiomas. Brain Pathology 19:357–364

Honegger J, Barocka A, Sadri B, Fahlbusch R (1998) Neuropsychological results of craniopharyngiomasurgery in adults: a prospective study. Surgical Neurology 50:19–28; discussion 28–19

Honegger J, Buchfelder M, Fahlbusch R (1999) Surgical treatment of craniopharyngiomas: endocrinological results. J Neurosurg 90(2):251–257

Hussain I, Eloy JA, Carmel PW, Liu JK (2013) Molecular oncogenesis of craniopharyngioma: current and future strategies for the development of targeted therapies. J Neurosurg 119(1):106–112

Ierardi DF, Fernandes MJ, Silva IR, Thomazini-Gouveia J, Silva NS, Dastoli P, Toledo SR, Cavalheiro S (2007) Apoptosis in alpha interferon (IFN-alpha) intratumoral chemotherapy for cystic craniopharyngiomas. Childs Nerv Syst 23(9):1041–1046

Indelicato DJ, Flampouri S, Rotondo RL, Bradley JA, Morris CG, Aldana PR, Sandler E, Mendenhall NP (2014) Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy. Acta Oncol 53(10):1298–1304

Inge TH, Pfluger P, Zeller M, Rose SR, Burget L, Sundararajan S, Daniels SR, Tschöp MH (2007) Gastric bypass surgery for treatment of hypothalamic obesity after craniopharyngioma therapy. Nature Clinical Practice. Endocrinology & Metabolism 3:606–609

Israel ZH, Pomeranz S (1995) Intracranial craniopharyngioma seeding following radical resection. Pediatr Neurosurg 22(4):210–213

Ito M, Jamshidi J, Yamanaka K (2001) Does craniopharyngioma metastasize? Case report and review of the literature. Neurosurgery 48(4):933–935

Jakacki RI, Cohen BH, Jamison C, Mathews VP, Arenson E, Longee DC, Hilden J, Cornelius A, Needle M, Heilman D, Boaz JC, Luerssen TG (2000) Phase II evaluation of interferon-alpha-2a for progressive or recurrent craniopharyngiomas. J Neurosurg 92: 255–260

Kalapurakal JA, Goldman S, Hsieh YC, Tomita T, Marymont MH (2000) Clinical outcome in children with recurrent craniopharyngioma after primary surgery. Cancer J 6(6):388–393

Kato K, Nakatani Y, Kanno H, Inayama Y, Ijiri R, Nagahara N, Miyake T, Tanaka M, Ito Y, Aida N, Tachibana K, Sekido K, Tanaka Y (2004) Possible linkage between specific histological structures and aberrant reactivation of the Wnt pathway in adamantinomatous craniopharyngioma. J Pathol 203(3): 814–821

Khoo LT, Flagel J, Liker M, Levy M (2001) Craniopharyngiomas: surgical management. In: Petrovich P, Brady LW, Apuzzo ML, Bamberg M (eds) Combined modality therapy of central nervous system tumors. Springer, Berlin, pp 187–214

Kobayashi T, Tanaka T, Kida Y (1994) Stereotactic gamma radiosurgery of craniopharyngiomas. Pediatr Neurosurg 21(Suppl 1):69–74

Koutourousiou M, Gardner PA, Fernandez-Miranda JC, Tyler-Kabara EC, Wang EW, Snyderman CH (2013) Endoscopic endonasal surgery for craniopharyngiomas: surgical outcome in 64 patients. J Neurosurg 119(5):1194–1207

Kristopaitis T, Thomas C, Petruzzelli GJ, Lee JM (2000) Malignant craniopharyngioma. Arch Pathol Lab Med 124(9):1356–1360

Laws ER (1994) Transsphenoidal removal of craniopharyngioma. Pediatr Neurosurg 21(Suppl 1):57–63

Leber KA, Bergloff J, Pendl G (1998) Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. J Neurosurg 88(1):43–50

Lee HC, Curry DL, Stern JS (1989) Direct effect of CNS on insulin hypersecretion in obese Zucker rats: involvement of vagus nerve. American Journal of Physiology 256:E439–E444

Lee JH, Kim CY, Kim DG, Jung HW (1999) Postoperative ectopic seeding of craniopharyngioma. Case illustration. J Neurosurg 90(4):796

Leksell L, Lidén K (1952) A therapeutic trial with radioactive isotope in cystic brain tumor: radioisotope techniques I. Medical and Physiological Application 1:1–4

Li K, Lu X, Yang N, Zheng J, Huang B, Li L (2015) Association of pituitary stalk management with endocrine outcomes and recurrence in microsurgery of craniopharyngiomas: a meta-analysis. Clin Neurol Neurosurg 136:20–24

Lin LL, El Naqa I, Leonard JR, Park TS, Hollander AS, Michalski JM, Mansur DB (2008) Long-term outcome in children treated for craniopharyngioma with and without radiotherapy. Journal of Neurosurgery Pediatrics 1:126–130

Linnert M, Gehl J (2009) Bleomycin treatment of brain tumors: an evaluation. Anticancer Drugs 20(3): 157–164

Lunsford LD, Pollock BE, Kondziolka DS, Levine G, Flickinger JC (1994) Stereotactic options in the management of craniopharyngioma. Pediatr Neurosurg 21(Suppl 1):90–97

Lustig RH (2002) Hypothalamic obesity: the sixth cranial endocrinopahty. The Endocrinologist 12:210–217

Lustig RH (2007) The efferent arm of the energy balance regulatory pathway: neuroendocrinology and pathology. In: Donahoue PA (ed) Obesity and energy metabolism: research and clinical applications. Humana, Totowa, NJ, pp 69–86

Lustig RH (2008) Hypothalamic obesity: causes, consequences, treatment. Pediatr Endocrinol Rev 6(2): 220–227

Lustig RH, Post SR, Srivannaboon K, Rose SR, Danish RK, Burghen GA, . . . Merchant TE (2003) Risk factors for the development of obesity in children surviving brain tumors. J Clin Endocrinol Metab 88(2): 611–616

Lustig RH, Rose SR, Burghen GA, Velasquez-Mieyer P, Broome DC, Smith K, Li H, Hudson MM,Heideman RL, Kun LE (1999) Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. Journal of Pediatrics 135:162–168

Luu QT, Loredo LN, Archambeau JO, Yonemoto LT, Slater JM, Slater JD (2006) Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. Cancer J 12(2):155–159

Malik JM, Cosgrove GR, VandenBerg SR (1992) Remote recurrence of craniopharyngioma in the epidural space. Case report. J Neurosurg 77(5):804–807

Mason PW, Krawiecki N, Meacham LR (2002) The use of dextroamphetamine to treat obesity and hyperphagia in children treated for craniopharyngioma. Archives of Pediatric and Adolescent Medicine 156:887–892

Matsuo M, Yonemitsu N, Zaitsu M, Ishii K, Hamasaki Y, Fukutama K et al (2001) Expression of prostaglandin H synthetase-2 in human brain tumors. Acta Neuopathol, 102(2):181–187

May JA, Krieger MD, Bowen I, Geffner ME (2006) Craniopharyngioma in childhood. Adv Pediatr 53:183–209

Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, . . . Kun LE (2002) Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. Int J Radiat Oncol Biol Phys 53(3):533–542

Merchant TE, Kun LE, Hua CH, Wu S, Xiong X, Sanford RA, Boop FA (2013) Disease control after reduced volume conformal and intensity modulated radiation therapy for childhood craniopharyngioma. Int J Radiat Oncol Biol Phys 85(4):e187–e192

Miller DC (1994) Pathology of craniopharyngiomas: clinical import of pathological findings. Pediatr Neurosurg 21(Suppl 1):11–17

Minniti G, Saran F, Traish D, Soomal R, Sardell S, Gonsalves A, . . . Brada M (2007) Fractionated stereotactic conformal radiotherapy following conservative surgery in the control of craniopharyngiomas. Radiother Oncol 82(1):90–95

Mokry M (1999) Craniopharyngiomas: a six year experience with Gamma Knife radiosurgery. Stereotact Funct Neurosurg 72(Suppl 1):140–149

Moore K, Couldwell WT (2000) Craniopharyngioma. In: Bernstein M, Berger MS (eds) Neuro-oncology: the essentials. Thieme, New York

Muller HL (2014) Craniopharyngioma. Endocr Rev 35(3):513–543

Muller HL, Gebhardt U, Etavard-Gorris N, Korenke E, Warmuth-Metz M, Kolb R, . . . Calaminus G (2004) Prognosis and sequela in patients with childhood craniopharyngioma – results of HIT-ENDO and update on KRANIOPHARYNGEOM 2000. Klin Padiatr 216(6):43–348

Norris JS, Pavaresh M, Afshar F (1998) Primary transsphenoidal microsurgery in the treatment of craniopharyngiomas. Br J Neurosurg 12(4):305–312

Nozaki M1, Tada M, Matsumoto R, Sawamura Y, Abe H, Iggo RD (1998) Rare occurrence of inactivating p53 gene mutations in primary non-astrocytic tumors of the central nervous system: reappraisal by yeast functional assay. Acta Neuropathol 95(3):291–6

Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS (2015) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008–2012. Neuro Oncol 17(Suppl 4):iv1–iv62

Pekmezci M, Louie J, Gupta N, Bloomer MM, Tihan T (2010) Clinicopathological characteristics of adamantinomatous and papillary craniopharyngiomas: University of California, San Francisco experience 1985–2005. Neurosurgery 67(5):1341–1349

Pierre-Kahn A, Sainte-Rose C, Renier D (1994) Surgical approach to children with craniopharyngiomas and severely impaired vision: special considerations. Pediatr Neurosurg 21(Suppl 1):50–56

Pollock BE, Lunsford LD, Kondziolka D, Levine G, Flickinger JC (1995) Phosphorus-32 intracavitary irradiation of cystic craniopharyngiomas: current technique and long-term results. Int J Radiat Oncol Biol Phys 33:437–446

Poretti A, Grotzer MA, Ribi K, Schonle E, Boltshauser E (2004) Outcome of craniopharyngioma in children: long-term complications and quality of life. Dev Med Child Neurol 46(4):220–229

Prabhu VC, Brown HG (2005) The pathogenesis of craniopharyngiomas. Childs Nerv Syst 21(8–9):622–627

Preeyasombat C, Bacchetti P, Lazar AA, Lustig RH (2005) Racial and etiopathologic dichotomies in insulin secretion and resistance in obese children. Journal of Pediatrics 146:474–481

Prieto R, Pascual JM (2013) Craniopharyngiomas with a mixed histological pattern: the missing link to the intriguing pathogenesis of adamantinomatous and squamous-papillary varieties? Neuropathology 33(6): 682–686

Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, Zerah M, Bezerra M, Renier D, Pierre-Kahn A, Sainte-Rose C (2007) Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. Journal of Neurosurgery 106:3–12

Raghavan R, Dickey WT Jr, Margraf LR, White CL 3rd, Coimbra C, Hynan LS, Rushing EJ (2000) Proliferative activity in craniopharyngiomas: clinicopathological correlations in adults and children. Surg Neurol 54:241–247

Ragoowansi AT, Piepgras DG (1991) Postoperative ectopic craniopharyngioma. Case report. J Neurosurg 74(4):653–655

Regine WF, Mohiuddin M, Kramer S (1993) Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. Radiother Oncol 27(1):13–21

Rienstein S, Adams EF, Pilzer D, Goldring AA, Goldman B, Friedman E (2003) Comparative genomic hybridization analysis of craniopharyngiomas. J Neurosurg 98(1):162–164

Rilliet B, de Paul Djientcheu V, Vernet O, Montes J, Farmer JP, Bertrand G (1999) Craniopharyngiomas, results in children and adolescents operated through a transsphenoidal approach compared with an intracranial approach. Front Radiat Ther Oncol 33:114–122

Riva D, Pantaleoni C, Devoti M, Saletti V, Nichelli F, Giorgi C (1998) Late neuropsychological and behavioural outcome of children surgically treated for craniopharyngioma. Childs Nerv Syst 14(4–5):179–184

Rose SR, Lustig RH, Pitukcheewanont P, Broome DC, Burghen GA, Li H, Hudson MM, Kun LE, Heideman RL (1999) Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. J Clin Endocrinol Metab 84(12):4472–4479

Rose SR, Lustig RH, Pitukcheewanont P, Broome DC, Burghen GA, Li H, Hudson MM, Kun LE, Heideman RL (1999b) Hidden central hypothyroidism in survivors of childhood cancer. Journal of Clincal Endocrinology and Metabolism 84:4472–4479

Rose SR, Danish RK, Kearney NS, Schreiber RE, Lustig RH, Burghen GA, Hudson MM (2005) ACTH deficiency in childhood cancer survivors. Pediatr Blood Cancer 45(6):808–813

Samii M, Tatagiba M (1997) Surgical management of craniopharyngiomas: a review. Neurol Med Chir (Tokyo) 37(2):141–149

Sanford RA (1994) Craniopharyngioma: results of survey of the American Society of Pediatric Neurosurgery. Pediatr Neurosurg 21(Suppl 1):39–43

Sanford RA, Muhlbauer MS (1991) Craniopharyngioma in children. Neurol Clin 9(2):453–465

Sarubi JC, Bei H, Adams EF, Boson WL, Friedman E, Brandão K, Kalapothakis E, Miranda D, Valle FL, Sarquis MS, De Marco L (2001) Clonal composition of human adamantinomatous craniopharyngiomas and somatic mutation analyses of the patched (PTCH), Gsalpha and Gi2alpha genes. Neurosci Lett 310(1): 5–8, Neurosci Lett. 310(1):5–8

Schofl C, Schleth A, Berger D, Terkamp C, Von Zur Muhlen A, Brabant G (2002) Sympathoadrenal counterregulation in patients with hypothalamic craniopharyngioma. Journal of Clincal Endocrinology and Metabolism 87: 624–629

Shi XE, Wu B, Fan T, Zhou ZQ, Zhang YL (2008) Craniopharyngioma: surgical experience of 309 cases in China. Clin Neurol Neurosurg 110(2):151–159

Sidawy MK, Jannotta FS (1997) Intraoperative cytologic diagnosis of lesions of the central nervous system. Am J Clin Pathol 108:S56–S66

Smith D, Finucane F, Phillips J, Baylis PH, Finucane J, Tormey W, Thompson CJ (2004) Abnormal regulation of thirst and vasopressin secretion following surgery for craniopharyngioma. Clinical Endocrinology 61:273–279

Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT (2004) Features of the metabolic syndrome after craniopharyngioma. Journal of Clinical Endocrinology and Metabolism 89:81–86

Stafford SL, Pollock BE, Leavitt JA, Foote RL, Brown PD, Link MJ, Gorman DA, Schomberg PJ (2003) A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 55(5):1177–1181

Steinbok P, Hukin J (2010) Intracystic treatments for craniopharyngioma. Neurosurg Focus 28(4):E13

Sterkenberg AS, Hofmann A, Gebhardt U, Warmuth-Metz M, Daubenbüchel AM, Muller HL (2015) Survival, hypothalamic obesity, and neuropsychologic/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. Neuro Oncol 17(7):1029–1038

Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwein JW, Moshang T, Rorke LB, Phillips PC, Sutton LN, Shu HK (2004) Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. Int J Radiat Oncol Biol Phys 58(3):714–720

Suit HD, Goitein M, Tepper J, Koehler AM, Schmidt RA, Schneider R (1975) Exploratory study of proton radiation therapy using large field techniques and fractionated dose schedules. Cancer 35(6):1646–1657

Takahashi H, Nakazawa S, Shimura T (1985) Evaluation of postoperative intratumoral injection of bleomycin for craniopharyngioma in children. J Neurosurg 62(1):120–127

Takamaru KI, Ohmitsu M, Li FQ (2008) An oncogenic hub: beta-catenin as a molecular target for cancer therapeutics. Handbook of Experimental Pharmacology 186:261–284

Thapar K, Stefaneanu L, Kovacs K, Scheithauer BW, Ricardo VL, Muller PJ, Laws ER (1994) Estrogen receptor gene expression in craniopharyngiomas: an in situ hybridization study. Neurosurgery 35:1012–1017

Tomita T, McLone DG (1993) Radical resections of childhood craniopharyngiomas. Pediatr Neurosurg 19(1): 6–14

Van Effenterre R, Boch AL (2002) Craniopharyngioma in adults and children: a study of 122 surgical cases. J Neurosurg 97(1):3–11

Veeravagu A, Lee M, Jiang B, Chang SD (2010) The role of radiosurgery in the treatment of craniopharyngiomas. Neurosurg Focus d28(4):E11

Vidal S, Kovacs K, Lloyd RV, Meyer FB, Scheithauer BW (2002) Angiogenesis in patients wtih craniopharyngiomas: correlation with treatment and outcome. Cancer 94(3):738–745

Villani RM, Tomei G, Bello L, Sganzerla E, Ambrosi B, Re T, Giovanelli Barilari M (1997) Long-term results of treatment for craniopharyngioma in children. Childs Nerv Syst 13(7):397–405

Voges J, Sturm V, Lehrke R, Treuer H, Gauss C, Berthold F (1997) Cystic craniopharyngioma: long-term results after intracavitary irradiation with stereotactically applied colloidal beta emitting radioactive sources. Neurosurgery 40:263–269

Weiner HL, Wisoff JH, Rosenberg ME, Kupersmith MJ, Cohen H, Zagzag D, Shiminski-Maher T, Flamm ES, Epstein FJ, Miller DC (1994) Craniopharyngiomas: a clinicopathological analysis of factors predictive of recurrence and functional outcome. Neurosurgery 35(6):1001–1010

Weiss M, Sutton L, Marcial V, Fowble B, Packer R, Zimmerman R, Schut L, Bruce D, D'Angio G (1989) The role of radiation therapy in the management of childhood craniopharyngioma. Int J Radiat Oncol Biol Phys 17(6):1313–1321

Wilson JD, Foster DW, Kronenberg HM, Larsen PR (1998) Williams textbook of endocrinology. W.B. Saunders, Philadelphia

Winkfield KM, Linsenmeier C, Yock TI, Grant PE, Yeap BY, Butler WE, Tarbell NJ (2009) Surveillance of craniopharyngioma cyst growth in children treated with proton radiotherapy. Int J Radiat Oncol Biol Phys 73(3):716–721

Wisoff J, Donahue B (2015) Craniopharyngiomas. In: Albright AL, Pollack IF, Adelson PD (eds) Principles and practice of pediatric neurosurgery, 3rd edn. Thieme, New York

Yasargil MG, Curcic M, Kis M, Siegenthaler G, Teddy PJ, Roth P (1990) Total removal of craniopharyngiomas. Approaches and long-term results in 144 patients. J Neurosurg 73(1):3–11

Yeung JT, Pollack IF, Panigrahy A, Jakacki RI (2012) Pegylated interferon-α-2b for children with recurrent craniopharyngioma. J Neurosurg Pediatr 10:498–503

Yu X, Liu Z, Li S (2000) Combined treatment with stereotactic intracavitary irradiation and gamma knife surgery for craniopharyngiomas. Stereotact Funct Neurosurg 75(2–3):117–122

Yuen KC, Koltowska-Häggström M, Cook DM, Fox JL, Jönsson PJ, Geffner ME, Abs R (2013) Clinical characteristics and effects of GH replacement therapy in adults with childhood-onset craniopharyngioma compared with those in adults with other causes of childhood-onset hypothalamic-pituitary dysfunction. Eur J Endocrinol 169:511–519

Yuen KC, Koltowska-Häggström M, Cook DM, Fox JL, Jönsson PJ, Geffner ME, Abs R (2014) Primary treatment regimen and diabetes insipidus as predictors of health outcomes in adults with childhood-onset craniopharyngioma. J Clin Endocrinol Metab 99(4): 1227–1235

Zhou ZQ, Shi XE (2004) Changes of hypothalamus-pituitary hormones in patients after total removal of craniopharyngiomas. Chin Med J (Engl) 117(3): 357–360

Zuccaro G (2005) Radical resection of craniopharyngioma. Childs Nerv Syst 21(8–9):679–690

Zuccaro G, Jaimovich R, Mantese B, Monges J (1996) Complications in paediatric craniopharyngioma treatment. Childs Nerv Syst 12(7):385–390

Zuhur SS, Müslüman AM, Tanık C, Karaman O, Oztürk FY, Ozderya A, Ozkayalar H, Aydın Y, Altuntaş Y (2011) MGMT immunoexpression in adamantinomatous craniopharyngiomas. Pituitary 14(4):323–327

Neuronal Tumors

8

Dario J. Englot, Edward F. Chang, and Nalin Gupta

Contents

D.J. Englot, MD, PhD
Department of Neurological Surgery,
University of California San Francisco,
505 Parnassus Ave., Rm M779,
San Francisco, CA 94143, USA
e-mail: englot@gmail.com

E.F. Chang, MD
Departments of Neurological Surgery & Physiology,
University of California San Francisco,
505 Parnassus Ave., Rm M779, San Francisco,
CA 94143, USA
e-mail: edward.chang@ucsf.edu

N. Gupta, MD, PhD (✉)
Division of Pediatric Neurosurgery, Departments of Neurological Surgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA
e-mail: nalin.gupta@ucsf.edu

8.1 Introduction

Neuronal tumors are rare, typically slow-growing tumors which usually carry a good prognosis. Gangliocytomas, gangliogliomas, and dysembryoplastic neuroepithelial tumors (DNETs) present in late childhood or early adulthood are most often found in the supratentorial compartment and are commonly accompanied by intractable epilepsy. Surgical gross total resection (GTR) is typically curative and results in favorable seizure control, although tumor progression and persistent seizures are possible with subtotal resection (STR). It is important to distinguish these tumors from low-grade astrocytomas in

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_8

order to identify appropriate therapy. Central neurocytomas are lobulated, well-circumscribed masses seen in early adulthood, most often found in the lateral ventricles in proximity to the foramen of Monro. Patients usually present with symptoms attributable to raised intracranial pressure secondary to obstructive hydrocephalus. Complete surgical resection carries a favorable prognosis and also has the benefit of reopening CSF pathways, but can be difficult to achieve in some cases. Malignant transformation occurs in only a small minority of neuronal tumors, but has been reported in all tumor types. Although rare, tumor recurrence is seen, necessitating adjuvant therapy such as chemotherapy, radiation therapy, or radiosurgery in addition to surgical resection.

8.2 Ganglioglioma and Gangliocytoma

Ganglioglioma and gangliocytoma belong to a family of rare, slow-growing, neuronal tumors. The term "ganglioglioma" was first introduced by Courville in 1930 to describe the mixed neuronal and glial elements typically seen in this tumor (Courville 1930). Although there are pathological differences between ganglioglioma and gangliocytoma, the natural history and biology of these two subtypes appear to be quite similar.

8.2.1 Epidemiology

Gangliogliomas are rare, representing less than 0.5 % of all central nervous system (CNS) tumors and approximately 1–2 % of all brain tumors (Kalyan-Raman and Olivero 1987; Zentner et al. 1994; Compton et al. 2012). The mean or median age at diagnosis ranged from 8 to 25 years in a group of 206 patients, and the male/female ratio varies among different series from 0.9:1 to 1.9:1, with most studies supporting a slight male predominance (Lang et al. 1993; Prayson et al. 1995; Hirose et al. 1997; Compton et al. 2012). In one series of 99 children with ganglioglioma, the mean age was 9.5 years, with an approximately equal number of males and females (Johnson et al. 1997).

8.2.2 Pathology

Gangliogliomas can occur throughout the CNS, although they occur mostly in the supratentorial region, primarily the temporal lobe. The frontal lobes and the floor of the third ventricle are also common locations for these tumors (Shono et al. 2007; El Khashab et al. 2009; Lou et al. 2014). Less frequently, they can occur in the cerebellum, brain stem, spinal cord, pituitary, and pineal regions (Kalyan-Raman and Olivero 1987; Hirose et al. 1997; Jallo et al. 2004; Baussard et al. 2007; Zhang et al. 2013b).

8.2.2.1 Gross Appearance

These tumors can be either solid or cystic. If cystic in nature, there is often an associated mural nodule (the solid tumor component is located eccentrically at the margin of the cyst) (Shono et al. 2007). The tumor itself is firm and typically well demarcated from the surrounding brain tissue. Some tumors contain varying degrees of calcification. Significant mass effect, hemorrhage, and necrosis are rare.

8.2.2.2 Histopathology

Gangliocytomas consist of groups of large, multipolar neurons with dysplastic features. The surrounding stroma contains nonneoplastic glial elements and a network of reticulin fibers (Fig. 8.1b). Gangliocytomas are classified as WHO grade I tumors. Gangliogliomas are also classified as WHO grade I tumors, but in contrast to gangliocytomas, contain neoplastic astrocytes or other glial cells (Louis et al. 2007). Grading of gangliogliomas has typically been assigned based on characteristics of the glial component of the neoplasm. However, the standard criteria that are used to grade astrocytomas (e.g., mitotic activity, microvascular proliferation, and necrosis) appear to less reliably predict the clinical behavior of gangliogliomas (Luyken et al. 2003).

The 4th edition of the WHO classification does not include grade II as a designation for gangliogliomas (Louis et al. 2007). In this edition, gangliogliomas are designated WHO grade I and anaplastic gangliogliomas are designated WHO grade III. Grade III neoplasms are characterized

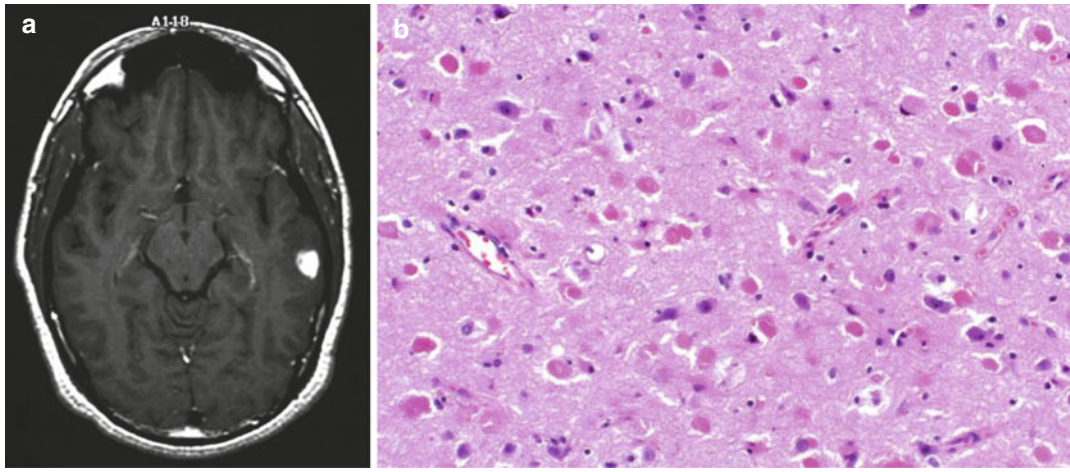

Fig. 8.1 Ganglioglioma. (**a**) T1-weighted axial MRI with gadolinium of a ganglioglioma in the left temporal lobe. Nodular enhancement is seen. (**b**) Hematoxylin and eosin staining reveals large, dysplastic neurons and a neoplastic glial component. Necrosis is not seen

by additional features such as atypia (increased cellularity, conspicuous pleomorphism), microvascular proliferation, or an elevated MIB-1 labeling index. Necrosis is absent unless the glial component undergoes malignant transformation. Tumors with evidence of malignant transformation are considered anaplastic gangliogliomas, WHO grade III.

8.2.2.3 Immunohistochemistry and Electron Microscopy

Immunohistochemical staining techniques are crucial for identifying the neuronal and astrocytic features within these tumors. Positive staining for synaptophysin, neuropeptides, and biogenic amines are associated with a neuronal phenotype. Similarly, positive staining for glial fibrillary acid protein (GFAP) identifies the astrocytic component. Electron microscopy is also helpful to identify additional neuronal features such as dense core granules and synaptic junctions (Hirose et al. 1997; Gelabert-Gonzalez et al. 2010).

8.2.2.4 Cytogenetics

Molecular cytogenetic data regarding ganglioglioma are scarce, but a few abnormal karyotypes have been observed. Specific cytogenetic abnormalities include a ring chromosome 1, trisomy of chromosomes 5–7, and deletion of chromosome 6 (Neumann et al. 1993; Xu et al. 2014). Analysis for microsatellite marker instability in tumor DNA from six gangliogliomas found no abnormalities (Zhu et al. 1996). One series of ganglioglioma patients reported a comparatively higher frequency of splice-site-associated single-nucleotide polymorphism in the tuberous sclerosis 2 gene (*TSC2*) (Platten et al. 1997). This may suggest an underlying genetic susceptibility for sporadic ganglioglioma, although the underlying biologic mechanism is unknown. More recently described variants, papillary glioneuronal tumor and rosette-forming glioneuronal tumor (WHO grade I), have been mostly described in adults, although a recent systematic review also identified a number of children with these tumors (Schlamann et al. 2014). Chromosomal and structural alterations involving only chromosome 7 with breakpoints at 7p22 have been reported in the papillary glioneuronal tumor variant (Faria et al. 2008).

8.2.3 Clinical Features

Seizure is the most common presenting symptom of gangliogliomas. The seizure history is often longstanding, with a mean duration prior to diagnosis ranging from 6 to 25 years (Prayson et al.

1995; Luyken et al. 2003; Southwell et al. 2012). In one series of patients, temporal lobe gangliogliomas represent 40 % of all tumors causing chronic temporal lobe epilepsy (Blumcke et al. 1999). Patients with brain stem lesions commonly present with involvement of the motor tracts: weakness, spasticity, and gait disturbance (Gopalakrishnan et al. 2013). Gangliogliomas of the spinal cord may involve the entire spinal cord and typically produce scoliosis, gait disturbance, and progressive weakness (Hamburger et al. 1997; Jallo et al. 2004). These symptoms can be very longstanding before a diagnosis is reached. Patients with midline tumors may develop symptoms and signs of hydrocephalus, such as headache, papilledema, alterations in the level of consciousness, and nausea/vomiting (Haddad et al. 1992; Deling et al. 2013; Zhang et al. 2013a).

8.2.4 Natural History

Gangliogliomas are indolent, slow-growing tumors. Without resection, patients often have prolonged courses of disease, depending on the location of the primary mass (Selch et al. 1998). Anaplastic glial changes in ganglioglioma, as well as high MIB-1 labeling indices, may be markers for more aggressive tumor behavior (Hirose et al. 1997; Scoccianti et al. 2012). Malignant transformation is relatively rare, occurring in less than 3 % of gangliogliomas (Hakim et al. 1997; DeMarchi et al. 2011).

8.2.5 Diagnosis and Neuroimaging

Neuroimaging is the initial step in diagnosis, as no specific laboratory tests are available. A CT scan, if performed as a screening test, reveals an iso- to hypodense solid or cystic mass (Adachi and Yagishita 2008). Cysts may be associated with a mural nodule, although both cyst and nodule are well circumscribed. Calcifications may be present and contrast enhancement is usually seen, but occasionally can be minimal or absent (Lagares et al. 2001). MRI is the best imaging modality and is required to adequately delineate the mass. Tumors are usually hypointense on T1-weighted images and hyperintense on T2-weighted images (Zhang et al. 2008). Mass effect and edema are typically minimal. Contrast enhancement varies in intensity and may be nodular, rim-like, or entirely solid (Figs. 8.1a and 8.2). Syringobulbia or syringomyelia can be seen with spinal cord gangliogliomas (Park et al. 1993; Hamburger et al. 1997; Jallo et al. 2004). MR spectroscopy is usually of limited value due to the indolent nature of these tumors.

8.2.6 Treatment

Complete surgical resection is the treatment of choice and when achievable is usually curative (Sutton et al. 1987; Compton et al. 2012). The neoplasm itself contains no functioning nervous tissue, but potential eloquence of surrounding parenchyma must be considered in surgical planning (Southwell et al. 2012). A postoperative MRI is useful to assess the extent of resection. Subsequent surveillance imaging should be done to evaluate for recurrence, which can occur in a

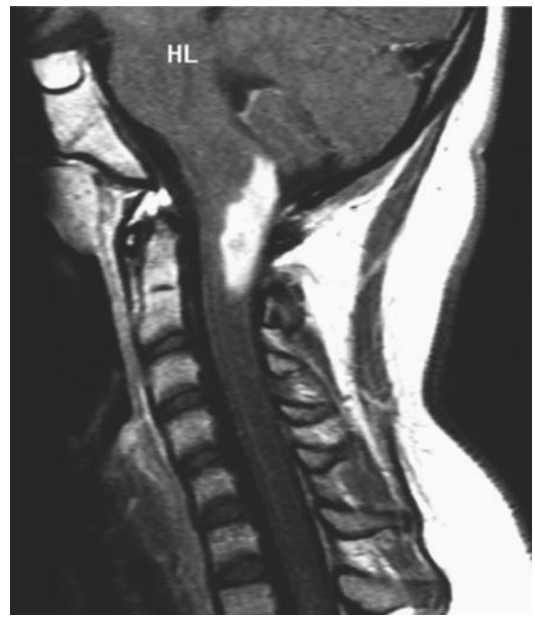

Fig. 8.2 An unusual case of a ganglioglioma of the upper cervical spinal cord. The patient is a 14-year-old girl who presented with paresthesias over the left side of the neck. The sagittal T1-weighted post-contrast MRI shows a well-demarcated mass arising in the dorsal portion of the spinal cord

small percentage of patients. Radiation therapy should be considered for tumor recurrence when further resection is not feasible. Tumors with malignant features (anaplastic features, high MIB-1 labeling index) may require radiation therapy as an adjuvant therapy, regardless of the extent of resection (Hakim et al. 1997; DeMarchi et al. 2011). Radiation therapy for benign lesions may delay time to progression in patients with unresectable disease, but the impact of radiotherapy on progression-free survival for incompletely resected benign tumors remains uncertain (Lang et al. 1993; Compton et al. 2012). Because the role of radiation therapy for subtotally resected, low-grade tumors is unclear, the risks and benefits of radiotherapy should be carefully weighed.

8.2.7 Outcome

The prognosis following GTR is excellent (Khajavi et al. 1995; Compton et al. 2012; Englot et al. 2012a; Southwell et al. 2012). In one surgical series of 88 patients with a median follow-up of nearly 12 years, 15-year overall survival was 94 % and 10-year progression-free survival was 37 %, with progression being dramatically affected by the extent of the initial resection (Compton et al. 2012). Tumor location is a significant predictor of outcome, most likely because it predicts resectability. Patients who undergo a subtotal excision (STR), most commonly seen in patients with midline tumors, are at higher risk of tumor progression or recurrence (Haddad et al. 1992; Compton et al. 2012). The importance of anaplasia as a prognostic feature is unclear, with different series demonstrating conflicting results (Kalyan-Raman and Olivero 1987; Lang et al. 1993; DeMarchi et al. 2011; Selvanathan et al. 2011). A retrospective analysis in one series of 34 patients, however, did demonstrate a correlation between improved survival and degree of resection as well as tumor grade (Selch et al. 1998). In a large series reported by Luyken et al., the rate of 7.5-year, progression-free survival was 97 % (Luyken et al. 2003). Risk factors for recurrence or malignant progression were residual tumor, frontal tumor location, and a higher-grade lesion. The survival outcomes are also acceptable for gangliogliomas involving the posterior fossa (Baussard et al. 2007) or spinal cord (Jallo et al. 2004).

For patients with tumor-associated epilepsy, seizure control improves dramatically after tumor resection (Englot et al. 2012a; Wallace et al. 2013). GTR appears to be the most important treatment-related factor (Benifla et al. 2006; Giulioni et al. 2006; Park et al. 2008; Southwell et al. 2012). In a recent series of 66 patients with ganglioglioma, 49 of which presented with epilepsy, and 85 % of patients with a seizure history were free of seizures after surgery (Southwell et al. 2012). Ninety-six percent of individuals in whom GTR was achieved were seizure-free, but only 54 % of the group had STR. A recent systematic review and meta-analysis found that postoperative seizure freedom in glioneuronal tumor resection was predicted by GTR, the absence of generalized seizures, and a shorter history of epilepsy (Englot et al. 2012a). Because seizure outcomes are improved in those patients with a shorter duration of epilepsy, early surgical intervention should be considered, particularly in patients with medically refractory epilepsy.

8.3 Dysembryoplastic Neuroepithelial Tumor

Dysembryoplastic neuroepithelial tumor (DNET) is a benign glioneuronal neoplasm that most commonly occurs in the supratentorial compartment. It was first described by Daumas-Duport and Scheithauer in 1988 (Daumas-Duport et al. 1988). The initial report described 39 children with a morphologically distinct brain tumor and intractable partial seizures.

8.3.1 Epidemiology

DNET most commonly affects children and young adults in the second and third decade of life, with a peak in late childhood to early adolescence (Daumas-Duport and Varlet 2003). The incidence of DNET is not accurately known, but available reports suggest it affects 0.6–3 % of individuals with a primary brain tumor (Morris et al. 1993; Wolf et al. 1995; Rickert and Paulus 2001; Rashidi et al. 2003). In a

retrospective review of all neuroepithelial tumors at a single institution, DNETs were found in 0.6% of patients including all ages, in 1.2% of patients under age 20 years, and in 0.2% of patients over 20 years of age (Daumas-Duport et al. 1988). Males are more frequently affected than females (Daumas-Duport et al. 1988; Rickert and Paulus 2001).

8.3.2 Pathology

8.3.2.1 Gross Appearance

DNET arises from and expands the cortex, although the underlying white matter may also be involved, and it has traditionally been viewed as a benign "quasihamartomatous" tumor (Daumas-Duport 1993; Ray et al. 2009). Distended cortical ribbons consisting of gelatinous glioneuronal elements and smaller, firmer glial nodules are seen during surgery.

8.3.2.2 Histopathology

The characteristic pathologic feature is the glioneuronal element which consists of columns of axon bundles lined with small S100-positive and GFAP-negative oligodendroglia-like cells (Fig. 8.3b). Oligodendroglia-like cells have minimal cytoplasm and are rich in mucopolysaccharides. Mature neuronal cells are found interspersed within the tumor and adjacent cortical dysplasia can be found. Associated cortical dysplasias are commonly observed with DNET (Fay-McClymont et al. 2012).

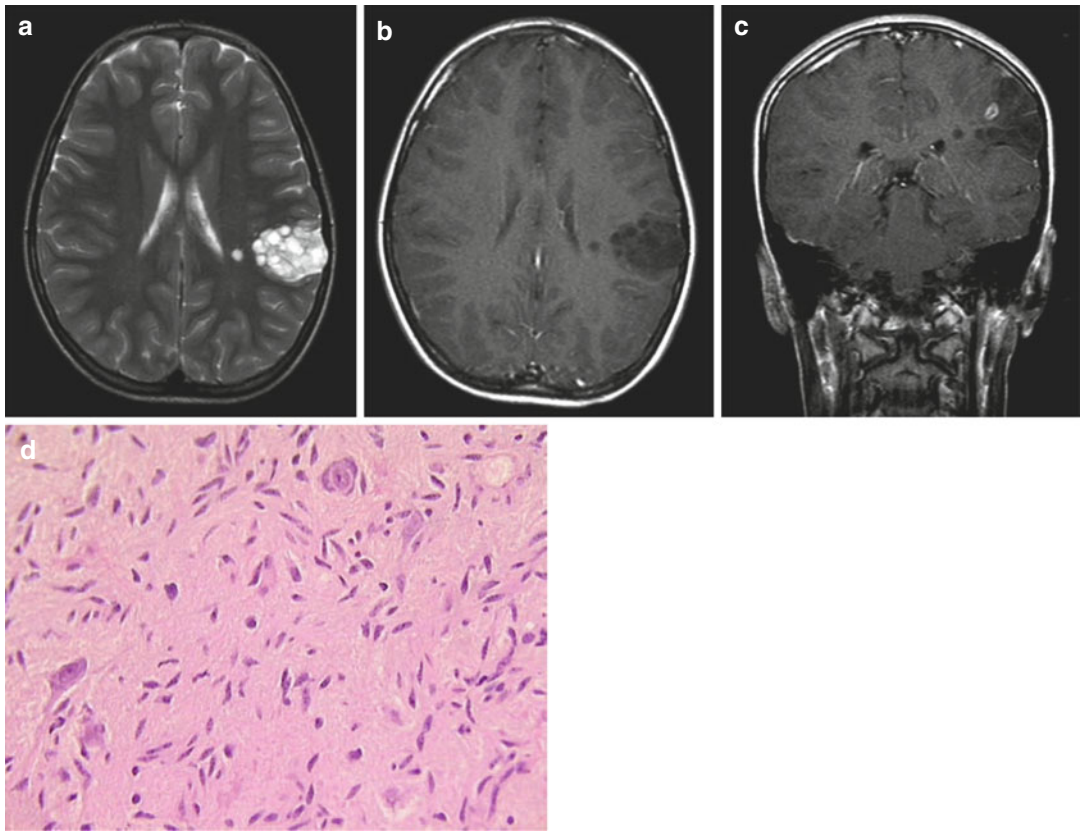

Fig. 8.3 Dysembryoplastic neuroepithelial tumor (DNET). (**a**) T2-weighted axial MRI of a left parietal DNET demonstrates a typical "bubbly" appearance. The majority of the mass does not enhance following contrast (**b**), although a small focus of enhancement was noted along one margin of the tumor (**c**). No peritumoral edema is seen. (**d**) H & E staining in a complex form of DNET shows nuclear atypia of glioneuronal elements. Astrocytic, oligodendrocytic, and neuronal components are present to varying degrees

Smaller glial nodules are found along the tumor borders of the complex variant of DNETs. In contrast to gangliogliomas, atypical neurons resembling ganglion cells and perivascular lymphocytes are not found with DNETs (Daumas-Duport 1993; Hirose et al. 1994; Raymond et al. 1994; Fay-McClymont et al. 2012). DNETs are classified as WHO grade I, and although rare, malignant transformation has been observed (Ray et al. 2009; Mano et al. 2013).

8.3.2.3 Immunohistochemistry and Molecular Genetics

Neuronal elements stain positive for synaptophysin and neuronal nuclear antigen (NeuN) (Wolf et al. 1997; Brandes et al. 2000). Glial nodules stain positive for GFAP. The proliferation potential is very low and MIB-1 labeling indices vary from 0 to 8 % (Prayson and Estes 1992; Daumas-Duport 1993; Taratuto et al. 1995). Molecular genetic abnormalities have not been well studied, but one study identified certain tumors with *IDH1* mutation, 1p/19q loss, isolated loss 9q, and/or *PTEN* loss, which were not associated with tumor type or location or higher cell proliferation (Fay-McClymont et al. 2012). DNETs have been reported in patients with neurofibromatosis type I, although the overall frequency is unknown, and the lack of *NF1* gene loss in some of these tumors puts into question whether they are truly associated with defects in NF1 expression (Lellouch-Tubiana et al. 1995; Fedi et al. 2004).

8.3.3 Clinical Features

DNETs are associated with chronic, intractable partial seizures and are present in 25 % of all lesions resected for medically refractory epilepsy (Wolf et al. 1995; Pasquier et al. 1996; Chang et al. 2010). Most DNETs are located in the supratentorial region, especially the temporal lobe; however, other locations corresponding to the topography of the secondary germinal layers have been described, including the basal ganglia, thalamus, cerebellum, and pons (Leung et al. 1994; Kuchelmeister et al. 1995; Cervera-Pierot et al. 1997). Multifocal locations have been described, including both supratentorial and infratentorial (including both the cerebellum and brain stem) lesions in the same patient (Leung et al. 1994; Sharma et al. 2009).

8.3.4 Natural History

Untreated lesions often do not grow, but without resection, medically intractable seizures are likely to persist (Chang et al. 2010; Thom et al. 2011). Tumor progression is rare with partially resected DNETs, but does occur, and may suggest malignant transformation (Daumas-Duport 1993; Raymond et al. 1994; Taratuto et al. 1995; Mano et al. 2013; Kim et al. 2014). Subtotally resected lesions can remain quiescent for extended periods of time.

8.3.5 Diagnosis and Neuroimaging

Appearance on unenhanced CT ranges from iso- to hypodense, often with calcifications and occasionally with true cyst formation. One-third of tumors show contrast enhancement and the overlying calvarium may be remodeled, consistent with the chronic nature of the tumor (Daumas-Duport 1993; Raymond et al. 1995; Stanescu Cosson et al. 2001). DNETs are cortically based and may appear as macrogyri. Usually, the lesion involves the thickness of the normal cortex, although it can extend into the white matter. With MR imaging, the tumor is hypointense on T1-weighted and hyperintense on T2-weighted images (Fig. 8.3). No peritumoral edema or mass effect is usually seen. Enhancement is seen in one-third of tumors (Fig. 8.3c) (Daumas-Duport 1993; Raymond et al. 1995; Campos et al. 2009; Mano et al. 2013).

A definitive diagnosis of DNET is difficult to obtain with neuroimaging alone. However, the combination of partial seizures before age of 20 years, lack of progressive neurologic deficit, cortical involvement on MRI, absence of mass effect, or edema on CT or MRI is highly suggestive of DNET (Daumas-Duport 1993; Lang et al. 1993; Fernandez et al. 2003).

8.3.6 Treatment

Surgical GTR is typically curative. Recurrence has been reported rarely; therefore, radiation or chemotherapy is usually not indicated, except in cases of rare malignant lesions (Raymond et al. 1995; Maher et al. 2008; Mano et al. 2013). It is important to differentiate DNET from oligodendroglioma to avoid unnecessarily aggressive therapy.

8.3.7 Outcome

Neither clinical nor radiographic tumor progression is seen in the majority of patients, even with subtotal resection (Daumas-Duport et al. 1988; Daumas-Duport 1993; Raymond et al. 1994; Taratuto et al. 1995; Chang et al. 2010). Resection results in an approximately 83 % rate of seizure control across the literature, as observed in a recent systematic review (Englot et al. 2012a). In one report of 50 patients with DNET-related epilepsy, 87 % achieved seizure freedom after surgery (Chang et al. 2010). Seizure freedom was predicted by GTR, achieved in approximately 80 % of surgeries, and this outcome remained resilient at a median follow-up of greater than 5 years. Currently, no agreement exists over whether removal of the tumor alone (lesionectomy) or extended resection to include neighboring dysplastic cortex results in the best seizure control (Nolan et al. 2004; Chan et al. 2006; Giulioni et al. 2006; Minkin et al. 2008; Englot et al. 2012b).

8.4 Central Neurocytoma

8.4.1 Epidemiology

Central neurocytomas are rare CNS neoplasms and compromise only 0.25–0.5 % of brain tumors and are tumors of adolescents and young adults (Hassoun et al. 1993; Yang et al. 2015). In one series of 207 cases, the mean age of presentation was 29 years, with a range of 8 days to 67 years (Hassoun et al. 1993). Approximately 70 % of patients present between the ages of 20 and 40 years, and the incidence is similar in males and females (Vasiljevic et al. 2013).

8.4.2 Pathology

8.4.2.1 Gross Appearance

Central neurocytomas are lobulated, well-circumscribed masses that are gray in color, similar to the normal cortex (Bonney et al. 2015). They typically occur in close proximity to the foramen of Monro and may be attached to the septum pellucidum. Necrosis and cyst formation are frequently seen, and some neurocytomas are very vascular. Intratumoral hemorrhage is unusual.

8.4.2.2 Histopathology

The histopathologic appearance of a central neurocytoma can be similar to that of an oligodendroglioma (von Deimling et al. 1990; Schild et al. 1997; Bonney et al. 2015). Both neoplasms have small uniform cells with rounded nuclei and scant cytoplasm resembling perinuclear halos (the so-called “fried egg” appearance). It is quite likely that many intraventricular tumors previously diagnosed as oligodendrogliomas may actually have been central neurocytomas (von Deimling et al. 1990; Schild et al. 1997). The cytoplasm is ill defined and the nuclei are round to slightly lobulated (Fig. 8.4b). The tumor cells are dense in some areas and alternate with anuclear, less dense tumor parts. In particular the anuclear areas may have a fine fibrillary matrix. A delicate pattern of blood vessels forms a branching network in pattern similar to oligodendrogliomas. Focal calcification can be seen. Mitotic figures are absent or infrequent and endothelial proliferation and necrosis are uncommon. A variant, extraventricular neurocytoma (WHO grade II) usually occurs in adults and can sometimes be difficult to distinguish from oligodendroglioma (Mut et al. 2005; Sweiss et al. 2015).

8.4.2.3 Immunohistochemistry and Electron Microscopy

Immunostaining for neuron-specific enolase (NSE) and synaptophysin confirms the neuronal origin of these tumors (von Deimling et al.

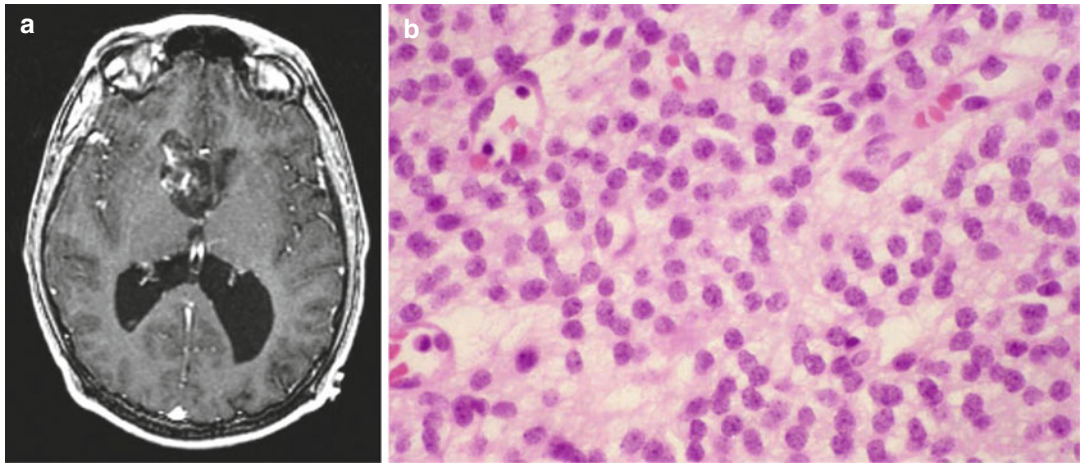

Fig. 8.4 Central neurocytoma. (**a**) T1-weighted axial MRI with gadolinium of a typical central neurocytoma arising in the frontal horn of the right lateral ventricle. A heterogeneous pattern of enhancement is seen. (**b**) H & E staining demonstrates cells with uniform, round to oval nuclei with speckled chromatin and occasional nucleolus. Anaplastic features are not seen

1991; Bonney et al. 2015). Positive staining with GFAP may represent neoplastic or reactive astrocytes. It has been suggested that central neurocytomas originate from bipotential (neuronal and astrocytic) progenitor cells in the periventricular region which persist into adulthood (von Deimling et al. 1991). An ultrastructural feature that sometimes distinguishes central neurocytomas from oligodendroglioma is the high degree of neuronal maturation. Electron microscopy demonstrates clear and dense-core vesicles, microtubules, and synapse formation.

8.4.2.4 Cytogenetics and Molecular Genetics

Comparative genomic hybridization (CGH) analysis was used to identify losses and gains in DNA sequences in ten histologically confirmed central neurocytomas (Yin et al. 2000). Genomic alterations were found in six tumors. Gain in genetic material was found for chromosomes 2p and 10q in four tumors, chromosome 18q in three tumors, and in chromosome 13q in two tumors. Gains in chromosome 7 were reported in three out seven central neurocytomas using fluorescence in situ hybridization (FISH) (Taruscio et al. 1997). Loss of 1p/19q has been described in a subset of extraventricular but not intraventricular neurocytomas and may be associated with aggressive histology in these tumors (Rodriguez et al. 2009).

It has been proposed that central neurocytoma originates from an adult neuronal progenitor cell. A significant overlap in the antigen profile and gene expression was observed in tumor specimens and native neuronal progenitor cells. GDF8, PDGF-D, neuregulin 2 (NRG2), IGF2, and JAG1 were overexpressed in tumors, suggesting that central neurocytoma is characterized by the concurrent overactivation of these pathways, which may drive neurocytoma expansion, while restricting tumor progenitor phenotype (Sim et al. 2006). One recent report identified genes highly expressed in five neurocytomas compared to the normal brain, including several in the Wnt/β-catenin and sonic hedgehog (SHH) signaling pathways, as well as genes mainly linked to calcium function or maintenance of neural progenitors (Vasiljevic et al. 2013).

8.4.3 Clinical Features

Patients most often present with symptoms attributable to raised intracranial pressure secondary to obstructive hydrocephalus (Yang et al. 2015). As expected, these consist of headaches and visual changes; the duration of clinical symptoms and

signs is typically less than 6 months. In one study, 93 % of patients complained of headaches, 37 % had visual changes, and 30 % experienced nausea and vomiting at presentation, while individuals less commonly complained of paresthesias (19 %), lethargy (11 %), balance problems (11 %), and tinnitus (7 %) (Schild et al. 1997). On physical exam, common presenting signs include papilledema and ataxia (Schild et al. 1997; Yang et al. 2015).

8.4.4 Natural History

While most central neurocytomas are benign, they can recur and even disseminate along the CSF pathways (Eng et al. 1997; Kim et al. 2013). Anaplasia has been demonstrated in central neurocytomas, marked by increased proliferative potential, and it is associated with worse long-term survival and local tumor control (Choudhri et al. 2015). An increase in GFAP positivity and vascular proliferation may suggest a more malignant course (Elek et al. 1999).

Most reports indicate that central neurocytomas are relatively slow growing, with the exception of atypical variants (Soylemezoglu et al. 1997; Sharma et al. 1998; Choudhri et al. 2015). Markers of proliferation have been studied in order to clarify the biological behavior of neurocytomas. In one study of 36 central neurocytomas, it was found that MIB-1 index under 2 % had a 22 % relapse rate, compared to a relapse rate of 63 % when the MIB-1 index was over 2 % for the observation period of 150 months (Soylemezoglu et al. 1997). With longer follow-up, tumors with an increasing MIB-1 index may relapse. This is illustrated in a case report of a patient with a recurrent central neurocytoma that had a fourfold increase in MIB-1 index after a 9-year disease-free interval (Christov et al. 1999). Necrosis and increased mitotic figures have also been reported in tumors with high-growth potential (Choudhri et al. 2015). Atypical (or anaplastic) neurocytomas (either in an intra- or extraventricular location) are now typically defined as having a high proliferative index (MIB-1 index >2 %) and may also have vascular proliferation, increased mitotic figures, and necrosis (Choudhri et al. 2015).

8.4.5 Diagnosis and Neuroimaging

CT scans demonstrate an iso- or slightly hyperdense mass within the body of the lateral ventricles near the foramen of Monro (Donoho and Zada 2015). Areas of hypodensity represent cystic degeneration. About one-half of central neurocytomas demonstrate calcification on CT imaging (Hassoun et al. 1993). These tumors are thought to arise from septal nuclei and have broad-based attachments to the superior and lateral walls of the ventricle. Obstruction of the interventricular foramen of Monro by tumor mass usually results in hydrocephalus. Contrast enhancement is mild to moderate for most central neurocytomas.

MRI reveals an isointense mass on T1-weighted images, with a soap-bubble multicystic appearance on T2-weighted images (Donoho and Zada 2015). Most central neurocytomas are isointense on T2-weighted images. Moderate heterogeneous gadolinium enhancement is seen (Fig. 8.4a) (Wichmann et al. 1991; Donoho and Zada 2015). Catheter angiography is rarely performed for central neurocytomas, but if obtained shows a homogenous vascular blush. On occasion, tumors can be relatively avascular (Taratuto et al. 1995; Ashkan et al. 2000). Arterial supply is from the posterior and anterior choroidal, pericallosal, and lenticulostriate vessels.

Central neurocytomas in the lateral ventricle of young adults must be distinguished from oligodendroglioma, subependymal giant cell astrocytoma, ependymoma, and low-grade or pilocytic astrocytoma. The typical central neurocytoma is located in the supratentorial ventricular system, in the anterior half of the lateral ventricle.

8.4.6 Treatment

8.4.6.1 Surgery

Complete surgical resection is the treatment of choice and also has the benefit of reopening CSF pathways in patients with hydrocephalus. Clinical reports indicate that gross-total resection confers long-term control for most central neurocytomas, but complete resection can be challenging, and may only be achieved in approximately one-half of cases (Schild et al. 1997; Kim et al.

2015; Thawani and Lee 2015). In one large multi-institutional database study of 82 resections for neurocytoma, gross-total tumor removal was reported in 48 % of patients (Lubrano et al. 2013).

Preoperative CSF shunting is rarely indicated, but if the patient continues to have hydrocephalus postoperatively, a permanent shunt is required. A third ventriculostomy can be useful in patients with noncommunicating hydrocephalus and was successful in 86 % of patients with intraventricular tumors in one report (Buxton et al. 2001). After completion of tumor resection, CSF may be drained via an external ventricular drain until returns are nearly clear.

8.4.6.2 Radiation Therapy and Radiosurgery

Radiotherapy after GTR is not indicated, as such surgery results in long-term tumor control for most patients. The use of fractionated conventional radiation or stereotactic radiation for residual or recurrent neurocytoma is variable among centers, and little consensus exists regarding adjuvant treatment strategy (Garcia et al. 2014; Barani et al. 2015). Among series utilizing conventional radiation, local control is reported in anywhere from 40 to 100 % of patients, with a median follow-up of 19–171 months across studies (Fujimaki et al. 1997; Sharma et al. 1998; Leenstra et al. 2007; Chen et al. 2008; Paek et al. 2008). Tumor control with stereotactic radiosurgery has been reported to be higher, 80–100 % across studies, with median follow-up of 30–72 months (Martin et al. 2003; Yen et al. 2007; Matsunaga et al. 2010; Genc et al. 2011; Karlsson et al. 2012). A few systematic reviews have examined conventional radiation versus radiosurgery in the treatment of neurocytoma, finding low rates of tumor regrowth with either modality (Rades and Schild 2006; Park and Steven 2012; Garcia et al. 2014). In a recent systematic review, local tumor control rates of 93 % and 88 % were observed in the radiosurgery and conventional radiation subgroups, respectively, with fewer complications reported with radiosurgery (Garcia et al. 2014). Although it is not a first-line option, radiosurgery should be considered for residual or recurrent tumors, or for those patients whose tumors are located in regions that preclude open surgical resection, and the role of conventional radiation in these lesions deserves further exploration.

8.4.6.3 Chemotherapy

The experience with chemotherapy for central neurocytoma is more limited, reported in a few case studies as adjunctive therapy to surgery and radiation (Patel et al. 2013; Thawani and Lee 2015). A variety of agents have been used, including carmustine, lomustine, vincristine, etoposide, cisplatin, cyclophosphamide, topotecan, and carboplatin, but responses have not been well documented (Schild et al. 1997; Brandes et al. 2000; von Koch et al. 2003; Patel et al. 2013). In the series of Schild et al., four patients received chemotherapy after radiation and none experienced tumor progression (Schild et al. 1997). Another study used chemotherapy in the treatment of recurrent/progressive central neurocytoma in three patients (Brandes et al. 2000). Stabilization was observed in two of them and the other had a complete remission. Follow-up was limited to 15, 18, and 36 months, but the responses were maintained. Most other reports regarding chemotherapy in this disorder are single-patient case studies, and no known studies compared the efficacy with chemotherapy versus radiation as adjuvant therapy in neurocytoma.

8.4.7 Outcome

Central neurocytomas have a favorable prognosis, but in some cases the clinical course can be more aggressive. Histological features of anaplasia predict biologic behavior in some but not all studies, and proliferation markers might be more useful in predicting relapse. The most important therapeutic modality remains surgery. A safe maximal resection confers the best long-term outcome. In one study of 82 patients receiving surgery for neurocytoma, 5-year progression-free survival rate was 92 % with GTR, compared with 55 % in individuals who had STR (Lubrano et al. 2013). In cases of STR, radiosurgery or standard external beam radiation can be considered or radiation can be delayed until tumor progression

occurs. One large series of 50 patients found that the 10-year survival rate was about 83 % and the local control rate was 60 % (Leenstra et al. 2007). These authors found that patients whose tumors have a low mitotic index (e.g., less than three per ten high-power fields) have much higher survival and local control rates compared to those whose tumors have a higher mitotic index. Reoperation for recurrence should be considered if the procedure can be performed safely. Chemotherapy has been used for recurrent central neurocytomas that cannot be resected, although long-term responses are unknown. Despite good outcomes, long-term follow-up is important as recurrence can occur long after surgery (Bertalanffy et al. 2005).

Conclusion

Neuronal tumors are rare and usually carry a good prognosis. Gangliocytomas, gangliogliomas, and DNETs present in late childhood or early adulthood and are commonly accompanied by intractable epilepsy. Complete surgical resection is typically curative and results in improved seizure control. It is important to distinguish these tumors from low-grade astrocytomas to prevent aggressive management. However, malignant transformations have been seen in all tumor types, particularly ganglioglioma. Central neurocytomas are seen in early adulthood and present with hydrocephalus due to ventricular outflow obstruction. Although rare, tumor recurrence and progression is seen, and adjuvant therapy such as chemotherapy, radiation therapy, or radiosurgery may be necessary in addition to surgical resection.

References

Adachi Y, Yagishita A (2008) Gangliogliomas: characteristic imaging findings and role in the temporal lobe epilepsy. Neuroradiology 50:829–834. doi:10.1007/s00234-008-0410-x

Ashkan K, Casey AT, D'Arrigo C, Harkness WF, Thomas DG (2000) Benign central neurocytoma. Cancer 89:1111–1120

Barani IJ, Raleigh DR, Larson D (2015) The management of central neurocytoma: radiotherapy. Neurosurg Clin N Am 26:45–56. doi:10.1016/j.nec.2014.09.014

Baussard B, Di Rocco F, Garnett MR et al (2007) Pediatric infratentorial gangliogliomas: a retrospective series. J Neurosurg 107:286–291

Benifla M, Otsubo H, Ochi A et al (2006) Temporal lobe surgery for intractable epilepsy in children: an analysis of outcomes in 126 children. Neurosurgery 59:1203–1213; discussion 1213–1204

Bertalanffy A, Roessler K, Koperek O, Gelpi E, Prayer D, Knosp E (2005) Recurrent central neurocytomas. Cancer 104:135–142

Blumcke I, Lobach M, Wolf HK, Wiestler OD (1999) Evidence for developmental precursor lesions in epilepsy-associated glioneuronal tumors. Microsc Res Tech 46:53–58

Bonney PA, Boettcher LB, Krysiak RS 3rd, Fung KM, Sughrue ME (2015) Histology and molecular aspects of central neurocytoma. Neurosurg Clin N Am 26:21–29. doi:10.1016/j.nec.2014.09.001

Brandes AA, Amista P, Gardiman M et al (2000) Chemotherapy in patients with recurrent and progressive central neurocytoma. Cancer 88:169–174

Buxton N, Ho KJ, Macarthur D, Vloeberghs M, Punt J, Robertson I (2001) Neuroendoscopic third ventriculostomy for hydrocephalus in adults: report of a single unit's experience with 63 cases. Surg Neurol 55:74–78

Campos AR, Clusmann H, von Lehe M, Niehusmann P, Becker AJ, Schramm J, Urbach H (2009) Simple and complex dysembryoplastic neuroepithelial tumors (DNT) variants: clinical profile, MRI, and histopathology. Neuroradiology 51:433–443. doi:10.1007/s00234-009-0511-1

Cervera-Pierot P, Varlet P, Chodkiewicz JP, Daumas-Duport C (1997) Dysembryoplastic neuroepithelial tumors located in the caudate nucleus area: report of four cases. Neurosurgery 40:1065–1069; discussion 1069–1070

Chan CH, Bittar RG, Davis GA, Kalnins RM, Fabinyi GC (2006) Long-term seizure outcome following surgery for dysembryoplastic neuroepithelial tumor. J Neurosurg 104:62–69

Chang EF, Christie C, Sullivan JE et al (2010) Seizure control outcomes after resection of dysembryoplastic neuroepithelial tumor in 50 patients. J Neurosurg Pediatr 5:123–130. doi:10.3171/2009.8.PEDS09368

Chen CM, Chen KH, Jung SM, Hsu HC, Wang CM (2008) Central neurocytoma: 9 case series and review. Surg Neurol 70:204–209. doi:10.1016/j.surneu.2007.04.023

Choudhri O, Razavi SM, Vogel H, Li G (2015) Atypical and rare variants of central neurocytomas. Neurosurg Clin N Am 26:91–98. doi:10.1016/j.nec.2014.09.003

Christov C, Adle-Biassette H, Le Guerinel C (1999) Recurrent central neurocytoma with marked increase in MIB-1 labelling index. Br J Neurosurg 13:496–499

Compton JJ, Laack NN, Eckel LJ, Schomas DA, Giannini C, Meyer FB (2012) Long-term outcomes for low-grade intracranial ganglioglioma: 30-year experience from the Mayo Clinic. J Neurosurg 117:825–830. doi:10.3171/2012.7.JNS111260

Courville CB (1930) Ganglioglioma: tumor of the central nervous system. Review of the literature and report of two cases. Arch Neurol Psychiatry 24:438–491

Daumas-Duport C (1993) Dysembryoplastic neuroepithelial tumours. Brain Pathol 3:283–295

Daumas-Duport C, Varlet P (2003) Dysembryoplastic neuroepithelial tumors. Rev Neurol (Paris) 159: 622–636

Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, Laws ER Jr, Vedrenne C (1988) Dysembryoplastic neuroepithelial tumor: a surgically curable tumor of young patients with intractable partial seizures. Report of thirty-nine cases. Neurosurgery 23:545–556

Deling L, Nan J, Yongji T, Shuqing Y, Zhixian G, Jisheng W, Liwei Z (2013) Intraventricular ganglioglioma prognosis and hydrocephalus: the largest case series and systematic literature review. Acta Neurochir (Wien) 155:1253–1260. doi:10.1007/s00701-013-1728-7

DeMarchi R, Abu-Abed S, Munoz D, Loch Macdonald R (2011) Malignant ganglioglioma: case report and review of literature. J Neurooncol 101:311–318. doi:10.1007/s11060-010-0248-z

Donoho D, Zada G (2015) Imaging of central neurocytomas. Neurosurg Clin N Am 26:11–19. doi:10.1016/j.nec.2014.09.012

El Khashab M, Gargan L, Margraf L et al (2009) Predictors of tumor progression among children with gangliogliomas. Clinical article. J Neurosurg Pediatr 3:461–466. doi:10.3171/2009.2.PEDS0861

Elek G, Slowik F, Eross L, Toth S, Szabo Z, Balint K (1999) Central neurocytoma with malignant course. Neuronal and glial differentiation and craniospinal dissemination. Pathol Oncol Res 5:155–159

Eng DY, DeMonte F, Ginsberg L, Fuller GN, Jaeckle K (1997) Craniospinal dissemination of central neurocytoma. Report of two cases. J Neurosurg 86: 547–552

Englot DJ, Berger MS, Barbaro NM, Chang EF (2012a) Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. Epilepsia 53:51–57. doi:10.1111/j.1528-1167.2011.03269.x

Englot DJ, Han SJ, Berger MS, Barbaro NM, Chang EF (2012b) Extent of surgical resection predicts seizure freedom in low-grade temporal lobe brain tumors. Neurosurgery 70:921–928. doi:10.1227/NEU.0b013e31823c3a30; discussion 928

Faria C, Miguens J, Antunes JL et al (2008) Genetic alterations in a papillary glioneuronal tumor. J Neurosurg Pediatr 1:99–102

Fay-McClymont TB, Hrabok M, Sherman EM et al (2012) Systematic review and case series of neuropsychological functioning after epilepsy surgery in children with dysembryoplastic neuroepithelial tumors (DNET). Epilepsy Behav 23:481–486. doi:10.1016/j.yebeh.2011.12.011

Fedi M, Anne Mitchell L, Kalnins RM et al (2004) Glioneuronal tumours in neurofibromatosis type 1: MRI-pathological study. J Clin Neurosci 11:745–747. doi:10.1016/j.jocn.2003.10.017

Fernandez C, Girard N, Paz Paredes A, Bouvier-Labit C, Lena G, Figarella-Branger D (2003) The usefulness of MR imaging in the diagnosis of dysembryoplastic neuroepithelial tumor in children: a study of 14 cases. AJNR Am J Neuroradiol 24:829–834

Fujimaki T, Matsuno A, Sasaki T et al (1997) Proliferative activity of central neurocytoma: measurement of tumor volume doubling time, MIB-1 staining index and bromodeoxyuridine labeling index. J Neurooncol 32:103–109

Garcia RM, Ivan ME, Oh T, Barani I, Parsa AT (2014) Intraventricular neurocytomas: a systematic review of stereotactic radiosurgery and fractionated conventional radiotherapy for residual or recurrent tumors. Clin Neurol Neurosurg 117:55–64. doi:10.1016/j.clineuro.2013.11.028

Gelabert-Gonzalez M, Serramito-Garcia R, Arcos-Algaba A (2010) Desmoplastic infantile and non-infantile ganglioglioma. Review of the literature. Neurosurg Rev 34:151–158. doi:10.1007/s10143-010-0303-4

Genc A, Bozkurt SU, Karabagli P, Seker A, Bayri Y, Konya D, Kilic T (2011) Gamma knife radiosurgery for cranial neurocytomas. J Neurooncol 105:647–657. doi:10.1007/s11060-011-0635-0

Giulioni M, Gardella E, Rubboli G et al (2006) Lesionectomy in epileptogenic gangliogliomas: seizure outcome and surgical results. J Clin Neurosci 13:529–535

Gopalakrishnan CV, Shrivastava A, Nair S, Radhakrishnan N (2013) Brainstem ganglioglioma in an infant: case report and review of literature. J Pediatr Neurosci 8:41–45. doi:10.4103/1817-1745.111422

Haddad SF, Moore SA, Menezes AH, VanGilder JC (1992) Ganglioglioma: 13 years of experience. Neurosurgery 31:171–178

Hakim R, Loeffler JS, Anthony DC, Black PM (1997) Gangliogliomas in adults. Cancer 79:127–131

Hamburger C, Buttner A, Weis S (1997) Ganglioglioma of the spinal cord: report of two rare cases and review of the literature. Neurosurgery 41:1410–1415; discussion 1415–1416

Hassoun J, Soylemezoglu F, Gambarelli D, Figarella-Branger D, von Ammon K, Kleihues P (1993) Central neurocytoma: a synopsis of clinical and histological features. Brain Pathol 3:297–306

Hirose T, Scheithauer BW, Lopes MB, VandenBerg SR (1994) Dysembryoplastic neuroeptihelial tumor (DNT): an immunohistochemical and ultrastructural study. J Neuropathol Exp Neurol 53:184–195

Hirose T, Scheithauer BW, Lopes MB, Gerber HA, Altermatt HJ, VandenBerg SR (1997) Ganglioglioma: an ultrastructural and immunohistochemical study. Cancer 79:989–1003

Jallo GI, Freed D, Epstein FJ (2004) Spinal cord gangliogliomas: a review of 56 patients. J Neurooncol 68:71–77

Johnson JH Jr, Hariharan S, Berman J, Sutton LN, Rorke LB, Molloy P, Phillips PC (1997) Clinical outcome of pediatric gangliogliomas: ninety-nine cases over 20 years. Pediatr Neurosurg 27:203–207

Kalyan-Raman UP, Olivero WC (1987) Ganglioglioma: a correlative clinicopathological and radiological study of ten surgically treated cases with follow-up. Neurosurgery 20:428–433

Karlsson B, Guo WY, Kejia T et al (2012) Gamma Knife surgery for central neurocytomas. J Neurosurg 117(Suppl):96–101. doi:10.3171/2012.6.GKS12214

Khajavi K, Comair YG, Prayson RA, Wyllie E, Palmer J, Estes ML, Hahn JF (1995) Childhood ganglioglioma and medically intractable epilepsy. A clinicopathological study of 15 patients and a review of the literature. Pediatr Neurosurg 22:181–188

Kim JW, Kim DG, Chung HT et al (2013) Radiosurgery for central neurocytoma: long-term outcome and failure pattern. J Neurooncol 115:505–511. doi:10.1007/s11060-013-1253-9

Kim AH, Thompson EA, Governale LS et al (2014) Recurrence after gross-total resection of low-grade pediatric brain tumors: the frequency and timing of postoperative imaging. J Neurosurg Pediatr 14:356–364. doi:10.3171/2014.6.PEDS1321

Kim CY, Kim DG, Joo JD, Kim YH (2015) Clinical outcome and quality of life after treatment of patients with central neurocytoma. Neurosurg Clin N Am 26:83–90. doi:10.1016/j.nec.2014.09.007

Kuchelmeister K, Demirel T, Schlorer E, Bergmann M, Gullotta F (1995) Dysembryoplastic neuroepithelial tumour of the cerebellum. Acta Neuropathol 89:385–390

Lagares A, Gomez PA, Lobato RD, Ricoy JR, Ramos A, de la Lama A (2001) Ganglioglioma of the brainstem: report of three cases and review of the literature. Surg Neurol 56:315–322; discussion 322–314

Lang FF, Epstein FJ, Ransohoff J, Allen JC, Wisoff J, Abbott IR, Miller DC (1993) Central nervous system gangliogliomas. Part 2: clinical outcome. J Neurosurg 79:867–873

Leenstra JL, Rodriguez FJ, Frechette CM et al (2007) Central neurocytoma: management recommendations based on a 35-year experience. Int J Radiat Oncol Biol Phys 67:1145–1154

Lellouch-Tubiana A, Bourgeois M, Vekemans M, Robain O (1995) Dysembryoplastic neuroepithelial tumors in two children with neurofibromatosis type 1. Acta Neuropathol 90:319–322

Leung SY, Gwi E, Ng HK, Fung CF, Yam KY (1994) Dysembryoplastic neuroepithelial tumor. A tumor with small neuronal cells resembling oligodendroglioma. Am J Surg Pathol 18:604–614

Lou X, Gui QP, Sun L, Wu NZ, Lyu JH, Ma L (2014) Comparisons of MR findings between supratentorial and infratentorial gangliogliomas. Clin Neuroradiol. doi:10.1007/s00062-014-0333-3

Louis DN, Ohgaki H, Wiestler OD et al (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109

Lubrano V, Francois P, Loundou A, Vasiljevic A, Roche PH, French Society of N (2013) Outcomes after surgery for central neurocytoma: results of a French multicentre retrospective study. Acta Neurochir (Wien) 155:1261–1269. doi:10.1007/s00701-013-1732-y

Luyken C, Blumcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, Schramm J (2003) The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. Epilepsia 44:822–830

Maher CO, White JB, Scheithauer BW, Raffel C (2008) Recurrence of dysembryoplastic neuroepithelial tumor following resection. Pediatr Neurosurg 44:333–336

Mano Y, Kumabe T, Shibahara I, Saito R, Sonoda Y, Watanabe M, Tominaga T (2013) Dynamic changes in magnetic resonance imaging appearance of dysembryoplastic neuroepithelial tumor with or without malignant transformation. J Neurosurg Pediatr 11:518–525. doi:10.3171/2013.1.PEDS11449

Martin JM, Katati M, Lopez E et al (2003) Linear accelerator radiosurgery in treatment of central neurocytomas. Acta Neurochir (Wien) 145:749–754. doi:10.1007/s00701-003-0076-4; discussion 754

Matsunaga S, Shuto T, Suenaga J, Inomori S, Fujino H (2010) Gamma knife radiosurgery for central neurocytomas. Neurol Med Chir (Tokyo) 50:107–112; discussion 112–103

Minkin K, Klein O, Mancini J, Lena G (2008) Surgical strategies and seizure control in pediatric patients with dysembryoplastic neuroepithelial tumors: a single-institution experience. J Neurosurg Pediatr 1:206–210

Morris HH, Estes ML, Gilmore R, Van Ness PC, Barnett GH, Turnbull J (1993) Chronic intractable epilepsy as the only symptom of primary brain tumor. Epilepsia 34:1038–1043

Mut M, Guler-Tezel G, Lopes MB, Bilginer B, Ziyal I, Ozcan OE (2005) Challenging diagnosis: oligodendroglioma versus extraventricular neurocytoma. Clin Neuropathol 24:225–229

Neumann E, Kalousek DK, Norman MG, Steinbok P, Cochrane DD, Goddard K (1993) Cytogenetic analysis of 109 pediatric central nervous system tumors. Cancer Genet Cytogenet 71:40–49

Nolan MA, Sakuta R, Chuang N et al (2004) Dysembryoplastic neuroepithelial tumors in childhood: long-term outcome and prognostic features. Neurology 62:2270–2276

Paek SH, Han JH, Kim JW et al (2008) Long-term outcome of conventional radiation therapy for central neurocytoma. J Neurooncol 90:25–30. doi:10.1007/s11060-008-9622-5

Park HK, Steven DC (2012) Stereotactic radiosurgery for central neurocytoma: a quantitative systematic review. J Neurooncol 108:115–121. doi:10.1007/s11060-012-0849-9

Park SH, Chi JG, Cho BK, Wang KC (1993) Spinal cord ganglioglioma in childhood. Pathol Res Pract 189:189–196

Park YS, Kim DS, Shim KW, Kim JH, Choi JU (2008) Factors contributing to resectability and seizure outcomes in 44 patients with ganglioglioma. Clin Neurol Neurosurg 110:667–673

Pasquier B, Bost F, Peoc'h M, Barnoud R, Pasquier D (1996) Neuropathologic data in drug-resistant partial epilepsy. Report of a series of 195 cases. Ann Pathol 16:174–181

Patel DM, Schmidt RF, Liu JK (2013) Update on the diagnosis, pathogenesis, and treatment strategies for central neurocytoma. J Clin Neurosci 20:1193–1199. doi:10.1016/j.jocn.2013.01.001

Platten M, Meyer-Puttlitz B, Blumcke I et al (1997) A novel splice site associated polymorphism in the tuberous sclerosis 2 (TSC2) gene may predispose to the development of sporadic gangliogliomas. J Neuropathol Exp Neurol 56:806–810

Prayson RA, Estes ML (1992) Dysembryoplastic neuroepithelial tumor. Am J Clin Pathol 97:398–401

Prayson RA, Khajavi K, Comair YG (1995) Cortical architectural abnormalities and MIB1 immunoreactivity in gangliogliomas: a study of 60 patients with intracranial tumors. J Neuropathol Exp Neurol 54:513–520

Rades D, Schild SE (2006) Value of postoperative stereotactic radiosurgery and conventional radiotherapy for incompletely resected typical neurocytomas. Cancer 106:1140–1143. doi:10.1002/cncr.21628

Rashidi M, DaSilva VR, Minagar A, Rutka JT (2003) Nonmalignant pediatric brain tumors. Curr Neurol Neurosci Rep 3:200–205

Ray WZ, Blackburn SL, Casavilca-Zambrano S et al (2009) Clinicopathologic features of recurrent dysembryoplastic neuroepithelial tumor and rare malignant transformation: a report of 5 cases and review of the literature. J Neurooncol 94:283–292. doi:10.1007/s11060-009-9849-9

Raymond AA, Halpin SF, Alsanjari N et al (1994) Dysembryoplastic neuroepithelial tumor. Features in 16 patients. Brain 117(Pt 3):461–475

Raymond AA, Fish DR, Sisodiya SM, Alsanjari N, Stevens JM, Shorvon SD (1995) Abnormalities of gyration, heterotopias, tuberous sclerosis, focal cortical dysplasia, microdysgenesis, dysembryoplastic neuroepithelial tumour and dysgenesis of the archicortex in epilepsy. Clinical, EEG and neuroimaging features in 100 adult patients. Brain 118(Pt 3):629–660

Rickert CH, Paulus W (2001) Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst 17:503–511. doi:10.1007/s003810100496

Rodriguez FJ, Mota RA, Scheithauer BW et al (2009) Interphase cytogenetics for 1p19q and t(1;19)(q10;p10) may distinguish prognostically relevant subgroups in extraventricular neurocytoma. Brain Pathol 19:623–629. doi:10.1111/j.1750-3639.2008.00206.x

Schild SE, Scheithauer BW, Haddock MG, Schiff D, Burger PC, Wong WW, Lyons MK (1997) Central neurocytomas. Cancer 79:790–795

Schlamann A, von Bueren AO, Hagel C, Zwiener I, Seidel C, Kortmann RD, Muller K (2014) An individual patient data meta-analysis on characteristics and outcome of patients with papillary glioneuronal tumor, rosette glioneuronal tumor with neuropil-like islands and rosette forming glioneuronal tumor of the fourth ventricle. PLoS One 9:e101211. doi:10.1371/journal.pone.0101211

Scoccianti S, Giordano F, Agresti B et al (2012) Pediatric primary anaplastic ganglioglioma: a case report and review of the literature. Pediatr Neurosurg 48:35–41. doi:10.1159/000340067

Selch MT, Goy BW, Lee SP, El-Sadin S, Kincaid P, Park SH, Withers HR (1998) Gangliogliomas: experience with 34 patients and review of the literature. Am J Clin Oncol 21:557–564

Selvanathan SK, Hammouche S, Salminen HJ, Jenkinson MD (2011) Outcome and prognostic features in anaplastic ganglioglioma: analysis of cases from the SEER database. J Neurooncol 105:539–545. doi:10.1007/s11060-011-0615-4

Sharma MC, Rathore A, Karak AK, Sarkar C (1998) A study of proliferative markers in central neurocytoma. Pathology 30:355–359

Sharma MC, Jain D, Gupta A et al (2009) Dysembryoplastic neuroepithelial tumor: a clinicopathological study of 32 cases. Neurosurg Rev 32:161–169. doi:10.1007/s10143-008-0181-1; discussion 169–170

Shono T, Tosaka M, Matsumoto K et al (2007) Ganglioglioma in the third ventricle: report on two cases. Neurosurg Rev 30:253–258. doi:10.1007/s10143-007-0090-8; discussion 258

Sim FJ, Keyoung HM, Goldman JE, Kim DK, Jung HW, Roy NS, Goldman SA (2006) Neurocytoma is a tumor of adult neuronal progenitor cells. J Neurosci 26:12544–12555

Southwell DG, Garcia PA, Berger MS, Barbaro NM, Chang EF (2012) Long-term seizure control outcomes after resection of gangliogliomas. Neurosurgery 70:1406–1413. doi:10.1227/NEU.0b013e3182500a4c; discussion 1413–1404

Soylemezoglu F, Scheithauer BW, Esteve J, Kleihues P (1997) Atypical central neurocytoma. J Neuropathol Exp Neurol 56:551–556

Stanescu Cosson R, Varlet P, Beuvon F et al (2001) Dysembryoplastic neuroepithelial tumors: CT, MR findings and imaging follow-up: a study of 53 cases. J Neuroradiol 28:230–240

Sutton LN, Packer RJ, Zimmerman RA, Bruce DA, Schut L (1987) Cerebral gangliogliomas of childhood. Prog Exp Tumor Res 30:239–246

Sweiss FB, Lee M, Sherman JH (2015) Extraventricular neurocytomas. Neurosurg Clin N Am 26:99–104. doi:10.1016/j.nec.2014.09.004

Taratuto AL, Pomata H, Sevlever G, Gallo G, Monges J (1995) Dysembryoplastic neuroepithelial tumor: morphological, immunocytochemical, and deoxyribonucleic acid analyses in a pediatric series. Neurosurgery 36:474–481

Taruscio D, Danesi R, Montaldi A, Cerasoli S, Cenacchi G, Giangaspero F (1997) Nonrandom gain of chromosome 7 in central neurocytoma: a chromosomal analysis and fluorescence in situ hybridization study. Virchows Arch 430:47–51

Thawani JP, Lee JY (2015) The management of residual or recurrent central neurocytoma. Neurosurg Clin N Am 26:67–81. doi:10.1016/j.nec.2014.09.002

Thom M, Toma A, An S et al (2011) One hundred and one dysembryoplastic neuroepithelial tumors: an adult epilepsy series with immunohistochemical, molecular genetic, and clinical correlations and a review of the literature. J Neuropathol Exp Neurol 70:859–878. doi:10.1097/NEN.0b013e3182302475

Vasiljevic A, Champier J, Figarella-Branger D, Wierinckx A, Jouvet A, Fevre-Montange M (2013) Molecular characterization of central neurocytomas: potential markers for tumor typing and progression. Neuropathology 33:149–161. doi:10.1111/j.1440-1789.2012.01338.x

von Deimling A, Janzer R, Kleihues P, Wiestler OD (1990) Patterns of differentiation in central neurocytoma. An immunohistochemical study of eleven biopsies. Acta Neuropathol 79:473–479

von Deimling A, Kleihues P, Saremaslani P, Yasargil MG, Spoerri O, Sudhof TC, Wiestler OD (1991) Histogenesis and differentiation potential of central neurocytomas. Lab Invest 64:585–591

von Koch CS, Schmidt MH, Uyehara-Lock JH, Berger MS, Chang SM (2003) The role of PCV chemotherapy in the treatment of central neurocytoma: illustration of a case and review of the literature. Surg Neurol 60:560–565

Wallace D, Ruban D, Kanner A et al (2013) Temporal lobe gangliogliomas associated with chronic epilepsy: long-term surgical outcomes. Clin Neurol Neurosurg 115:472–476. doi:10.1016/j.clineuro.2012.05.034

Wichmann W, Schubiger O, von Deimling A, Schenker C, Valavanis A (1991) Neuroradiology of central neurocytoma. Neuroradiology 33:143–148

Wolf HK, Wellmer J, Muller MB, Wiestler OD, Hufnagel A, Pietsch T (1995) Glioneuronal malformative lesions and dysembryoplastic neuroepithelial tumors in patients with chronic pharmacoresistant epilepsies. J Neuropathol Exp Neurol 54:245–254

Wolf HK, Buslei R, Blumcke I, Wiestler OD, Pietsch T (1997) Neural antigens in oligodendrogliomas and dysembryoplastic neuroepithelial tumors. Acta Neuropathol 94:436–443

Xu LX, Holland H, Kirsten H et al (2014) Three gangliogliomas: results of GTG-banding, SKY, genome-wide high resolution SNP-array, gene expression and review of the literature. Neuropathology. doi:10.1111/neup.12176

Yang I, Ung N, Chung LK, Nagasawa DT, Thill K, Park J, Tenn S (2015) Clinical manifestations of central neurocytoma. Neurosurg Clin N Am 26:5–10. doi:10.1016/j.nec.2014.09.011

Yen CP, Sheehan J, Patterson G, Steiner L (2007) Gamma knife surgery for neurocytoma. J Neurosurg 107: 7–12

Yin XL, Pang JC, Hui AB, Ng HK (2000) Detection of chromosomal imbalances in central neurocytomas by using comparative genomic hybridization. J Neurosurg 93:77–81

Zentner J, Wolf HK, Ostertun B, Hufnagel A, Campos MG, Solymosi L, Schramm J (1994) Gangliogliomas: clinical, radiological, and histopathological findings in 51 patients. J Neurol Neurosurg Psychiatry 57:1497–1502

Zhang D, Henning TD, Zou LG et al (2008) Intracranial ganglioglioma: clinicopathological and MRI findings in 16 patients. Clin Radiol 63:80–91. doi:10.1016/j.crad.2007.06.010

Zhang J, Babu R, McLendon RE, Friedman AH, Adamson C (2013a) A comprehensive analysis of 41 patients with rosette-forming glioneuronal tumors of the fourth ventricle. J Clin Neurosci 20:335–341. doi:10.1016/j.jocn.2012.09.003

Zhang S, Wang X, Liu X, Ju Y, Hui X (2013b) Brainstem gangliogliomas: a retrospective series. J Neurosurg 118:884–888. doi:10.3171/2013.1.JNS121323

Zhu J, Guo SZ, Beggs AH et al (1996) Microsatellite instability analysis of primary human brain tumors. Oncogene 12:1417–1423

Choroid Plexus Tumors

9

Nalin Gupta

Contents

9.1 Introduction

The choroid plexus has the highly specialized function of producing cerebrospinal fluid (CSF). It is anatomically localized to the parenchymal/ventricular junction in all four ventricles. The choroid plexus itself is derived from the ventricular epithelium along certain segments of the neural tube, and there is a common ontogeny between choroid epithelium and cells of glial origin which can lead to diagnostic confusion. Tumors arising from the choroid plexus can display a benign or malignant phenotype, but conversion to a malignant phenotype is a rare event (Chow et al. 1999; Jeibmann et al. 2007). Guerard was the first to describe a choroid plexus tumor in 1833. The first surgical resection was reported by Bielschowsky and Unger in 1906. Thereafter, both Cushing and Dandy reported their experiences with this unusual tumor (Dandy 1922; Davis and Cushing 1925).

9.2 Epidemiology

Choroid plexus papilloma (CPP) and choroid plexus carcinoma (CPC) are rare, comprising only 0.5–0.6 % of all brain tumors. Although found in all age groups, choroid plexus neoplasms are primarily a tumor of childhood. Laurence, in his review of all published cases prior to 1974, reported that 45 % presented in the first year of life, while 74 % were in the first

N. Gupta, MD, PhD
Division of Pediatric Neurosurgery, Departments of Neurological Surgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA
e-mail: nalin.gupta@ucsf.edu

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_9

decade (Laurence 1974). In another paper that compiled information from many other studies, Wolff et al. reported a male to female ratio of 1.2:1, and a median age at diagnosis of 3.5 years (Wolff et al. 2002). There was also a notable difference in tumor location and age with supratentorial tumors (lateral and third ventricles) occurring mostly in infants (median age at diagnosis in this group of 1.5 years), while the median ages at diagnosis of tumors located in the fourth ventricle and cerebellopontine angle (CPA) were 22.5 and 35.5 years, respectively.

As expected, pediatric centers report that a higher percentage (1.8–2.9 %) of their cases are choroid plexus tumors (Asai et al. 1989; Ellenbogen et al. 1989; Sarkar et al. 1999). In two reviews describing tumors occurring in the first year of life, choroid plexus tumors comprised 14 and 12.8 % of all cases (Galassi et al. 1989; Haddad et al. 1991). The majority of the series noted here have not reported any predilection for right or left ventricle or sex. Laurence did report that 50 % of cases reviewed were situated in the lateral ventricles, 37 % in the fourth ventricle, 9 % in the third ventricle, and the remainder in other locations. Other series have confirmed this geographic distribution. CPCs, while rare, comprise 29–39 % of all choroid neoplasms (Ellenbogen et al. 1989; Johnson 1989; St Clair et al. 1991).

9.3 Pathology

9.3.1 Gross Appearance

CPP is frequently described as "cauliflower-like." Indeed, these tumors have a similar appearance to the soft fronds of normal choroid plexus. The shape is roughly globular, with an irregular surface and intervening encapsulated areas. Evidence of previous hemorrhage is sometimes noted. Since papillomas are benign, they tend to expand the ventricle rather than invade the adjacent brain tissue. Nevertheless, the proximity of these tumors to deep-seated structures such as the internal cerebral veins and limbic structures can make their removal difficult. CPCs are less well differentiated and the papillary structure can be absent. There is often brain invasion, which is evident at a gross and microscopic level. For very rapidly growing CPCs, there can be a "pseudoplane" surrounding the mass. This can facilitate surgical resection by revealing the boundary between the tumor and the surrounding tissues.

9.3.2 Histopathology

CPP is a WHO grade I tumor, and its microscopic appearance recapitulates the normal choroid plexus. There are many papillae covered with a simple cuboidal or columnar epithelia. The stroma of these fibrovascular structures is composed of connective tissue and small blood vessels. The presence of the connective tissue stroma is notable mainly because it allows one to distinguish between CPP and papillary forms of ependymoma (whose stroma is composed of fibrillary neuroglia). In addition, choroid epithelial cells do not contain cilia or blepharoplasts as do ependymal cells. Mitotic figures are rare.

Villous hypertrophy of the choroid plexus is a poorly defined entity. Characteristically, the choroid plexus of both lateral ventricles is enlarged and is associated with hydrocephalus from birth. Russell and Rubinstein comment that the hydrocephalus is related to hyperactivity of the choroid while the cytological appearance of the tissue is normal (McLendon et al. 2006). Other authors have used villous hypertrophy synonymously with bilateral CPP, but this is not accurate in the strictest sense if histologic evidence of neoplastic growth is not present, and expansion of the choroid plexus occurs diffusely (Hirano et al. 1994).

CPCs are WHO grade III tumors and are diagnosed on the basis of their microscopic appearance (Gopal et al. 2008). Two major features accompany malignancy. First is the presence of brain invasion by the tumor. This usually involves transgression of the ependymal lining and extension into the paraventricular parenchyma. Second, cytological criteria of malignancy – nuclear atypia, increased nuclear to cytoplasmic ratio, prominent mitotic figures, and necrosis – are present in association with a loss of normal papillary

architecture. Rarely, if a tumor demonstrates some atypical features without evidence of invasion, it can be designated as an atypical papilloma. The epithelial nature of the frank malignancy can create confusion, since other tumors such as metastatic adenocarcinoma, papillary meningioma, and atypical teratoid/rhabdoid tumors (ATRT) can be histologically similar. If the tumor arises in a young patient, then chance of the tumor being metastatic from a primary source outside the CNS is extremely low. Electron microscopy can reveal details such as cilia, which are normally not present in choroid plexus tumors. Grossly, these tumors tend to be softer and more friable than papillomas. While carcinomas rarely metastasize from the intracranial or intraspinal compartment, they can disseminate throughout the CSF pathways (McComb and Burger 1983).

An intermediate entity, the atypical CPP, is identified as a WHO grade II neoplasm, but the diagnostic criteria are poorly defined (Paulus and Brandner 2007). The number of mitotic figures in a high-power field, or two other cytological features such as increased cellularity, nuclear pleomorphism, and/or necrosis, has been proposed as a characteristic of atypical papillomas, but this requires validation (Jeibmann et al. 2007). It is likely, however, that a biological spectrum exists for tumors identified as papillomas, and the clinician should be alert to unusual pathologic features that would prompt closer surveillance imaging in the postoperative period (Merino et al. 2015).

9.3.3 Immunohistochemistry

Only a few immunohistochemical stains have been found to be helpful. The calcium-binding protein S-100 is positive in the vast majority of choroid tumors (Paulus and Janisch 1990; Ho et al. 1991). This is of limited value since glial tissues and normal choroid express S-100 in a parallel fashion with glial fibrillary acid protein (GFAP). Other markers such as vimentin, GFAP, and cytokeratins can be positive, but they also lack specificity (Mannoji and Becker 1988; Cruz-Sanchez et al. 1989). Prealbumin, or transthyretin (TTR), was initially believed to be a specific marker, but another report noted that 20 % of choroid tumors were TTR negative (Herbert et al. 1990; Paulus and Janisch 1990). These investigators did find that prognostic information could be gleaned from immunohistochemical data. A poor prognosis was found in those tumors with less than 50 % of the cells in a given tumor heavily stained for S-100. In addition, absence of TTR-positive cells correlated with a poor prognosis. Cellular proliferation, as measured by Ki-67/MIB-1 labeling, is low with papillomas and significantly higher for carcinomas (Vajtai et al. 1996).

Using a microarray approach, Hasselblatt et al. identified a number of genes that appeared to be overexpressed in choroid plexus tumors (Hasselblatt et al. 2006). Two in particular, Kir7.1 (a potassium channel gene) and stanniocalcin-1, demonstrated high specificity and were proposed as markers for these tumors, but require confirmation by other groups. Finally, Judkins et al. noted that the *SMARCB1* gene product was expressed in the majority of CPCs, but not in atypical teratoid/rhabdoid tumors, so this marker may be useful to distinguish between these tumor types (Judkins et al. 2005).

9.3.4 Genetics

The cause of choroid plexus tumors is unknown. One report has mentioned two cases occurring in one family, but a hereditary basis has not been observed for most cases (Zwetsloot et al. 1991). There are historical data linking SV40, a primate DNA virus, with choroid plexus tumor etiology. Large T antigen, the major regulator of late viral gene products of the SV40 virus, when expressed in mice induces the formation of choroid plexus neoplasms (Brinster et al. 1984). Using PCR, SV40 DNA sequences were demonstrated in 50 % of choroid plexus tumors and the majority of ependymomas (Bergsagel et al. 1992). However, more recent studies suggest that these findings may represent a technical error related to sample contamination (Dang-Tan et al. 2004).

In one report, positive nuclear staining for the *TP53* tumor suppressor gene was identified in 10 of 11 CPCs, but in only 1 of 12 CPPs (Carlotti

et al. 2002). A *TP53* mutation in this setting leads to a loss of normal gene function but an increased half-life of the protein. Germline mutations in *TP53* can also lead to the development of CPCs (Krutilkova et al. 2005).

Experiments in mice showed that the expression of transgenes of the viral oncoproteins E6 and E7 from human papillomavirus produced tumors in 71 % of offspring, and 26 % of the tumors were choroid plexus tumors (Arbeit et al. 1993). Finally, mice that overexpress the *E2F1* gene in glial cells develop tumors such as medulloblastoma, CPCs, and primitive neuroectodermal tumors (PNETs) at an early age (Olson et al. 2007).

A subset of central PNETs, CPCs, and medulloblastomas were recently shown to have frequent mutations in the *SMARCB1* gene, which encodes for a component of the ATP-dependent chromatin remodeling complex (Sevenet et al. 1999a). The same authors have proposed that constitutional mutations in this gene lead to a greater incidence of renal and extrarenal malignant rhabdoid tumors, CPCs, central PNETs, and medulloblastomas: a complex they have coined the "rhabdoid predisposition syndrome" (Sevenet et al. 1999b). The penetration of the disease is high, with many probands developing malignant tumors before 3 years of age. Some pathologic data also suggest a connection between malignant rhabdoid tumors and CPCs (Wyatt-Ashmead et al. 2001).

A number of chromosomal abnormalities have been identified in both CPP and CPC. Tumors with a gain of 9p and loss of 10q are associated with longer survival (Rickert et al. 2002). Surprisingly, even benign CPP (32 of 34 cases) demonstrated chromosomal aberration. The patterns of aberrations in CPP differ from those observed in CPC.

9.4 Clinical Features

Hydrocephalus is the presenting symptom in the vast majority of patients with choroid plexus tumors. It is caused by both overproduction of CSF and, in certain cases, the obstruction of CSF pathways, although it appears that overproduction is the major factor (Eisenberg et al. 1974). Resolution of hydrocephalus has been reported after complete tumor removal, suggesting that CSF hypersecretion was responsible for ventriculomegaly (Matson and Crofton 1960; Wilkins and Rutledge 1961; Gudeman et al. 1979). Variations are likely to exist since a normal rate of CSF production has been reported in a patient with a papilloma (Sahar et al. 1980).

The most common presentation of choroid plexus neoplasms is related to increased intracranial pressure secondary to obstructive hydrocephalus and/or CSF overproduction (Laurence 1974; Humphreys et al. 1987; Ellenbogen et al. 1989). Since the majority of cases occur in infants and young children, the characteristic features are those associated with raised intracranial pressure: nausea/vomiting, irritability, headache, macrocephaly, papilledema, and a decreased level of consciousness. The duration of symptoms reported in this series varied from 2 months in those patients younger than 2 years of age to 6 months on average in those patients older than 2 years. Although choroid neoplasms are viewed as slow-growing tumors, a more acute clinical course occurs in up to a quarter of patients with presenting signs of stupor or coma. Rapid decompensation can occur either from massive hydrocephalus or from tumoral hemorrhage. In Ellenbogen's series, of 21 patients who had CSF examined, 2 were found to have grossly bloody fluid. Lateralizing signs are found in a minority of patients and are usually related to asymmetrical ventricular dilatation. Hydrocephalus was present in 78 % of cases at the Hospital for Sick Children and in 95 % of cases at the Children's Hospital in Boston (Humphreys et al. 1987; Ellenbogen et al. 1989).

9.5 Diagnosis and Neuroimaging

Since most patients present with hydrocephalus and increased intracranial pressure, there is no role for sampling CSF at diagnosis. There is little information that can be gained from CSF sampling, and there are reports of disastrous outcomes in some patients following lumbar puncture (Laurence 1974). No specific laboratory

tests are available to diagnose these tumors. Other benign lesions of the choroid plexus such as choroid plexus cysts, villous hyperplasia, and lipomas can usually be distinguished on the basis of their appearance on magnetic resonance (MR) imaging (Naeini et al. 2009).

9.5.1 Computed Tomography

The typical features of CPP are present on a computed tomography (CT) scan. The mass is well demarcated from the brain, lobulated, and often has punctate calcification. These tumors enhance homogeneously after contrast, reflecting a luxuriant blood supply. Since they arise from the choroid plexus, their location is almost always intraventricular. An enlarged choroidal artery leading into the tumor mass can sometimes be seen in postcontrast images. At times, the massive size of these lesions may obscure the site of origin. Some carcinomas display a diffuse border between the tumor and normal brain that may reflect areas of brain invasion. On the basis of CT, certain features distinguish a suspected choroid tumor from other possibilities. Cerebellar astrocytomas tend to be less homogeneously staining and often have cystic areas. Medulloblastomas are characterized by a more heterogeneous appearance, although they also stain vividly with contrast and may cause confusion with a fourth ventricle choroid papilloma. Finally, ependymomas arise physically in similar locations but tend to enhance inhomogeneously.

9.5.2 Magnetic Resonance Imaging

Papillomas are isointense to brain on T1-weighted MR images (Fig. 9.1a). Areas of high signal indicate hemorrhage or necrosis. Following gadolinium administration, the tumor enhances brightly (Fig. 9.1b, c), although this can be patchy in nature, reflecting areas of high flow. T2-weighted images demonstrate an intermediate to high signal intensity with areas of heterogeneous internal signal (Coates et al. 1989). As with CT, an enlarged choroidal artery is often noted, especially with larger tumors. The vascularity of these tumors is easily demonstrated with specific perfusion sequences (Fig. 9.2). With CPC, the boundary between the tumor and surrounding brain can be indistinct in areas, but this is not a universal finding (Meyers et al. 2004). Substantial brain edema surrounding a CPC is often observed (Fig. 9.3). MR spectroscopy of CPP and CPC is characterized by a prominent choline peak and absence of *N*-acetyl aspartate (Horska et al. 2001). Myoinositol level is also reported to be specifically increased in CPPs (Krieger et al. 2005).

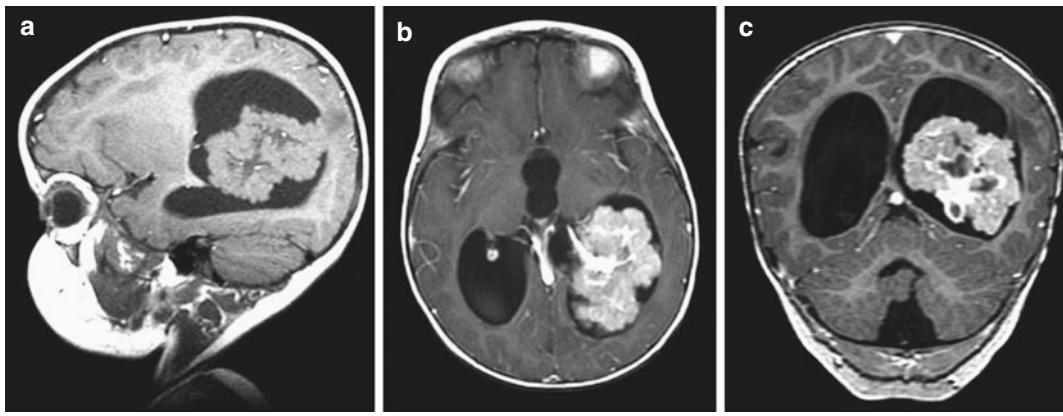

Fig. 9.1 A large choroid plexus papilloma. (**a**) A sagittal precontrast T1-weighted MRI demonstrates a large lobulated mass within the lateral ventricle with associated enlargement of the ventricle. (**b**, **c**) Following contrast, the mass enhances brightly. Note that the papilloma is well demarcated from the ventricular wall

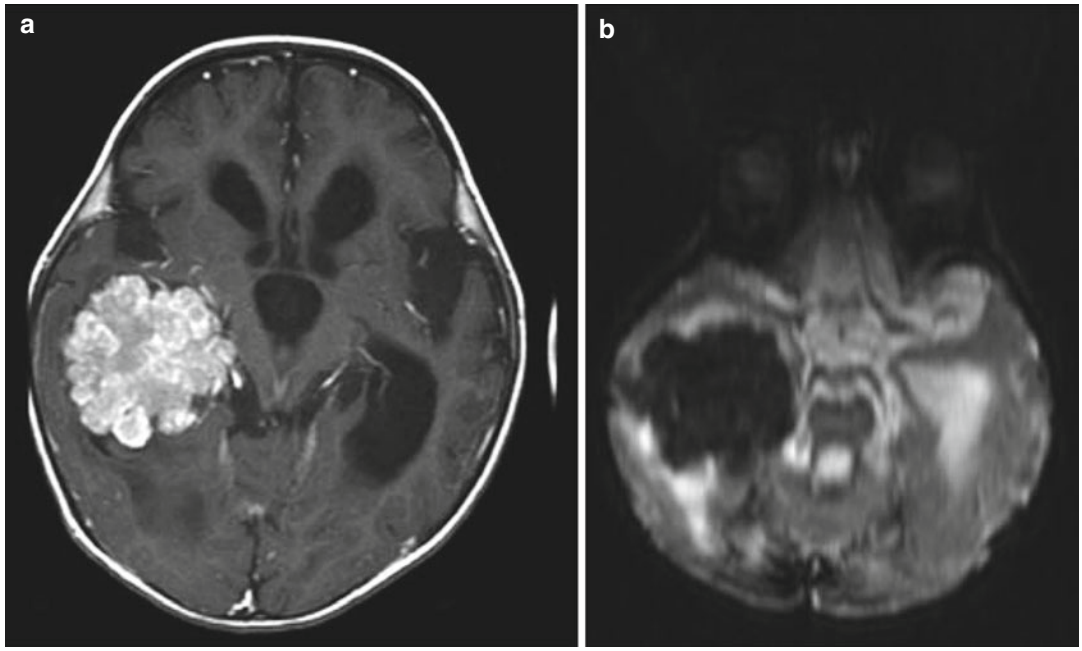

Fig. 9.2 (**a**) An axial postcontrast image shows a large choroid plexus papilloma within the temporal horn of the lateral ventricle. (**b**) The perfusion sequence results in a "negative" image with increased vascularity depicted as a dark area. The mass is considerably darker than the adjacent brain tissue

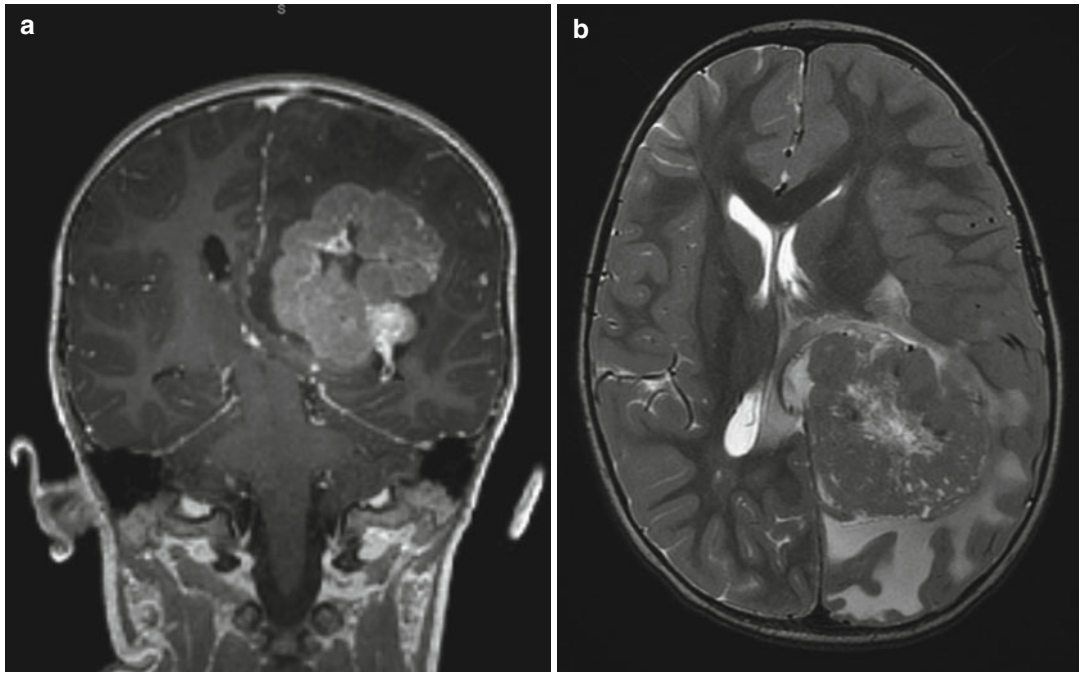

Fig. 9.3 (**a**) A coronal postcontrast MR image showing a large parietal choroid plexus carcinoma. The vascular pedicle can be seen at its most inferior portion adjacent to the atrium of the lateral ventricle. (**b**) An axial T2-weighted image showing the extent of the mass effect and peritumoral edema

9.6 Treatment

9.6.1 Preoperative Planning and Treatment

Since most patients present with symptoms of intracranial hypertension, treatment of hydrocephalus goes along with planning for the actual tumor resection. Unless the patient is rapidly deteriorating, urgent CSF drainage is not necessary. At the time of surgery, a ventricular drain is usually placed in order to reduce brain tension and allow sufficient retraction. An external ventricular drain may be left in place after surgery in order to monitor ICP and to determine if shunting is required in the early postoperative period. Matson and others have reported that the successful removal of a tumor obviates the need for shunting. However, it is likely that other factors such as ventricular bleeding, postoperative changes, or meningitis can also render the patient shunt dependent. Ellenbogen's series noted that 37 % of surviving patients required shunting (Ellenbogen et al. 1989). Two other series reported much higher rates of shunt dependency, ranging from 57 % to 78 % of cases reported (Humphreys et al. 1987; Lena et al. 1990). There is some evidence that patients with larger tumors, or hydrocephalus present prior to surgery, are at higher risk for requiring permanent CSF diversion (Safaee et al. 2013 #154).

Conventional catheter angiography is not required for diagnosis. Rather, its primary role is as a preoperative adjunct to define the blood supply and can be combined with embolization to reduce tumor vascularity. Angiography clearly indicates that the vascular supply of papillomas is from normal choroidal vessels, which often enlarge as the tumor grows. Tumors of the lateral ventricle or third ventricle are generally supplied by branches of the anterior or posterior choroidal arteries. Mass effect tends to displace the internal occipital artery and the basal vein of Rosenthal in an inferior direction. A fourth ventricle tumor receives its blood supply from medullary or vermian branches of the posteroinferior cerebellar artery.

9.6.2 Operative Treatment

The goal of surgery is gross total resection (GTR), as measured by postoperative MR imaging. As with most intracranial tumors, the exact approach is determined by avoiding eloquent tissue (primary motor or sensory cortex, speech centers, and visual cortex). The two features of choroid plexus tumors that can make resection exceedingly difficult are (1) profuse vascularity and (2) large size. The tumor's arterial vessels arborize rapidly, and so control of hemorrhage within the tumor requires slow and tedious dissection. The most effective strategy focuses on initial exposure of the feeding artery and its ligation (Fig. 9.4). In general, en bloc excision is recommended (Raimondi and Gutierrez 1975). For lateral ventricle papillomas, a cerebral incision posterior to the angular gyrus allows access to the entire trigone and permits the pedicle of the tumor to be identified and coagulated. For more anteriorly located tumors, an incision can be made in the frontal convolutions and the lateral ventricle approached from an anterolateral direction. Lateral ventricle tumors can also be approached through a cerebrotomy through the superior or middle temporal gyrus.

Third ventricle tumors are rare and are approached usually through a midline transcallosal route. The anterior aspect of the ventricle is entered through a generous opening in the corpus callosum extending from the rostrum to the supraoptic recess. In this way, the tumor can be separated from the choroid of the tela choroidea where it is usually attached and the accompanying bridging vessels can be identified and divided.

Fourth ventricle tumors almost always produce triventricular obstructive hydrocephalus and may require preoperative shunting and stabilization as noted earlier. Tumors in this location arise from the caudal part of the roof of the fourth ventricle and may extend into the lateral recesses, or through the foramen of Magendie. The approach is through a standard midline posterior fossa craniotomy exposing the vermis and tonsils. The blood supply from branches of the PICA is visualized from a medial vantage.

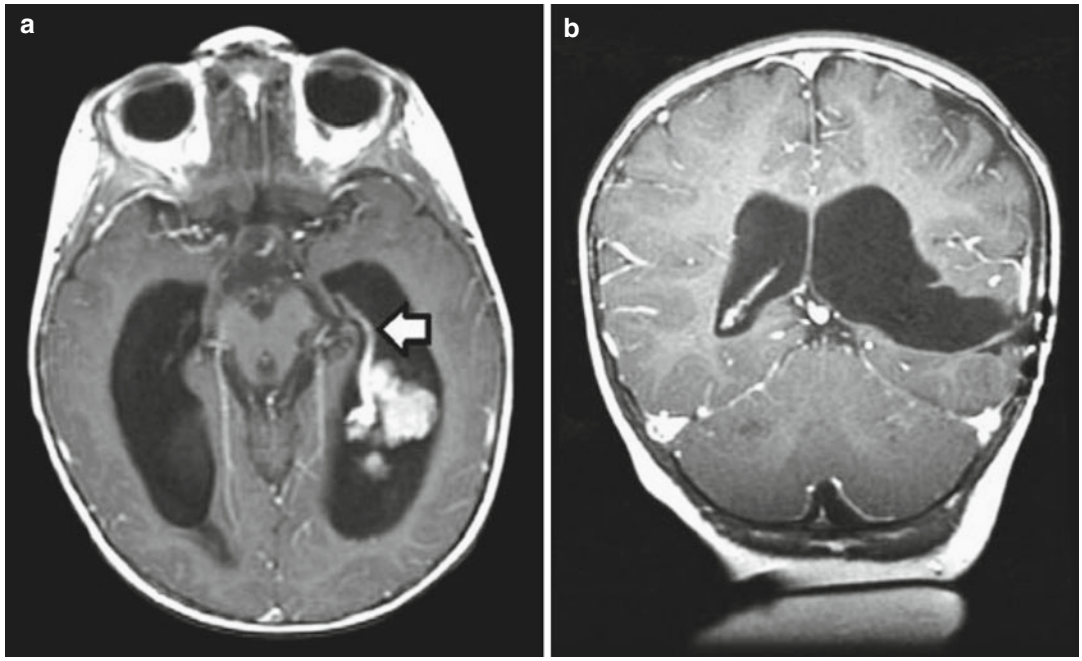

Fig. 9.4 The same case as shown in Fig. 9.1. (**a**) The axial T1-weighted image clearly shows an enlarged choroidal artery leading into the tumor. (**b**) The postoperative coronal MRI image shows the route through the temporal lobe used to access initially the feeding artery and then the tumor itself. Once the blood supply was interrupted, the tumor removal proceeded uneventfully

9.6.3 Choroid Plexus Carcinomas

In a recent systematic review, GTR clearly had a favorable impact upon survival for CPCs (Sun et al 2014). Nevertheless, GTR with carcinoma is achieved in less than 50 % of cases. Combined with adjunctive therapy, either radiation or chemotherapy, survival following GTR ranges from 67 % to 91 % (Fitzpatrick et al. 2002). Technical considerations with CPC include the expected increased tumor vascularity as well as additional difficulties relating to the lack of a well-developed plane between the brain and tumor and excessive friability of the tumor tissue. The rate of recurrence associated with GTR alone suggests that adjunctive therapy is useful, although definitive guidelines are not available (Fitzpatrick et al. 2002; Sun et al. 2014).

Most chemotherapy regimens rely upon cyclophosphamide, etoposide, vincristine, and a platinum agent (St Clair et al. 1991; Packer et al. 1992; Berger et al. 1998). Wolff et al. noted that only 8 of 22 carcinomas responded to chemotherapy, a disappointing observation (Wolff et al. 2002). Use of combination chemotherapy (ifosfamide, carboplatin, and etoposide) after an initial surgical procedure was found to reduce tumor volume and allow a more complete resection during a second-stage operation (St Clair et al. 1991; Razzaq and Cohen 1997; Lafay-Cousin et al. 2011). Importantly, the vascularity of the tumor appeared to be greatly reduced, as measured blood loss during the second procedure was on an average 15 % of blood volume compared to an average of 64 % of blood volume during the first procedure. Recent meta-analyses have noted that administration of chemotherapy resulted in a survival advantage for patients with completely or incompletely resected carcinomas and that second-look surgery is of benefit for those patients with incompletely resected CPCs (Wrede et al. 2005, 2007). Chemotherapy was also beneficial in the subgroup of patients who did not receive radiation. These observations, although retrospective in nature, suggest that aggressive therapy including chemotherapy and further attempts to remove any remaining tumor should be pursued when possible.

Postoperative radiation is usually recommended if the child is over 3 years of age, although this therapy has not been subjected to a clinical trial. Radiation is also used in the presence of leptomeningeal dissemination, subtotal resection (STR), and drop metastases. In one series, ten patients with CPC were treated with either chemotherapy or craniospinal radiation (Chow et al. 1999). Some of these patients demonstrated no evidence of disease following chemotherapy alone, but others required radiation to achieve disease control. The authors do suggest that radiation can be used as salvage therapy, but whether radiation for all patients with carcinoma would reduce the relapse rate remains unclear. Certainly, this should be judiciously used in children under 3 years of age. Fitzpatrick et al. noted that following STR, radiation therapy, either alone or in combination with chemotherapy, offered a survival advantage (Fitzpatrick et al. 2002). The question of which adjunctive therapy to use following GTR remains unclear, although the presence of relapse despite chemotherapy and radiation suggests that surgery alone is not sufficient for CPC. Wolff et al. support this view and state that GTR alone is insufficient for carcinoma and should be supplemented with radiation (Wolff et al. 1999). The role of conformal radiation and radiosurgery is unknown, nor is the role of intrathecal chemotherapy. The experience reported by Packer suggests that disease relapse confers a poor prognosis (Packer et al. 1992).

9.7 Outcome

Almost all patients with CPP can expect an excellent long-term survival. The survival for CPC, however, is much worse. In one meta-analysis, the 1-, 5-, and 10-year survival for CPP was 90, 81, and 77 %, compared to only 71, 41, and 35 % for CPC (Wolff et al. 2002). A prospective international study reported 5-year overall survival of 100 %, 89 %, and 36 % for CPPs, atypical CPPs, and CPCs, respectively. In another large series of grade I CPPs, only 12 of 124 patients recurred during a mean follow-up period of 59 months (Jeibmann et al. 2007). Of the 124 papillomas, 21 were described as having atypical histology. Six of these 21 tumors recurred, compared to 6 of the 103 tumors with normal histology. In the same series, 2 of the 103 papillomas progressed to carcinomas, which is a rare event. The extent of surgery is the most important treatment variable impacting long-term survival for both papilloma and carcinoma patients (Ellenbogen et al. 1989; Packer et al. 1992; Wolff et al. 2002). The overall survival rate in Ellenbogen's series was 88 % for patients with CPP and 50 % for those with carcinomas (Ellenbogen et al. 1989).

Packer et al. reported that GTR for carcinoma without adjuvant therapy offers the highest likelihood of success (Packer et al. 1992). Four of five patients who underwent GTR remained disease-free at a median of 45 months after diagnosis. Five of six patients who had an STR suffered a relapse. Two other reports, however, noted that 5-year survival following GTR of carcinomas ranged from 26 % to 40 % (Berger et al. 1998; Pencalet et al. 1998). Berger et al. also noted that surgery was the most important prognostic factor for CPC. The meta-analysis by Wrede et al. confirmed the utility of chemotherapy and/or radiation for CPC (Wrede et al. 2007). A brief report noted that the 5-year survival for patients with carcinoma who were treated with GTR followed by radiation was 68 %, compared to 16 % for those not irradiated (Wolff et al. 1999). The two groups were not exactly comparable, but the clear suggestion is that surgery alone is insufficient to prevent recurrence of carcinomas.

Although papillomas are histologically benign and potentially curable, morbidity and mortality are significant concerns. With respect to operative mortality, modern series provide figures of 8–9.5 % (Humphreys et al. 1987; Lena et al. 1990). In the series from the Hospital for Sick Children, the cumulative mortality was 36 %, the majority of which (six of eight) occurred in patients below 12 months of age. Morbidity remains an important problem. In one series 33 % of patients with papillomas had persisting motor sequelae and psychomotor retardation (Lena et al. 1990). In another series, 26 % of patients were classified as having a fair or poor recovery (Ellenbogen et al. 1989).

Tabori's analysis of CPC outcome as a function of TP53 status was striking (Tabori et al.

2010). Of the 26 patients with CPC, 38 % had immunopositivity for TP53 which correlated strongly with TP53 mutations. The overall 5-year survival for patients with TP53 immunonegativity was 82 % as compared to 0 % for patients with TP53 immunopositivity. A more detailed analysis of a 100 patients revealed subgroups within CPC, although patients with more than two copies of mutant *TP53* had worse overall survival (Merino et al. 2015). These data appear to support a strong genetic determinant of tumor phenotype. These data suggest that patients in higher risk groups should be treated more aggressively.

As noted earlier, the treatment of hydrocephalus goes hand-in-hand with the treatment of choroid neoplasms, and associated complications can occur. One significant complication is the presence of large subdural collections that may develop following tumor resection, caused by a persistent venticulosubdural fistula. Boyd and Steinbok appear to have dealt with this problem by applying pial sutures at the conclusion of the procedure (Boyd and Steinbok 1987). The role of preoperative shunting in the causation of this entity is unclear.

Conclusions

Choroid plexus tumors represent a rare but well-defined subset of brain tumors that occur mainly in young children. Surgical resection for papilloma is usually curative, while adjuvant therapy for carcinoma should include chemotherapy and/or radiation. The long-term survival for carcinoma remains poor, particularly for those tumors with *TP53* mutations. The overall functional outcome can be excellent, but the potential for neurologic morbidity should be recognized early even for benign tumors.

References

Arbeit JM, Munger K, Howley PM, Hanahan D (1993) Neuroepithelial carcinomas in mice transgenic with human papillomavirus type 16 E6/E7 ORFs. Am J Pathol 142:1187–1197

Asai A, Hoffman HJ, Hendrick EB, Humphreys RP, Becker LE (1989) Primary intracranial neoplasms in the first year of life. Childs Nerv Syst 5:230–233

Berger C, Thiesse P, Lellouch-Tubiana A, Kalifa C, Pierre-Kahn A, Bouffet E (1998) Choroid plexus carcinomas in childhood: clinical features and prognostic factors. Neurosurgery 42:470–475

Bergsagel DJ, Finegold MJ, Butel JS, Kupsky WJ, Garcea RL (1992) DNA sequences similar to those of simian virus 40 in ependymomas and choroid plexus tumors of childhood. N Engl J Med 326:988–993

Boyd MC, Steinbok P (1987) Choroid plexus tumors: problems in diagnosis and management. J Neurosurg 66:800–805

Brinster RL, Chen HY, Messing A, van Dyke T, Levine AJ, Palmiter RD (1984) Transgenic mice harboring SV40 T-antigen genes develop characteristic brain tumors. Cell 37:367–379

Carlotti CG Jr, Salhia B, Weitzman S, Greenberg M, Dirks PB, Mason W, Becker LE, Rutka JT (2002) Evaluation of proliferative index and cell cycle protein expression in choroid plexus tumors in children. Acta Neuropathol 103:1–10

Chow E, Jenkins JJ, Burger PC, Reardon DA, Langston JW, Sanford RA, Heideman RL, Kun LE, Merchant TE (1999) Malignant evolution of choroid plexus papilloma. Pediatr Neurosurg 31:127–130

Coates TL, Hinshaw DB Jr, Peckman N, Thompson JR, Hasso AN, Holshouser BA, Knierim DS (1989) Pediatric choroid plexus neoplasms: MR, CT, and pathologic correlation. Radiology 173:81–88

Cruz-Sanchez FF, Rossi ML, Hughes JT, Coakham HB, Figols J, Eynaud PM (1989) Choroid plexus papillomas: an immunohistological study of 16 cases. Histopathology 15:61–69

Dandy W (1922) Diagnosis, localization, and removal of tumours of the third ventricle. Bull Johns Hopkins Hosp 33:188–189

Dang-Tan T, Mahmud SM, Puntoni R, Franco EL (2004) Polio vaccines, Simian Virus 40, and human cancer, the epidemiologic evidence for a causal association. Oncogene 23(38):6535–6540

Davis LE, Cushing H (1925) Papillomas of the choroid plexus with a report of six cases. Arch Neurol Psychiatry 13:681–710

Eisenberg HM, McComb JG, Lorenzo AV (1974) Cerebrospinal fluid overproduction and hydrocephalus associated with choroid plexus papilloma. J Neurosurg 40:381–385

Ellenbogen RG, Winston KR, Kupsky WJ (1989) Tumors of the choroid plexus in children. Neurosurgery 25:327–335

Fitzpatrick LK, Aronson LJ, Cohen KJ (2002) Is there a requirement for adjuvant therapy for choroid plexus carcinoma that has been completely resected? J Neurooncol 57:123–126

Galassi E, Godano U, Cavallo M, Donati R, Nasi MT (1989) Intracranial tumors during the 1st year of life. Childs Nerv Syst 5:288–298

Gopal P, Parker JR, Debski R, Parker JC Jr (2008) Choroid plexus carcinoma. Arch Pathol Lab Med 132:1350–1354

Gudeman SK, Sullivan HG, Rosner MJ, Becker DP (1979) Surgical removal of bilateral papillomas of the choroid

plexus of the lateral ventricles with resolution of hydrocephalus. Case report. J Neurosurg 50:677–681
Haddad SF, Menezes AH, Bell WE, Godersky JC, Afifi AK, Bale JF (1991) Brain tumors occurring before 1 year of age: a retrospective reviews of 22 cases in an 11-year period (1977–1987). Neurosurgery 29:8–13
Hasselblatt M, Bohm C, Tatenhorst L, Dinh V, Newrzella D, Keyvani K, Jeibmann A, Buerger H, Rickert CH, Paulus W (2006) Identification of novel diagnostic markers for choroid plexus tumors: a microarray-based approach. Am J Surg Pathol 30:66–74
Herbert J, Cavallaro T, Dwork AJ (1990) A marker for primary choroid plexus neoplasms. Am J Pathol 136:1317–1325
Hirano H, Hirahara K, Asakura T, Shimozuru T, Kadota K, Kasamo S, Shimohonji M, Kimotsuki K, Goto M (1994) Hydrocephalus due to villous hypertrophy of the choroid plexus in the lateral ventricles. Case report. J Neurosurg 80:321–323
Ho DM, Wong TT, Liu HC (1991) Choroid plexus tumors in childhood. Histopathologic study and clinicopathological correlation. Childs Nerv Syst 7:437–441
Horska A, Ulug AM, Melhem ER, Filippi CG, Burger PC, Edgar MA, Souweidane MM, Carson BS, Barker PB (2001) Proton magnetic resonance spectroscopy of choroid plexus tumors in children. J Magn Reson Imaging 14:78–82
Humphreys RP, Nemoto S, Hendrick EB, Hoffman HJ (1987) Childhood choroid plexus tumors. Concepts Pediatr Neurosurg 7:1–18
Jeibmann A, Wrede B, Peters O, Wolff JE, Paulus W, Hasselblatt M (2007) Malignant progression in choroid plexus papillomas. J Neurosurg 107:199–202
Johnson DL (1989) Management of choroid plexus tumors in children. Pediatr Neurosci 15:195–206
Judkins AR, Burger PC, Hamilton RL, Kleinschmidt-DeMasters B, Perry A, Pomeroy SL, Rosenblum MK, Yachnis AT, Zhou H, Rorke LB, Biegel JA (2005) INI1 protein expression distinguishes atypical teratoid/rhabdoid tumor from choroid plexus carcinoma. J Neuropathol Exp Neurol 64:391–397
Krieger MD, Panigrahy A, McComb JG, Nelson MD, Liu X, Gonzalez-Gomez I, Gilles F, Bluml S (2005) Differentiation of choroid plexus tumors by advanced magnetic resonance spectroscopy. Neurosurg Focus 18:E4
Krutilkova V, Trkova M, Fleitz J, Gregor V, Novotna K, Krepelova A, Sumerauer D, Kodet R, Siruckova S, Plevova P, Bendova S, Hedvicakova P, Foreman NK, Sedlacek Z (2005) Identification of five new families strengthens the link between childhood choroid plexus carcinoma and germline TP53 mutations. Eur J Cancer 41:1597–1603
Lafay-Cousin L, Keene D, Carret AS, Fryer C, Brossard J, Crooks B, Eisenstat D, Johnston D, Larouche V, Silva M, Wilson B, Zelcer S, Bartels U, Bouffet E (2011) Choroid plexus tumors in children less than 36 months: the Canadian Pediatric Brain Tumor Consortium (CPBTC) experience. Childs Nerv Syst 27(2):259–264
Laurence KM (1974) The biology of choroid plexus papilloma and carcinoma of the lateral ventricle. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology. Elsevier, New York, pp 555–595
Lena G, Genitori L, Molina J, Legatte JR, Choux M (1990) Choroid plexus tumours in children. Review of 24 cases. Acta Neurochir 106:68–72
Mannoji H, Becker LE (1988) Ependymal and choroid plexus tumors. Cytokeratin and GFAP expression. Cancer 61:1377–1385
Matson DD, Crofton FD (1960) Papilloma of choroid plexus in childhood. J Neurosurg 17:1002–1027
McComb RD, Burger PC (1983) Choroid plexus carcinoma. Report of a case with immunohistochemical and ultrastructural observations. Cancer 51: 470–475
McLendon RE, Rosenblum MK, Bigner DD (eds) (2006) Russell and Rubenstein's pathology of tumors of the nervous system. Arnold, London
Merino DM, Shlien A, Villani A, Pienkowska M, Mack S, Ramaswamy V, Shih D, Tatevossian R, Novokmet A, Choufani S, Dvir R, Ben-Arush M, Harris BT, Hwang EI, Lulla R, Pfister SM, Achatz MI, Jabado N, Finlay JL, Weksberg R, Bouffet E, Hawkins C, Taylor MD, Tabori U, Ellison DW, Gilbertson RJ, Malkin D (2015) Molecular characterization of choroid plexus tumors reveals novel clinically relevant subgroups. Clin Cancer Res 21(1):184–192
Meyers SP, Khademian ZP, Chuang SH, Pollack IF, Korones DN, Zimmerman RA (2004) Choroid plexus carcinomas in children: MRI features and patient outcomes. Neuroradiology 46:770–780
Naeini RM, Yoo JH, Hunter JV (2009) Spectrum of choroid plexus lesions in children. AJR Am J Roentgenol 192:32–40
Olson MV, Johnson DG, Jiang H, Xu J, Alonso MM, Aldape KD, Fuller GN, Bekele BN, Yung WK, Gomez-Manzano C, Fueyo J (2007) Transgenic E2F1 expression in the mouse brain induces a human-like bimodal pattern of tumors. Cancer Res 67:4005–4009
Packer RJ, Perilongo G, Johnson D, Sutton LN, Vezina G, Zimmerman RA, Ryan J, Reaman G, Schut L (1992) Choroid plexus carcinoma of childhood. Cancer 69:580–585
Paulus W, Brandner S (2007) Choroid plexus tumours. In: Louis DN, Ohgaki H, Wiestler OD, Cavanee WK (eds) WHO classification of tumours of the central nervous system. IARC, Lyon, pp 81–85
Paulus W, Janisch W (1990) Clinicopathologic correlations in epithelial choroid plexus neoplasms: a study of 52 cases. Acta Neuropathol 80:635–641
Pencalet P, Sainte-Rose C, Lellouch-Tubiana A, Kalifa C, Brunelle F, Sgouros S, Meyer P, Cinalli G, Zerah M, Pierre-Kahn A, Renier D (1998) Papillomas and carcinomas of the choroid plexus in children. J Neurosurg 88:521–528
Raimondi AJ, Gutierrez FA (1975) Diagnosis and surgical treatment of choroid plexus papillomas. Childs Brain 1:81–115

Razzaq AA, Cohen AR (1997) Neoadjuvant chemotherapy for hypervascular malignant brain tumors of childhood. Pediatr Neurosurg 27:296–303

Rickert CH, Wiestler OD, Paulus W (2002) Chromosomal imbalances in choroid plexus tumors. Am J Pathol 160:1105–1113

Safaee M, Clark AJ, Bloch O, Oh MC, Singh A, Auguste KI, Gupta N, McDermott M, Aghi MK, Berger MS, Parsa AT (2013) Surgical outcomes in choroid plexus papillomas: an institutional experience. J Neuro Oncol 113:117–125

Sahar A, Feinsod M, Beller AJ (1980) Choroid plexus papilloma: hydrocephalus and cerebrospinal fluid dynamics. Surg Neurol 13:476–478

Sarkar C, Sharma MC, Gaikwad S, Sharma C, Singh VP (1999) Choroid plexus papilloma: a clinicopathological study of 23 cases. Surg Neurol 52:37–39

Sevenet N, Lellouch-Tubiana A, Schofield D, Hoang-Xuan K, Gessler M, Birnbaum D, Jeanpierre C, Jouvet A, Delattre O (1999a) Spectrum of hSNF5/INI1 somatic mutations in human cancer and genotype-phenotype correlations. Hum Mol Genet 8:2359–2368

Sevenet N, Sheridan E, Amram D, Schneider P, Handgretinger R, Delattre O (1999b) Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancers. Am J Hum Genet 65:1342–1348

St Clair SK, Humphreys RP, Pillay PK, Hoffman HJ, Blaser SI, Becker LE (1991) Current management of choroid plexus carcinoma in children. Pediatr Neurosurg 17:225–233

Sun MZ, Ivan ME, Clark AJ, Oh MC, Delance AR, Safaee M, Kaur G, Bloch O, Oh T, Molinaro A, Gupta N, Parsa AT (2014) Gross total resection improves overall survival in children with choroid plexus carcinoma. J Neuro Oncol 116:179–185

Tabori U, Shlien A, Baskin B, Levitt S, Ray P, Alon N, Hawkins C, Bouffet E, Pienkowska M, Lafay-Cousin L, Gozali A, Zhukova N, Shane L, Gonzalez I, Finlay J, Malkin D (2010) TP53 alterations determine clinical subgroups and survival of patients with choroid plexus tumors. J Clin Oncol 28(12): 1995–2001

Vajtai I, Varga Z, Aguzzi A (1996) MIB-1 immunoreactivity reveals different labelling in low grade and in malignant epithelial neoplasms of the choroid plexus. Histopathology 29:147–151

Wilkins RH, Rutledge BJ (1961) Papillomas of the choroid plexus. J Neurosurg 18:14–18

Wolff JE, Sajedi M, Coppes MJ, Anderson RA, Egeler RM (1999) Radiation therapy and survival in choroid plexus carcinoma. Lancet 353:2126

Wolff JE, Sajedi M, Brant R, Coppes MJ, Egeler RM (2002) Choroid plexus tumours. Br J Cancer 87:1086–1091

Wrede B, Liu P, Ater J, Wolff JE (2005) Second surgery and the prognosis of choroid plexus carcinoma–results of a meta-analysis of individual cases. Anticancer Res 25:4429–4433

Wrede B, Liu P, Wolff JE (2007) Chemotherapy improves the survival of patients with choroid plexus carcinoma: a meta-analysis of individual cases with choroid plexus tumors. J Neuro Oncol 85:345–351

Wyatt-Ashmead J, Kleinschmidt-DeMasters B, Mierau GW, Malkin D, Orsini E, McGavran L, Foreman NK (2001) Choroid plexus carcinomas and rhabdoid tumors: phenotypic and genotypic overlap. Pediatr Dev Pathol 4:545–549

Zwetsloot CP, Kros JM, Paz y Gueze HD (1991) Familial occurrence of tumours of the choroid plexus. J Med Genet 28:492–494

Intramedullary Spinal Cord Tumors

10

Jonathan D. Breshears, Peter P. Sun, and Kurtis I. Auguste

Contents

J.D. Breshears, MD, PhD
Department of Neurological Surgery,
University of California San Francisco,
505 Parnassus Ave., Rm M787,
San Francisco, CA 94143, USA
e-mail: jonathan.breshears@ucsf.edu

P.P. Sun, MD
Department of Neurological Surgery,
UCSF Benioff Children's Hospital Oakland,
747 52nd St, Oakland, CA 94143, USA
e-mail: psun@mail.cho.org

K.I. Auguste, MD (✉)
Departments of Neurological Surgery and Pediatrics,
University of California San Francisco & UCSF
Benioff Children's Hospital, 550 16th St. 4th Floor,
San Francisco, CA, USA

UCSF Benioff Children's Hospital Oakland,
Oakland, CA, USA
e-mail: kurtis.auguste@ucsf.edu

10.1 Introduction

Intramedullary spinal cord tumors (IMSCT) are rare lesions in the pediatric population, accounting for 4–8 % of central nervous system tumors in children (Bowers and Weprin 2003; DeSousa et al. 1979; Barker et al. 1976). They represent 55 % of intradural tumors in this age group (Yamamoto and Raffel 1999). They occur with an approximate incidence of 1 in 100,000, with 100–200 cases of pediatric IMSCTs diagnosed each year in the United States (Constantini and Epstein 1995; Constantini 1996). The majority of these lesions (nearly 60 %) are encountered in the cervical and thoracic regions and rarely involve the lumbar cord (Goh et al. 2000; Cooper 1989). They are distributed evenly between male and female patients (Goh et al. 1997). Primary glial tumors such as ependymomas and astrocytomas account for at least 80 % of IMSCTs (Cooper

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_10

1989; Cristante and Herrmann 1994; Epstein et al. 1993; Hoshimaru et al. 1999; McCormick et al. 1990b; Sandler et al. 1992). Other less common but reported pediatric IMSCT tumor types include ganglioglioma (Lang et al. 1993; Hayashi et al. 2011), oligodendroglioma (Miller 2000), and hemangioblastoma (Lang et al. 1993; Roonprapunt et al. 2001; Weil et al. 2003). Rarer still have been case reports of primitive neuroectodermal tumors (Alexiou et al. 2013), subependymoma (Miller and McCutcheon 2000), pleomorphic xanthoastrocytoma (Das et al. 2014), neurocytoma (Singh et al. 2007), schwannoma (Kim et al. 2009), teratoma (Isik et al. 2008), germinoma (Madhukar et al. 2013), and non-Hodgkin's lymphoma (Bhushanam et al. 2014).

While presenting symptoms are usually minimal and parents typically report symptoms for months or years prior to diagnosis, tumor size, location, and pathologic type all factor into their presentation (Kothbauer 2007). The common clinical features are pain, weakness, paresthesias, spinal deformity, sphincter disturbance, and cervicomedullary symptoms (Goh et al. 1997). Larger tumors, rostral tumors, and those with higher grades or hemorrhaging will commonly present sooner (Ito et al. 2013). Pain centered over the tumor's location is also a common complaint. For the cervical spine, neck pain, torticollis, and/or upper extremity weakness can be expected. Thoracic lesions can present with some form of scoliosis. Lower extremity weakness can occur as well but may do so over a more prolonged course of many months. Lesions involving the conus can ultimately lead to sphincter dysfunction, but bowel and bladder dysfunction are not common presenting symptoms for IMSCT (Houten and Weiner 2000). Slow progressive deterioration of neurologic function can also occur (Constantini 1996; Kothbauer 2007). The surgical objective for primary IMSCTs is gross total resection, but in some cases, achieving this goal may leave a patient with severe neurologic deficits. The location of the tumor, age of the patient, pathology, and ability to achieve a gross total resection (GTR) usually determine whether radiation or chemotherapy will be used.

10.2 Astrocytoma

Astrocytomas are the most common type of IMSCT in children, constituting approximately 60 % of these lesions (Epstein and Epstein 1981; Reimer and Onofrio 1985; Rossitch et al. 1990; Epstein et al. 1992, 1993). These tumors are most likely to occur in the cervicothoracic region. Intratumoral and satellite cysts, as well as associated hydromyelia, can be seen in the pilocytic subtypes (Baleriaux 1999). The most common astrocytoma subtype in children is pilocytic astrocytoma. Although low-grade lesions represent the majority of astrocytomas, high-grade tumors occur in 10–15 % of cases (Allen et al. 1998; DeSousa et al. 1979).

10.2.1 Epidemiology

Pilocytic astrocytomas (PA) of the spinal cord often occur in the first two decades of life. In the adult population, they occur in young patients (mean age 29 years) with a slightly higher predilection for males (Baleriaux 1999). Intramedullary spinal cord astrocytomas can be clustered with inherited syndromes such as Li–Fraumeni syndrome, Turcot's syndrome, tuberous sclerosis complex (TSC), Maffucci/Ollier disease, and neurofibromatosis types 1 and 2 (NF1 and NF2) (Mellon et al. 1988; Frappaz et al. 1999; van Nielen and de Jong 1999; Lee et al. 1996).

10.2.2 Pathology

10.2.2.1 Grading

Spinal cord astrocytomas are graded according to the WHO grading system based on the region of the tumor with the highest degree of histologic anaplasia (Louis et al. 2007). Grade I astrocytomas are most common in the pediatric population. Pilocytic astrocytoma, the most common grade I tumor, typically have cysts and contrast enhancement on imaging (Lee et al. 1996; Allen et al. 1998; Baleriaux 1999). Grade II astrocytomas are diffusely infiltrative with cytologic atypia, while grade III astrocytomas additionally

show anaplasia and mitotic activity. MIB-1 labeling index can be used to differentiate grade II and III tumors (Neder et al. 2004). Microvascular proliferation and/or necrosis is required for a grade IV designation.

10.2.2.2 Histopathology

PAs are characterized by elongated, "hairlike" cells with cytoplasmic Rosenthal fibers and granular eosinophilic bodies. Although occasional cellular pleomorphism, mitoses, vascular proliferation, and invasion of meninges can be detected, these histopathologic findings have not been determined to be prognostic and are not considered to be malignant findings.

Grade II diffuse astrocytomas of the spinal cord are infiltrative and produce a fusiform, enlarging process of the tumor. Typically these lesions are characterized by hypercellularity, nuclear pleomorphism, and a diffuse infiltrative growth pattern in the spinal cord. Diffuse spinal cord astrocytomas are differentiated by a fibrillary or gemistocytic neoplastic astrocyte with a background of loosely structured microcystic matrix. Higher-grade intramedullary spinal cord astrocytomas have increased cellularity, anaplastic features, mitotic activity, vascular proliferation, and areas of necrosis.

10.2.2.3 Molecular Biology and Genetics

Spinal cord astrocytomas in general are thought to arise from glial cell predecessors. These tumors are usually sporadic and are rarely associated with other genetic syndromes (Mellon et al. 1988; Frappaz et al. 1999; van Nielen and de Jong 1999). Genetic analyses of PAs have found numerous genetic aberrations, but previously no specific tumor suppressor or oncogene was identified (Ransom et al. 1992). Platelet-derived growth factor receptor (PDGFR) expression has been implicated in the development of spinal cord gliomas of all types (Ellis et al. 2012a, b).

Although a novel gene fusion at the *BRAF* locus was recently identified in pilocytic astrocytoma in the brain (Jones et al. 2008), there is little genetic data available for spinal cord astrocytomas. Nevertheless, it is likely that some of the genetic alterations described in intracranial astrocytoma play a role in the progression of spinal cord astrocytoma. Three general pathways for glioma progression are proposed: (1) astrocyte to infiltrating astrocytoma, (2) astrocytoma to anaplastic astrocytoma, and (3) anaplastic astrocytoma to glioblastoma. In the first, initial mutations in *p53* and losses of chromosome 17p and 22q have been implicated. Rubio and colleagues have shown that the *NF2* gene was not mutated in 30 astrocytomas examined, making it an unlikely candidate for the 22q locus lost during this transition (Rubio et al. 1994). In the progression from astrocytoma to anaplastic astrocytoma, genetic defects include retinoblastoma (*Rb*) gene mutations, chromosome 13q loss, P16 gene deletions, chromosome 9p loss, and chromosome 19q loss (von Deimling et al. 1995). The transition from anaplastic astrocytoma to glioblastoma has been shown to involve chromosome 10 loss and epidermal growth factor receptor (*EGFR*) gene amplification (Liu et al. 1997).

Several studies have identified the *PTEN* gene (also known as MMAC and TEP1) as one of the candidate chromosome 10 genes lost in glioblastoma (Liu et al. 1997; Parsons 2004). The gene encodes a tyrosine phosphatase, which is consistent with a tumor suppressor phenotype. When phosphatase activity is lost as a result of genetic mutation, signaling pathways can become activated constitutively, resulting in aberrant proliferation.

10.2.2.4 Association with Neurofibromatosis

There are two distinct types of neurofibromatosis, each affecting cells derived from the neural crest. NF1 is characterized by autosomal dominant inheritance with almost complete penetrance and variable expressivity (Ward and Gutmann 2005). NF1 is at least ten times more common than NF2. Spinal cord tumors in NF1 patients are usually astrocytomas, while ependymomas usually occur in patients with NF2 (Dow et al. 2005). In one small cohort of neurofibromatosis patients with IMSCTs, 3 had NF1, 5 had NF2, and 1 had an uncertain type (Lee et al. 1996). The reported incidence of IMSCTs in the

total neurofibromatosis population was approximately 19 % (9 out of 48). In 1997, Yagi and colleagues described a cohort of 44 adult patients with IMSCTs, 2 of whom had NF1 (Yagi et al. 1997). In both cases, the pathology of the lesion was astrocytoma (anaplastic astrocytoma and glioblastoma).

10.2.3 Clinical Features

The typical symptoms of an intramedullary spinal cord astrocytoma are shown in Table 10.1. They include gait disturbance, pain, reflex changes, motor or sensory symptoms, and bowel or bladder sphincter dysfunction (Steinbok et al. 1992; Constantini et al. 1996; Houten and Weiner 2000; Houten and Cooper 2000) Spinal deformity can be present in up to 30 % of patients (Epstein and Epstein 1981; Epstein et al. 1992; Steinbok et al. 1992). Intramedullary tumors involving the cervicomedullary junction can present with a myriad of symptoms, such as vomiting, choking, dysphagia, frequent respiratory infections due to chronic aspiration, dysarthria and dysphonic speech, sleep apnea, and failure to thrive (Abbott 1993; Robertson et al. 1994). A tumor in the cervical spinal cord can cause chronic neck pain, torticollis, progressive motor weakness, sensory changes, hyperreflexia, and, rarely, hydrocephalus (Abbott 1993; Robertson et al. 1994). Chronic pain at the level of the tumor can be present for months or years (Houten and Weiner 2000; Houten and Cooper 2000).

Table 10.1 Presenting symptoms of intramedullary spinal cord tumors in children

Pain
Motor regression
Weakness
Gait abnormality/deterioration
Torticollis
Progressive kyphoscoliosis
Hydrocephalus
Sphincter disturbance
Reflex changes
Sensory impairment

10.2.3.1 Diagnostic Imaging

MRI is the diagnostic tool of choice for all spinal tumors (Miyazawa et al. 2000; Sun et al. 2003). There is virtually no role for plain radiographs or computed tomography (CT) images because of the associated radiation exposure and limited anatomic detail seen. Astrocytomas are commonly located eccentrically within the spinal cord, and there is often heterogeneous contrast enhancement following injection of gadolinium (Baleriaux 1999; Osborn 1994) (Figs. 10.3 and 10.4). Diffusion tensor imaging (DTI) can be helpful in defining the relationship of the lesion to critical spinal pathway. In a series of ten patients, tractography was capable of demonstrating fiber splaying/displacement versus pathway infiltration. This information contributed to the decision between aggressive resection compared to debulking and biopsy (Choudhri et al. 2014). DTI and perfusion-weighted imaging (PWI) can be helpful in differentiating IMSCTs from other tumorlike lesions in the cervical cord (Liu et al. 2014). Approximately 75 % of astrocytomas occur in the cervicothoracic region, 20 % in the distal spinal cord, and 5 % in the filum terminale (Osborn 1994). Unlike ependymomas, which typically span three to four vertebral bodies, spinal cord astrocytomas are more extensive spanning several levels to holocord (Baleriaux 1999; Osborn 1994; Ebner et al. 2012).

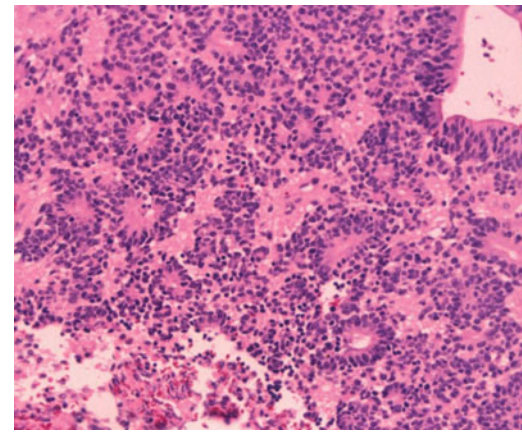

Fig. 10.1 Histological features of ependymoma. This image illustrates the ependymal rosettes which are formed from columnar cells arranged around a central lumen. Also in the top right hand corner, a pseudorosette, cells arranged radially around a blood vessels, can be appreciated

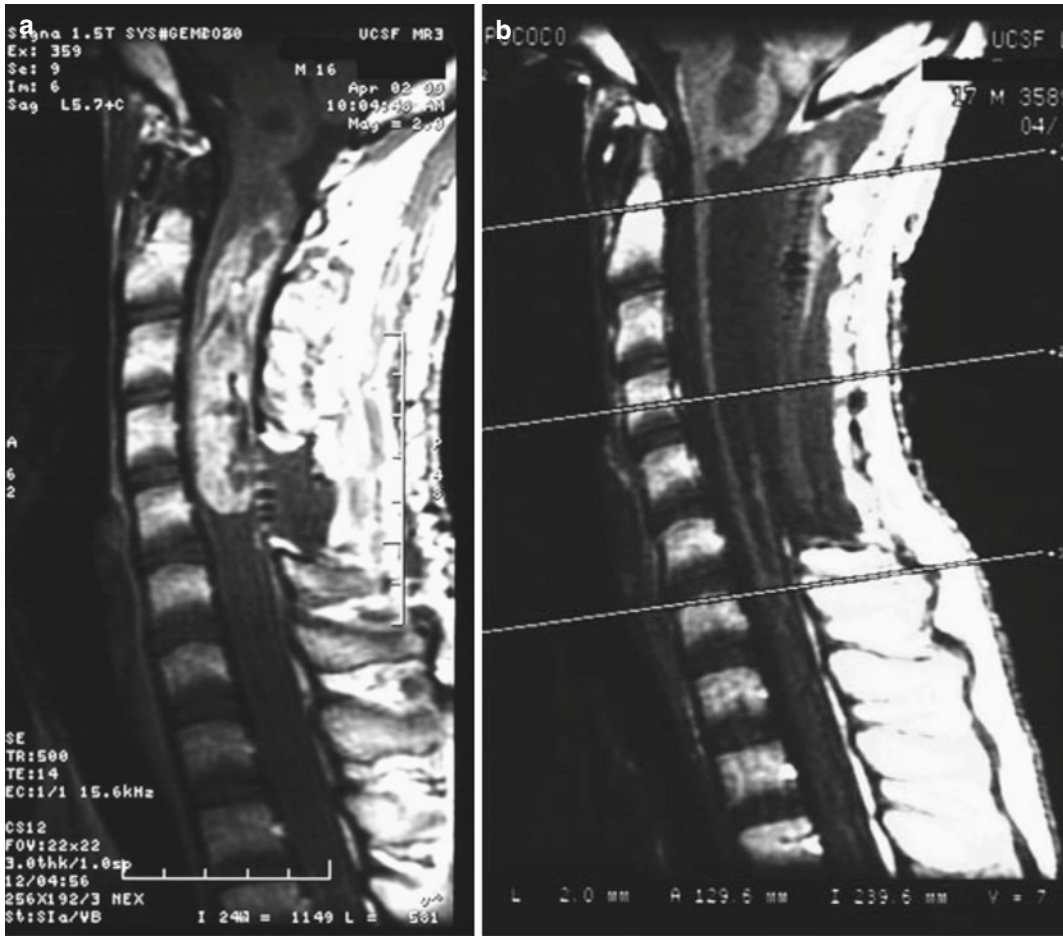

Fig. 10.2 A 17-year-old male presented with left-arm numbness and tingling. (**a**) The preoperative MRI scan reveals an intramedullary cervical cord mass in the sagittal T1-weighted image with contrast. Gross total resection was achieved, and pathology was consistent with a grade II ependymoma. (**b**) A postoperative MRI showed resection of the mass with no evidence of residual tumor as demonstrated in the sagittal T1-weighted image with contrast

Although MRI has improved our ability to identify the exact location of IMSCTs, a precise histopathologic diagnosis requires tissue biopsy (Kopelson and Linggood 1982; McCormick et al. 1990a; Hulshof et al. 1993; Minehan et al. 1995; Lee et al. 1996; Innocenzi et al. 1997; Jallo et al. 2001).

10.3 Ependymoma

10.3.1 Epidemiology

Ependymomas are thought to arise from the ependymal lining of the ventricles and central canal and can occur both in the brain and spinal cord. The majority of ependymomas are sporadic, but they can also be associated with NF2. In children, ependymomas usually arise in the cervical region and occur less frequently than astrocytomas (McCormick et al. 1990b; Brotchi et al. 1991; Fine et al. 1995; Goh et al. 1997; Miller 2000; Schwartz and McCormick 2000; Hanbali et al. 2002). Miller identified only 16 ependymomas out of 117 (14 %) cases of pediatric IMSCTs (Miller 2000). Although intramedullary ependymomas are the most common spinal cord tumor in adults (Mork and Loken 1977; Sonneland et al. 1985; Helseth and Mork 1989; Whitaker et al. 1991; Clover et al. 1993; Hulshof et al. 1993; Hoshimaru et al. 1999; Schwartz and McCormick 2000; Chang et al. 2002; Hanbali et al. 2002; Parsa et al. 2004),

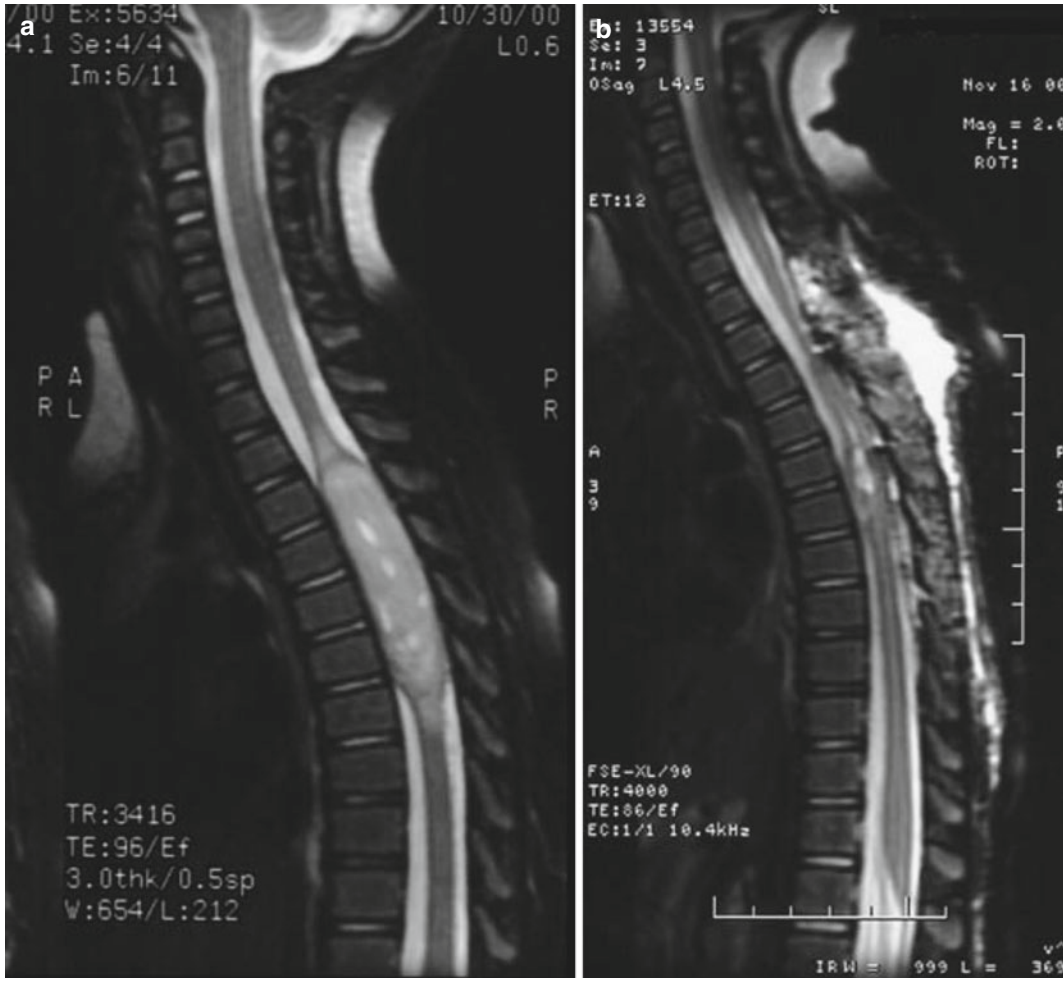

Fig. 10.3 A 3-year-old girl presented with 6 months of intermittent, worsening back pain. (**a**) The MRI scan revealed a large intramedullary mass extending from T3 to T7, shown here in a sagittal T2-weighted image. The histology was consistent with pilocytic astrocytoma. (**b**) The postoperative MRI scan demonstrates removal of the centrally located tumor. Nodular enhancement in the area of the surgery is seen in a sagittal T2-weighted image. Although nodular enhancement was present in the first imaging, subsequent MRIs showed complete resolution 6 months after resection

they are less common in the pediatric population (Constantini et al. 1996; Miller 2000; Constantini 1996) In their series of pediatric IMSCTs, Constantini and colleagues did not find any ependymomas in children less than 3 years of age (Constantini et al. 1996).

10.3.2 Pathology

10.3.2.1 Grading

The World Health Organization (WHO) classification of CNS tumors (Kleihues et al. 2002; Louis et al. 2007) divides ependymomas into four types: subependymoma (grade I), myxopapillary ependymoma (grade I), benign or "classic" ependymoma (grade II), and anaplastic ependymoma (grade III). Subependymomas are considered benign, slow-growing, and intraventricular tumors and have a good prognosis, although they are rarely encountered in the spinal cord. Myxopapillary ependymomas are unique tumors because they usually arise from the filum terminale or conus medullaris (Sonneland et al. 1985). Nearly all are histologically benign and are associated with a good long-term survival (Mork and

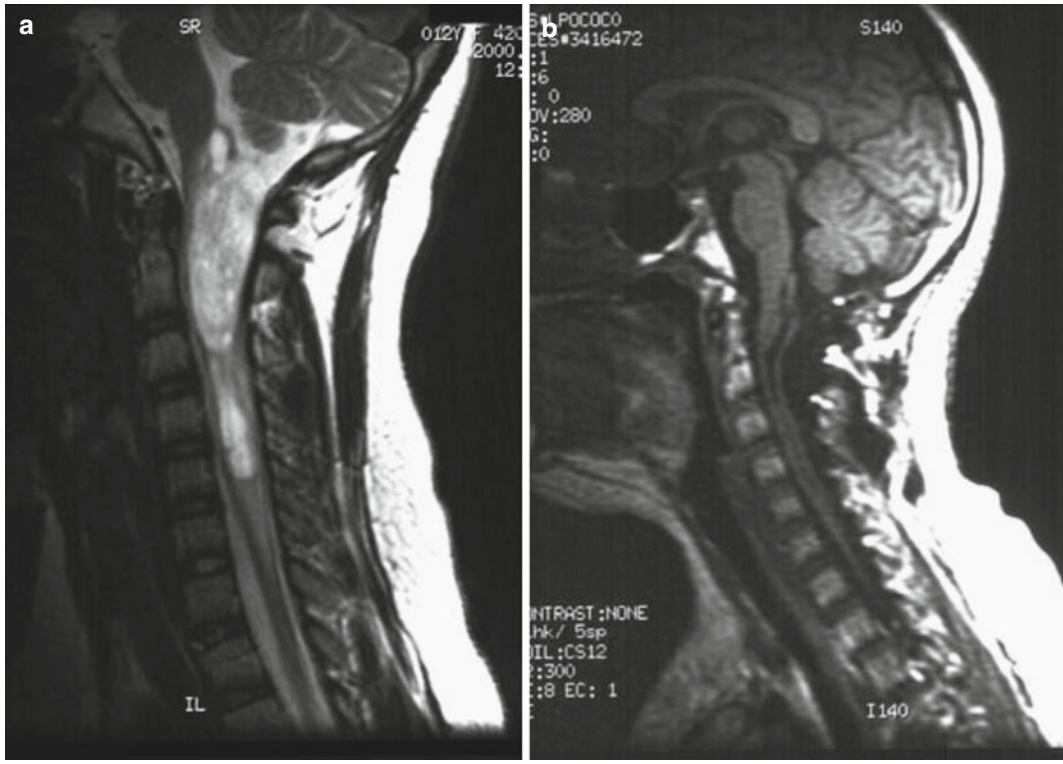

Fig. 10.4 A 12-year-old girl presented with a 3-month history of progressive right arm weakness and clumsiness. (**a**) The preoperative MRI scan revealed an intramedullary spinal cord tumor extending from the cervicomedullary junction to C4, as shown in sagittal T2-weighted image. Histology was consistent with a pilocytic astrocytoma. (**b**) The postoperative MRI demonstrates that the enhancing mass has been resected, as shown in the sagittal T1-weighted image

Loken 1977; Cooper 1989; McCormick et al. 1990b; Epstein et al. 1993; Chang et al. 2002; Hanbali et al. 2002; Russell 1989). Although most spinal cord ependymomas in children are grade II tumors, anaplastic ependymomas do occur infrequently and are believed to arise from the malignant transformation of lower-grade tumors (Kleihues et al. 2002).

10.3.2.2 Histopathology

Subependymomas are characterized by clusters of glial cells in a dense fibrillary matrix and are often associated with small cysts. Ependymomas are highly cellular tumors, irrespective of their grade. Myxopapillary ependymomas are characterized by cuboidal or elongated tumor cells arranged in a papillary and radial pattern around the vascular and stromal cores. Little mitotic activity is present, but a matrix of abundant mucin can accumulate between myxopapillary ependymoma cells and vessels.

The gross appearance of grade II spinal cord ependymomas is that of a soft, red or grayish-purple, somewhat friable mass (McCormick et al. 1990b; Schwartz and McCormick 2000; Sun et al. 2003). Cystic degeneration and hemorrhage are common in these vascular tumors (Sun et al. 2003). Although unencapsulated, these tumors are usually well circumscribed and do not infiltrate adjacent spinal cord tissue (Goh et al. 1997; Parsa et al. 2004; Parsa and McCormick 2005). Microscopic features include pseudorosettes and perivascular clustering and cuffing and immunoreactivity for glial fibrillary acidic protein (GFAP). Pseudorosettes are formed by clustering of cuboidal or columnar cells in a radial pattern around the blood vessels (Fig. 10.1). True rosettes, which appear as a ring of several nuclei from which interlacing neurofibrils converge in the center, can also be present (Schwartz and McCormick 2000). Mitotic figures are rare, but

an occasional nonpalisading focus of necrosis can be found in low-grade ependymomas. As measured by MIB-1 immunohistochemistry, the proliferative activity of spinal cord ependymoma is significantly lower than that of intracranial ependymoma. Proliferative indices greater than 2.0 % may be associated with an increased risk of recurrence (Iwasaki et al. 2000). The atypical variants clear cell ependymoma and tanycytic ependymoma can mimic oligodendroglioma and astrocytoma, respectively (Goh et al. 1997).

Anaplastic ependymomas differ from grade II ependymomas. While grade II ependymomas morphologically appear similar to nonneoplastic ependymal cells, anaplastic ependymomas demonstrate clear evidence of malignancy such as increased mitotic activity, increased cellularity with microvascular proliferation, and pseudopalisading necrosis. Anaplastic ependymomas can be extremely invasive and are poorly differentiated.

10.3.2.3 Molecular Biology and Genetics

Myxopapillary ependymomas have a much higher propensity for aneuploidy or polyploidy, especially of chromosome 7, when compared to other ependymomas (Gilhuis et al. 2004; Santi et al. 2005). Anaplastic ependymomas (WHO grade III) of the spinal cord are rare, and genetic alterations remain largely undefined (Ebert et al. 1999).

Molecular and genetic events associated with spinal ependymoma have been described. Ebert and colleagues analyzed 62 ependymal tumors, including myxopapillary ependymomas, subependymomas, classic ependymomas, and anaplastic ependymoma. They showed allelic loss of chromosomes 10q (5 out of 56) and 22q (12 out of 54) (Ebert et al. 1999). Somatic mutations of the *NF2* gene were detected in six of the tumors examined, and in each case the tumor was from a grade II spinal cord ependymoma. These results were confirmed by another group which also found mutations in the *NF2*. In addition, loss of heterozygosity (LOH) of 22q was present in all spinal intramedullary ependymomas ($n=6$) (Lamszus et al. 2001). Allelic loss on 22q was also frequently observed and was more common in intramedullary spinal ependymomas than in tumors in other locations (Lamszus et al. 2001).

In a report of 22 pediatric ependymomas, LOH at chromosome 22 was observed in two cases, deletions of chromosome 17 in another two cases, and the deletion or rearrangement of chromosome 6 in another five cases (Kramer et al. 1998). In addition, a low-penetrance ependymoma susceptibility locus has been mapped to chromosome 22q11 (Hulsebos et al. 1999; Ammerlaan et al. 2005), suggesting the role of alternative predisposing genes apart from *NF2*.

Overall, 75 % of all ependymomas display chromosomal aberrations or rearrangements over several different chromosomes, the most frequent LOHs being found on the long arms of chromosomes 6 (30.3 %), 9 (27.3 %), and 17 (Huang et al. 2003). In 18 pediatric ependymomas, von Haken and colleagues reported a 50 % incidence of allelic mutations on the short arm of chromosome 17 (von Haken et al. 1996). LOH was also detected on 3p14 (13.3 %), 10q23 (10.3 %), and 11q (18.2 %). Monosomy of chromosome 22 is present in approximately 30 % of ependymomas (Scheil et al. 2001), with aberrations or alterations of 22q existing in up to 40 % of all ependymomas.

Another distinction between spinal and cranial ependymoma may lie in the methylation of particular tumor-related genes. A study examining the methylation of a putative tumor suppressor gene, *HIC-1* on chromosome 17p13.3, showed a significant correlation between hypermethylation of *HIC-1* and cranial localization ($p=0.019$, $n=52$) (Waha et al. 2004). Losses in chromosomes 1p and 16q, which occur in other CNS tumors, have not been found in ependymoma (Bijlsma et al. 1995). The apparent genetic differences between ependymomas in the brain and those in the spine suggest that different molecular mechanisms exist that lead to the pathogenesis of each. Because primary brain and spine tumors are rarely, if ever, associated with each other, these distinctions may indicate the need to reclassify spinal ependymoma separately from intracranial ependymoma.

10.3.2.4 Association with Neurofibromatosis Type 2

NF2 is a rare autosomal dominant genetic disorder associated with tumors of the CNS (see Chap. 12) (Mulvihill et al. 1990). Its prevalence is 1 in 40,000 individuals (Evans et al. 1992), and is caused by a mutation of the *NF2* tumor suppressor gene (also known as *merlin* or *schwannomin*) located on chromosome 22 (Rouleau et al. 1987, 1993; Trofatter et al. 1993). Patients with NF2 have a high incidence of several CNS tumors, including vestibular schwannomas and meningiomas (Martuza and Eldridge 1988). Several authors have also noted an association between NF2 and intramedullary spinal cord ependymomas (Martuza and Eldridge 1988; Rodriguez and Berthrong 1966; Mautner et al. 1993; Lee et al. 1996; Lamszus et al. 2001; Egelhoff et al. 1992). NF2 patients represent approximately 2.5 % of patients with IMSCTs, yet only 0.03 % of the population (Lee et al. 1996). In addition, in one small study, 71 % of patients with intramedullary spinal cord ependymomas and no other clinical features of NF2 were shown to possess mutations in the *NF2* gene (Birch et al. 1996). More recently, Garcia and Guttman investigated the mechanism by which the *NF2* protein Merlin regulates spinal neural differentiation and glial proliferation. They demonstrated that Merlin negative regulates these cell functions in a manner dependent on ErbB2, and they further observed increased Erb2 activation in NF2-associated ependymomas; they further hypothesize that ErbB2 may be a rational therapeutic target for medical therapy for NF2-associated spinal ependymoma (Garcia et al. 2014).

10.3.3 Clinical Features

Arising from ependymal cells lining the central canal, intramedullary ependymomas are well circumscribed, slow-growing tumors usually located in the center of the cervical spinal cord and cause symmetric expansion of the cord (McCormick et al. 1990a; Brotchi et al. 1991; Fine et al. 1995; Goh et al. 1997; Miller 2000; Schwartz and McCormick 2000; Hanbali et al. 2002). Patients typically complain of dysesthesia correlating to the level of the tumor for months to years prior to diagnosis. Other symptoms include paresthesia, radicular pain, bowel and bladder dysfunction, and other sensory disturbances (Rawlings et al. 1988; McCormick and Stein 1990; McCormick et al. 1990b; Clover et al. 1993; Epstein et al. 1993; Hulshof et al. 1993; Asazuma et al. 1999; Hoshimaru et al. 1999; Schwartz and McCormick 2000; Chang et al. 2002; Hanbali et al. 2002; Peker et al. 2004; Shrivastava et al. 2005). Children most often present with pain, weakness, gait abnormality, torticollis, or progressive kyphoscoliosis (Constantini et al. 1996, 2000). Hydrocephalus also is more common in pediatric patients with intramedullary spinal cord ependymomas than in adult patients and may require cerebrospinal fluid (CSF) shunting (Houten and Weiner 2000; Houten and Cooper 2000). A sudden decline in neurologic function may occur following intratumoral hemorrhage (McCormick et al. 1990b). Motor impairment usually occurs late in the disease progression as the expanding tumor thins the surrounding spinal cord to a few millimeters (Epstein et al. 1993) (Table 10.1). This differs from intramedullary astrocytomas, which tend to present with pain and progressive motor dysfunction over a shorter time (Epstein et al. 1993).

10.3.4 Diagnostic Imaging

The anatomic features of spinal cord tumors are best evaluated with magnetic resonance imaging (MRI) (Miyazawa et al. 2000; Sun et al. 2003). Intramedullary spinal cord ependymomas are typically centrally located lesions with sharply defined rostral and caudal margins, enhancing borders, and typically spanning three to four vertebral body segments (Baleriaux 1999; Miyazawa et al. 2000). Spinal cord ependymomas commonly demonstrate symmetric enlargement of the spinal cord, unlike astrocytomas, which exhibit a nodular or asymmetric pattern of growth (Kopelson and Linggood 1982; McCormick et al. 1990a; Hulshof et al. 1993; Minehan et al. 1995; Lee et al. 1996; Innocenzi et al. 1997; Iwasaki et al. 2000; Miyazawa et al. 2000; Jallo et al. 2001).

Table 10.2 Magnetic resonance imaging of intramedullary spinal cord tumors

	Ependymomas	Astrocytomas
Location	Centrally located; mostly in the cervical spine but in children also present in the conus	Eccentrically located, usually widens the spinal cord, 75 % of astrocytomas in the cervical and thoracic regions, 20 % in the distal cord, 5 % in the filum terminale
T1	Isointense/hypointense	Isointense/hypointense
T1 with contrast	Axial view – cord symmetrically expanded. Enhances with contrast but less than astrocytomas	Ill-defined borders axial view – cord asymmetrical, "lumpy"; heterogeneous, moderate, partial contrast enhancement

Spinal cord ependymomas are isointense on T1-weighted MR images and slightly hyperintense on T2-weighted MR images (Miyazawa et al. 2000; Sun et al. 2003) (Table 10.2). However, signal heterogeneity can occur with cyst formation, necrosis, or hemorrhage (Miyazawa et al. 2000). A "cap sign" is typically associated with spinal cord ependymomas and represents areas of low signal density on either border of the tumor mass itself. This "cap" hypointensity at the tumor margin is often due to hemosiderin deposits from secondary, chronic hemorrhage (Baleriaux 1999; Miyazawa et al. 2000; Chang et al. 2002). Almost all intramedullary ependymomas enhance with contrast, but to a lesser degree than intracranial ependymomas (Sun et al. 2003) (Fig. 10.2). Occasionally, these spinal cord ependymomas can present with subarachnoid hemorrhage.

Spinal cord ependymoma-related cysts are common and are classified into three types: cystic tumors from tumor necrosis and hemorrhage, syrinx formation from disturbances of CSF formation, and rostral and caudal cysts from reactive products of IMSCTs (Sun et al. 2003). Ependymoma-associated cysts appear hypointense on T1-weighted MR images and hyperintense on T2-weighted images (Sun et al. 2003). These cysts are also centrally located and cause symmetric expansion of the spinal cord (Sun et al. 2003). A tumor-associated syrinx has similar MR characteristics to CSF and is present in over 50 % of spinal cord ependymomas (Chang et al. 2002). Multivariate analysis has determined that the presence of syringohydromyelia strongly favors a diagnosis of ependymoma over astrocytoma (Kim et al. 2014). The majority of rostral and caudal cysts are also hypointense on T1-weighted MR images and hyperintense on T2-weighted MR images (Sun et al. 2003).

10.4 Von Hippel–Lindau Disease and Spinal Hemangioblastoma

Hemangioblastomas are benign (WHO grade I) vascular tumors predominantly found in the cerebellum and spinal cord (see Chap. 12). First described by Arvid Lindau as cystic lesions in the cerebellum, CNS hemangioblastomas are usually sporadic, but 20–30 % of cases occur in association with von Hippel–Lindau (VHL) disease (Glasker 2005). VHL is an autosomal dominant disorder with 90 % penetrance attributable to loss of a tumor suppressor gene on chromosome 3p25–26 (Kley et al. 1995). The *VHL* gene encodes for a protein required for oxygen-dependent degradation of hypoxia-inducible factor-1 alpha (HIF-1a). Dysfunction or absence of the *VHL* gene product leads to constitutive overexpression of HIF-1a, which then leads to increased levels of vascular endothelial growth factor (VEGF) and other pro-angiogenic signals (Kim and Kaelin 2004). Additional information is provided in Chap. 12.6.

Lesions associated with VHL include CNS hemangioblastoma, retinal angioma, renal cysts, renal cell carcinoma, pancreatic cysts, pheochromocytoma, and epididymal cystadenoma (Glavac et al. 1996). VHL families can be grouped according to the presence or absence of pheochromocytomas (Neumann et al. 1995). Nearly all families with pheochromocytomas have missense mutations of the VHL gene. Using tissue

microdissection, Vortmeyer and colleagues have demonstrated consistent LOH at the VHL gene locus in the stromal cells, implicating these cells in the pathogenesis of hemangioblastoma (Vortmeyer et al. 1997).

CNS hemangioblastoma occurs in both type I (without pheochromocytoma) and type II (with pheochromocytoma) VHL disease. Common sites include the posterior fossa (80 %) and the spinal cord (20 %). VHL-related hemangioblastomas have been reported to harbor germline mutations (94 %) and LOH (62 %) at the *VHL* gene (Glasker et al. 1999, 2001; Glasker 2005). Over 150 different germline mutations have been identified and include deletion and missense and nonsense frameshift mutations. The resultant biallelic inactivation of the *VHL* gene suggests a "2-hit" model of tumorigenesis in VHL patients. VHL patients are usually heterozygous for the germline VHL mutant, and a "second hit" at the remaining wild-type *VHL* gene then causes neoplastic progression. In contrast, sporadic hemangioblastomas contain only 50 % LOH and 23 % germline mutations at the *VHL* gene, suggesting alternate pathways to biallelic inactivation and tumorigenesis in sporadic cases (Glasker 2005).

Other mutations and sites of LOH have been implicated in the development of sporadic hemangioblastomas. LOH of chromosome 22q13 was found in 5 of 8 patients with non-VHL-related hemangioblastoma, with only 3 of 8 patients harboring LOH at chromosome 3p21–23 (Beckner et al. 2004). Differences in the molecular and genetic origins of hemangioblastoma may indicate differences between patients with VHL disease and CNS hemangioblastomas and those with sporadic CNS hemangioblastomas.

10.5 Other Intramedullary Spinal Cord Tumors and Lesions

Inclusion tumors and cysts, metastases, nerve sheath tumors, neurocytoma, and melanocytoma account for much of the remainder of intramedullary mass lesions. Approximately 4 % of apparent IMSCTs are nonneoplastic lesions (Lee et al. 1998). Lipomas are the most common developmental lesion and account for about 1 % of all intramedullary spinal cord masses (Lee et al. 1998).

10.6 Treatment

Surgery is the treatment of choice for IMSCTs, and excellent results are associated with gross total resection (Houten and Weiner 2000; Iwasaki et al. 2000). Although the outcome for low-grade spinal cord astrocytomas is better in children than in adults, the prognosis for spinal cord astrocytomas is not as favorable as that of ependymoma (Goh et al. 1997; Houten and Weiner 2000; Iwasaki et al. 2000; Hanbali et al. 2002; Houten and Cooper 2000). Radical resection has been shown to prolong survival for non-disseminated WHO grades II and III astrocytomas, but must be weighed against the risk of causing neurologic deficits. GTR currently has no role in treatment of WHO grade IV tumors. Adjuvant radiotherapy is commonly used in cases of malignant astrocytomas or subtotally resected tumors. Little is known about the utility of chemotherapy for spinal cord astrocytoma or ependymoma.

10.6.1 Surgery

10.6.1.1 Surgical Principles

Surgery is effective for diffusely infiltrating spinal cord astrocytomas, and often a tissue diagnosis is all that can be safely accomplished (Houten and Weiner 2000; Houten and Cooper 2000). Pilocytic spinal cord astrocytomas, however, can be completely resected. The goal of surgery for intramedullary ependymoma is gross total resection (GTR) and preservation of neurologic function (Cooper 1989; McCormick et al. 1990a, b; McCormick and Stein 1990; Epstein et al. 1993; Cristante and Herrmann 1994; Chang et al. 2002; Peker et al. 2004). Ependymomas are typically non-infiltrative lesions that cause compression of the adjacent cord parenchyma, and the presence of a well-defined interface between the spinal cord and the tumor facilitates surgical resection (Sandalcioglu et al. 2005). An adequate myelotomy is necessary

to fully expose the tumor and allow an accurate tissue diagnosis (Hanbali et al. 2002). An intraoperative frozen section diagnosis consistent with ependymoma should prompt an attempt at GTR. Conversely, identification of a malignant tumor requires that the surgeon carefully weigh the risks versus benefits of further resection, factoring in the WHO grade, intraoperative appearance, quality of tumor margins, and stability of neuromonitoring signals. The presence of a syrinx may improve the chances of a GTR, but it cannot be used as an independent predictor of outcome (Samii and Klekamp 1994; Chang et al. 2002; Peker et al. 2004).

10.6.1.2 Surgical Approach

Pediatric IMSCTs are approached by performing a laminectomy or, more commonly, an osteoplastic laminotomy. The osteoplastic technique has been associated with decreased rates of progressive kyphotic deformity requiring fusion (McGirt et al. 2008b). It involves removal of the bony lamina to expose the dura and spinal cord at the relevant levels as indicated by the preoperative MRI, followed by replacement of the posterior bony elements after the tumor resection is completed. To expose the dura, parallel cuts are made in the lamina of the involved spinal segments with either a high-speed side-cutting drill or rongeurs. The supraspinous and intraspinous ligaments are then sharply dissected at the caudal end of the laminoplasty flap prior to its elevation. Following tumor resection, the flap is resecured with sutures or plates (metal or absorbable). Preservation of the posterior tension band in this manner restores the normal anatomy after tumor resection, may promote bony fusion, and minimizes the potential for spinal deformity (Houten and Weiner 2000; Houten and Cooper 2000; Raimondi et al. 1976); (Constantini et al. 1996, 2000).

Several risk factors for development of a progressive spinal deformity have been identified, including preoperative scoliotic deformity, an increasing number of resections, an age less than 13 years, tumor-associated syrinx, surgery involving more than four levels, surgery spanning the thoracolumbar junction, and adjuvant radiotherapy (Yao et al. 2007; Ahmed et al. 2014a; Knafo et al. 2014; McGirt et al. 2008c). For multilevel surgery, data suggests that in situ fusion can decrease the risk of postresection deformity by 30 % and as much as 42 % in skeletally mature children (Anakwenze et al. 2011). Intraoperative localizing x-rays are crucial to identify the correct level of surgery. Once the dura is exposed, intraoperative ultrasonography improves the accuracy of surgical exposure and identification of the intramedullary tumor, which in turn reduces the size of the dural opening and myelotomy (Epstein et al. 1993; Maiuri et al. 2000; Hanbali et al. 2002; Brunberg et al. 1991; Raghavendra et al. 1984).

During tumor resection, real-time neurophysiologic monitoring is critical adjunct. Common modalities of monitoring include motor evoked potentials (MEPs), somatosensory evoked potentials (SSEPs), and measurement of D-waves (Nash et al. 1977; Morota et al. 1997; Goh et al. 2000; Calancie et al. 1998; Jones et al. 1996; Pechstein et al. 1996; Costa et al. 2013). Intraoperative changes in these signals can predict postoperative deficits (Quinones-Hinojosa et al. 2005; Cheng et al. 2014b). Neurophysiology can also be useful in delineating an appropriate entry point by mapping the dorsal surface of the spinal cord (Auguste and Gupta 2006; Cheng et al. 2014b). A bipolar stimulator can be swept from a lateral to medial direction until no SSEPs are recorded. This is then delineated as "septum," and the process is confirmed from the contralateral side. This is especially helpful in cases where the tumor does not extend to the cord surface or if the anatomy is rotated or distorted.

The technique of tumor removal is determined by the surgical objective, tumor size, and gross and histological characteristics of the tumor. If no physical plane is present between the tumor and surrounding spinal cord, then it is likely that an infiltrative tumor is present. A biopsy is performed to establish a histological diagnosis. If an infiltrating or malignant astrocytoma is identified and is consistent with the intraoperative findings, further tumor removal may not be warranted. If tumor is easily identified, then continued removal is reasonable with close attention paid to motor

and sensory evoked potentials. A reduction in these signals can predict postoperative deficits (Asazuma et al. 1999; Quinones-Hinojosa et al. 2005; Cheng et al. 2014a). Uncertainty of spinal cord–tumor interface should signal an end to tumor resection (Asazuma et al. 1999). On the other hand, ependymomas appear with a smooth, reddish-gray glistening tumor surface, which is sharply demarcated from the surrounding spinal cord. Large tumors may require internal decompression with an ultrasonic aspirator or laser, and the surgical goal in these cases is gross total resection.

10.6.1.3 Postoperative Management

Postoperatively, early mobilization is encouraged to prevent complications of recumbency such as deep venous thrombosis and pneumonia (Smith et al. 2004). Patients with severe motor deficits are particularly vulnerable to thromboembolic complications. Compression stockings are routinely used, and subcutaneous heparin (Epstein 2005) is begun on the second postoperative day in these patients. Orthostatic hypotension may occasionally occur following removal of upper thoracic and cervical intramedullary neoplasms. This is usually a self-limited problem that can be managed with liberalization of fluids and more gradual mobilization. A posterior fossa syndrome occasionally occurs following removal of a high cervical intramedullary neoplasm. Neck pain and stiffness can be managed with steroids and anti-inflammatory medications, although a lumbar puncture may sometimes be required to exclude a diagnosis of meningitis (Cooper and Epstein 1985; McCormick and Stein 1990). Early and aggressive use of physical and occupational therapy results in a better functional recovery.

Despite evidence to support a GTR, there is a risk of recurrence (Whitaker et al. 1991; Chang et al. 2002). Long-term clinical and radiographic follow-up is warranted in these patients (Sandalcioglu et al. 2005). An early postoperative MRI establishes the completeness of resection and serves as a baseline against which further studies can be compared. GTR is defined as more than 90% tumor removal, subtotal resection (STR) as 50–90%, and partial as less than 50%. Serial gadolinium-enhanced MRIs are obtained because radiographic tumor recurrence usually precedes clinical symptoms (Chang et al. 2002; Hanbali et al. 2002). Serial radiographs should be obtained in high-risk patients to monitor for development of a progressive kyphotic deformity.

10.6.2 Radiation

Radiation therapy plays an adjunctive role in the treatment of malignant tumors and incompletely resected low-grade astrocytomas (Isaacson 2000; Guss et al. 2013). Low-grade astrocytomas and ependymomas that undergo GTR can be followed with serial imaging only. Radiotherapy in young children is associated with significant adverse effects, and therefore it is preferable to avoid or delay radiation therapy as long as possible in low-grade tumors (Rousseau et al. 1994; Perilongo et al. 1997; Prados et al. 1997; Gornet et al. 1999; Zuccaro et al. 1999; Grill et al. 2001; Teo et al. 2003; Valera et al. 2003).

GTR of grade II intramedullary ependymomas provides better long-term tumor control compared to STR and radiation therapy (McCormick et al. 1990b; Epstein et al. 1993; Hulshof et al. 1993; Cristante and Herrmann 1994; Hoshimaru et al. 1999; Lee et al. 2013). Although some authors recommend that radiation therapy is unnecessary following gross total resection (Cooper and Epstein 1985; Cooper 1989; McCormick et al. 1990b; Epstein et al. 1993; Hulshof et al. 1993; Samii and Klekamp 1994; Isaacson 2000; Kothbauer 2007), some studies have reported a 5–10% recurrence rate following surgery (Guidetti et al. 1981; Cooper 1989; Hulshof et al. 1993; Chang et al. 2002). Surgery followed by external beam radiotherapy has been shown to result in 84% local control of tumor for IMSCT of multiple tumor types (O'Sullivan et al. 1994).

Subtotal resection, as expected, has a very high recurrence rate (Cooper 1989; Linstadt et al. 1989; Chang et al. 2002). The data supporting postoperative radiation after STR is largely based on studies with small patient populations, limited

follow-up, and inadequate controls treated without radiation therapy (Isaacson 2000; O'Sullivan et al. 1994). Despite these limitations, the overall results suggest that radiation may be beneficial after STR of spinal cord ependymomas (Kopelson and Linggood 1982; Garcia 1985; Shaw et al. 1986; Cooper 1989; Linstadt et al. 1989; Guss et al. 2013). The usual dose delivered is approximately 5,000 cGy in 180–200 cGy fractions using external beam radiation therapy. In some cases, reoperation and another attempt at GTR should be considered if a recurrent tumor is more accessible or better defined from the normal spinal cord (Cooper 1989; Chamberlain 2002b; Hanbali et al. 2002).

Patients who present with focal disease usually recur locally and do not manifest late dissemination (Chamberlain 2002a, b). Craniospinal radiation is only indicated for the rare patient who presents with multifocal disease (Garrett and Simpson 1983; Linstadt et al. 1989; Hulshof et al. 1993). Although the outcome is worse for this subgroup, good control rates have been reported (Garcia 1985; Linstadt et al. 1989).

10.6.3 Chemotherapy

Currently, chemotherapy is not routinely used in the initial treatment of IMSCTs, although some clinicians consider the use of chemotherapy for recurrence or in combination with radiation therapy for high-grade or incompletely resected tumors. Very little published data exists to provide insight into the impact of chemotherapy on outcomes, and chemotherapy regimens are typically based on those with some demonstrated activity in the setting of intracranial disease. Objective radiographic responses for supratentorial ependymoma have been observed with the use of combination platinum agent with etoposide, but the effect of chemotherapy on survival and functional outcome is still unclear (Massimino et al. 2002; Valera et al. 2003). The prospect of preoperative chemotherapy for second-look surgery has been explored in small trials with mixed results (Foreman et al. 1996; Schiffer and Giordana 1998; Chamberlain 2001; Valera et al. 2003). Also, because of the desire to avoid or delay radiation therapy in young children under 3 years of age, adjuvant chemotherapy may have a potential role (Prados et al. 1997). In a series of adult patients with recurrent spinal low-grade astrocytoma treated with temozolomide, there was a modest effect (Chamberlain 2008).

Chemotherapy guidelines for pediatric IMSCTs have been mainly derived from the clinical experience with intracranial ependymomas and low-grade astrocytomas. No randomized clinical trials have been performed (Kothbauer 2007). Etoposide, a topoisomerase II inhibitor, has been used to treat recurrent intramedullary ependymomas. This drug appeared to be well tolerated with modest toxicity (Chamberlain 2002a, b). Further trials are needed to determine the efficacy of this potential therapy for recurrent and refractory intramedullary ependymomas. Fakhreddine and colleagues demonstrated an association between chemotherapy (primarily temozolomide) and improved progression-free survival, but not overall survival, in infiltrative astrocytomas (Fakhreddine et al. 2013). They saw no association between extent of resection or adjunctive radiotherapy and outcome in these patients (Fakhreddine et al. 2013).

10.6.4 Disease Control

The WHO grade of the tumor and neurologic status of the patient at the time of surgery are the primary determinants of oncologic prognosis in children with IMSCTs (Cristante and Herrmann 1994; Karikari et al. 2011). Over time, outcomes have improved in these patients. In 1992, Sandler reported a 5-year survival of 57 % in patients with grade I or II spinal cord astrocytomas (Sandler et al. 1992). With radical resection, Ahmed et al. reported long-term survival rates of 75 % and 64 % at 10 and 20 years, respectively, in a cohort of 55 IMSCT patients that included predominantly astrocytomas (Ahmed et al. 2014b). Another group also reported that children with non-disseminated anaplastic astrocytomas may have increased survival with radical resection

(McGirt et al. 2008d). Children with JPAs have better prognoses than those with diffuse spinal cord astrocytomas (Houten and Weiner 2000). Patients with WHO grade IV astrocytomas, unsurprisingly, do very poorly with no correlation between the extent of resection and survival (Fig. 10.5) (McGirt et al. 2008d).

The most important determinant in the treatment of ependymomas is the extent of resection (Nazar et al. 1990; Rousseau et al. 1994; Pollack et al. 1995; Perilongo et al. 1997; Schiffer and Giordana 1998; Souweidane et al. 1998; Chamberlain 2001; Grill et al. 2001; Teo et al. 2003; Valera et al. 2003; Lee et al. 2013). It should be noted that late recurrences can occur, even up to 12 years after surgery (Linstadt et al. 1989). As noted earlier, GTR results in cure or long-term control more frequently than STR and radiation. Regardless of whether radiation is used following surgery, long-term imaging surveillance is required.

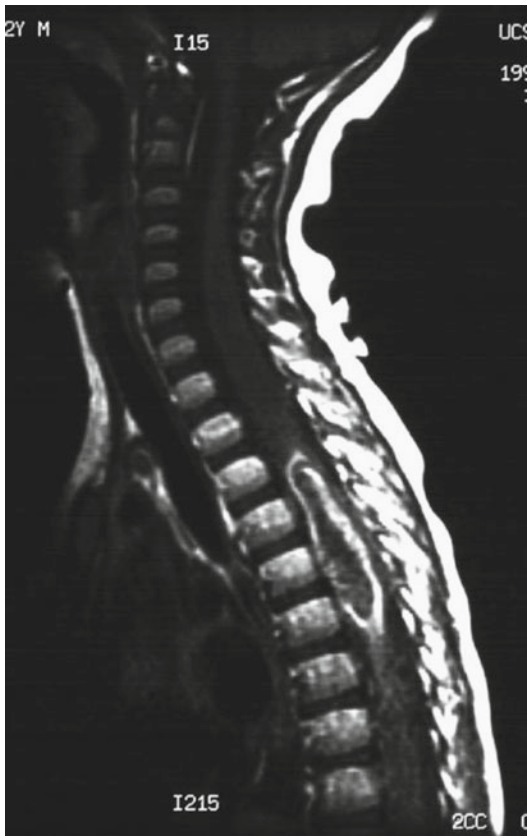

Fig. 10.5 A 2-year-old boy presented with several weeks of slowly progressive disuse of his lower extremities. The preoperative MRI demonstrated a 6 cm intramedullary thoracic cord mass from T3 to T7 with marked edema spanning the entire length of the spinal cord. Histopathology showed the tumor to be a grade III oligoastrocytoma. The patient's tumor progressed despite treatment

10.6.5 Functional Outcome

Children tolerate surgery for IMSCT very well, and their overall quality of life years after surgery is comparable to normal, healthy cohorts (Schneider et al. 2014). The strongest predictor of postoperative functional outcome is preoperative functional ability (Cooper 1989; McCormick and Stein 1990; McCormick et al. 1990b; Epstein et al. 1993; Cristante and Herrmann 1994; Hoshimaru et al. 1999; Chang et al. 2002; Sandalcioglu et al. 2005). While significant improvement of a severe or long-standing preoperative neurologic deficit rarely occurs (Chang et al. 2002), fortunately the incidence of permanent extremity paralysis after resection is also rare (Constantini et al. 2000; McGirt et al. 2008a). Surgical morbidity is greater in patients with more significant preoperative deficits (Hoshimaru et al. 1999; Chang et al. 2002; Hanbali et al. 2002; Peker et al. 2004). A shorter duration of preoperative symptoms may favor improvement even in patients with a significant preoperative deficit (Hoshimaru et al. 1999). In general, most patients note sensory loss in the early postoperative period, most likely as a result of the midline myelotomy, transient edema, or vascular compromise (McCormick and Stein 1990; Epstein et al. 1993). These deficits usually resolve within 3 months (Hoshimaru et al. 1999; Peker et al. 2004), although sensory ability may not return to preoperative baseline (McCormick and Stein 1990).

Additional surgical morbidity is directly related to the location of the tumor and the presence of spinal cord atrophy and arachnoid scarring (Cooper 1989; McCormick and Stein 1990; Cristante and Herrmann 1994; Samii and Klekamp 1994; Hoshimaru et al. 1999). A thoracic location has been correlated with a decline

in postoperative function (Cristante and Herrmann 1994; Hoshimaru et al. 1999; Hanbali et al. 2002; Sandalcioglu et al. 2005), perhaps due to a more tenuous blood supply in this region.

Conclusions

Early diagnosis of IMSCTs plays an important role in the management of these lesions and as a factor in long-term outcome. Because preoperative functional status is a significant prognostic factor, early diagnosis and surgical intervention are critical to the successful treatment of these tumors. Unexplained and chronic back pain in a child should be investigated immediately with a high-quality MRI with gadolinium. For intramedullary ependymomas, the extent of surgical resection is the strongest predictor of long-term survival. Adjuvant therapy should be reserved for malignant, disseminated, or progressive subtotally resected tumors.

A postoperative MRI scan and serial imaging are important for long-term follow-up of patients who have an IMSCT. New adjuvant therapeutic agents will likely play an increasing role in the treatment of spinal cord astrocytomas in children. Finally, improved knowledge of the genetic and molecular features of these tumors made possible through analysis of small tissue specimens will allow the identification of new therapeutic targets.

References

Abbott R (1993) Tumors of the medulla. Neurosurg Clin N Am 4(3):519–527

Ahmed R, Menezes AH, Awe OO, Mahaney KB, Torner JC, Weinstein SL (2014a) Long-term incidence and risk factors for development of spinal deformity following resection of pediatric intramedullary spinal cord tumors. J Neurosurg Pediatr 13(6):613–621. doi:10.3171/2014.1.PEDS13317

Ahmed R, Menezes AH, Awe OO, Torner JC (2014b) Long-term disease and neurological outcomes in patients with pediatric intramedullary spinal cord tumors. J Neurosurg Pediatr 13(6):600–612. doi:10.3171/2014.1.PEDS13316

Alexiou GA, Siozos G, Stefanaki K, Moschovi M, Prodromou N (2013) Intramedullary spinal cord primitive neuroectodermal tumor presenting with hydrocephalus. J Child Neurol 28(2):246–250. doi:10.1177/0883073812441061

Allen JC, Aviner S, Yates AJ, Boyett JM, Cherlow JM, Turski PA, Epstein F, Finlay JL (1998) Treatment of high-grade spinal cord astrocytoma of childhood with "8-in-1" chemotherapy and radiotherapy: a pilot study of CCG-945. Children's Cancer Group. J Neurosurg 88(2):215–220. doi:10.3171/jns.1998.88.2.0215

Ammerlaan AC, de Bustos C, Ararou A, Buckley PG, Mantripragada KK, Verstegen MJ, Hulsebos TJ, Dumanski JP (2005) Localization of a putative low-penetrance ependymoma susceptibility locus to 22q11 using a chromosome 22 tiling-path genomic microarray. Gene Chromosome Cancer 43(4):329–338. doi:10.1002/gcc.20207

Anakwenze OA, Auerbach JD, Buck DW, Garg S, Simon SL, Sutton LN, Sponseller PD, Dormans JP (2011) The role of concurrent fusion to prevent spinal deformity after intramedullary spinal cord tumor excision in children. J Pediatr Orthop 31(5):475–479. doi:10.1097/BPO.0b013e318220bb46

Asazuma T, Toyama Y, Suzuki N, Fujimura Y, Hirabayshi K (1999) Ependymomas of the spinal cord and cauda equina: an analysis of 26 cases and a review of the literature. Spinal Cord 37(11):753–759

Auguste KI, Gupta N (2006) Pediatric intramedullary spinal cord tumors. Neurosurg Clin N Am 17(1):51–61. doi:10.1016/j.nec.2005.10.004

Baleriaux DL (1999) Spinal cord tumors. Eur Radiol 9(7):1252–1258. doi:10.1007/s003300050831

Barker DJ, Weller RO, Garfield JS (1976) Epidemiology of primary tumours of the brain and spinal cord: a regional survey in southern England. J Neurol Neurosurg Psychiatry 39(3):290–296

Beckner ME, Sasatomi E, Swalsky PA, Hamilton RL, Pollack IF, Finkelstein SD (2004) Loss of heterozygosity reveals non-VHL allelic loss in hemangioblastomas at 22q13. Hum Pathol 35(9):1105–1111

Bhushanam TV, Rajesh A, Linga VG, Uppin MS, Malik M (2014) Primary intramedullary non-Hodgkin's lymphoma in an immunocompetent child. Spinal Cord 52(Suppl 2):S21–S23. doi:10.1038/sc.2014.96

Bijlsma EK, Voesten AM, Bijleveld EH, Troost D, Westerveld A, Merel P, Thomas G, Hulsebos TJ (1995) Molecular analysis of genetic changes in ependymomas. Gene Chromosome Cancer 13(4):272–277

Birch BD, Johnson JP, Parsa A, Desai RD, Yoon JT, Lycette CA, Li YM, Bruce JN (1996) Frequent type 2 neurofibromatosis gene transcript mutations in sporadic intramedullary spinal cord ependymomas. Neurosurgery 39(1):135–140

Bowers DC, Weprin BE (2003) Intramedullary spinal cord tumors. Curr Treat Options Neurol 5(3):207–212

Brotchi J, Dewitte O, Levivier M, Baleriaux D, Vandesteene A, Raftopoulos C, Flament-Durand J, Noterman J (1991) A survey of 65 tumors within the spinal cord: surgical results and the importance of preoperative magnetic resonance imaging. Neurosurgery 29(5):651–656, discussion 656–657

Brunberg JA, DiPietro MA, Venes JL, Dauser RC, Muraszko KM, Berkey GS, D'Amato CJ, Rubin JM (1991) Intramedullary lesions of the pediatric spinal cord: correlation of findings from MR imaging, intraoperative sonography, surgery, and histologic study. Radiology 181(2):573–579. doi:10.1148/radiology.181.2.1924807

Calancie B, Harris W, Broton JG, Alexeeva N, Green BA (1998) "Threshold-level" multipulse transcranial electrical stimulation of motor cortex for intraoperative monitoring of spinal motor tracts: description of method and comparison to somatosensory evoked potential monitoring. J Neurosurg 88(3):457–470. doi:10.3171/jns.1998.88.3.0457

Chamberlain MC (2001) Recurrent intracranial ependymoma in children: salvage therapy with oral etoposide. Pediatr Neurol 24(2):117–121

Chamberlain MC (2002a) Etoposide for recurrent spinal cord ependymoma. Neurology 58(8):1310–1311

Chamberlain MC (2002b) Salvage chemotherapy for recurrent spinal cord ependymoma. Cancer 95(5):997–1002. doi:10.1002/cncr.10826

Chamberlain MC (2008) Temozolomide for recurrent low-grade spina cord gliomas in adults. Cancer 113:1019–1024

Chang UK, Choe WJ, Chung SK, Chung CK, Kim HJ (2002) Surgical outcome and prognostic factors of spinal intramedullary ependymomas in adults. J Neuro Oncol 57(2):133–139

Cheng JS, Ivan ME, Stapleton CJ, Quinones-Hinojosa A, Gupta N, Auguste KI (2014a) Intraoperative changes in transcranial motor evoked potentials and somatosensory evoked potentials predicting outcome in children with intramedullary spinal cord tumors. J Neurosurg Pediatr 13 (6):591–9. doi:10.3171/2014.2.PEDS1392

Cheng JS, Ivan ME, Stapleton CJ, Quinones-Hinojosa A, Gupta N, Auguste KI (2014b) Intraoperative changes in transcranial motor evoked potentials and somatosensory evoked potentials predicting outcome in children with intramedullary spinal cord tumors. J Neurosurg Pediatr 13(6):591–9. doi: 10.3171/2014.2.PEDS1392.

Choudhri AF, Whitehead MT, Klimo P Jr, Montgomery BK, Boop FA (2014) Diffusion tensor imaging to guide surgical planning in intramedullary spinal cord tumors in children. Neuroradiology 56(2):169–174. doi:10.1007/s00234-013-1316-9

Clover LL, Hazuka MB, Kinzie JJ (1993) Spinal cord ependymomas treated with surgery and radiation therapy. A review of 11 cases. Am J Clin Oncol 16(4): 350–353

Constantini SEF (1996) Intraspinal tumors in infants and children. In: Youmans J (ed) Neurological surgery, vol 4. Saunders, Philadelphia, pp 3123–3133

Constantini S, Epstein F (1995) Intraspinal tumors in children and infants. In: Youmans J (ed) Neurological surgery. WB Saunders, Philadelphia, pp 3132–3167

Constantini S, Houten J, Miller DC, Freed D, Ozek MM, Rorke LB, Allen JC, Epstein FJ (1996) Intramedullary spinal cord tumors in children under the age of 3 years. J Neurosurg 85(6):1036–1043. doi:10.3171/jns.1996.85.6.1036

Constantini S, Miller DC, Allen JC, Rorke LB, Freed D, Epstein FJ (2000) Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg 93(2 Suppl):183–193

Cooper PR (1989) Outcome after operative treatment of intramedullary spinal cord tumors in adults: intermediate and long-term results in 51 patients. Neurosurgery 25(6):855–859

Cooper PR, Epstein F (1985) Radical resection of intramedullary spinal cord tumors in adults. Recent experience in 29 patients. J Neurosurg 63(4):492–499. doi:10.3171/jns.1985.63.4.0492

Costa P, Peretta P, Faccani G (2013) Relevance of intraoperative D wave in spine and spinal cord surgeries. Eur Spine J 22(4):840–848. doi:10.1007/s00586-012-2576-5

Cristante L, Herrmann HD (1994) Surgical management of intramedullary spinal cord tumors: functional outcome and sources of morbidity. Neurosurgery 35(1):69–74, discussion 74–66

Das S, Yip S, Hukin J, Cochrane D, Dunham C (2014) Pleomorphic xanthoastrocytoma of the spinal cord: case report and literature review. Clin Neuropathol. doi:10.5414/NP300689

DeSousa AL, Kalsbeck JE, Mealey J Jr, Campbell RL, Hockey A (1979) Intraspinal tumors in children. A review of 81 cases. J Neurosurg 51(4):437–445. doi:10.3171/jns.1979.51.4.0437

Dow G, Biggs N, Evans G, Gillespie J, Ramsden R, King A (2005) Spinal tumors in neurofibromatosis type 2. Is emerging knowledge of genotype predictive of natural history? J Neurosurg Spine 2(5):574–579. doi:10.3171/spi.2005.2.5.0574

Ebert C, von Haken M, Meyer-Puttlitz B, Wiestler OD, Reifenberger G, Pietsch T, von Deimling A (1999) Molecular genetic analysis of ependymal tumors. NF2 mutations and chromosome 22q loss occur preferentially in intramedullary spinal ependymomas. Am J Pathol 155(2):627–632. doi:10.1016/S0002-9440(10)65158-9

Ebner FH, Schittenhelm J, Roser F, Scheel-Walter H, Tatagiba M, Schuhmann MU (2012) Management of holocord pilocytic astrocytomas in children and adolescents: an update. Pediatr Neurosurg 48(3):133–140. doi:10.1159/000345593

Egelhoff JC, Bates DJ, Ross JS, Rothner AD, Cohen BH (1992) Spinal MR findings in neurofibromatosis types 1 and 2. AJNR Am J Neuroradiol 13(4):1071–1077

Ellis JA, Canoll P, McCormick PC 2nd, Feldstein NA, Anderson RC, Angevine PD, Kaiser MG, McCormick PC, Bruce JN, Ogden AT (2012a) Platelet-derived growth factor receptor (PDGFR) expression in primary spinal cord gliomas. J Neuro Oncol 106(2):235–242. doi:10.1007/s11060-011-0666-6

Ellis JA, Castelli M, Bruce JN, Canoll P, Ogden AT (2012b) Retroviral delivery of platelet-derived growth factor to spinal cord progenitor cells drives the formation of

intramedullary gliomas. Neurosurgery 70(1):198–204. doi:10.1227/NEU.0b013e31822ce963, discussion 204
Epstein NE (2005) A review of the risks and benefits of differing prophylaxis regimens for the treatment of deep venous thrombosis and pulmonary embolism in neurosurgery. Surg Neurol 64(4):295–301. doi:10.1016/j.surneu.2005.04.039, discussion 302
Epstein F, Epstein N (1981) Surgical management of holocord intramedullary spinal cord astrocytomas in children. J Neurosurg 54(6):829–832. doi:10.3171/jns.1981.54.6.0829
Epstein FJ, Farmer JP, Freed D (1992) Adult intramedullary astrocytomas of the spinal cord. J Neurosurg 77(3):355–359. doi:10.3171/jns.1992.77.3.0355
Epstein FJ, Farmer JP, Freed D (1993) Adult intramedullary spinal cord ependymomas: the result of surgery in 38 patients. J Neurosurg 79(2):204–209. doi:10.3171/jns.1993.79.2.0204
Evans DG, Huson SM, Donnai D, Neary W, Blair V, Teare D, Newton V, Strachan T, Ramsden R, Harris R (1992) A genetic study of type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity. J Med Genet 29(12):841–846
Fakhreddine MH, Mahajan A, Penas-Prado M, Weinberg J, McCutcheon IE, Puduvalli V, Brown PD (2013) Treatment, prognostic factors, and outcomes in spinal cord astrocytomas. Neuro-Oncology 15(4):406–412. doi:10.1093/neuonc/nos309
Fine MJ, Kricheff II, Freed D, Epstein FJ (1995) Spinal cord ependymomas: MR imaging features. Radiology 197(3):655–658. doi:10.1148/radiology.197.3.7480734
Foreman NK, Love S, Thorne R (1996) Intracranial ependymomas: analysis of prognostic factors in a population-based series. Pediatr Neurosurg 24(3):119–125
Frappaz D, Ricci AC, Kohler R, Bret P, Mottolese C (1999) Diffuse brain stem tumor in an adolescent with multiple enchondromatosis (Ollier's disease). Childs Nerv Syst 15(5):222–225. doi:10.1007/s003810050377
Garcia DM (1985) Primary spinal cord tumors treated with surgery and postoperative irradiation. Int J Radiat Oncol Biol Phys 11(11):1933–1939
Garcia C, Guttman DH (2014) Nf2/Merlin controls spinal cord neural progenitor function in a Rac1/ErbB2 dependent manner. PLoS One 9:e97320
Garrett PG, Simpson WJ (1983) Ependymomas: results of radiation treatment. Int J Radiat Oncol Biol Phys 9(8):1121–1124
Gilhuis HJ, van der Laak J, Wesseling P, Boerman RH, Beute G, Teepen JL, Grotenhuis JA, Kappelle AC (2004) Inverse correlation between genetic aberrations and malignancy grade in ependymal tumors: a paradox? J Neuro Oncol 66(1–2):111–116
Glasker S (2005) Central nervous system manifestations in VHL: genetics, pathology and clinical phenotypic features. Familial Cancer 4(1):37–42. doi:10.1007/s10689-004-5347-6
Glasker S, Bender BU, Apel TW, Natt E, van Velthoven V, Scheremet R, Zentner J, Neumann HP (1999) The impact of molecular genetic analysis of the VHL gene in patients with haemangioblastomas of the central nervous system. J Neurol Neurosurg Psychiatry 67(6):758–762
Glasker S, Bender BU, Apel TW, van Velthoven V, Mulligan LM, Zentner J, Neumann HP (2001) Reconsideration of biallelic inactivation of the VHL tumour suppressor gene in hemangioblastomas of the central nervous system. J Neurol Neurosurg Psychiatry 70(5):644–648
Glavac D, Neumann HP, Wittke C, Jaenig H, Masek O, Streicher T, Pausch F, Engelhardt D, Plate KH, Hofler H, Chen F, Zbar B, Brauch H (1996) Mutations in the VHL tumor suppressor gene and associated lesions in families with von Hippel-Lindau disease from central Europe. Hum Genet 98(3):271–280
Goh KY, Velasquez L, Epstein FJ (1997) Pediatric intramedullary spinal cord tumors: is surgery alone enough? Pediatr Neurosurg 27(1):34–39
Goh KYC, Muszynski CA, Teo JGC, Constantini S, Epstein FJ (2000) Excision of intramedullary tumours. In: Black PM, Kaye AH (eds) Operative neurosurgery. Churchill, London, pp 1947–1960
Grill J, Le Deley MC, Gambarelli D, Raquin MA, Couanet D, Pierre-Kahn A, Habrand JL, Doz F, Frappaz D, Gentet JC, Edan C, Chastagner P, Kalifa C (2001) Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. J Clin Oncol 19(5):1288–1296
Guidetti B, Mercuri S, Vagnozzi R (1981) Long-term results of the surgical treatment of 129 intramedullary spinal gliomas. J Neurosurg 54(3):323–330. doi:10.3171/jns.1981.54.3.0323
Guss ZD, Moningi S, Jallo GI, Cohen KJ, Wharam MD, Terezakis SA (2013) Management of pediatric spinal cord astrocytomas: outcomes with adjuvant radiation. Int J Radiat Oncol Biol Phys 85(5):1307–1311. doi:10.1016/j.ijrobp.2012.11.022
Hanbali F, Fourney DR, Marmor E, Suki D, Rhines LD, Weinberg JS, McCutcheon IE, Suk I, Gokaslan ZL (2002) Spinal cord ependymoma: radical surgical resection and outcome. Neurosurgery 51(5):1162–1172, discussion 1172–1164
Hayashi Y, Nakada M, Mohri M, Murakami H, Kawahara N, Hamada J (2011) Ganglioglioma of the thoracolumbar spinal cord in a patient with neurofibromatosis type 1: a case report and literature review. Pediatr Neurosurg 47(3):210–213. doi:10.1159/000331569
Helseth A, Mork SJ (1989) Primary intraspinal neoplasms in Norway, 1955 to 1986. A population-based survey of 467 patients. J Neurosurg 71(6):842–845. doi:10.3171/jns.1989.71.6.0842
Hoshimaru M, Koyama T, Hashimoto N, Kikuchi H (1999) Results of microsurgical treatment for intramedullary spinal cord ependymomas: analysis of 36 cases. Neurosurgery 44(2):264–269
Houten JK, Cooper PR (2000) Spinal cord astrocytomas: presentation, management and outcome. J Neuro Oncol 47(3):219–224

Houten JK, Weiner HL (2000) Pediatric intramedullary spinal cord tumors: special considerations. J Neuro Oncol 47(3):225–230

Huang B, Starostik P, Schraut H, Krauss J, Sorensen N, Roggendorf W (2003) Human ependymomas reveal frequent deletions on chromosomes 6 and 9. Acta Neuropathol 106(4):357–362. doi:10.1007/s00401-003-0739-5

Hulsebos TJ, Oskam NT, Bijleveld EH, Westerveld A, Hermsen MA, van den Ouweland AM, Hamel BC, Tijssen CC (1999) Evidence for an ependymoma tumour suppressor gene in chromosome region 22pter-22q11.2. Br J Cancer 81(7):1150–1154. doi:10.1038/sj.bjc.6690822

Hulshof MC, Menten J, Dito JJ, Dreissen JJ, van den Bergh R, Gonzalez Gonzalez D (1993) Treatment results in primary intraspinal gliomas. Radiother Oncol 29(3):294–300

Innocenzi G, Salvati M, Cervoni L, Delfini R, Cantore G (1997) Prognostic factors in intramedullary astrocytomas. Clin Neurol Neurosurg 99(1):1–5

Isaacson SR (2000) Radiation therapy and the management of intramedullary spinal cord tumors. J Neuro Oncol 47(3):231–238

Isik N, Balak N, Silav G, Elmaci I (2008) Pediatric intramedullary teratomas. Neuropediatrics 39(4):196–199. doi:10.1055/s-0028-1112116

Ito T, Sawakami K, Ishikawa S, Hirano T, Endo N, Kakita A, Takahashi H (2013) Progression of paralysis is the most useful factor for differentiating malignant from benign intramedullary tumors. Spinal Cord 51(4):319–321. doi:10.1038/sc.2012.152

Iwasaki Y, Hida K, Sawamura Y, Abe H (2000) Spinal intramedullary ependymomas: surgical results and immunohistochemical analysis of tumour proliferation activity. Br J Neurosurg 14(4):331–336

Jallo GI, Danish S, Velasquez L, Epstein F (2001) Intramedullary low-grade astrocytomas: long-term outcome following radical surgery. J Neuro Oncol 53(1):61–66

Jones SJ, Harrison R, Koh KF, Mendoza N, Crockard HA (1996) Motor evoked potential monitoring during spinal surgery: responses of distal limb muscles to transcranial cortical stimulation with pulse trains. Electroencephalogr Clin Neurophysiol 100(5):375–383

Jones DT, Kocialkowski S, Liu L, Pearson DM, Backlund LM, Ichimura K, Collins VP (2008) Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 68(21):8673–8677. doi:10.1158/0008-5472.CAN-08-2097

Karikari IO, Nimjee SM, Hodges TR, Cutrell E, Hughes BD, Powers CJ, Mehta AI, Hardin C, Bagley CA, Isaacs RE, Haglund MM, Friedman AH (2011) Impact of tumor histology on resectability and neurological outcome in primary intramedullary spinal cord tumors: a single-center experience with 102 patients. Neurosurgery 68(1):188–197. doi:10.1227/NEU.0b013e3181fe3794, discussion 197

Kim WY, Kaelin WG (2004) Role of VHL gene mutation in human cancer. J Clin Oncol 22(24):4991–5004. doi:10.1200/JCO.2004.05.061

Kim NR, Suh YL, Shin HJ (2009) Thoracic pediatric intramedullary schwannoma: report of a case. Pediatr Neurosurg 45(5):396–401. doi:10.1159/000260911

Kim DH, Kim JH, Choi SH, Sohn CH, Yun TJ, Kim CH, Chang KH (2014) Differentiation between intramedullary spinal ependymoma and astrocytoma: comparative MRI analysis. Clin Radiol 69(1):29–35. doi:10.1016/j.crad.2013.07.017

Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, Cavenee WK (2002) The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol 61(3):215–225, discussion 226–219

Kley N, Whaley J, Seizinger BR (1995) Neurofibromatosis type 2 and von Hippel-Lindau disease: from gene cloning to function. Glia 15(3):297–307. doi:10.1002/glia.440150310

Knafo S, Court C, Parker F (2014) Predicting sagittal deformity after surgery for intramedullary tumors. J Neurosurg Spine 21(3):342–347. doi:10.3171/2014.5.SPINE13886

Kopelson G, Linggood RM (1982) Intramedullary spinal cord astrocytoma versus glioblastoma: the prognostic importance of histologic grade. Cancer 50(4):732–735

Kothbauer KF (2007) Neurosurgical management of intramedullary spinal cord tumors in children. Pediatr Neurosurg 43(3):222–235. doi:10.1159/000098835

Kramer DL, Parmiter AH, Rorke LB, Sutton LN, Biegel JA (1998) Molecular cytogenetic studies of pediatric ependymomas. J Neuro Oncol 37(1):25–33

Lamszus K, Lachenmayer L, Heinemann U, Kluwe L, Finckh U, Hoppner W, Stavrou D, Fillbrandt R, Westphal M (2001) Molecular genetic alterations on chromosomes 11 and 22 in ependymomas. Int J Cancer 91(6):803–808

Lang FF, Epstein FJ, Ransohoff J, Allen JC, Wisoff J, Abbott IR, Miller DC (1993) Central nervous system gangliogliomas. Part 2: clinical outcome. J Neurosurg 79(6):867–873. doi:10.3171/jns.1993.79.6.0867

Lee M, Rezai AR, Freed D, Epstein FJ (1996) Intramedullary spinal cord tumors in neurofibromatosis. Neurosurgery 38(1):32–37

Lee M, Epstein FJ, Rezai AR, Zagzag D (1998) Nonneoplastic intramedullary spinal cord lesions mimicking tumors. Neurosurgery 43(4):788–794, discussion 794–785

Lee SH, Chung CK, Kim CH, Yoon SH, Hyun SJ, Kim KJ, Kim ES, Eoh W, Kim HJ (2013) Long-term outcomes of surgical resection with or without adjuvant radiation therapy for treatment of spinal ependymoma: a retrospective multicenter study by the Korea Spinal Oncology Research Group. Neuro-Oncology 15(7):921–929. doi:10.1093/neuonc/not038

Linstadt DE, Wara WM, Leibel SA, Gutin PH, Wilson CB, Sheline GE (1989) Postoperative radiotherapy of primary spinal cord tumors. Int J Radiat Oncol Biol Phys 16(6):1397–1403

Liu W, James CD, Frederick L, Alderete BE, Jenkins RB (1997) PTEN/MMAC1 mutations and EGFR amplification in glioblastomas. Cancer Res 57(23):5254–5257

Liu X, Tian W, Kolar B, Hu R, Huang Y, Huang J, Ekholm S (2014) Advanced MR diffusion tensor imaging and perfusion weighted imaging of intramedullary tumors and tumor like lesions in the cervicomedullary junction region and the cervical spinal cord. J Neuro Oncol 116(3):559–566. doi:10.1007/s11060-013-1323-z

Louis DNOH, Wiestler OD, Cavenee WK (2007) WHO classification of tumors of the central nervous system. International Agency for Research on Cancer, Lyon

Madhukar M, Maller VG, Choudhary AK, Iantosca MR, Specht CS, Dias MS (2013) Primary intramedullary spinal cord germinoma. J Neurosurg Pediatr 11(5):605–609. doi:10.3171/2013.1.PEDS12402

Maiuri F, Iaconetta G, Gallicchio B, Stella L (2000) Intraoperative sonography for spinal tumors. Correlations with MR findings and surgery. J Neurosurg Sci 44(3):115–122

Martuza RL, Eldridge R (1988) Neurofibromatosis 2 (bilateral acoustic neurofibromatosis). N Engl J Med 318(11):684–688. doi:10.1056/NEJM198803173181106

Massimino M, Spreafico F, Cefalo G, Riccardi R, Tesoro-Tess JD, Gandola L, Riva D, Ruggiero A, Valentini L, Mazza E, Genitori L, Di Rocco C, Navarria P, Casanova M, Ferrari A, Luksch R, Terenziani M, Balestrini MR, Colosimo C, Fossati-Bellani F (2002) High response rate to cisplatin/etoposide regimen in childhood low-grade glioma. J Clin Oncol 20(20): 4209–4216

Mautner VF, Tatagiba M, Guthoff R, Samii M, Pulst SM (1993) Neurofibromatosis 2 in the pediatric age group. Neurosurgery 33(1):92–96

McCormick PC, Stein BM (1990) Intramedullary tumors in adults. Neurosurg Clin N Am 1(3):609–630

McCormick PC, Post KD, Stein BM (1990a) Intradural extramedullary tumors in adults. Neurosurg Clin N Am 1(3):591–608

McCormick PC, Torres R, Post KD, Stein BM (1990b) Intramedullary ependymoma of the spinal cord. J Neurosurg 72(4):523–532. doi:10.3171/jns.1990.72.4.0523

McGirt MJ, Chaichana KL, Atiba A, Attenello F, Yao KC, Jallo GI (2008a) Resection of intramedullary spinal cord tumors in children: assessment of long-term motor and sensory deficits. J Neurosurg Pediatr 1(1):63–67. doi:10.3171/PED-08/01/063

McGirt MJ, Chaichana KL, Atiba A, Bydon A, Witham TF, Yao KC, Jallo GI (2008b) Incidence of spinal deformity after resection of intramedullary spinal cord tumors in children who underwent laminectomy compared with laminoplasty. J Neurosurg Pediatr 1(1):57–62. doi:10.3171/PED-08/01/057

McGirt MJ, Chaichana KL, Attenello F, Witham T, Bydon A, Yao KC, Jallo GI (2008c) Spinal deformity after resection of cervical intramedullary spinal cord tumors in children. Childs Nerv Syst 24(6):735–739. doi:10.1007/s00381-007-0513-4

McGirt MJ, Goldstein IM, Chaichana KL, Tobias ME, Kothbauer KF, Jallo GI (2008d) Extent of surgical resection of malignant astrocytomas of the spinal cord: outcome analysis of 35 patients. Neurosurgery 63(1): 55–60. doi:10.1227/01.NEU.0000335070.37943.09, discussion 60–51

Mellon CD, Carter JE, Owen DB (1988) Ollier's disease and Maffucci's syndrome: distinct entities or a continuum. Case report: enchondromatosis complicated by an intracranial glioma. J Neurol 235(6):376–378

Miller DC (2000) Surgical pathology of intramedullary spinal cord neoplasms. J Neuro Oncol 47(3): 189–194

Miller DJ, McCutcheon IE (2000) Hemangioblastomas and other uncommon intramedullary tumors. J Neuro Oncol 47(3):253–270

Minehan KJ, Shaw EG, Scheithauer BW, Davis DL, Onofrio BM (1995) Spinal cord astrocytoma: pathological and treatment considerations. J Neurosurg 83(4):590–595. doi:10.3171/jns.1995.83.4.0590

Miyazawa N, Hida K, Iwasaki Y, Koyanagi I, Abe H (2000) MRI at 1.5 T of intramedullary ependymoma and classification of pattern of contrast enhancement. Neuroradiology 42(11):828–832

Mork SJ, Loken AC (1977) Ependymoma: a follow-up study of 101 cases. Cancer 40(2):907–915

Morota N, Deletis V, Constantini S, Kofler M, Cohen H, Epstein FJ (1997) The role of motor evoked potentials during surgery for intramedullary spinal cord tumors. Neurosurgery 41(6):1327–1336

Mulvihill JJ, Parry DM, Sherman JL, Pikus A, Kaiser-Kupfer MI, Eldridge R (1990) NIH conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. Ann Intern Med 113(1):39–52

Nash CL Jr, Lorig RA, Schatzinger LA, Brown RH (1977) Spinal cord monitoring during operative treatment of the spine. Clin Orthop Relat Res 126:100–105

Nazar GB, Hoffman HJ, Becker LE, Jenkin D, Humphreys RP, Hendrick EB (1990) Infratentorial ependymomas in childhood: prognostic factors and treatment. J Neurosurg 72(3):408–417. doi:10.3171/jns.1990.72.3.0408

Neder L, Colli BO, Machado HR, Carlotti CG Jr, Santos AC, Chimelli L (2004) MIB-1 labeling index in astrocytic tumors – a clinicopathologic study. Clin Neuropathol 23(6):262–270

Neumann HP, Lips CJ, Hsia YE, Zbar B (1995) Von Hippel-Lindau syndrome. Brain Pathol 5(2):181–193

O'Sullivan C, Jenkin RD, Doherty MA, Hoffman HJ, Greenberg ML (1994) Spinal cord tumors in children: long-term results of combined surgical and radiation treatment. J Neurosurg 81(4):507–512. doi:10.3171/jns.1994.81.4.0507

Osborn A (1994) Diagnostic neuroradiology. Mosby, St. Louis

Parsa AT, McCormick PC (2005) Spinal axis tumors. In: Berger M, Prados M (eds) Textbook of neuro-oncology. Elsevier Saunders, Philadelphia, pp 476–484

Parsa AT, Lee J, Parney IF, Weinstein P, McCormick PC, Ames C (2004) Spinal cord and intradural-extraparenchymal spinal tumors: current best care practices and strategies. J Neuro Oncol 69(1–3):291–318

Parsons R (2004) Human cancer, PTEN and the PI-3 kinase pathway. Semin Cell Dev Biol 15(2):171–176

Pechstein U, Cedzich C, Nadstawek J, Schramm J (1996) Transcranial high-frequency repetitive electrical stimulation for recording myogenic motor evoked potentials with the patient under general anesthesia. Neurosurgery 39(2):335–343, discussion 343–334

Peker S, Ozgen S, Ozek MM, Pamir MN (2004) Surgical treatment of intramedullary spinal cord ependymomas: can outcome be predicted by tumor parameters? J Spinal Disord Tech 17(6):516–521

Perilongo G, Massimino M, Sotti G, Belfontali T, Masiero L, Rigobello L, Garre L, Carli M, Lombardi F, Solero C, Sainati L, Canale V, del Prever AB, Giangaspero F, Andreussi L, Mazza C, Madon E (1997) Analyses of prognostic factors in a retrospective review of 92 children with ependymoma: Italian Pediatric Neuro-oncology Group. Med Pediatr Oncol 29(2):79–85

Pollack IF, Gerszten PC, Martinez AJ, Lo KH, Shultz B, Albright AL, Janosky J, Deutsch M (1995) Intracranial ependymomas of childhood: long-term outcome and prognostic factors. Neurosurgery 37(4):655–666, discussion 666–657

Prados MD, Edwards MS, Rabbitt J, Lamborn K, Davis RL, Levin VA (1997) Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. J Neuro Oncol 32(3):235–241

Quinones-Hinojosa A, Lyon R, Zada G, Lamborn KR, Gupta N, Parsa AT, McDermott MW, Weinstein PR (2005) Changes in transcranial motor evoked potentials during intramedullary spinal cord tumor resection correlate with postoperative motor function. Neurosurgery 56(5):982–993, discussion 982–993

Raghavendra BN, Epstein FJ, McCleary L (1984) Intramedullary spinal cord tumors in children: localization by intraoperative sonography. AJNR Am J Neuroradiol 5(4):395–397

Raimondi AJ, Gutierrez FA, Di Rocco C (1976) Laminotomy and total reconstruction of the posterior spinal arch for spinal canal surgery in childhood. J Neurosurg 45(5):555–560. doi:10.3171/jns.1976.45.5.0555

Ransom DT, Ritland SR, Kimmel DW, Moertel CA, Dahl RJ, Scheithauer BW, Kelly PJ, Jenkins RB (1992) Cytogenetic and loss of heterozygosity studies in ependymomas, pilocytic astrocytomas, and oligodendrogliomas. Gene Chromosome Cancer 5(4):348–356

Rawlings CE 3rd, Giangaspero F, Burger PC, Bullard DE (1988) Ependymomas: a clinicopathologic study. Surg Neurol 29(4):271–281

Reimer R, Onofrio BM (1985) Astrocytomas of the spinal cord in children and adolescents. J Neurosurg 63(5):669–675. doi:10.3171/jns.1985.63.5.0669

Robertson PL, Allen JC, Abbott IR, Miller DC, Fidel J, Epstein FJ (1994) Cervicomedullary tumors in children: a distinct subset of brainstem gliomas. Neurology 44(10):1798–1803

Rodriguez HA, Berthrong M (1966) Multiple primary intracranial tumors in von Recklinghausen's neurofibromatosis. Arch Neurol 14(5):467–475

Roonprapunt C, Silvera VM, Setton A, Freed D, Epstein FJ, Jallo GI (2001) Surgical management of isolated hemangioblastomas of the spinal cord. Neurosurgery 49(2):321–327, discussion 327–328

Rossitch E Jr, Zeidman SM, Burger PC, Curnes JT, Harsh C, Anscher M, Oakes WJ (1990) Clinical and pathological analysis of spinal cord astrocytomas in children. Neurosurgery 27(2):193–196

Rouleau GA, Wertelecki W, Haines JL, Hobbs WJ, Trofatter JA, Seizinger BR, Martuza RL, Superneau DW, Conneally PM, Gusella JF (1987) Genetic linkage of bilateral acoustic neurofibromatosis to a DNA marker on chromosome 22. Nature 329(6136):246–248. doi:10.1038/329246a0

Rouleau GA, Merel P, Lutchman M, Sanson M, Zucman J, Marineau C, Hoang-Xuan K, Demczuk S, Desmaze C, Plougastel B et al (1993) Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. Nature 363(6429):515–521. doi:10.1038/363515a0

Rousseau P, Habrand JL, Sarrazin D, Kalifa C, Terrier-Lacombe MJ, Rekacewicz C, Rey A (1994) Treatment of intracranial ependymomas of children: review of a 15-year experience. Int J Radiat Oncol Biol Phys 28(2):381–386

Rubio MP, Correa KM, Ramesh V, MacCollin MM, Jacoby LB, von Deimling A, Gusella JF, Louis DN (1994) Analysis of the neurofibromatosis 2 gene in human ependymomas and astrocytomas. Cancer Res 54(1):45–47

Russell DSRL (1989) Pathology of tumors of the nervous system. Williams & Wilkins, Baltimore

Samii M, Klekamp J (1994) Surgical results of 100 intramedullary tumors in relation to accompanying syringomyelia. Neurosurgery 35(5):865–873, discussion 873

Sandalcioglu IE, Gasser T, Asgari S, Lazorisak A, Engelhorn T, Egelhof T, Stolke D, Wiedemayer H (2005) Functional outcome after surgical treatment of intramedullary spinal cord tumors: experience with 78 patients. Spinal Cord 43(1):34–41. doi:10.1038/sj.sc.3101668

Sandler HM, Papadopoulos SM, Thornton AF Jr, Ross DA (1992) Spinal cord astrocytomas: results of therapy. Neurosurgery 30(4):490–493

Santi M, Quezado M, Ronchetti R, Rushing EJ (2005) Analysis of chromosome 7 in adult and pediatric ependymomas using chromogenic in situ hybridization. J Neuro Oncol 72(1):25–28. doi:10.1007/s11060-004-3117-9

Scheil S, Bruderlein S, Eicker M, Herms J, Herold-Mende C, Steiner HH, Barth TF, Moller P (2001) Low frequency of chromosomal imbalances in anaplastic ependymomas as detected by comparative genomic hybridization. Brain Pathol 11(2):133–143

Schiffer D, Giordana MT (1998) Prognosis of ependymoma. Childs Nerv Syst 14(8):357–361. doi:10.1007/s003810050244

Schneider C, Hidalgo ET, Schmitt-Mechelke T, Kothbauer KF (2014) Quality of life after surgical treatment of primary intramedullary spinal cord tumors in children. J Neurosurg Pediatr 13(2):170–177. doi:10.3171/2013.11.PEDS13346

Schwartz TH, McCormick PC (2000) Intramedullary ependymomas: clinical presentation, surgical treatment strategies and prognosis. J Neuro Oncol 47(3):211–218

Shaw EG, Evans RG, Scheithauer BW, Ilstrup DM, Earle JD (1986) Radiotherapeutic management of adult intraspinal ependymomas. Int J Radiat Oncol Biol Phys 12(3):323–327

Shrivastava RK, Epstein FJ, Perin NI, Post KD, Jallo GI (2005) Intramedullary spinal cord tumors in patients older than 50 years of age: management and outcome analysis. J Neurosurg Spine 2(3):249–255. doi:10.3171/spi.2005.2.3.0249

Singh A, Chand K, Singh H, Sarkar C, Sharma MC (2007) Atypical neurocytoma of the spinal cord in a young child. Childs Nerv Syst 23(2):207–211. doi:10.1007/s00381-006-0141-4

Smith SF, Simpson JM, Sekhon LH (2004) Prophylaxis for deep venous thrombosis in neurosurgical oncology: review of 2779 admissions over a 9-year period. Neurosurg Focus 17(4):E4

Sonneland PR, Scheithauer BW, Onofrio BM (1985) Myxopapillary ependymoma. A clinicopathologic and immunocytochemical study of 77 cases. Cancer 56(4):883–893

Souweidane MM, Bouffet E, Finlay J (1998) The role of chemotherapy in newly diagnosed ependymoma of childhood. Pediatr Neurosurg 28(5):273–278

Steinbok P, Cochrane DD, Poskitt K (1992) Intramedullary spinal cord tumors in children. Neurosurg Clin N Am 3(4):931–945

Sun B, Wang C, Wang J, Liu A (2003) MRI features of intramedullary spinal cord ependymomas. J Neuroimaging 13(4):346–351

Teo C, Nakaji P, Symons P, Tobias V, Cohn R, Smee R (2003) Ependymoma. Childs Nerv Syst 19(5–6):270–285. doi:10.1007/s00381-003-0753-x

Trofatter JA, MacCollin MM, Rutter JL, Murrell JR, Duyao MP, Parry DM, Eldridge R, Kley N, Menon AG, Pulaski K et al (1993) A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. Cell 75(4):826

Valera ET, Serafini LN, Machado HR, Tone LG (2003) Complete surgical resection in children with low-grade astrocytomas after neoadjuvant chemotherapy. Childs Nerv Syst 19(2):86–90. doi:10.1007/s00381-002-0704-y

van Nielen KM, de Jong BM (1999) A case of Ollier's disease associated with two intracerebral low-grade gliomas. Clin Neurol Neurosurg 101(2):106–110

von Deimling A, Louis DN, Wiestler OD (1995) Molecular pathways in the formation of gliomas. Glia 15(3):328–338. doi:10.1002/glia.440150312

von Haken MS, White EC, Daneshvar-Shyesther L, Sih S, Choi E, Kalra R, Cogen PH (1996) Molecular genetic analysis of chromosome arm 17p and chromosome arm 22q DNA sequences in sporadic pediatric ependymomas. Gene Chromosome Cancer 17(1):37–44. doi:10.1002/(SICI)1098-2264(199609)17:1<37::AID-GCC6>3.0.CO;2-3

Vortmeyer AO, Gnarra JR, Emmert-Buck MR, Katz D, Linehan WM, Oldfield EH, Zhuang Z (1997) von Hippel-Lindau gene deletion detected in the stromal cell component of a cerebellar hemangioblastoma associated with von Hippel-Lindau disease. Hum Pathol 28(5):540–543

Waha A, Koch A, Hartmann W, Mack H, Schramm J, Sorensen N, Berthold F, Wiestler OD, Pietsch T, Waha A (2004) Analysis of HIC-1 methylation and transcription in human ependymomas. Int J Cancer 110(4):542–549. doi:10.1002/ijc.20165

Ward BA, Gutmann DH (2005) Neurofibromatosis 1: from lab bench to clinic. Pediatr Neurol 32(4):221–228. doi:10.1016/j.pediatrneurol.2004.11.002

Weil RJ, Lonser RR, DeVroom HL, Wanebo JE, Oldfield EH (2003) Surgical management of brainstem hemangioblastomas in patients with von Hippel-Lindau disease. J Neurosurg 98(1):95–105. doi:10.3171/jns.2003.98.1.0095

Whitaker SJ, Bessell EM, Ashley SE, Bloom HJ, Bell BA, Brada M (1991) Postoperative radiotherapy in the management of spinal cord ependymoma. J Neurosurg 74(5):720–728. doi:10.3171/jns.1991.74.5.0720

Yagi T, Ohata K, Haque M, Hakuba A (1997) Intramedullary spinal cord tumour associated with neurofibromatosis type 1. Acta Neurochir (Wien) 139(11):1055–1060

Yamamoto Y, Raffel C (1999) Spinal extradural neoplasms and intradural neoplasms. In: Albright AL, Pollack IF, Adelson PD (eds) Principles and practice of pediatric neurosurgery. Thieme, New York, pp 685–696

Yao KC, McGirt MJ, Chaichana KL, Constantini S, Jallo GI (2007) Risk factors for progressive spinal deformity following resection of intramedullary spinal cord tumors in children: an analysis of 161 consecutive cases. J Neurosurg 107(6 Suppl):463–468. doi:10.3171/PED-07/12/463

Zuccaro G, Sosa F, Cuccia V, Lubieniecky F, Monges J (1999) Lateral ventricle tumors in children: a series of 54 cases. Childs Nerv Syst 15(11–12):774–785. doi:10.1007/s003810050470

Rare Tumors

11

Sunanda Pejavar and Daphne A. Haas-Kogan

Contents

S. Pejavar, MD
Department of Radiation Oncology,
Sharp Memorial Hospital, 7901 Frost Street,
San Diego, CA 92123, USA
e-mail: sunanda.pejavar@sharp.com

D.A. Haas-Kogan, MD (✉)
Department of Radiation Oncology,
Brigham and Women's Hospital, Dana-Farber Cancer Institute & Boston Children's Hospital,
450 Brookline Ave. D1622,
Boston, MA 02215-5418, USA
e-mail: dhaas-kogan@lroc.harvard.edu

11.1 Meningiomas

11.1.1 Epidemiology

Meningiomas are primarily benign tumors that arise from arachnoid cap cells of the meninges. Although they account for approximately 30 % of primary central nervous system (CNS) tumors in adults, these tumors are rare in children and adolescents. Pediatric meningiomas comprise only 1.5–2 % of all meningiomas and less than 5 % of pediatric CNS neoplasms (Gao et al. 2009). Unlike adult series, in which the female-to-male ratio is 2:1, most series on pediatric meningiomas report a slight male preponderance (Caroli et al. 2006).

Most children with meningiomas are diagnosed in the first or second decades of life, and the mean age at presentation is 11 years (Caroli et al. 2006). Although many of these tumors develop spontaneously, ionizing radiation and neurofibromatosis

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_11

type 2 (NF2) are well-known risk factors. Children with prior cranial radiation exposure have nearly a ten-fold greater risk of meningioma development (Menon et al. 2009), and approximately 50 % of patients with NF2 are diagnosed with meningiomas (Goutagny and Kalamarides 2010). Patients with radiation-induced or neurofibromatosis-associated meningiomas are generally diagnosed at a later age than those with spontaneously occurring tumors (Greene et al. 2008).

Most pediatric meningiomas are found in supratentorial locations, but they may also be infratentorial, intraorbital, or intraventricular. Both infratentorial and intraventricular meningiomas are more common in children than adults. Infratentorial tumors are noted in 19 % of cases found in children under the age of 15 (Erdincler et al. 1998) versus 8–10 % in adults (Di Rocco and Di Rienzo 1999). The incidence of intraventricular meningiomas in children is 10 % (Germano et al. 1994) compared with less than 2 % in adults (Liu et al. 2006). Third ventricular tumors are rare (Martínez-Lage et al. 1993), as are orbital tumors, which have been associated exclusively with neurofibromatosis in one series (Greene et al. 2008). Meningiomas without dural attachment are also common in children, as are tumors with large cystic components (Ferrante et al. 1989; Tufan et al. 2005).

11.1.2 Histopathology

The World Health Organization (WHO) Classification of Tumours of the Central Nervous System (Louis et al. 2007) separates meningiomas into three grades (Table 11.1). Most pediatric meningiomas are WHO grade I (80 %) (Kotecha et al. 2011). Some series have reported that meningiomas in children and adolescents have higher rates of atypical and malignant features (6–10 %), higher rates of brain invasion, and poorer prognosis (Arivazhagan et al. 2008; Perry et al. 2001) compared with meningiomas in adults; however, this remains a controversial issue (Caroli et al. 2006). Of benign meningiomas, fibrous (24 %), transitional (12 %), and meningothelial (12 %) subtypes are the most common, but the significance of meningioma subtype on outcome is not known. A WHO classification update, with planned release in 2016, will incorporate brain invasion into the criteria for atypical meningioma. Thus, even if otherwise benign, brain invasion will qualify as atypical meningioma, WHO grade II. This is of particular significance for children because pediatric meningiomas more frequently display perivascular spread along Virchow-Robin spaces; however, this pattern alone should not be mistaken for brain invasion (Dr. Arie Perry, UCSF, personal communication).

Table 11.1 World Health Organization (WHO) classification for meningiomas (Louis et al. 2007)

WHO grade I	Benign meningiomas: with low risk of recurrence and/or low risk of aggressive growth
WHO grade II	Atypical meningiomas: with increased mitotic activity or three or more of the following features, increased cellularity, small cells with high nucleus-to-cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheetlike growth, and foci of spontaneous or geographic necrosis
WHO grade III	Anaplastic (malignant) meningiomas: exhibit frank histologic features of malignancy far in excess of the abnormalities present in atypical meningiomas

11.1.3 Clinical Features

Children with meningiomas often experience insidious, nonspecific symptoms and signs related to increased intracranial pressure. Therefore, they generally present with a relatively long duration of symptoms (average 6–10 months) and large tumors at diagnosis (Arivazhagan et al. 2008).

Headache (91 %) and vomiting (70 %) are the most common presenting complaints in adolescents. In infants, a tense or bulging fontanel can be seen (Amirjamshidi et al. 2000). Other patients present with distinct neurologic symptoms related to tumor location, such as motor deficits or hemiparesis (20 %) (Erdincler et al. 1998). A large number of patients develop visual deficits (51 %) or cranial neuropathies (64 %) due to the high incidence of skull base and infratentorial tumors (Arivazhagan et al. 2008). Epilepsy is relatively uncommon in the pediatric population and occurs in 20–30 % of patients (Erdincler et al. 1998; Amirjamshidi et al. 2000).

11.1.4 Diagnosis and Neuroimaging

Magnetic resonance imaging (MRI) is the mainstay of diagnosis of intracranial meningioma. Tumors show intense enhancement upon administration of gadolinium contrast agent and are frequently cystic and calcified. An enhancing dural tail can be seen (Fig. 11.1), but is less common in children than in adults. Other studies, including contrast-enhanced computed tomography (CT) scans and plain films, may serve to confirm the diagnosis. On a brain CT scan, a meningioma appears as a dural-based tumor that usually compresses, but does not invade the brain. It is usually intensely and homogenously enhancing and may be surrounded by extensive edema. On a plain radiograph, intracranial calcifications and hyperostosis may be seen.

Conventional catheter angiography typically shows a delayed vascular blush and a "sunburst" pattern of feeding meningeal arteries. This modality was used in the past for diagnosis; however, it is now limited to those cases in which preoperative embolization is being considered. Catheter angiography, magnetic resonance arteriography (MRA), and magnetic resonance venography (MRV) are important tools in planning surgery by determining vascularity of the tumor, impingement on critical vascular structures, and patency of involved dural sinuses.

11.1.5 Treatment

Surgical gross total resection (GTR) is the primary treatment objective in children. In various series, GTR was accomplished in 65–86 % of cases (Erdincler et al. 1998; Tufan et al. 2005; Arivazhagan et al. 2008; Caroli et al. 2006). Specific surgical challenges in children include the proximity of the tumor to vital structures, larger tumor size at diagnosis, and lower blood volume. Multiple staged resections are sometimes necessary, particularly when significant perioperative blood loss occurs.

Preoperative embolization of meningiomas is shown to decrease tumor vascularity and reduce blood loss during surgery in adults, although there is no data specifically pertaining to children (Oka et al. 1998). Pediatric patients may have an increased risk of morbidity from this procedure due to their smaller caliber vessels.

Adjuvant chemotherapy and radiotherapy have limited roles in the treatment of pediatric meningioma, and their use varies widely between institutions. The benefits of radiation therapy must be balanced against the risks of long-term sequelae, particularly in infants and young children, whose brains are particularly vulnerable to the effects of radiation. The Children's Cancer and Leukemia Group (CCLG)

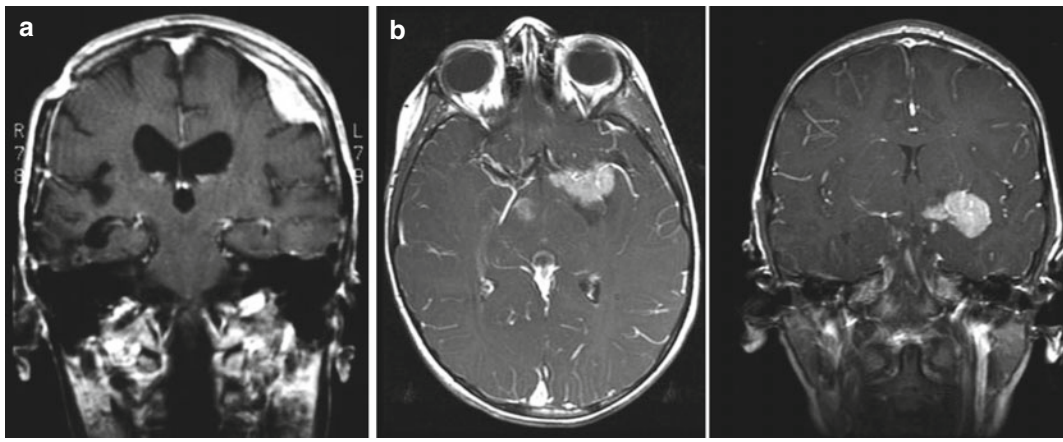

Fig. 11.1 (**a**) A T1-weighted MR image following contrast administration showing a dural-based convexity meningioma with an enhancing "tail." (**b**) T1-weighted postcontrast MR images (axial and coronal) of a 6-year-old girl with a very unusual meningioma located in the Sylvian fissure without a defined dural attachment point

suggests consideration of radiation therapy in patients with WHO grade I and II meningiomas who experience multiple recurrences not amenable to further surgery, evidence of clinically relevant progression that threatens vital functions after subtotal resection, and in all WHO grade III tumors at diagnosis (Traunecker et al. 2008). However, a meta-analysis reported in the *Lancet* in 2011 showed no benefit to upfront radiation therapy, even in WHO grade III tumors, and therefore aggressive surgical management with close observation was recommended (Kotecha et al. 2011). Data on the use of stereotactic radiosurgery in children is limited, but radiosurgery has been reported as a successful treatment for recurrent tumor in a few series (Li and Zhao 2009). The use of drug therapy in the treatment of meningioma has been disappointing in adults, and therefore, chemotherapy is not routinely used in children with meningiomas.

11.1.6 Outcome

Extent of tumor resection is described as the most significant prognostic factor (Kotecha et al. 2011). Reviews of the literature show that almost all children who experienced a recurrence had a malignant histologic variant or a subtotal resection. In some series, pediatric meningiomas are reported as behaving more aggressive and carrying a worse prognosis compared with adult meningiomas (Mehta et al. 2009); however, this is controversial. In general, children with typical benign meningioma and complete removal show a good prognosis, similar to their adult counterparts.

11.2 Pediatric Pituitary Adenoma

11.2.1 Epidemiology

Pituitary adenomas account for only 1–10 % of all childhood brain tumors and between 3 % and 6 % of all surgically treated pituitary tumors (Mindermann and Wilson 1995). Variation in reported incidence is related to the lack of consensus on an age cutoff for pediatric tumors. The majority of children present with hormone-secreting tumors. Nonfunctioning adenomas are rare in children and only make up 3–6 % of tumors in this population, compared with one-third of adenomas found in adult series (Partington et al. 1994; Mindermann and Wilson 1995; Webb and Prayson 2008).

The most common functioning adenomas in children are prolactinomas (45–53 %), followed by adrenocorticotropic hormone (ACTH)-secreting adenomas or corticotroph adenomas (25–33 %), and finally growth hormone (GH)-secreting adenomas or somatotroph adenomas (8–15 %). Thyroid hormone-secreting tumors or thyrotroph adenomas are extremely rare, and only a few pediatric cases have been reported in the literature. The vast majority of cases present in adolescence; only 25 % of pediatric patients with pituitary adenomas are under the age of 12 (Partington et al. 1994; Mindermann and Wilson 1995). When stratified into prepubescent (age 0–11), pubescent (age 12–17), and postpubescent (age 18–19) groups, there is a characteristic distribution by tumor type (Table 11.2). Corticotroph adenomas are most commonly seen in the youngest age group, found in over 50 % of prepubescent children diagnosed with pituitary adenomas.

Table 11.2 Occurrence of pediatric pituitary adenoma by age group (Kunwar and Wilson 1999)

	No. of patients (%)			
Adenoma subtype	Age 0–11	Age 12–17	Age 18–19	Total
Prolactinoma	5 (16.1)	61 (59.8)	12 (70.6)	78 (52.0)
Corticotroph adenoma	22 (71.0)	31 (30.4)	3 (17.6)	56 (37.3)
Somatotroph adenoma	2 (6.4)	8 (7.8)	2 (11.8)	12 (8.0)
Endocrine inactive	2 (6.4)	2 (2.0)	0	4 (2.7)
Total[a]	31 (20.7)	102 (68.0)	17 (11.3)	150 (100)

[a]Numbers represent total of each age group. Percentages represent the number out of 150 patients

Somatotroph adenomas are equally distributed among the three age groups. The distribution of the various adenomas in the postpubescent group mimics that in adults.

Multiple large series have shown a female preponderance in pediatric pituitary adenomas (Maira and Anile 1990; Kane et al. 1994; Mindermann and Wilson 1995; Webb and Prayson 2008). The vast majority of prolactinomas occur in females (80 % females vs. 20 % males), and slightly more corticotroph adenomas occur in females than in males. On the other hand, pure somatotroph adenomas are more common in males.

11.2.2 Histopathology

Most pituitary adenomas are benign tumors arising from epithelial cells of the adenohypophysis. Tumor development occurs as a monoclonal process influenced by a multitude of factors, including hormones, gene mutations, or heredity. The exact pathophysiologic mechanism, however, is unknown. Pituitary adenomas can occur sporadically or as components of hereditary syndromes. Prolactinomas, corticotroph adenomas, and somatotroph adenomas are common in patients with multiple endocrine neoplasia syndrome type 1 (MEN-1). Somatotroph adenomas are also associated with several other hereditary conditions, including McCune Albright syndrome or the Carney complex (Lafferty and Chrousos 1999).

There is some discrepancy among studies regarding the ratio of macroadenomas (>1 cm) to microadenomas. Most studies document either equal distribution between the two types or a slightly higher incidence of macroadenomas in the pediatric population (range 36–78 %). The size of the tumor appears to be related to secretory function, with the vast majority of somatotroph and thyrotroph adenomas presenting as macroadenomas and corticotroph adenomas presenting as microadenomas. Hormonally inactive adenomas often present as macroadenomas.

11.2.3 Clinical Features

Presenting symptoms in patients with pituitary adenomas depend both on tumor size and on secretory capability. Headaches and visual deficits are common in children with macroadenomas. Because pediatric patients have a preponderance for functioning adenomas, the majority of children also present with endocrine dysfunction (75 %) (Pandey et al. 2005). This dysfunction manifests as specific clinical signs related to hormone hypersecretion from the tumor, as well as disruptions in growth or sexual maturation related to compression of normal pituitary tissue. The pituitary gland shows a predictable sequence of secretory failure (Kunwar and Wilson 1999). GH-releasing cells are extremely vulnerable to compression and are almost always the first cells to exhibit hormone hyposecretion. Therefore, children with adenomas other than somatotroph adenomas usually present with short stature or growth retardation. Gonadotropin-releasing cells are also susceptible to compression, although to a lesser degree than GH-secreting cells, and menstrual irregularity is a common complaint in adolescent girls with pituitary adenomas. Thyroid-stimulating hormone (TSH) is affected late and only with relatively large tumors.

Prolactinomas can present with different signs and symptoms depending on the age and sex of the child. Prepubertal children present with nonspecific symptoms of headache, visual disturbances, and growth failure, mentioned earlier. Common complaints by postpubertal females are amenorrhea and galactorrhea. These tumors are rare in males, but may present with pubertal arrest, hypogonadism, or gynecomastia. Because prolactinomas arise from cells in the same lineage as somatotrophs and thyrotrophs, these tumors may also stain for and secrete GH and TSH.

Cushing's syndrome is the most common presentation of corticotroph adenomas. Approximately 90 % of children over the age of 5 years diagnosed with Cushing's syndrome have ACTH-secreting adenomas (Lafferty and Chrousos 1999). These patients experience weight gain (50 %) with purplish striae, easy

bruising, moon facies, growth retardation, and sometimes hypertension and insulin resistance. Prepubertal children may present with hirsutism and premature pubarche, while postpubertal children often have pubertal arrest. Unlike adults, proximal myopathy is uncommon in children, and weight gain tends to be generalized rather than centripetal (Lafferty and Chrousos 1999). Neuropsychiatric problems such as compulsive behavior and overachievement in school tend to dominate in the pediatric population, as opposed to depression and memory loss which are common in adults.

Somatotroph adenomas generally cause rapid growth and gigantism in children with open epiphyseal plates. Occasionally, these tumors also cause weight gain, premature puberty, or menstrual irregularities. In older children, who have undergone epiphyseal fusion, symptoms tend to mimic those in adults. These patients may present with glucose intolerance, acromegalic features such as coarse facies and enlarged hands and feet, nausea, and respiratory difficulty.

Nonfunctioning adenomas, which are uncommon in children, present with generalized symptoms of headache, visual disturbance, growth retardation, and pubertal arrest. Thyrotroph adenomas, which are exceedingly rare, may present with hyperthyroidism or nonspecific findings similar to those patients with nonfunctioning adenomas.

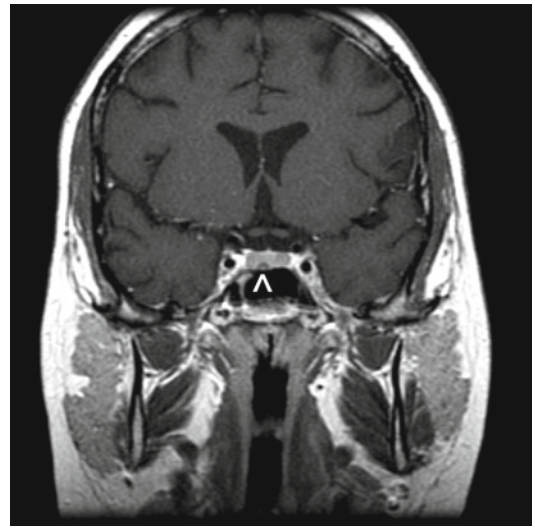

Fig. 11.2 A teenage girl presenting with Cushing's disease secondary to a hormone-secreting corticotroph microadenoma. A T1-weighted coronal MR image shows a small lesion (*arrowhead*) that is hypointense relative to the pituitary gland. The normal pituitary gland is usually brighter than a small pituitary adenoma following contrast

11.2.4 Diagnosis and Neuroimaging

11.2.4.1 Imaging

Pituitary adenomas are diagnosed by both imaging and biochemical studies. MRI with gadolinium is the imaging modality of choice and has 72 % sensitivity in the diagnosis of adenomas (Devoe et al. 1997). On T1-weighted images, pituitary adenomas are hypoenhancing, compared with normal anterior pituitary tissue that appears slightly hyperintense relative to the rest of the brain (Fig. 11.2). Nonspecific signs may include a deviation of the pituitary stalk or an increase in the vertical height of the gland, although a normal pituitary gland in adolescent girls may appear enlarged and convex superiorly. Physiologic enlargement of the pituitary gland during puberty is frequently mistaken for a macroadenoma. Although MRI provides superior soft tissue contrast and resolution of the sella compared to CT, MRI is still only able to detect less than one-half of microadenomas.

Positron emission tomography (PET) scans and ultrasound may be useful in some cases, although these modalities have not been used yet in primary diagnosis. Ultrasound has shown promise during transsphenoidal surgery, particularly in patients with corticotroph adenomas (Ram et al. 1999). This modality provides good contrast between tumor and normal pituitary gland and has the potential to identify sellar or suprasellar structures with invasion or damage. In postoperative patients, PET can help differentiate recurrence from scarring.

11.2.4.2 Biochemical Tests

Hematologic tests depend on clinical presentation. Prolactin levels are checked in any patient with a suspected prolactinoma. A single elevated

level of greater than 200 in a patient with a 1 cm pituitary mass on imaging is adequate for a diagnosis of prolactinoma. Because moderately elevated levels can signify either a microadenoma or secondary hyperprolactinemia due to other causes such as functional pituitary stalk disconnection, a second, fasting level may be checked for confirmation and is usually drawn an hour after placing an indwelling cannula.

Suspected corticotroph adenomas warrant a workup that confirms the presence of Cushing's disease. Multiple 24 h urine free cortisol (UFC) levels are checked and adjusted for the child's body surface area. In addition, a dexamethasone suppression test can be administered and is positive for Cushing's disease if the patient's serum cortisol fails to drop the morning after receiving a dose of dexamethasone. Once Cushing's disease is diagnosed, further tests are ordered to confirm that the etiology is a corticotroph adenoma. A high-dose dexamethasone suppression test is positive if a patient's serum cortisol drops by 50 % the morning after a high dose of dexamethasone is administered and has 85 % sensitivity for diagnosis of corticotroph adenoma (Lafferty and Chrousos 1999). Additional tests involve injecting ovine corticotropin-releasing hormone and measuring ACTH simultaneously from central and peripheral sites. If ACTH is stimulated, the test has 97 % sensitivity for corticotroph adenoma. Alternatively, bilateral inferior petrosal sinuses can be sampled, and detection of ACTH both confirms the diagnosis and lateralizes the tumor with 75 % accuracy.

Biochemical tests for somatotroph adenomas include random measurements of GH and insulin-like growth factor (IGF-1). Elevations in both markers suggest a diagnosis of somatotroph adenoma, although IGF-1 can sometimes be elevated during normal puberty. An oral glucose tolerance test, during which GH shows failed suppression or a paradoxical rise, is also positive for a somatotroph adenoma. This test, however, has a high false-positive rate (Holl et al. 1999) and should be used in conjunction with other laboratory testing. Somatotroph adenomas also frequently express thyrotropin-releasing hormone (TRH) receptors, and therefore, the diagnosis can be confirmed by measuring GH stimulation after TRH administration.

Several tests may be used to help confirm the presence of a thyrotroph adenoma. Elevated free T4 and T3 without suppression of TSH support the diagnosis. However, additional tests differentiate an adenoma from central T4 resistance. Thyrotroph adenomas do not respond to TRH stimulation, and this test has a sensitivity of 71 % and specificity of 96 %. In addition, elevated alpha-glycoprotein subunit is a positive test and has 75 % sensitivity and 90 % specificity.

11.2.5 Treatment

11.2.5.1 Surgery

Surgical treatment for pituitary adenomas has been widely used during the past 50 years. Surgery has the advantage of rapidly lowering hormone levels in functioning adenomas and improving visual symptoms in patients with optic chiasm compression. Two general surgical approaches are used: transcranial/subfrontal or transsphenoidal. In some situations with very large tumors, a combination of approaches is needed. At present, the preferred technique is the transsphenoidal route in both adults and children. In several series, transsphenoidal surgery was used in children as the initial approach. This technique yielded positive results, and very few patients suffered postoperative complications or required a second intracranial procedure (Maira and Anile 1990; Partington et al. 1994). The transsphenoidal route has been used in children as young as 4 years old without difficulty (Haddad et al. 1991; Ludecke and Abe 2006). In patients with larger tumors, the transcranial route is often used. Specific indications include dumbbell-shaped tumors with extensive suprasellar component, multi-compartmental tumors, and unclear diagnoses (Pandey et al. 2005). However, morbidity is often higher in patients operated on via this route, and postoperative visual deterioration is more common.

Surgery as primary therapy is recommended for all pituitary adenomas except prolactinomas. Corticotroph adenomas usually present as

microadenomas, and therefore, hemihypophysectomy is often curative. However, this approach entails confirmation of the correct half of the anterior pituitary gland containing the microadenoma. In patients with functional corticotroph or somatotroph adenomas, 80 % will be cured following surgery alone (Mindermann and Wilson 1995). Although surgery is the preferred treatment for thyrotroph adenomas, these tumors are often large and invasive and therefore require adjuvant radiation therapy (Kunwar and Wilson 1999). While adult patients with asymptomatic, nonfunctioning adenomas are usually observed, pediatric patients are almost always treated surgically. This approach is primarily due to the fact that nonfunctioning adenomas are extremely rare in children and difficult to discern from craniopharyngiomas.

In children with prolactinomas, medical rather than surgical therapy is recommended as the initial treatment (CasaNueva et al. 2006). Surgery is reserved for individuals who have rapid visual decline (Fig. 11.3), are intolerant of the side effects of medication, or are unwilling to comply with lifelong pharmacologic therapy. Some studies do report good results in pediatric patients who undergo surgery for prolactin-secreting tumors; one large series reported an 82 % cure rate (Mindermann and Wilson 1995).

11.2.5.2 Medical Therapy

Prolactinomas are the only adenomas that can be managed initially with medical therapy. Dopamine agonists such as bromocriptine, pergolide, and cabergoline are effective for shrinking the tumor and normalizing prolactin levels. Side effects of these medicines, however, include gastrointestinal upset and orthostatic hypotension, and it is generally thought that these patients will require medical treatment for their entire lives. A recent review of pediatric pituitary adenomas, however, reported that 90 % of the patients with prolactinomas stopped dopamine agonist therapy and were recurrence-free after a median follow-up of 4 years (Steele et al 2010).

For other types of pituitary adenomas, medical therapy is indicated only in nonsurgical candidates or if surgical management is inadequate in controlling hormone levels. Adrenal blockade with ketoconazole is often required in patients with corticotroph adenomas, but is only used if surgery and postoperative radiation have failed. Somatostatin analogs such as octreotide and lanreotide have been used in adults with GH-secreting tumors and thyrotroph adenomas, although there is limited experience with these drugs in the pediatric population. These drugs show variable effects on both tumor shrinkage and hormone suppression.

11.2.5.3 Radiation Therapy

Radiation therapy as primary treatment for pituitary adenomas is not recommended in children due to the risk of long-term sequelae from radiation to the pituitary gland and normal brain. Moreover, normalization of hormone levels is usually suboptimal after radiation and requires years to take effect. Although external beam radiation therapy and radiosurgery are sometimes used in adults with unresectable tumors or residual disease after resection, they are rarely employed in the pediatric population.

11.2.6 Outcome

Pediatric pituitary adenomas are rarely fatal but can have significant effects on quality of life and sometimes lead to long-term complications caused by endocrine dysfunction. Treatment is almost always recommended for functional or symptomatic nonfunctional adenomas, but optimal management remains unknown.

Children who undergo surgical resection for functioning adenomas have cure rates of 80–90 % (Partington et al. 1994; Mindermann and Wilson 1995). Recurrence depends largely on the extent of resection (total vs. subtotal). Pediatric patients who undergo gross total resection have local recurrence rates of 1–5 %, while patients who undergo subtotal resections have recurrence rates greater than 60 % (Kane et al. 1994; Partington et al. 1994; Mindermann and Wilson 1995; Webb and Prayson 2008).

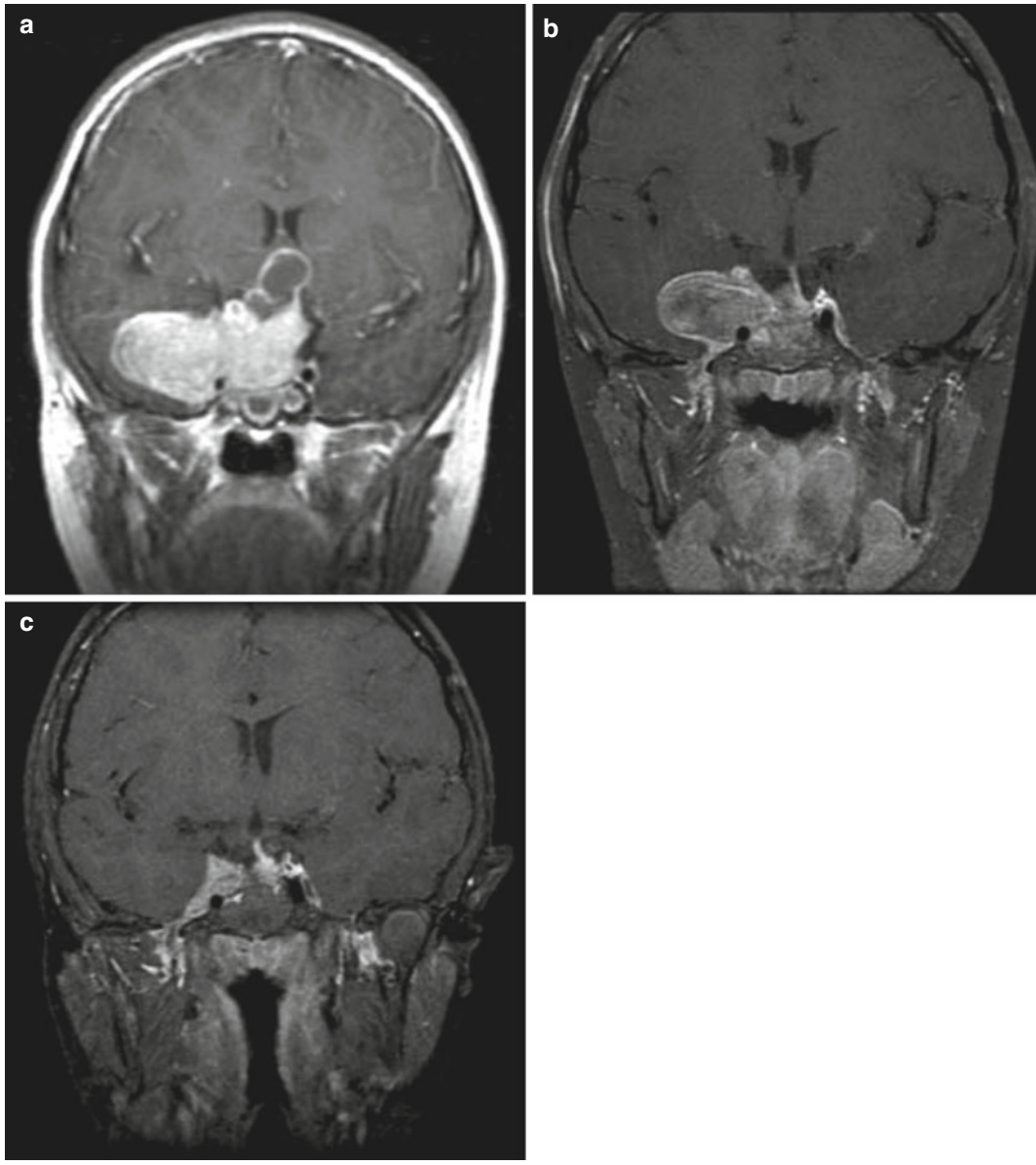

Fig. 11.3 A 5-year-old boy who presented with visual loss from a very large prolactinoma. The tumor was treated with subtotal surgical resection to decompress the optic chiasm and preserve visual function. The preoperative T1-weighted coronal MR image (**a**) shows a large multilobulated mass with poor visualization of the chiasm. The immediate postoperative scan (**b**) shows excellent decompression of the suprasellar tumor although the lateral portion remains. Two years later (**c**), after taking oral cabergoline, a much smaller residual tumor remains adjacent to the cavernous sinus. The patient has a partial GH deficiency, but otherwise has normal visual and endocrine function

When surgery is undertaken successfully, patients will often require hormone supplementation such as thyroid hormone or hydrocortisone for the duration of their lifetime. Surgical complications such as visual deficits or diabetes insipidus are rare and usually transient. However, pituitary apoplexy, a complication caused by sudden tumor hemorrhage or pituitary infarction, is found relatively often in pediatric patients after surgery or medical therapy (Bills et al. 1993; Knoepfelmacher et al. 2004; Semple et al. 2005).

11.3 Primary Central Nervous System Lymphoma

11.3.1 Epidemiology

Primary central nervous system lymphoma (PCNSL) is extremely rare in the pediatric population. In the Surveillance, Epidemiology, and End Results Program (SEER, USA 1973–1998), 1 % of all reported cases occurred in patients younger than 19 years, resulting in an estimated incidence of 15–20 cases per year (Kadan-Lottick et al. 2002). Children with congenital or acquired immunodeficiency are at an increased risk of developing this tumor (Roychowdhury et al. 2003; Newell et al. 2004), although there have been several sporadic cases of pediatric PCNSL reported in the literature.

11.3.2 Histopathology

Primary CNS lymphoma most frequently arises from B lymphocytes, and the majority of cases (69 %) are diffuse large B-cell lymphomas (Abla et al. 2006). The frequency of PCNSL in immunodeficient individuals suggests that the immune system may play a role in the pathogenesis of the neoplasms. Almost all patients with AIDS express Epstein-Barr viral genome in their tumors. Although the exact mechanism of tumorigenesis is not known, the tumor may arise from an Epstein-Barr virus-mediated malignant transformation and clonal expansion of B cells. Chromosomal abnormalities in both adults and children are not reported often. In one pediatric series, two of three patients with anaplastic T-cell lymphoma were found with t(2:5) translocations (Abla et al. 2006).

11.3.3 Clinical Features

PCNSL has been described as four distinct clinicopathologic entities: solitary or multiple intracranial lesions; diffuse periventricular or leptomeningeal disease; vitreous or uveal deposits; and intradural spinal cord tumors. In adults, signs and symptoms tend to correlate with location of involvement.

The majority of children present with intracranial, multifocal disease as opposed to solitary lesions. These patients may present with nonspecific symptoms related to increased intracranial pressure, such as headache, vomiting, or somnolence. Many children also present with either ataxia or hemiparesis, and other presenting symptoms in various series include paresthesias, nystagmus, decreased visual acuity, panhypopituitarism, or personality change.

11.3.4 Diagnosis and Neuroimaging

Diagnosis of PCNSL involves radiographic evaluation, cerebrospinal fluid testing, and histopathologic analysis. CT and MRI studies are used in both immunocompetent and immunocompromised patients with suspected PCNSL. Radiographic features seen in children are similar to those seen in adults (Schulman et al. 1991). In immunocompetent individuals, intracranial lesions appear as nonhemorrhagic masses in the deep white matter adjacent to the ventricular surfaces (Buhring et al. 2001). The tumors are generally hyperdense on CT images, hypointense on T2-weighted MR images, and homogeneously enhancing after administration of contrast agent (Fig. 11.4). Surrounding edema, calcification, necrosis, and ring enhancement are relatively infrequent in PCNSL. Leptomeningeal and vitreal disease are often missed on both CT and MRI.

Lumbar puncture is almost always performed on patients with suspected PCNSL if no mass effect is evident, and CSF evaluation includes cytology, flow cytometry, and immunophenotypic analysis. Elevated protein concentration and slight lymphocytic predominance are often seen. Glucose levels are usually normal, but may be low in patients with leptomeningeal disease. Although malignant lymphoid cells may be present in many patients, there is difficulty in differentiating between reactive and malignant cells or between medulloblastoma cells and malignant B cells. Immunophenotype testing using antibodies

against lymphocytic antigens is often useful in supporting the diagnosis of PCNSL and in distinguishing B-cell neoplasms from T-cell neoplasms. Stereotactic biopsy is the usual surgical technique used to establish a tissue diagnosis.

11.3.5 Treatment

The role of surgery in the treatment of PCNSL is usually limited to stereotactic biopsy. Complete resection is generally not possible because of the tumor's deep location, multifocality, and extensive infiltration into the surrounding brain. Moreover, patients treated with surgical excision alone have a poor prognosis, with a median survival of less than 5 months (Henry et al. 1974). Surgical intervention may be considered emergent in patients with impending herniation, significant mass effect, or hydrocephalus.

In adults, treatment for PCNSL is based on a combination of chemotherapy and cranial irradiation or intensive chemotherapy alone. Lymphoma is highly radiosensitive, and the disease will often show a rapid and complete radiographic and clinical response to radiation therapy; however, the vast majority of patients will relapse within 1 year. High-dose methotrexate (HD-MTX) is the most studied chemotherapeutic agent for PCNSL and has become the backbone of primary treatment. The combination of cranial irradiation and HD-MTX improves median survival to 3–4 years, but the role of radiation therapy remains controversial due to the high risk of neurotoxicity, particularly in older patients (Mohile and Abrey 2007; Batchelor and Loeffler 2006).

Because of the rarity of PCNSL in the pediatric population, the optimal therapeutic strategy is unknown. Several studies have shown positive long-term results in patients treated with chemotherapy alone. In a retrospective series consisting of patients treated mostly with HD-MTX and HD-Ara-C combinations, the 5-year event-free survival rate was 70 % (Abla et al. 2006). In a study from Korea, 5-year event-free and overall survival in patients treated with chemotherapy alone was 83 % (Yoon et al. 2012). In another series, 3-year overall survival was 82 % in pediatric patients with PCNSL, and the response rate in

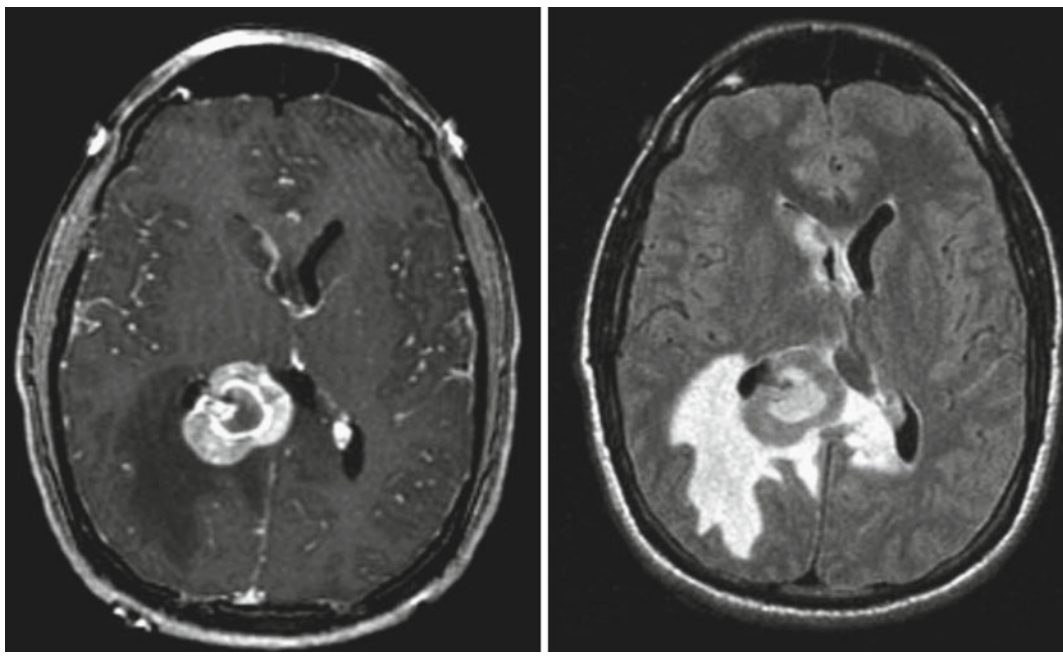

Fig. 11.4 Primary CNS lymphoma involving the right medial occipital lobe and corpus callosum. The tumor enhances (*left image*), but there is also a marked degree of white matter edema visible on the FLAIR image (*right image*)

patients who received chemotherapy alone was better than those who received combined chemoradiotherapy (Abla et al, 2011). Moreover, the majority of patients who relapsed after initial treatment were salvaged with chemotherapy alone, chemoradiation and/or autologous stem cell transplant. These results, as well as the known devastating late effects of cranial irradiation in children such as neurocognitive effects, endocrine aberrations, and secondary malignancy, suggest that pediatric patients with PCNSL may be treated upfront with chemotherapy as a single modality.

11.3.6 Outcome

Primary CNS lymphoma is generally thought to carry a poor prognosis and is fatal if left untreated. However, the prognosis of childhood PCNSL seems to be significantly better than in adults (McAllister et al. 2000; Abla et al. 2006). Some series suggest that this may be due to better tolerance of aggressive chemotherapeutic regimens, as well as biologically different tumors (Abla et al. 2011).

11.4 Hemangioblastoma

11.4.1 Epidemiology

Hemangioblastomas are benign tumors arising in the central nervous system. They are uncommon in the general population, but extremely rare in children under the age of 18, with an incidence of less than 1 per 1,000,000 (Ries et al. 2000; Fisher et al. 2002).

Although hemangioblastomas can occur as sporadic lesions, up to 50 % of cases are associated with von Hippel-Lindau disease (VHL) (Latif et al. 1993). This hereditary, autosomal dominant syndrome results from germline mutations on chromosome 3 that cause loss of function of the *VHL* tumor-suppressor gene (Zagzag et al. 2005). This condition predisposes patients to a variety of malignant and benign tumors, including hemangioblastomas, renal cysts and carcinomas, neuroendocrine tumors, and cystadenomas of the reproductive organs. In adults, the average age at diagnosis of VHL-associated hemangioblastomas is about 10 years less than that of sporadic cases (Maher et al. 1990). Therefore, the presence of multiple hemangioblastomas at a young age is highly suggestive of VHL.

11.4.2 Histopathology

Hemangioblastomas are vascular tumors and are composed mainly of normal-appearing capillary endothelial cells. Two additional distinct cellular types are often found, a perivascular endothelial cell with sparse cytoplasm and compact nuclei and a stromal cell with multiple vacuoles and lipid-rich eosinophilic cytoplasm. Two histologic subtypes of hemangioblastomas have been described: cellular and reticular. The reticular subtype is more common, but the cellular subtype has been found to have a higher incidence of recurrence (Hasselblatt et al. 2005).

11.4.3 Clinical Features

Most hemangioblastomas are found in the posterior fossa, although children and adolescents with VHL also frequently present with additional tumors in the spinal cord. Symptoms are generally a function of tumor size and anatomical location. Cerebellar lesions may cause ataxia and loss of coordination, brainstem tumors may cause cranial neuropathies or motor deficits, and spinal cord neoplasms initially cause pain followed by neurologic dysfunction. Both intracranial and intraspinal hemangioblastomas occasionally cause spontaneous hemorrhage (Glasker et al. 1999), but the risk of bleeding with tumors smaller than 1.5 cm is virtually zero.

Symptoms are frequently related to the development of tumor-associated pseudocysts. The pathogenesis of these pseudocysts is not known, but it is postulated to be a result of transudation of fluid from tumor capillaries along gray matter near the central canal (Van Velthoven et al. 2003).

11.4.4 Diagnosis and Neuroimaging

Contrast-enhanced MRI is the gold standard for the diagnosis of hemangioblastoma (Lee et al. 1989). The tumor is usually hypointense or isointense on pregadolinium T1-weighted studies and hyperintense on T2-weighted images (Fig. 11.5). The characteristic appearance on a contrast CT scan is a uniformly enhancing tumor nodule adjacent to a hypodense cyst. Cerebral and spinal angiography reveals a tumor blush, which may be useful to surgeons in determining vascular supply to the tumor.

Because of the high incidence of VHL in pediatric patients with hemangioblastoma, these

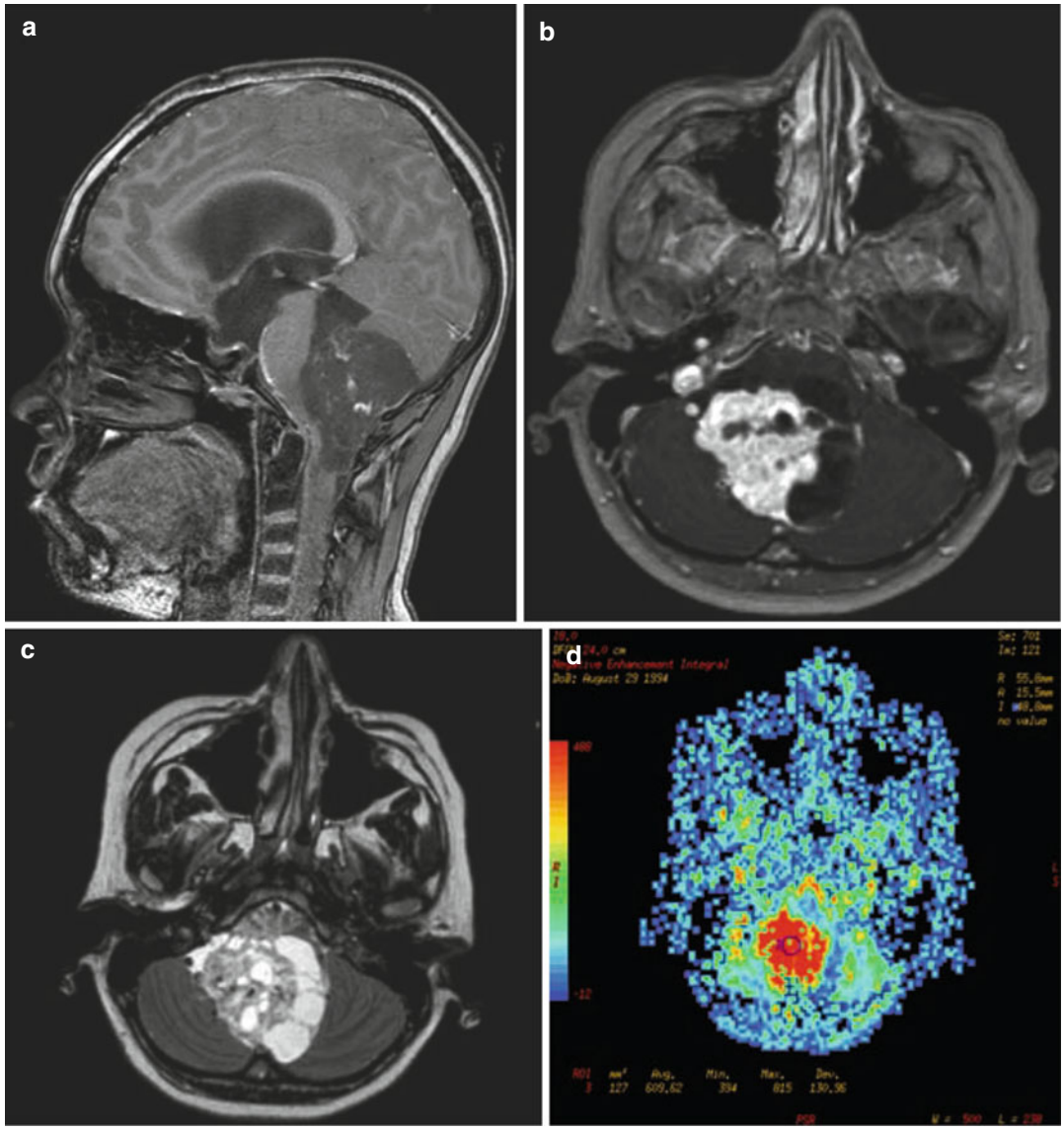

Fig. 11.5 A posterior fossa hemangioblastoma in an 8-year-old boy who presented with worsening headaches. (**a**) On this sagittal T1-weighted image, the tumor is noted to fill and obstruct the fourth ventricle and cause hydrocephalus. (**b**) A postcontrast T1-weighted axial image shows a well-defined mass arising in the cerebellum. There is a cyst associated with the medial border of the tumor. (**c**) Prominent flow voids which represent large blood vessels are seen along the lateral border of the tumor in this T2-weighted axial image. (**d**) The vascularity of these tumors is emphasized by a perfusion sequence

patients should undergo complete neural axis imaging in order to rule out multiple lesions. It is recommended that they undergo genetic testing for germline mutations of the VHL gene, as this will have consequences for further treatment planning. In addition, abdominal imaging, ophthalmological evaluation, urine analyses for catecholamines, and urological assessment are recommended in order to identify other sequelae of the VHL disease complex.

11.4.5 Treatment

Because hemangioblastomas are generally benign, microneurosurgery is considered the standard of care in adults. Children and adolescents with VHL syndrome, however, may present with multiple tumors that affect the brain and spinal cord and are therefore rarely cured with surgery. Currently, there is no data on adequate management of these patients. Staged surgical procedures are sometimes recommended in those with symptomatic lesions or tumors with radiographic progression.

Preoperative endovascular embolization is used in adults in order to decrease tumor vascularity and risk of hemorrhage during surgery (Eskridge et al. 1996; Takeuchi et al. 2001); however, this procedure may pose an increased risk of morbidity in children due to smaller vessel caliber. Stereotactic radiosurgery and antiangiogenic therapy have recently been described in adult patients, but no data are available in the pediatric population.

11.4.6 Outcome

Long-term results of hemangioblastoma management are generally favorable, and complete surgical resection generally results in cure. In adults, the overall risk of local recurrence is low. However, children and patients with known VHL have higher rates of recurrence after surgical resection.

Conclusions

Many rare and unusual CNS tumors arise in children. While surgical management is often preferred, definitive treatment must always be individualized. In certain situations, treatment is extrapolated from related tumor type in adults. The prognosis of rare tumors is variable.

References

Abla O, Sandlund JT, Sung L, Brock P, Corbett R, Kirov I, Griffin TC, Blaser S, Weitzman S (2006) A case series of pediatric primary central nervous system lymphoma: favorable outcome without cranial irradiation. Pediatr Blood Cancer 47:880–885

Abla O, Weitzman S, Blay JY, O'Neill BP, Abrey LE, Neuwelt E, Doolittle ND, Baehring J, Pradhan K, Martin SE, Guerrera M, Shah S, Ghesquieres H, Silver M, Betensky RA, Batchelor T (2011) Primary CNS lymphoma in children and adolescents: a descriptive analysis from the International Primary CNS Lymphoma Collaborative Group (IPCG). Clin Cancer Res 17(2):346–352

Amirjamshidi A, Mehrazin M, Abbassioun K (2000) Meningiomas of the central nervous system occurring below the age of 17: report of 24 cases not associated with neurofibromatosis and review of literature. Childs Nerv Syst 16:406–416

Arivazhagan A, Devi BI, Kolluri SV, Abraham RG, Sampath S, Chandramouli BA (2008) Pediatric intracranial meningiomas–do they differ from their counterparts in adults? Pediatr Neurosurg 44:43–48

Batchelor T, Loeffler JS (2006) Primary CNS lymphoma. J Clin Oncol 24:1281–1288

Bills DC, Meyer FB, Laws ER Jr, Davis DH, Ebersold MJ, Scheithauer BW, Ilstrup DM, Abboud CF (1993) A retrospective analysis of pituitary apoplexy. Neurosurgery 33:602–608; discussion 608–609

Buhring U, Herrlinger U, Krings T, Thiex R, Weller M, Kuker W (2001) MRI features of primary central nervous system lymphomas at presentation. Neurology 57:393–396

Caroli E, Russillo M, Ferrante L (2006) Intracranial meningiomas in children: report of 27 new cases and critical analysis of 440 cases reported in the literature. J Child Neurol 21(1):31–36

Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JA, Giustina A (2006) Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol 65(2):265–273

Devoe DJ, Miller WL, Conte FA, Kaplan SL, Grumbach MM, Rosenthal SM, Wilson CB, Gitelman SE (1997) Long-term outcome in children and adolescents after transsphenoidal surgery for Cushing's disease. J Clin Endocrinol Metabol 82:3196–3202

Di Rocco C, Di Rienzo A (1999) Meningiomas in childhood. Crit Rev Neurosurg 9:180–188

Erdincler P, Lena G, Sarioglu AC, Kuday C, Choux M (1998) Intracranial meningiomas in children: review of 29 cases. Surg Neurol 49:136–140; discussion 140–141

Eskridge JM, McAuliffe W, Harris B, Kim DK, Scott J, Winn HR (1996) Preoperative endovascular embolization of craniospinal hemangioblastomas. AJNR Am J Neuroradiol 17:525–531

Ferrante L, Acqui M, Artico M, Mastronardi L, Rocchi G, Fortuna A (1989) Cerebral meningiomas in children. Childs Nerv Syst 5:83–86

Fisher PG, Tontiplaphol A, Pearlman EM, Duffner PK, Hyder DJ, Stolle CA, Vortmeyer AO, Zhuang Z (2002) Childhood cerebellar hemangioblastoma does not predict germline or somatic mutations in the von Hippel-Lindau tumor suppressor gene. Ann Neurol 51:257–260

Gao X, Zhang R, Mao Y, Wang Y (2009) Childhood and juvenile meningiomas. Childs Nerv Syst 25(12):1571–1580

Germano IM, Edwards MS, Davis RL, Schiffer D (1994) Intracranial meningiomas of the first two decades of life. J Neurosurg 80:447–453

Glasker S, Bender BU, Apel TW, Natt E, van Velthoven V, Scheremet R, Zentner J, Neumann HP (1999) The impact of molecular genetic analysis of the VHL gene in patients with haemangioblastomas of the central nervous system. J Neurol Neurosurg Psychiatry 67:758–762

Goutagny S, Kalamarides M (2010) Meningiomas and neurofibromatosis. J Neurooncol 99(3):341–347

Greene S, Nair N, Ojemann JG, Ellenbogen RG, Avellino AM (2008) Meningiomas in children. Pediatr Neurosurg 44:9–13

Haddad SF, VanGilder JC, Menezes AH (1991) Pediatric pituitary tumors. Neurosurgery 29:509–514

Hasselblatt M, Jeibmann A, Gerss J, Behrens C, Rama B, Wassmann H, Paulus W (2005) Cellular and reticular variants of haemangioblastoma revisited: a clinicopathologic study of 88 cases. Neuropathol Appl Neurobiol 31:618–622

Henry JM, Heffner RR Jr, Dillard SH, Earle KM, Davis RL (1974) Primary malignant lymphomas of the central nervous system. Cancer 34:1293–1302

Holl RW, Bucher P, Sorgo W, Heinze E, Homoki J, Debatin KM (1999) Suppression of growth hormone by oral glucose in the evaluation of tall stature. Horm Res 51:20–24

Kadan-Lottick NS, Skluzacek MC, Gurney JG (2002) Decreasing incidence rates of primary central nervous system lymphoma. Cancer 95(1):193–202

Kane LA, Leinung MC, Scheithauer BW, Bergstralh EJ, Laws ER Jr, Groover RV, Kovacs K, Horvath E, Zimmerman D (1994 October) Pituitary adenomas in childhood and adolescence. J Clin Endocrinol Metab. 79(4):1135–1140

Knoepfelmacher M, Gomes MC, Melo ME, Mendonca BB (2004) Pituitary apoplexy during therapy with cabergoline in an adolescent male with prolactin-secreting macroadenoma. Pituitary 7:83–87

Kotecha RS, Pascoe EM, Rushing EJ, Rorke-Adams LB, Zwerdling T, Gao X, Li X, Greene S, Amirjamshidi A, Kim SK, Lima MA, Hung PC, Lakhdar F, Mehta N, Liu Y, Devi BI, Sudhir BJ, Lund-Johansen M, Gjerris F, Cole CH, Gottardo NG (2011) Meningiomas in children and adolescents: a meta-analysis of individual patient data. Lancet Oncol 12(13):1229–1239

Kunwar S, Wilson CB (1999) Pediatric pituitary adenomas. J Clin Endocrinol Metabol 84:4385–4389

Lafferty AR, Chrousos GP (1999) Pituitary tumors in children and adolescents. J Clin Endocrinol Metabol 84:4317–4323

Latif F, Duh FM, Gnarra J, Tory K, Kuzmin I, Yao M, Stackhouse T, Modi W, Geil L, Schmidt L et al (1993) von Hippel-Lindau syndrome: cloning and identification of the plasma membrane Ca(++)-transporting ATPase isoform 2 gene that resides in the von Hippel-Lindau gene region. Cancer Res 53:861–867

Lee SR, Sanches J, Mark AS, Dillon WP, Norman D, Newton TH (1989) Posterior fossa hemangioblastomas: MR imaging. Radiology 171:463–468

Li X, Zhao J (2009) Intracranial meningiomas of childhood and adolescence: report of 34 cases with follow-up. Childs Nerv Syst 25(11):1411–1417

Liu M, Wei Y, Liu Y, Zhu S, Li X (2006) Intraventricular meningiomas: a report of 25 cases. Neurosurg Rev 29(1):36–40

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) (2007) WHO classification of tumors of the central nervous system. International Agency for Research on Cancer, Lyon

Ludecke DK, Abe T (2006) Transsphenoidal microsurgery for newly diagnosed acromegaly: a personal view after more than 1, 000 operations. Neuroendocrinology 83:230–239

Maira G, Anile C (1990) Pituitary adenomas in childhood and adolescence. Can J Neurol Sci 17:83–87

Martínez-Lage JF, Poza M, Alcaraz J, Molina E (1993) Giant meningioma of the III ventricle in a child: case report and review of the literature. Childs Nerv Syst 9(5):306–308

McAllister LD, Doolittle ND, Guastadisegni PE, Kraemer DF, Lacy CA, Crossen JR, Neuwelt EA (2000) Cognitive outcomes and long-term follow-up results after enhanced chemotherapy delivery for primary central nervous system lymphoma. Neurosurgery 46:51–60; discussion 60–61

Maher ER, Yates JR, Harries R, Benjamin C, Harris R, Moore AT, Ferguson-Smith MA (1990) Clinical features and natural history of von Hippel-Lindau disease. Q J Med 77: 1151–1163

Mehta N, Bhagwati S, Parulekar G (2009) Meningiomas in children: a study of 18 cases. J Pediatr Neurosci 4(2):61

Menon G, Nair S, Sudhir J, Rao BR, Mathew A, Bahuleyan B (2009) Childhood and adolescent meningiomas: a report of 38 cases and review of literature. Acta Neurochir 151:239–244

Mindermann T, Wilson CB (1995) Pediatric pituitary adenomas. Neurosurgery 36:259–268; discussion 269

Mohile NA, Abrey LE (2007) Primary central nervous system lymphoma. Neurol Clin 25(4):1193–1207

Newell ME, Hoy JF, Cooper SG, DeGraaff B, Grulich AE, Bryant M, Millar JL, Brew BJ, Quinn DI (2004) Human immunodeficiency virus-related primary central nervous system lymphoma: factors influencing survival in 111 patients. Cancer 100:2627–2636

Oka H, Kurata A, Kawano N, Saegusa H, Kobayashi I, Ohmomo T, Miyasaka Y, Fujii K (1998) Preoperative superselective embolization of skull-base meningiomas: indications and limitations. J Neurooncology 40:67–71

Pandey P, Ojha BK, Mahapatra AK (2005) Pediatric pituitary adenoma: a series of 42 patients. J Clin Neurosci 12:124–127

Partington MD, Davis DH, Laws ER Jr, Scheithauer BW (1994) Pituitary adenomas in childhood and adolescence. Results of transsphenoidal surgery. J Neurosurg 80:209–216

Perry A, Giannini C, Raghavan R, Scheithauer BW, Banerjee R, Margraf L, Bowers DC, Lytle RA, Newsham IF, Gutmann DH (2001) Aggressive phenotypic and genotypic features in pediatric and NF2-associated meningiomas: a clinicopathologic study of 53 cases. J Neuropathol Exp Neurol 60:994–1003

Ram Z, Bruck B, Hadani M (1999) Ultrasound in pituitary tumor surgery. Pituitary 2:133–138

Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, Vernon SW, Cronin K, Edwards BK (2000) The annual report to the nation on the status of cancer, 1973–1997, with a special section on colorectal cancer. Cancer 88:2398–2424

Roychowdhury S, Peng R, Baiocchi RA, Bhatt D, Vourganti S, Grecula J, Gupta N, Eisenbeis CF, Nuovo GJ, Yang W, Schmalbrock P, Ferketich A, Moeschberger M, Porcu P, Barth RF, Caligiuri MA (2003) Experimental treatment of Epstein–Barr virus-associated primary central nervous system lymphoma. Cancer Res 63:965–971

Schulman H, Hertzanu Y, Maor E, Hadar A (1991) Primary lymphoma of brain in childhood. Pediatr Radiol 21:434–435

Semple PL, Webb MK, de Villiers JC, Laws ER Jr (2005) Pituitary apoplexy. Neurosurgery 56:65–72; discussion 72–73

Steele CA, MacFarlane IA, Blair J, Cuthbertson DJ, Didi M, Mallucci C, Javadpour M, Daousi C (2010) Pituitary adenomas in childhood, adolescence and young adulthood: presentation, management, endocrine and metabolic outcomes. Eur J Endocrinol 163(4):515–522

Takeuchi S, Tanaka R, Fujii Y, Abe H, Ito Y (2001) Surgical treatment of hemangioblastomas with presurgical endovascular embolization. Neurol Med Chir 41:246–251; discussion 251–252

Traunecker H, Mallucci C, Grundy R, Pizer B, Saran F (2008) Children's Cancer and Leukaemia Group (CCLG): guidelines for the management of intracranial meningioma in children and young people. Br J Neurosurg 22(1):13–25

Tufan K, Dogulu F, Kurt G, Emmez H, Ceviker N, Baykaner MK (2005) Intracranial meningiomas of childhood and adolescence. Pediatr Neurosurg 41:1–7

Van Velthoven V, Reinacher PC, Klisch J, Neumann HP, Glasker S (2003) Treatment of intramedullary hemangioblastomas, with special attention to von Hippel-Lindau disease. Neurosurgery 53:1306–1313; discussion 1313–1314

Webb C, Prayson RA (2008) Pediatric pituitary adenomas. Arch Pathol Lab Med 132:77–80

Yoon JH, Kang HJ, Kim H, Lee JW, Park JD, Park KD, Shin HY, Ahn HS (2012) Successful treatment of primary central nervous system lymphoma without irradiation in children: single center experience. J Korean Med Sci 27(11):1378–1384

Zagzag D, Krishnamachary B, Yee H, Okuyama H, Chiriboga L, Ali MA, Melamed J, Semenza GL (2005) Stromal cell-derived factor-1alpha and CXCR4 expression in hemangioblastoma and clear cell-renal cell carcinoma: von Hippel-Lindau loss-of-function induces expression of a ligand and its receptor. Cancer Res 65:6178–6188

Neurocutaneous Syndromes and Associated CNS Tumors

12

Alexei Polishchuk, Daphne A. Haas-Kogan, and Sabine Mueller

Contents

A. Polishchuk, MD
Department of Radiation Oncology,
University of California San Francisco,
1600 Divisadero Street, Suite H1031,
San Francisco, CA 94115, USA
e-mail: Alexei.Polishchuk@ucsf.edu

D.A. Haas-Kogan, MD
Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston Children's Hospital,
450 Brookline Ave. D1622,
Boston, MA 02215-5418, USA
e-mail: dhaas-kogan@lroc.harvard.edu

S. Mueller (✉)
Departments of Neurology, Neurosurgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital,
625 Nelson Rising Lane, Room 402C,
Sandler Neuroscience Building,
San Francisco, CA 94115, USA
e-mail: sabine.mueller@ucsf.edu

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_12

12.1 Introduction

In the Greek language, *Phakos* means spot, mole, or lentil, and phakomatosis suggests the presence of a congenital lesion or birthmark (Berg 1991). Historically, this term was applied to a group of genetic disorders defined by the involvement of the central nervous system (CNS), skin, and one or more body systems. Over time, this group expanded to include over 40 entities, each with its own specific features (Chalhub 1976). This chapter reviews six of the more common neurocutaneous syndromes and the current designation for these disorders, with a particular emphasis on the CNS tumors occurring in each disease: neurofibromatosis types 1 (NF1) and 2 (NF2), tuberous sclerosis (TS), ataxia telangiectasia (AT), von Hippel–Lindau (VHL), and Sturge–Weber syndrome (SWS). Other comprehensive reviews discuss each entity in detail (Ranger et al. 2014; Lin and Gutmann 2013; Karajannis and Ferner 2015; Rovira et al. 2014; Chaudhary and Al-Baradie 2014; Vortmeyer et al. 2013; Sudarsanam and Ardern-Holmes 2014). More up-to-date information on current molecular genetics is also available through the Online Mendelian Inheritance in Man website (http://www.ncbi.nlm.nih.gov/omim/).

Dysplasia caused by specific genetic alterations within normal ectodermal tissue is thought to give rise to the abnormalities seen in the skin and neural tissues of individuals with neurocutaneous syndromes. The same underlying molecular defects predispose affected individuals to further genetic alterations and increased risk of developing a neoplasm. The molecular mechanisms leading to marked variations in disease phenotype remain incompletely understood, but may depend on specific mutation features in the syndrome genes (Sharif et al. 2011; Upadhyaya et al. 2007) as well as on yet unknown modifier genes and environmental factors (Sabbagh et al. 2009). Clinical characterization of these syndromes has improved, accelerated by advances in imaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI) (Cai et al. 2009; Kalantari and Salamon 2008; van Engelen et al. 2008). Imaging is now essential to identify major and minor criteria used for the diagnosis of neurocutaneous syndromes. In many patients, the neuroradiographic features often precede clinically significant findings or patient symptoms. Advanced imaging techniques are also being incorporated into syndrome-specific response criteria for design of new clinical trials in phakomatoses (Widemann et al. 2013).

Research discoveries revealing the molecular pathogenesis of these disorders have spurred multiple clinical trials of targeted therapies tailored to syndrome-specific aberrant signaling pathways. Clinical success using this strategy has revolutionized the management of vestibular schwannomas in NF2 (bevacizumab) and subependymal giant cell astrocytomas in TS (mTOR inhibitors) (Plotkin and Stemmer-Rachamimov 2009; Franz et al. 2013). Numerous other rationally selected, targeted molecular therapies are being evaluated in clinical trials for tumors occurring in patients with neurocutaneous syndromes.

There are several reasons why oncologists should be familiar with the neurocutaneous syndromes. First, these patients are at increased risk of developing CNS tumors. Second, the natural history of these tumors often differs from sporadically occurring versions of the same tumors (Oh et al. 2011; Listernick et al. 2007; Shamji and Benoit 2007). Finally, the incidence of these inherited syndromes is relatively high. Similar to other genetic syndromes and heritable diseases, great variability exists among patients with phakomatoses due in part to mosaicism, expressivity, and genetic penetrance. Such variability exists among patients afflicted with the same neurocutaneous syndrome, even within a single family and among monozygotic twins (Rieley et al. 2011). Genotype–phenotype correlation studies have given further insight into these diseases but have been disappointing with regard to predicting outcome based on specifically identified mutations (Sabbagh et al. 2013; van Slegtenhorst et al. 1999; Becker-Catania et al. 2000). Further complexity is added by spontaneous mutations that result in neurocutaneous syndromes that lack a family history but incur subsequent risk for patients and their progeny.

12.2 Neurofibromatosis Type 1

12.2.1 Epidemiology

NF1, historically known as von Recklinghausen's disease, is an autosomal dominant disease with an estimated incidence of 1:3000–4000, with equal sex distribution, and no apparent ethnic predisposition (Szudek et al. 2000; Korf 2002). It is one of the most common single-gene disorders, with as many as 50 % of cases arising sporadically due to new mutations. The disorder has a high phenotypic inheritance, and therefore, unaffected parents have a low risk of recurrence. Most cases of NF1 can be detected in infancy based on skin abnormalities, which, although subtle, usually intensify with age, especially after puberty. NF1 exhibits nearly 100 % penetrance by 8 years of age (DeBella et al. 2000).

12.2.2 Genetics and Molecular Biology

The *NF1* gene maps to chromosome 17q11.2 and consists of 57 constitutive exons spread over 350 kb of genomic DNA. More than 200 different mutations have been observed in patients with NF1 (Pros et al. 2008). The *NF1* gene encodes for a 2818 amino acid protein referred to as neurofibromin; is expressed in Schwann cells, oligodendrocytes, and neurons; and acts as a tumor suppressor gene. The protein contains a large amino acid segment exhibiting homology to the functional domain of the p21ras GTPase-activating protein. p21ras GTPase inactivates the oncogene p21ras by stimulating its GTPase activity, thus converting the active form of p21ras into its inactive form. Mutations of neurofibromin leading to low or absent expression allow constitutive activation of p21ras and probably account for the many phenotypic abnormalities seen in NF1, including benign and malignant neoplasms. Germline mutation in the *NF1* gene constitutes the first hit in the 2-hit cancer theory. Malignant transformation occurs with additional genetic changes such as mutations in *TP53* or loss of *CDKN2A* or *PTEN* (reviewed in Laycock-van Spyk et al. 2011). Inactivation of neurofibromin has also been shown to alter cellular cAMP levels in neurons via ras-dependent signaling through PKCζ (Anastasaki and Gutmann 2014). It has been suggested that such molecular signaling abnormalities may also underlie the learning disabilities well-described in approximately half of all patients with NF1 (Diggs-Andrews and Gutmann 2013; Szudek et al. 2000).

12.2.3 Diagnostic Criteria and Clinical Features

The clinical features of NF1 are divided into major and minor subgroups (Table 12.1). The most recognizable clinical feature of NF1 is the café au lait spot, a smooth, nonraised, brown discoloration of the skin, which appears before adulthood in 95 % of patients with NF1. Dermal neurofibromas, which arise from Schwann cells, occur in >99 % of patients. These tumors appear during adolescence and increase in number and size with age. Other manifestations seen in patients with NF1 include axillary freckling, Lisch nodules (pigmented hamartomas of the iris), optic gliomas, and bone dysplasias (Szudek et al. 2000; Korf 2002). Other associated symptoms include

Table 12.1 Major and minor features of NF1

Major features	Minor features
Café au lait spots and skin freckling	Macrocephaly
Peripheral neurofibromas	Short stature as growth hormone deficiency found in NF1 patients that do not even have hypothalamic lesions
Lisch nodules (iris hamartomas)	Hypsarrhythmia
Plexiform neurofibromas	Intellectual difficulties (e.g., learning difficulties)
CNS tumors (optic gliomas, spinal neurofibromas)	Epilepsy
Distinctive osseous lesions (ribbon ribs, sphenoid wing dysplasia, pseudarthroses, or thinning of long bone cortex)	Hypertension – may be due to aortic coarctation, renal artery stenosis, or pheochromocytoma

NIH Consensus Development Conference, Neurofibromatosis: Conference Statement, 1988

macrocephaly, vascular changes, short stature, scoliosis, and learning disabilities. As outlined in an earlier NIH meeting (NIH Consensus Development Conference, Neurofibromatosis: Conference Statement 1988), the diagnosis of NF1 is made if a patient has met two or more of the following criteria:

1. Six or more café au lait spots (greatest diameter >5 mm if prepubertal, >15 mm if postpubertal)
2. Two or more neurofibromas of any type or one or more plexiform neurofibromas
3. Freckling in the axilla or inguinal regions (Crowe's sign)
4. Two or more Lisch nodules (iris hamartomas)
5. An optic pathway tumor
6. A distinctive osseous lesion such as sphenoid wing dysplasia or thinning of the cortex of the long bones with or without pseudarthroses
7. First-degree relative (parent, sibling, or offspring) with NF1 by the aforementioned criteria

There is an increased incidence of specific CNS neoplasms in patients with NF1 (Korf 2000; Rosser and Packer 2002). The most common NF1-associated tumors are optic gliomas, especially chiasmatic gliomas, the majority of which are diagnosed in childhood (Turgut et al. 1991; Balestri et al. 1993). Studies suggest that up to 30 % of patients with optic pathway glioma have stigmata of NF1 (Dutton 1994) and 5–25 % of patients with NF1 have signs of optic pathway glioma (Listernick et al. 2007), suggesting that many NF1 patients are asymptomatic and, therefore, might never be diagnosed. If symptomatic, these tumors may present with decreased visual acuity, visual field defects, proptosis, and precocious puberty due to hypothalamic compression. To date, there is no consensus regarding the frequency of follow-up MRIs required, and it can vary from every 3 to 24 months (Listernick et al. 2007). Some studies argue that assessing the visual system is sufficient to follow these patients and that MRI studies are not indicated in patients with no clinical signs of disease progression (Listernick and Charrow 2004; Listernick et al. 2007).

In addition to optic gliomas, NF1 is associated with an increased incidence of parenchymal gliomas, particularly in the brainstem, cerebellar peduncles, globus pallidus, and midbrain. The biologic behavior of brainstem gliomas in patients with NF1 differs significantly from that of lesions with similar appearance in patients without NF1 (Pollack et al. 1996; Listernick et al. 1999). In general, patients with NF1 and brainstem gliomas have better outcomes than nonaffected children (Sevick et al. 1992; Listernick et al. 1994). A recent study identified 23 patients out of 125 with NF1 (18.4 %) who presented with brainstem mass lesions. Reported outcome was favorable; 17/23 untreated and 6/23 treated patients were alive with stable or decreased disease burden on MRI at median follow-up of 67 and 102 months, respectively. Only one previously untreated patient experienced disease progression (Ullrich et al. 2007). Brainstem tumors should not be confused with nonspecific white matter changes, which are frequently found on MRI in patients with NF1 and are of unknown clinical significance (Sevick et al. 1992; van Engelen et al. 2008). These unidentified bright objects are normally not associated with mass effect, edema, or contrast enhancement and tend to decrease in size over time. Besides astrocytomas, CNS neoplasms that occur at higher rates in NF1 patients are ependymomas, meningiomas, and medulloblastomas.

NF1 patients develop not only CNS lesions but also peripheral nervous system tumors. Neurofibromas and schwannomas arise most commonly from major peripheral nerves particularly radial and ulnar nerves. The incidence of symptomatic neurofibromas in NF1 patients is 4 %, and the incidence of asymptomatic but radiographically evident tumors is >25 %. Malignant transformation leads to malignant peripheral nerve sheath tumors. These tumors occur in less than 5 % of children with NF1, but are the leading cause of mortality in adults with NF1 (Rasmussen et al. 2001). Malignant peripheral nerve sheath tumors (MPNST) are chemoresistant sarcomas associated with poor 5-year survival rates despite aggressive therapy. The impact of NF1 diagnosis on the prognosis of

MPNST is controversial (LaFemina et al. 2013; Kolberg et al. 2013; Porter et al. 2009). The clinical signs associated with malignant transformation are rapid growth and/or pain. FDG-PET is increasingly relied upon to identify lesions suspicious for malignant transformation (Benz et al. 2010; Tsai et al. 2012). Surgical resection remains the mainstay of therapy. The other indication for surgical resection is a large tumor that creates a cosmetic problem. Patients with NF1 are also at risk for non-CNS tumors, including Wilm's tumor, rhabdomyosarcoma, leukemia, melanoma, medullary thyroid carcinoma, and pheochromocytoma.

12.2.4 Natural History and Prognosis

NF1 is a progressive disease that can affect almost any organ (Rasmussen et al. 2001; Korf 2002), and overall survival is less than that of the general population (Sorensen et al. 1986; Evans et al. 2011; Duong et al. 2011); however, outcomes remain highly variable even within individual families. The causes of death in NF1 patients include malignant peripheral nerve sheath tumors, CNS tumors, and systemic conditions such as hypertension due to the associated vasculopathies leading to renal artery stenosis. Patients with NF1 are 34 times more likely to have malignant connective tissue or soft tissue neoplasms than non-NF1 individuals (Rasmussen et al. 2001). In population-based cohorts that include children with NF1, a ~4000–8000-fold increased risk of death from MPNST is seen when compared to the non-NF1 population (Evans et al. 2011).

12.2.5 Laboratory Studies

A wide variety of mutations in the NF1 gene have been identified. Current molecular technology is able to identify NF1 mutations in greater than 95 % of cases (Messiaen et al. 2000). Next-generation sequencing has been successfully deployed in the molecular diagnosis of NF1 patients and may facilitate genotyping NF1 mosaic patients as well as identification of second-hit mutations in NF1-associated tumor specimens (Pasmant et al. 2015). However, to date, the majority of cases are identified on a clinical basis, and therefore genetic testing should be reserved for when there is uncertainty in the clinical diagnosis. Prenatal diagnosis is also available for couples with a positive family history of NF1.

12.2.6 Imaging Studies

With MR brain imaging, optic nerve gliomas are easily visible with enlargement of the optic nerve(s), chiasm, and/or optic tract (Fig. 12.1). Asymptomatic optic gliomas are present in up to 20 % of NF1 patients. The extent of involvement is often underestimated with T1-weighted images, while T2-weighted images provide better representation of the involved areas. Contrast enhancement can occur and may be heterogeneous or homogeneous. Brainstem gliomas are relatively common (Aoki et al. 1989; Balestri et al. 1993; Mukonoweshuro et al. 1999; Kornreich et al. 2001; Fischbein et al. 2000). Parenchymal tumors (usually astrocytomas) have a predilection for the thalami and basal ganglia and appear as T2 prolonging mass lesions with variable post-gadolinium enhancement.

Nonenhancing foci of T2 prolongation within deep gray nuclei and the white matter have a poorly understood underlying etiology (Billiet et al. 2014) and can be difficult to distinguish from suspected low-grade brainstem gliomas on MR imaging in the setting of NF1 (Hervey-Jumper et al. 2013). Their natural history is reflective of an indolent process with reports of spontaneous regression. These are most common in the globus pallidus, followed by the cerebellum and brainstem, internal capsules, centrum semiovale, and corpus callosum and occur in up to 60 % of NF1 patients (Fig. 12.2). The T2-weighted signal characteristics are variable.

MRI remains a mainstay modality for detection and surveillance of peripheral neurofibromas in NF1 patients. Recent reports suggest a promising role of whole-body MRI for rapid, comprehensive, and quantitative assessment of

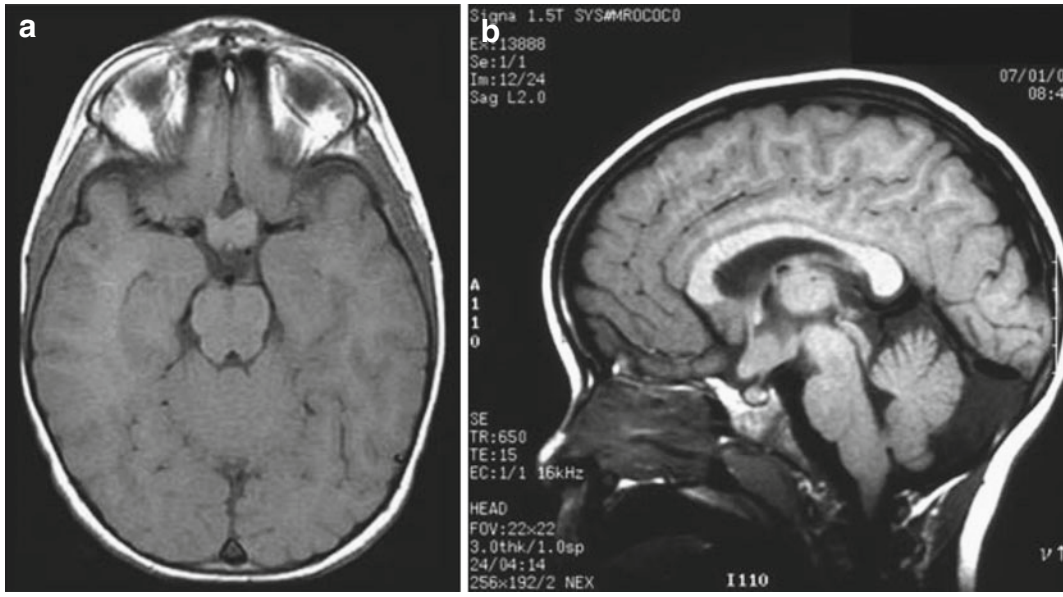

Fig. 12.1 Optic pathway gliomas associated with NF1. (**a**) The T1-weighted axial images show asymmetry of the optic chiasm with the left optic nerve being larger than the right. The mass did not enhance following gadolinium administration. (**b**) A sagittal T1-weighted image shows the thickened chiasm directly above the pituitary gland

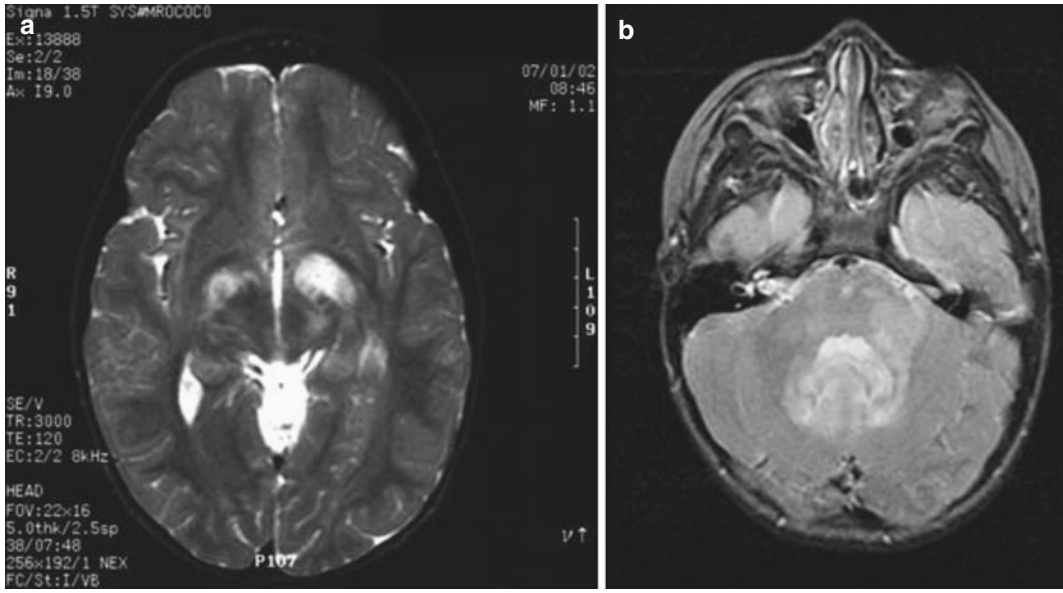

Fig. 12.2 White matter lesions associated with NF1. These lesions are best seen on T2-weighted images. (**a**) In this axial image, there are bilateral lesions (larger on the patient's left side) within the basal ganglia that do not produce much mass effect. These lesions do not enhance following gadolinium administration. (**b**) Similar lesions may be seen in the posterior fossa. Here, the area of T2 prolongation extends from the cerebellar peduncle toward the pons

neurofibroma tumor burden (Plotkin et al. 2012). FDG-PET imaging has shown promise in differentiating MPNST from non-degenerated neurofibromas in the setting of NF1 (Benz et al. 2010; Tsai et al. 2012).

12.2.7 Treatment

Patients with NF1 should have a thorough annual physical examination including visual field testing. Although the value of screening imaging studies is not proven, most patients at some point undergo a screening MRI of the brain and spine. Even if a mass is identified, treatment focuses on symptomatic lesions (Turgut et al. 1991; Pollack et al. 1996). Most optic pathway gliomas associated with NF1 are asymptomatic, and some have been noted to regress spontaneously (Parsa et al. 2001). Pathologically, these tumors are mainly pilocytic astrocytomas, classified as WHO grade I, with more indolent clinical courses than in non-NF1 patients. The role of surgery in patients with optic pathway gliomas remains controversial. Consensus for surgical intervention exists for single-nerve lesions, which cause disfiguring symptoms for patients. Surgery might also be beneficial if there are signs of increased intracranial pressure, mass effect, or hydrocephalus (Medlock et al. 1997; Astrup 2003). Rapidly growing tumors, more frequently located in the hypothalamus and chiasm, benefit from early surgical resection to preserve vision and reduce mass effect (Listernick et al. 2007).

Radiation therapy is discouraged in patients with NF1, mainly due to the development of neurovascular, endocrine and neuropsychological side effects as well as the high risk of developing secondary malignancies (Madden et al. 2014; Grill et al. 1999; Sharif et al. 2006). In a prospective trial of conformal radiation therapy for pediatric low-grade glioma that included 13 patients with NF1, the presence of NF1 was associated with lower baseline intellectual function as compared to non-NF1 patients and with a greater decline in behavioral assessment scores following radiation treatment (Merchant et al. 2009). With respect to secondary malignancy risk, one study showed that three out of five patients with NF1 and optic pathway glioma, who were treated with radiation therapy for disease progression, developed a secondary CNS tumor, whereas none of the patients with sporadic tumors developed a secondary tumor (Singhal et al. 2002). Similarly, in another study of neurofibromatosis patients treated with radiotherapy, local control was achieved with irradiation in three of five low-grade glioma patients, while two patients progressed to high-grade glioma in the radiation field (Wentworth et al. 2009). By contrast, a prospective study of radiation or chemotherapy for progressive pediatric low-grade glioma reported no untoward radiation-associated acute or late effects in ten NF1 patients who had received radiation therapy with a median follow-up of 5.2 years for this subgroup. Only three of these patients demonstrated post-radiation tumor progression (Hernaiz Driever and von Hornstein 2010).

Slow enlargement of optic pathway gliomas clearly demonstrated on serial imaging studies and accompanied by symptoms can be managed by systemic chemotherapy. A recent expert consensus statement recommends nonsurgical treatment of hypothalamic–chiasmatic low-grade gliomas if visual function is threatened or if symptomatic progression is documented. Surgical intervention was not recommended as frontline therapy in the majority of cases (Walker et al. 2013). A retrospective multicenter study of visual outcomes after chemotherapy in 115 patients with NF1-associated optic pathway glioma revealed improved and stable visual acuity after chemotherapy in 32 % and 40 % of patients, respectively (Fisher et al. 2012). A large phase II study found that 22 NF1 patients with low-grade gliomas who were treated with chemotherapy had better overall survival than non-NF1 patients (Gururangan et al. 2002). Patients were treated if they met one or more of the following criteria: (a) >25 % increase in the size of the tumor (Fig. 12.3a, b), (b) papilledema, (c) loss of vision, (d) increase in proptosis, or (e) increase in the diameter of the optic nerve >2 mm. An increased response rate following chemotherapy in NF1-associated pediatric low-grade gliomas as

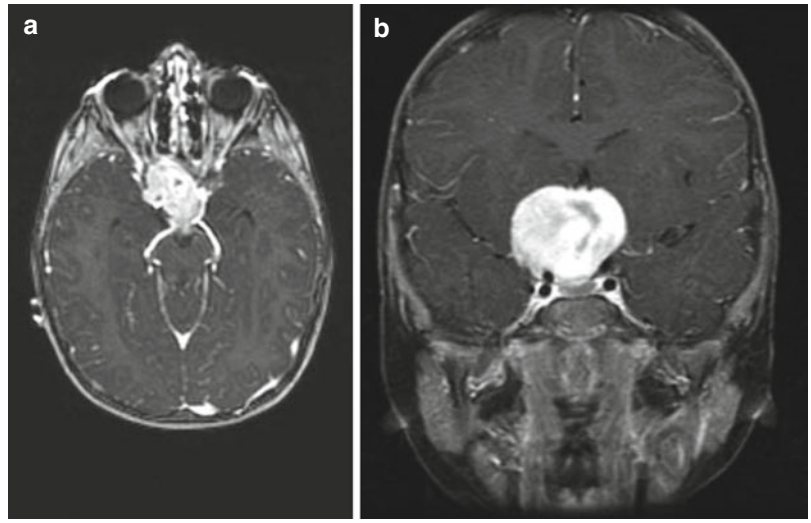

Fig. 12.3 Large optic pathway glioma in a patient with NF1. This 3-year-old-girl presented with visual loss and was noted to have an extremely large optic glioma as seen on axial (**a**) and coronal (**b**) T1-weighted images following contrast administration. The optic chiasm and nerves cannot be differentiated from the tumor. Because of the degree of visual loss, the patient underwent biopsy to confirm the diagnosis and then was started on chemotherapy

compared to sporadic pediatric low-grade gliomas was also observed in the long-term follow-up results of the large HIT-LGG-1996 protocol in Europe (Gnekow et al. 2012) and in preliminary results of the COG protocol A9952 (Kalamarides et al. 2012). It is yet unclear, however, whether the overall favorable prognosis of these lesions in the setting of NF1 is attributable predominantly to increased chemosensitivity versus an intrinsically indolent natural history.

Usually, protocols tailored for low-grade astrocytic tumors are used (see Chap. 1). There have been early reports of promising activity of bevacizumab associated with long-term survival in NF1-associated high-grade glioma (Theeler et al. 2014). Surgery is often required for plexiform neurofibromas that have become disfiguring or painful, and multiple targeted biologic-based approaches have been investigated in recent early phase trials. Unfortunately, many rationally selected agents failed translation from animal models to phase I and phase II trials in the setting of NF1 (Agarwal et al. 2014). However, there have been preliminary signs of promise in phase II trials of the farnesyltransferase inhibitor tipifarnib (Widemann et al. 2014a) and the c-Kit inhibitor imatinib (Robertson et al. 2012) in the treatment of NF1-associated neurofibromas. Encouraging preliminary results have also been seen in a trial of the MEK inhibitor selumetinib in NF1-associated inoperable plexiform neurofibromas (Widemann et al. 2014b). See http://www.ctf.org for ongoing NF1 patient trials.

12.3 Neurofibromatosis Type 2

12.3.1 Epidemiology

NF2 is inherited in an autosomal dominant manner with an incidence of 1:37,000 and has no gender predilection (Mautner et al. 1993; Parry et al. 1994). Generally NF2 patients become symptomatic at puberty or thereafter, but age of onset is highly variable. The mean age of onset of symptoms is approximately 17 years, usually with tinnitus and/or acute hearing loss due to vestibular tumors.

12.3.2 Molecular Biology and Cytogenetics

The *NF2* gene is located on chromosome 22q12, and the protein consists of 595 amino acids. It was identified in 1993 in two different laboratories and named *merlin* and *schwannomin* (Rouleau et al. 1993; Bianchi et al. 1994). The name merlin refers to a high degree of homology with a family of F-actin-binding proteins including *m*oesin, *e*zrin, and *r*adixin (De Vitis et al. 1996a, b).

Merlin localizes at the cell membrane and acts as a membrane-cytoskeletal linker. It can revert Ras-induced malignant phenotypes, indicating that the *NF2* gene product has a tumor suppressor activity. More recently, merlin has been shown to control a broad cellular proliferation signaling program through inhibition of the $CRL4^{DCAF1}$ E3 ubiquitin ligase and modulation of the Hippo signaling pathway by a variety of mechanisms (Cooper and Giancotti 2014; Karajannis and Ferner 2015). Multiple canonical downstream growth signaling pathways including Rac-PAK, PI3K-Akt, FAK-Src, and EGFR-Ras-Erk appear to be negatively regulated by active merlin. Mechanistic links between these canonical pathways and upstream events in the setting of merlin inactivation remain to be fully elucidated.

Despite considerable efforts, it also remains unclear if any of the known merlin-regulated signaling pathways are keys to the development of NF2-associated tumors (Scoles 2008). Mutations leading to the loss of merlin expression are the most common gene defect in meningiomas. A total of 50–60 % of all spontaneous meningiomas and NF2-associated meningiomas have mutations in the *NF2* gene. Schwannomas are caused by loss of merlin expression, whereas only 29–38 % of ependymomas show alteration in merlin expression (Lamszus et al. 2001; Rajaram et al. 2005). Mutations of the *NF2* gene occur not only in neoplasms associated with NF2 but also in 30 % of melanomas and 41 % of mesotheliomas (De Vitis et al. 1996a, b). It remains unclear why *NF2* mutations predispose to the formation of bilateral vestibular schwannomas.

Recently, a third disorder within neurofibromatosis was distinguished as schwannomatosis. This disorder is characterized by the presence of schwannomas of cranial nerves other than the vestibular nerve. This disorder has been associated with two genes on chromosome 22 near the *NF2* locus, *SMARCB1*, and *LZTR1* (Paganini et al. 2015).

12.3.3 Diagnostic Criteria and Clinical Features

Clinical criteria are used to diagnose NF2 (Table 12.2). Bilateral vestibular schwannomas, which are characteristic lesions in patients with NF2, usually present with tinnitus and/or hearing loss (Uppal and Coatesworth 2003). These tumors are found in 96 % of NF2 patients: bilateral in 90 %, and unilateral in 6 %. Vestibular schwannomas were formerly called acoustic neuromas, an inaccurate term because they arise from Schwann cells and typically involve the vestibular rather than the acoustic (cochlear) branch of the eighth cranial nerve. NF2 patients exhibit an overall predilection for tumors of the meninges and Schwann cells and may also present with facial nerve, trigeminal nerve, and multiple spinal nerve schwannomas, as well as meningiomas and retinal hamartomas. Symptoms at time of presentation include hearing loss, tinnitus, and disequilibrium from vestibular schwannomas. NF2 patients under 10 years of age present most commonly with visual deficits or rapidly growing skin tumors.

Table 12.2 NF2 diagnostic criteria

Primary criteria	Additional criteria
Bilateral eighth cranial nerve masses (vestibular schwannomas) seen with imaging techniques	Unilateral vestibular schwannoma *and* any two of glioma, meningioma, neurofibroma, schwannoma, or posterior subcapsular lenticular opacities
Family history of NF2 *and* unilateral vestibular schwannoma *or* any two of glioma, neurofibroma, meningioma, schwannoma, or posterior subcapsular lenticular opacities	Multiple (2 or more) meningiomas *and* unilateral vestibular schwannoma *or* any two of the following schwannoma, glioma, neurofibroma, or cataract

Modified NIH Consensus Criteria, Evans et al. (2005)

NF2 patients develop other central neurofibromas including paraspinal tumors that may compress the spinal cord and present with myelopathy. These lesions are surprisingly common (67–90 %) in patients with NF2 and are a source of major morbidity and mortality (Mautner et al. 1995; Dow et al. 2005). Additional lesions associated with NF2 include posterior subcapsular cataracts (63 %), retinal hamartomas, optic nerve sheath meningiomas, meningiomas, ependymomas (usually spinal cord), gliomas, and trigeminal schwannomas (Mautner et al. 1996).

12.3.4 Natural History and Prognosis

The mean age of onset of symptoms is 17 years, while the mean age of NF2 diagnosis is 22 years. Relentless progression of vestibular schwannomas and other tumors may lead to loss of vision, paresis, and eventual death from brainstem compression (Parry et al. 1994). Overall, NF2 patients have been demonstrated to have a decreased life expectancy as compared to the general population (Wilding et al. 2012). However, the prognosis for NF2 patients is variable, as a spectrum of phenotypes exists. The type of mutation in the *NF2* gene influences the disease severity. Constitutional nonsense and frameshift mutations that cause protein truncation confer a poorer phenotype (Baser et al. 2004; Selvanathan et al. 2010). Early detection offers distinct advantages to the patients as hearing preservation remains a challenge. The diagnosis of NF2 increases the likelihood of developing CNS tumors (schwannomas, meningiomas, gliomas, and neuromas) that may involve the brain, cranial nerves, or spinal cord.

12.3.5 Laboratory Studies

Laboratory diagnosis relies on the presence of DNA mutation in the *NF2* gene and requires linkage studies from DNA derived from at least two affected family members.

12.3.6 Imaging Studies

Schwannomas on CT head scanning are round or ovoid extra-axial masses. They are iso- to mildly hypodense on noncontrast CT scan, unless cystic or hemorrhagic. Meningiomas are dural-based, extra-axial masses, often with an associated dural tail. They are typically isodense to brain on nonenhanced CT scan (Aoki et al. 1989; Mautner et al. 1996; Fischbein et al. 2000).

On MR imaging, schwannomas are iso- to mildly hypointense compared to brain parenchyma on T1-weighted images. They are iso- to hyperintense to brain parenchyma on T2-weighted images. Intense homogeneous enhancement after contrast administration is typically seen (Fig. 12.4a), although areas of cystic change or hemorrhage may lead to heterogeneous enhancement. Large lesions may cause brainstem compression and/or hydrocephalus. The multilobulated-appearing vestibular schwannomas often seen in NF2 have recently been shown to consist of mixed cell populations bearing a variety of somatic NF2 mutations, suggestive of a collision between several distinct tumor clones, which

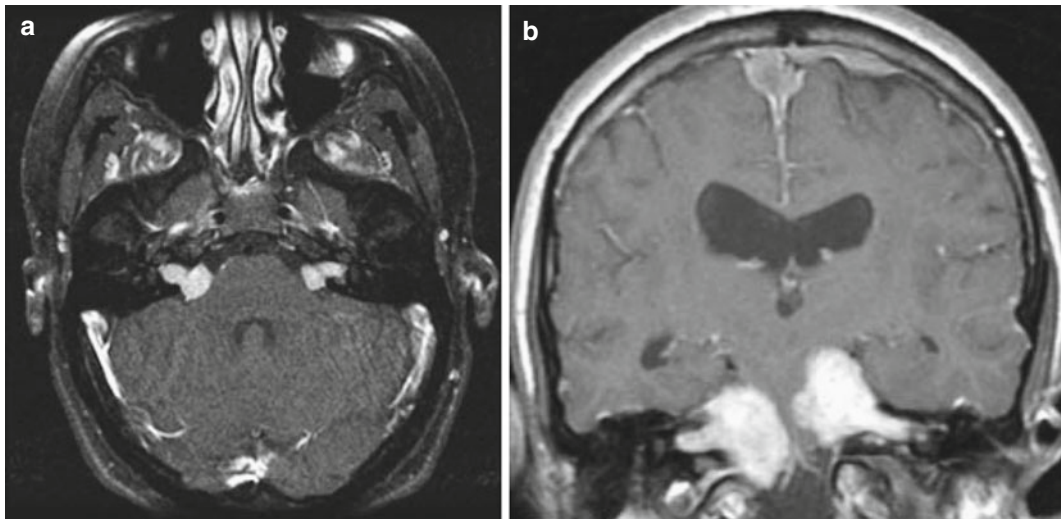

Fig. 12.4 NF2 tumors. (**a**) Typical appearance of bilateral vestibular schwannomas in a teenage girl. On this fat-suppressed T-weighted axial image, the tumors are clearly seen arising from the internal acoustic meatuses on either side. (**b**) This patient has much larger bilateral schwannomas although convexity and falcine meningiomas are also visualized

may account for their relative resistance to treatment (Dewan et al. 2015).

Similar to schwannomas, meningiomas are isointense to gray matter on T1- and T2-weighted images. They usually enhance intensely and homogeneously following gadolinium administration, and calcifications are common (Fig. 12.4b) (Mautner et al. 1996; Fischbein et al. 2000).

12.3.7 Treatment

The best approach to the management of schwannomas remains controversial, although expert consensus recommendations have been published (Blakeley et al. 2011). Hearing loss in the setting of vestibular schwannomas generally progresses slowly, and if the lesions are small and asymptomatic, patients can be followed by serial imaging studies. A natural history study performed on a large, newly diagnosed NF2 patient cohort with vestibular schwannomas showed rates of hearing decline of 5 % at 1 year, 13 % at 2 years, and 16 % at 3 years. Rates of radiographic tumor progression in this population were higher: 31 % at 1 year, 64 % at 2 years, and 79 % at 3 years (Plotkin et al. 2014). Any progression of symptoms such as hearing loss may be considered failure of conservative management. By contrast, large lesions >3 cm are approached with frontline surgery, and those with brainstem compression may require urgent surgical intervention (Blakeley et al. 2011).

Vestibular schwannoma surgery is challenging and often is performed by multidisciplinary teams of neurosurgeons and neuro-otologists. Several surgical approaches have been described including translabyrinthine, middle cranial fossa, and suboccipital, each with its own advantages and potential risks. Ipsilateral facial nerve damage has been reported in 17 % of patients undergoing removal of vestibular schwannomas greater than 2.5 cm (Grey et al. 1996). This complication can have significant impact on patient quality of life.

Recently, radiosurgery has become more popular in the management of vestibular schwannomas. The main goal of radiosurgery is tumor control, which appears to be decreased in the setting of NF2 as compared to patients with sporadic vestibular schwannomas. In one large retrospective single institutional series of NF2-associated vestibular schwannomas treated with radiosurgery, 8-year local control was 50 % and 3-year hearing preservation was 40 % (Rowe et al. 2008), though subsequent, smaller, series have reported more favorable tumor control outcomes (e.g., Mallory et al. 2014). While secondary malignancies and malignant transformation of vestibular schwannomas following radiosurgery are rare, the majority of described cases have been in the setting of preexisting NF2, suggesting that these patients are at an increased risk of radiation-induced cancer induction (Balasubramaniam et al. 2007).

The therapeutic landscape in NF2-associated lesions has recently been transformed by successes in early trials of targeted biologic therapies based on our evolving understanding of schwannoma biology and the signaling consequences of merlin loss. Schwannomas are known to express high levels of the pro-angiogenic signaling factor VEGF (Caye-Thomasen et al. 2003). In a pilot trial of the anti-VEGF antibody bevacizumab in ten NF2 patients with progressive vestibular schwannoma who were not candidates for standard therapy, six patients exhibited radiographic tumor responses, and four of seven hearing-evaluable patients had objective improvement in hearing (Plotkin and Stemmer-Rachamimov 2009). Similarly promising tumor and hearing response rates were seen in a larger bevacizumab-treated NF2 cohort with longer-term follow-up; however, continuous therapy was required for sustained responses (Plotkin et al. 2012). Unfortunately, in NF2-associated meningiomas, bevacizumab responses were transient and much less frequent, implicating signaling pathways other than VEGF in the growth of these entities (Nunes et al. 2013). Based on the finding that the EGFR signaling pathway was negatively regulated by NF2 (Curto et al. 2007), a recent phase II trial of the EGFR/ErbB2 inhibitor lapatinib in children and adults with NF2-associated vestibular schwannomas revealed volumetric responses in 24 % of patients and hearing responses in 31 % of patients with a median time to overall progression of 14 months (Karajannis et al. 2012). mTOR signaling was also shown to be dysregulated in preclinical models of NF2; however, a recent phase II study of the mTOR inhibitor everolimus in NF2-associated vestibular

schwannoma was negative (Karajannis et al. 2014). At this time, more clinical experience is warranted to better define the most effective treatment(s) and key criteria for initiating therapy. Multiple rationally informed clinical trials of a variety of targeted agents in NF2 including lapatinib, axitinib, everolimus, and bevacizumab are ongoing (Karajannis and Ferner 2015).

12.4 Tuberous Sclerosis Complex

12.4.1 Epidemiology

Tuberous sclerosis complex (TSC), previously known as Bourneville's disease, is an autosomal dominant disorder with a growing incidence currently estimated to be 1:6000 to 1:9000 due to improved diagnostic tests (Roach and Sparagana 2004). There is no race or gender predilection, and onset of symptoms varies from infancy to late childhood (Roach et al. 1998; Sparagana and Roach 2000).

12.4.2 Molecular Biology and Genetics

TSC is genetically heterogeneous with two implicated genes: TSC1 on chromosome 9q34 encodes hamartin, a 130 kDa tumor suppressor protein, and TSC2 on chromosome 16p13 encodes tuberin, a 200 kDa tumor suppressor protein. Both proteins form a ubiquitous intracellular complex called the TSC complex, which is involved in many cell regulatory processes.

Through the GTPase-activating function of tuberin, the TSC tumor suppressor complex drives the small GTPase, termed Ras homolog enhanced in brain (Rheb), into the inactive guanosine diphosphate-bound state. Rheb in the guanosine triphosphate-bound active state is a positive effector of *m*ammalian *t*arget *o*f *r*apamycin (mTOR). Mutations in either hamartin or tuberin drive Rheb into the guanosine triphosphate-bound state, which results in constitutive mTOR signaling. mTOR appears to mediate many of its effects on cell growth through the phosphorylation of the ribosomal protein S6 kinases (S6Ks) and the repressors of protein synthesis initiation factor eIF4E, the 4EBPs. The S6Ks act to increase cell growth and protein synthesis, whereas the 4EBPs serve to inhibit these processes. mTOR interacts with the S6Ks and 4EBPs through an associated protein, raptor.

Mutation of tuberin or hamartin leads to constitutive activation of mTOR, which results in the hamartomatous lesions in the brain, kidney, heart, lung, CNS, and other organs of the body. More aggressive tumors, such as angiomyolipomas, can also arise. Such mutations are commonly found in patients with TSC, but up to one third of clinically diagnosed patients have no discernable mutation (Jones et al. 2000). This might be in part due to somatic mosaicism. Reasons for the clinical variability associated with identical mutations remain elusive. Recent reports suggest that patients with mutations in *TSC1* gene are less severely affected than patients with mutations in the *TSC2* gene, a finding that provides some help when counseling parents (Jansen et al. 2008; van Eeghen et al. 2012).

12.4.3 Diagnostic Criteria and Clinical Features

TSC is characterized by seizures, behavioral problems, mental retardation, and development of benign tumors (hamartomas) in multiple organs. The classic TSC triad consists of seizures, mental retardation, and adenoma sebaceum (Hanno and Beck 1987; Curatolo 1996; Roach et al. 1998). Adenoma sebaceum are pathologically best characterized as facial angiofibromas. The CNS lesions seen with TSC include cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGA). Cortical tubers present a hallmark for the disease. They form during development and represent a disorder of neural proliferation. Recently updated diagnostic guidelines rely upon molecular testing and a variety of clinical criteria to establish the diagnosis of TSC (Table 12.3). A definite diagnosis of TSC requires identification of a pathogenic mutation in TSC1 or TSC2 or a

Table 12.3 Diagnostic criteria for tuberous sclerosis (Northrup and Krueger 2013)

Genetic diagnostic criteria:	
The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al. 2012, 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria and are not sufficient to make a definite diagnosis of TSC. Note that 10–25 % of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC or have any effect on the use of clinical diagnostic criteria to diagnose TSC	
Clinical diagnostic criteria:	
Major features	**Minor features**
1. Hypomelanotic macules (≥3, at least 5 mm diameter)	1. "Confetti" skin lesions
2. Angiofibroma (≥3) or fibrous cephalic plaque	2. Dental enamel pits (≥3)
3. Ungual fibromas (≥2)	3. Intraoral fibromas (≥2)
4. Shagreen patch	4. Retinal achromic patch
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Cortical dysplasias[a]	6. Nonrenal hamartomas
7. Subependymal nodules	
8. Subependymal giant cell astrocytoma	
9. Cardiac rhabdomyoma	
10. Lymphangioleiomyomatosis (LAM)[b]	
11. Angiomyolipomas (≥2)[b]	

Definite diagnosis: two major features or one major feature with ≥2 minor features. Possible diagnosis: either one major feature or ≥2 minor features

[a]Includes tubers and cerebral white matter radial migration lines

[b]A combination of the two major clinical features (LAM and lymphangioleiomyomatosis) without other features does not meet criteria for a definite diagnosis

combination of either two major features or one major feature and two minor features. For a probable diagnosis of TSC, one major feature or two or more minor features must be present.

Epilepsy is the most common neurological symptom associated with TSC, present in 60–90 % of cases, and often beginning in the first year of life (Jozwiak et al. 2000; Thiele 2004). In one analysis of 105 patients diagnosed with TSC, 47 % had abnormal cognitive function that was associated with refractory seizures and mutations in the *TSC2* gene (Winterkorn et al. 2007). Patients with tuberous sclerosis complex face a high risk of neuropsychiatric impairments: for example, the prevalence of autism spectrum disorders in TSC has recently been estimated to be as high as 25–50 % (de Vries et al. 2015).

Hypomelanotic lesions, ash-leaf macule depigmented nevi resembling vitiligo, may be noted at birth and can be seen in more than half of TSC patients before 2 years of age. These are best visualized with ultraviolet light (Wood lamp). Ash-leaf spots are seen in up to 90 % of patients with TSC. Facial angiofibromas (adenoma sebaceum) skin lesions consist of vascular and connective tissue elements. The red papular rash typically extends over the nose and down the nasolabial folds toward the chin, cheeks, and malar regions. Skin lesions gradually enlarge, manifesting ultimately in 90 or more percent of TSC patients (Northrup and Krueger 2013).

12.4.4 Natural History and Prognosis

The leading cause of morbidity and mortality in TSC patients is caused by neurologic manifestation of the disease followed by renal complications (Franz 2004). Refractory epilepsy is common and leads to poor cognitive outcome (Winterkorn et al.

2007). SEGAs can cause hydrocephalus and require surgical intervention (Cuccia et al. 2003). Additional abnormalities occur in the eyes, skin, kidneys, bones, heart, and lungs. Prognosis varies with the individual manifestations of the disease. Major causes of death in a large TSC Scottish cohort were renal disease, followed by brain tumors, pulmonary lymphangiomyomatosis, status epilepticus, and bronchopneumonia (Shepherd and Stephenson 1992). In severe cases, death occurs in the second decade of life (Curatolo 1996; Webb et al. 1996; Sparagana and Roach 2000).

12.4.5 Laboratory Studies

Molecular genetic testing has become available in clinical practice and may be helpful in young patients who are less than 2 years of age, since many of the clinical signs are not present until later in life. Recently updated consensus diagnostic criteria for TSC now include the identification of a pathogenic *TSC1* or *TSC2* mutation as sufficient for the formal diagnosis of tuberous sclerosis, independent of clinical findings (Table 12.3, Northrup and Krueger 2013). Various molecular assays reveal the presence of a mutation in 75–90% of cases (Northrup and Krueger 2013). According to recently updated TSC management guidelines, genetic testing is indicated for genetic counseling purposes or when the diagnosis of TS is suspected but cannot be clinically confirmed (Krueger and Northrup 2013).

12.4.6 Imaging Studies

In addition to the recent adoption of genetic testing to formally establish a diagnosis of TSC, clinical criteria are commonly used as detailed in Table 12.3.

Approximately 95% of patients with clinical features of TSC have abnormalities on CT scans (Menkes and Maria 2000). Typically, there are hypodense subependymal nodules lining the ventricles (Fig. 12.5a), usually calcified after the first year of life, and 50% of affected individuals demonstrate calcified cortical hamartomas. SEGAs located at or near the foramen of Monro enhance brightly following contrast administration. Calcified subependymal and cortical nodules are seen in 95% of individuals with TSC, leaving CT as a simpler diagnostic tool than MRI by obviating the need for general anesthesia in children (Braffman et al. 1990; Menor et al. 1992; Mukonoweshuro et al. 1999; Fischbein et al. 2000).

Brain MRI is preferable for defining the exact number and location of cerebral cortical and subcortical tubers, white matter lesions, and areas of heterotopias (Braffman et al. 1990; Menor et al. 1992; Mukonoweshuro et al. 2001; Fischbein et al. 2000). Tubers or sclerotic white patches involving the gyri or white matter occur mostly in the cerebrum, while cerebellar, brainstem, and spinal cord lesions occur less commonly. Cortical tubers and hamartomas change in appearance as the brain myelinates. They are initially hyperintense on T1-weighted images and hypointense on T2-weighted images, but as brain myelination progresses, this imaging pattern reverses. White matter lesions appear as hyperintense linear bands in cerebrum and cerebellum. In infants, bands are hypointense to unmyelinated white matter on T2-weighted images and are hyperintense to white matter in older children and adults (Fig. 12.5b). SEGAs at or near foramen of Monro display intense postcontrast enhancement, although the pattern can be heterogeneous (Fig. 12.5c). MR spectroscopy can be useful to distinguish them from cortical tubers.

Refinement of MRI techniques and interpretation to identify the location of epileptogenic lesions in TS patients remains an area of active research (Jahodova et al. 2014; Gallagher et al. 2009, 2010; Peters et al. 2013). PET/MRI fusion imaging has been studied to identify epileptogenic tubers with great promise for improving surgical cure rates for intractable epilepsy (Chandra et al. 2006).

12.4.7 Treatment

TSC affects multiple organs, and treatment recommendations vary according to each specific organ manifestation. Recently developed consensus surveillance and management guide-

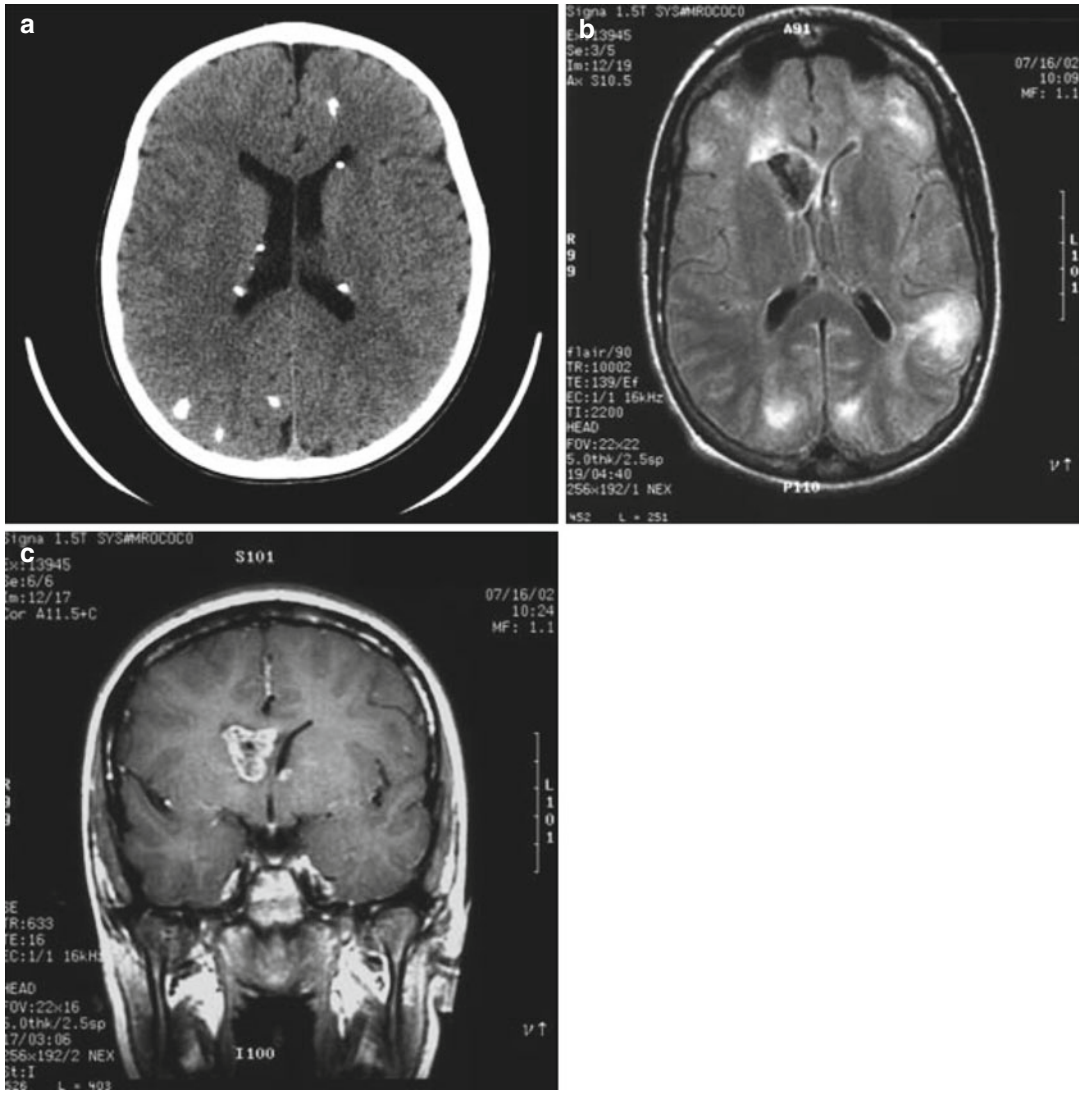

Fig. 12.5 Tuberous sclerosis complex. (**a**) Axial CT image of multiple calcified subependymal nodules. Other calcifications are also seen within the cortex. (**b**) Bilateral cortical tubers of varying sizes and a frontal subependymal giant cell astrocytoma (SEGA) are seen on this T2-weighted image. (**c**) A postcontrast T1-weighted coronal image from the same patient demonstrates the proximity of the tumor to the foramen of Monro

lines for TSC patients provide detailed recommendations for diagnosis, surveillance, and treatment of organ site-specific manifestations of TSC (Krueger and Northrup 2013). For diagnosis of CNS abnormalities, all TSC patients are recommended to have an initial MRI of the brain with and without gadolinium contrast to identify tubers, subependymal nodules, and subependymal giant cell astrocytomas. CT or cranial ultrasound are second-line diagnostic modalities. All pediatric patients are recommended to undergo a baseline EEG even in the absence of seizures. A baseline neuropsychiatric assessment and referral for specialized management is also strongly recommended in view of the risk of significant neuropsychiatric manifestations in TSC.

Neurologically asymptomatic patients with TSC should undergo neuroimaging surveillance every 1–3 years until the age of 25 and, if SEGAs are present, continuing into adulthood. Updated

treatment recommendations for TSC-associated SEGA have recently been published (Roth et al. 2013). Surgical resection is recommended for acutely symptomatic SEGAs, while growing or asymptomatic SEGAs can be managed by surgical resection or medical therapy with mTOR inhibitors. The efficacy of mTOR inhibition with everolimus in shrinking or stabilizing TS-associated SEGAs has been demonstrated in a randomized phase III trial (Franz et al. 2013) and has revolutionized the management paradigm for such patients. Early results (e.g., Krueger et al. 2010) suggest that mTOR inhibition may reduce seizure frequency in some TS patients; however, the efficacy of this approach awaits larger-scale prospective verification. Everolimus has also been shown to be efficacious in reducing the volume of renal angiomyolipomas in TS patients (Bissler et al. 2013).

Treatment and surveillance recommendations for extracranial manifestations of TS have also been updated at the 2012 International Tuberous Sclerosis Consensus Conference (Krueger and Northrup 2013). An organ site-specific summary of recommendations for newly diagnosed and established tuberous sclerosis patients is provided in Table 12.4.

12.5 Ataxia Telangiectasia

12.5.1 Epidemiology

Ataxia telangiectasia (AT) is an autosomal recessive disorder with an incidence of 1:40,000 to 1:80,000 and equal predilection in both sexes. Patients with AT may present during infancy with ataxia without any cutaneous manifestations, which may become apparent after 2 years of age (Gosink et al. 1999; Lavin 1999).

12.5.2 Molecular Biology and Genetics

The gene for AT has been mapped to the long arm of chromosome 11 (11q23.3). The ataxia telangiectasia mutated (*ATM*) gene is very large with 66 exons spanning 150 kb of the genome, which renders mutation analysis challenging (Bakkenist and Kastan 2003). The *ATM* gene product is a member of the phosphatidylinositol 3-kinase (PI3-kinase) family and is activated by autophosphorylation in response to DNA double-strand breaks, as well as by direct ATM protein oxidation (Guo et al. 2010) and by membrane receptors such as PDGFRβ (Kim et al. 2010). It contains a PI3-kinase domain, a putative leucine zipper, and a proline-rich region. The ATM protein detects DNA double-strand breaks and activates a number of substrates including p53, chk-2, nibrin, BRCA1, and TSC2, the latter serving to downregulate mTOR signaling (Ambrose and Gattia 2013; Kastan and Lim 2000; Shiloh 2003). ATM plays an important role in cellular responses to DNA damage, cell cycle control, and maintenance of telomere length and has recently been shown to be important for mitochondrial homeostasis (Ambrose et al. 2007; Eaton and Lin 2007). Additional roles of ATM outside of DNA repair, such as in regulation of synaptic vesicle trafficking and in epigenetics, are emerging and may be critical to fully understanding the neurodegenerative phenotype of its deficiency in humans (Herrup 2014).

Over 400 different mutations have been identified in AT patients. Database screening has revealed that most mutations are unique to a given family. Mutations are distributed anywhere in the gene, and no hotspots or high-frequency mutations have been reported (Concannon and Gatti 1997; Mitui et al. 2003). Approximately 90 % of mutations are of the frameshift or premature truncation type, making the majority null mutations. Missense mutations occur in 10 % of the known mutations among AT families (Chun and Gatti 2004; Nakamura et al. 2014). Increased variant protein expression and residual kinase activity have been shown to correlate with a milder phenotype and increased life expectancy in AT patients (Staples and McDermott 2008; Micol et al. 2011; Verhagen et al. 2011).

Table 12.4 Surveillance and management recommendations for newly diagnosed or suspected tuberous sclerosis complex (TSC)

Organ system or specialty area	Recommendation
Genetics	Obtain three-generation family history to assess for additional family members at risk of TSC
	Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed
	Offer genetic testing and family counseling, if not done previously, in individuals of reproductive age or newly considering having children
Brain	Perform magnetic resonance imaging (MRI) of the brain to assess for the presence of tubers, subependymal nodules (SEN), migrational defects, and subependymal giant cell astrocytoma (SEGA)
	Evaluate for TSC-associated neuropsychiatric disorder (TAND)
	During infancy, educate parents to recognize infantile spasms, even if none have occurred at the time of first diagnosis
	Obtain baseline routine electroencephalogram (EEG). If abnormal, especially if features of TAND are also present, follow up with a 24-h video EEG to assess for subclinical seizure activity
	Obtain magnetic resonance imaging (MRI) of the brain every 1–3 years in asymptomatic TSC patients younger than age 25 years to monitor for new occurrence of subependymal giant cell astrocytoma (SEGA). Patients with large or growing SEGA, or with SEGA causing ventricular enlargement but yet are still asymptomatic, should undergo MRI scans more frequently, and the patients and their families should be educated regarding the potential of new symptoms. Patients with asymptomatic SEGA in childhood should continue to be imaged periodically as adults to ensure there is no growth
	Surgical resection should be performed for acutely symptomatic SEGA. Cerebral spinal fluid diversion (shunt) may also be necessary. Either surgical resection or medical treatment with mammalian target of rapamycin complex (mTOR) inhibitors may be used for growing but otherwise asymptomatic SEGA. In determining the best treatment option, discussion of the complication risks, adverse effects, cost, length of treatment, and potential impact on TSC-associated comorbidities should be included in the decision-making process
	Perform screening for TSC-associated neuropsychiatric disorders (TAND) features at least annually at each clinical visit. Perform comprehensive formal evaluation for TAND at key developmental time points: infancy (0–3 years), preschool (3–6 years), pre-middle school (6–9 years), adolescence (12–16 years), early adulthood (18–25 years), and as needed thereafter. Management strategies should be based on the TAND profile of each patient and should be based on evidence-based good practice guidelines/practice parameters for individual disorders (e.g., autism spectrum disorder, attention deficit hyperactivity disorder, anxiety disorder). Always consider the need for an individual educational program (IEP). Sudden change in behavior should prompt medical/clinical evaluation to look at potential medical causes (e.g., SEGA, seizures, renal disease)
	Obtain routine electroencephalograph (EEG) in individuals with known or suspected seizure activity. The frequency of routine EEG should be determined by clinical need rather than a specific defined interval. Prolonged video EEG, 24 h or longer, is appropriate when seizure occurrence is unclear or when unexplained sleep, behavioral changes, or other alteration in cognitive or neurological function is present
	Vigabatrin is the recommended first-line therapy for infantile spasms. Adrenocorticotropin hormone (ACTH) can be used if treatment with vigabatrin is unsuccessful. Anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies. Epilepsy surgery should be considered for medically refractory TSC patients, but special consideration should be given to children at younger ages experiencing neurological regression and is best if performed at epilepsy centers with experience and expertise in TSC

(continued)

Table 12.4 (continued)

Organ system or specialty area	Recommendation
Kidney	Obtain MRI of the abdomen to assess for the presence of angiomyolipoma and renal cysts
	Screen for hypertension by obtaining an accurate blood pressure
	Evaluate renal function by determination of glomerular filtration rate (GFR)
	Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1–3 years throughout the lifetime of the patient
	Assess renal function (including determination of glomerular filtration rate (GFR)) and blood pressure at least annually
	Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy is to be avoided. For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first-line therapy. Selective embolization or kidney-sparing resection is acceptable second-line therapy for asymptomatic angiomyolipoma
Lung	Perform baseline pulmonary function testing (pulmonary function testing and 6-min walk test) and high-resolution chest computed tomography (HRCT), even if asymptomatic, in patients at risk of developing lymphangioleiomyomatosis (LAM), typically females 18 years or older. Adult males, if symptomatic, should also undergo testing
	Provide counsel on smoking risks and estrogen use in adolescent and adult females
	Perform clinical screening for lymphangioleiomyomatosis (LAM) symptoms, including exertional dyspnea and shortness of breath, at each clinic visit. Counseling regarding smoking risk and estrogen use should be reviewed at each clinic visit for individuals at risk of LAM
	Obtain high-resolution computed tomography (HRCT) every 5–10 year in asymptomatic individuals at risk of LAM if there is no evidence of lung cysts on their baseline HRCT. Individuals with lung cysts detected on HRCT should have annual pulmonary function testing (pulmonary function testing and 6-min walk) and HRCT interval reduced to every 2–3 years
	mTOR inhibitors may be used to treat LAM patients with moderate to severe lung disease or rapid progression. TSC patients with LAM are candidates for lung transplantation, but TSC comorbidities may impact transplant suitability
Skin	Perform a detailed clinical dermatologic inspection/exam
	Perform a detailed clinical dermatologic inspection/exam annually
	Rapidly changing, disfiguring, or symptomatic TSC-associated skin lesions should be treated as appropriate for the lesion and clinical context, using approaches such as surgical excision, laser(s), or possibly topical mTOR inhibitor

Teeth	Perform a detailed clinical dental inspection/exam
	Perform a detailed clinical dental inspection/exam at minimum every 6 months and panoramic radiographs by age 7 years, if not performed previously
	Symptomatic or deforming dental lesions, oral fibromas, and bony jaw lesions should be treated with surgical excision or curettage when present
Heart	Consider fetal echocardiography to detect individuals with high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound
	Obtain an echocardiogram in pediatric patients, especially if younger than 3 years of age
	Obtain an electrocardiogram (ECG) in all ages to assess for underlying conduction defects
	Obtain an echocardiogram every 1–3 years in asymptomatic pediatric patients until regression of cardiac rhabdomyomas is documented. More frequent or advanced diagnostic assessment may be required for symptomatic patients
	Obtain electrocardiogram (ECG) every 3–5 years in asymptomatic patients of all ages to monitor for conduction defects. More frequent or advanced diagnostic assessment such as ambulatory and event monitoring may be required for symptomatic patients
Eye	Perform a complete ophthalmologic evaluation, including dilated funduscopy, to assess for retinal lesions and visual field deficits
	Perform annual ophthalmologic evaluation in patients with previously identified ophthalmologic lesions or vision symptoms at the baseline evaluation. More frequent assessment, including those treated with vigabatrin, is of limited benefit and not recommended unless new clinical concerns arise

12.5.3 Diagnostic Criteria and Clinical Features

AT is the most common ataxia in infancy (Kamiya et al. 2001), although the initial manifestations of cerebellar ataxia may not be noted until early walking. AT is a common cause of progressive ataxia in children younger than 10 years of age, second only to tumors of the posterior fossa. Ataxia is generally the presenting symptom of AT. Oculomotor apraxia is a distinguishing feature of the disease, which is often present prior to the cutaneous findings.

Telangiectasias are a second major clinical manifestation of the disease (Table 12.5). Progressive oculocutaneous telangiectasias represent a key feature of AT. Bulbar conjunctivae telangiectasias first appear between 2 and 8 years of age and subsequently involve the ears, eyelids, malar prominences, neck, antecubital and popliteal fossae, as well as dorsum of hands and palate. Initially they appear as bright-red, thick, symmetrical streaks that resemble atypical conjunctivitis and only later become frank telangiectasias. These skin lesions become more prominent with sunlight exposure and age. Premature aging of hair and skin is frequent.

Patients with AT have a high tendency to develop chronic sinopulmonary infections. The immunodeficiency involves both cellular and humoral immunities. Absence of the tonsils, adenoids, lymphoid tissue, and thymus gland is commonly seen in AT. The incidence of cancer in AT is approximately 100-fold higher than in matched populations. These neoplasms consist of non-Hodgkin's lymphoma, leukemia, and other solid tumors.

Table 12.5 Clinical features for ataxia telangiectasia (Menkes and Maria 2000)

Clinical features
Slowly progressive cerebellar ataxia
Choreoathetosis
Telangiectasia of the skin and conjunctiva
Susceptibility to sinobronchopulmonary infections
Cancer (non-Hodgkin's lymphoma, leukemias, solid tumors)

12.5.4 Natural History and Prognosis

Neurologic deterioration is progressive, and by the end of the first decade of life, children are confined to wheelchairs with myoclonic jerks, drooling, choreoathetosis, oculomotor abnormalities, and dysarthric speech (Paller 1987). Eighty-five percent of AT patients develop choreoathetosis, apraxia of eye movements, and nystagmus. The progressive cerebellar neurodegeneration is the most debilitating feature of AT. Over time patients also develop peripheral neuropathy and eventually spinal muscular atrophy. Intelligence is usually normal in young children but deteriorates with disease progression (Menkes and Maria 2000).

Growth retardation occurs in 72 % of patients with AT. Progeric changes have been noted in almost 90 % of AT patients with early loss of subcutaneous fat, loss of skin elasticity, and premature graying of hair by adolescence (Paller 1987). AT patients are immunodeficient with compromised humoral immune surveillance and cellular immunity. Specifically, AT patients have IgA deficiencies that predispose them to infectious agents that enter through exposed sites. Consequently, they tend to suffer recurrent bacterial and viral sinopulmonary infections that can be life-threatening (Paller 1987). Molecular mechanisms underlying this immunodeficient phenotype are gradually being unraveled (Jiang et al. 2015).

Children with AT have an increased incidence of cancer, primarily lymphoid tumors, due to acute sensitivity to ionizing radiation and defective cell cycle checkpoints (Kamiya et al. 2001). AT patients are 40–100 times more likely to develop leukemias, lymphomas, lymphosarcomas, and Hodgkin's disease, leading to neoplastic development in 30 % of patients. Lymphoreticular malignancies predominate in younger patients, whereas epithelial malignancies occur most frequently in adult patients (Suarez and Mahlaoui 2015; Paller 1987). Not surprisingly, death frequently occurs in late childhood or early teenage years. Mean age of death is 14 years (Kamiya et al. 2001) due to malignancy or complications from pulmonary infection and respiratory insufficiency.

A milder, adult-onset "variant" phenotype of AT has also been described, frequently presenting with extrapyramidal signs and more gradual or delayed development of ataxia (Saunders-Pullman et al. 2012; Verhagen et al. 2009). These patients may have a longer life span compared with individuals with classic AT, but remain at elevated risk for malignancy relative to the unaffected general population.

Some penetrance appears in AT heterozygotes leading to intermediate radiosensitivity and increased risk of cancer, particularly breast cancer. ATM heterozygotes have a ninefold increased risk of developing breast cancer, characterized by bilateral disease and early age of onset (Lavin et al. 1999).

12.5.5 Laboratory Studies

Highly elevated serum α-fetoprotein is detected in nearly 95 % of AT cases, and this laboratory marker often precedes the appearance of telangiectasias by several years (Menkes and Maria 2000). Patients with variant AT may have normal or more mildly elevated AFP levels (Saunders-Pullman et al. 2012).

AT patients may also display elevated levels of carcinoembryonic antigen (CEA) and low or absent total IgA or IgE levels. Markedly decreased serum IgA (<80 mg/L) and IgE (<3 mg/L) levels are seen in 70–90 % of AT patients. Conversely, IgM, IgG1, and IgG3 levels tend to be high (Menkes and Maria 2000). Elevated hepatic transaminases are seen in 40–50 % of patients, and glucose intolerance is seen in 50 % of patients. An unusual form of adolescent diabetes is observed in which hyperglycemia occurs with rare glycosuria, absent ketosis, insulin hypersecretion, and peripheral insulin resistance.

Chromosomal abnormalities occur 2–18 times more frequently in AT patients than in normal individuals, with chromosomal abnormalities observed in 80 % of AT patients. Rearrangements of chromosomes 7 and 14, and especially 14:14 translocations may anticipate the development of lymphoreticular malignancies (Lavin et al. 1999). Analysis of amniotic fluid allows prenatal diagnosis using measurements of α-fetoprotein and high-resolution chromosomal analysis. Diagnosis of AT may be confirmed by sequencing of the ATM locus in patients with clinical features of the syndrome and supported by cytogenetic studies showing chromosomal rearrangements and x-irradiation hypersensitivity of lymphocytes or fibroblasts derived from the patient.

12.5.6 Imaging Studies

MRI of the brain is normal with a well-formed cerebellum for many years after onset of ataxia. By 10 years of age, volume loss of the cerebellum often becomes apparent. Posterior fossa abnormalities include cerebellar atrophy, particularly of the anterior vermis, atrophy of the dentate, and atrophy of the olivary nuclei; spine MRI demonstrates degeneration of the posterior columns. These imaging findings correlate with well-described neuropathologic features of AT (Sahama et al. 2014a). In the cerebellum, there is a reduction in Purkinje cell number and atrophy of dentate nuclei. In addition, there is atrophy of anterior horn cells, demyelination of gracile fasciculi in the spinal cord, and appearance of nucleocytomegalic cells in the anterior pituitary. Preliminary studies with diffusion-weighted MRI techniques in AT patients have revealed signs of compromise in key cerebellar–corticomotor pathways, consistent with the ataxic phenotype (Sahama et al. 2014b). Cerebrovascular abnormalities can be noted on MRI in later stages of the disease (Habek et al. 2008).

12.5.7 Treatment

To date, there is no therapy available to cure or prevent progress of the disease, and interventions are mainly supportive. These efforts include prophylactic therapy for infections. Antibiotics and plasma gamma globulin infusions have been utilized for IgA deficiencies and intercurrent sinopulmonary infections. Thymus gland and bone

marrow transplantations have been reported as well. Judicious use of sunscreen is warranted to retard actinic-like skin progeric changes. Radiation therapy and radiomimetic chemotherapeutic agents should be avoided in treating lymphoreticular malignancies. Early pulmonary physiotherapy and physical therapy appropriate for the neurologic dysfunction should be instituted. Many treatments employed for ataxia, including acetylcholine, γ-aminobutyric acid, dopamine, diazepam, chlordiazepoxide, trihexyphenidyl, diphenhydramine, and haloperidol, have been ineffective, although a recent small study using amantadine sulfate has reported promising symptom response rates (Nissenkorn et al. 2013). A patient disabled with an extremely severe involuntary movement disorder responded well to dantrolene, a hydantoin compound. Corticosteroids have been shown to induce an alternate splice site in ATM expression and partially rescue the gene product's activity (Menotta et al. 2012). In small studies steroid preparations appear to mitigate and possibly delay symptom progression (Chessa et al. 2014). Neoplastic processes that require aggressive treatment with chemotherapy or radiation present a formidable challenge, given the high vulnerability to further oncologic insults in AT patients.

12.6 Von Hippel–Lindau Syndrome

12.6.1 Epidemiology

VHL is an autosomal dominant disorder with an incidence of 1:40,000 (Maher and Kaelin 1997). It exhibits 90% penetrance and equal incidence in males and females. Generally, VHL does not present during childhood, but more often during the second or third decade of life (Singh et al. 2001). Approximately 20% of cases are attributable to de novo mutations (Schmid et al. 2014).

12.6.2 Molecular Biology and Cytogenetics

The *VHL* gene maps to chromosome 3p25–p26 and is a putative tumor suppressor gene (Latif et al. 1993). Two VHL gene products have been identified that are translated from mRNAs generated from two alternative start codons. In most functional studies these two proteins are indistinguishable and, therefore, are referred to as one. The VHL protein (pVHL) lacks known enzymatic activity and instead is thought to function as a molecular adaptor in a variety of mechanistic roles (Frew and Krek 2008). Its most thoroughly understood role is in the oxygen-dependent ubiquitination for subsequent proteolytic degradation of the HIFα transcription factor family (Maxwell et al. 1999). These transcription factors control a variety of downstream pathways involved in cellular proliferation, angiogenesis, tumor invasion, and metastasis. HIFα-dependent signaling elements such as VEGF, PDGF, and TGFα have been implicated in VHL-associated neoplasia (Shen and Kaelin 2013). Recent findings have suggested that pVHL also modulates multiple HIFα-independent regulatory elements including NF-κB, p53, JunB, and others, which may also contribute to organ-specific tumorigenesis in the setting of VHL loss (Frew and Krek 2008).

For VHL, disease genotype–phenotype correlation has revealed a strong association of missense mutations with the presentation of pheochromocytoma (VHL Type 2), whereas null mutations carry a very low risk to develop these tumors (VHL Type 1) (Crossey et al. 1994; Chen et al. 1995). An extensive analysis of the VHL mutational spectrum in 945 families afflicted with the disorder has recently been published, revealing 1548 individual mutations of which approximately half were missense (Nordstrom-O'Brien et al. 2010).

12.6.3 Diagnostic Criteria and Clinical Features

Although it is classified as a neurocutaneous syndrome, VHL is not associated with any specific cutaneous lesion. VHL is a multisystem disorder with marked phenotypic variability (Table 12.6). The main pathological lesions are capillary hemangioblastomas that are highly vascularized benign tumors composed of pericytes and blood vessels. Patients with VHL are at risk of develop-

Table 12.6 Clinical features for von Hippel–Lindau

Clinical features
Cerebellar, retinal, and spinal cord hemangioblastoma
Renal cell carcinoma
Pheochromocytoma
Pancreatic neuroendocrine tumors
Pancreatic and renal cysts
Endolymphatic sac tumors
Polycythemia

ing benign and malignant tumors in the CNS, kidneys, retina, adrenal glands, pancreas, and reproductive adnexal organs. Retinal hemangioblastoma is often the first clinical sign and leads to diagnosis in 30 % of VHL patients (Joerger et al. 2005). Diagnostic features include a positive family history of VHL, identification of one CNS hemangioblastoma, or a single visceral lesion (Richard et al. 2000; Sims 2001). For example, a retinal or cerebellar hemangioblastoma, renal cell carcinoma, or pheochromocytoma in an at-risk individual would be an adequate criterion. In isolated cases with absent family histories, two or more retinal or cerebellar hemangioblastomas or a single hemangioblastoma and a visceral tumor are required for diagnosis. Multiple, frequent retinal angiomas may lead to retinal detachment, hemorrhage, and blindness if left untreated.

CNS hemangioblastomas occur most commonly in the cerebellum (44–72 %) and with a much lower incidence in the spinal cord (13–44 %) at a mean age of 33 years (Wanebo et al. 2003). These lesions are often multiple and are generally benign without metastases. Surgical excision results in excellent clinical outcome. Mean age of onset of cerebellar hemangioblastomas in VHL is considerably younger than in sporadic cases (Richard et al. 2000; Sims 2001). Cerebellar hemangioblastomas are found in approximately 75 % of patients with VHL. However, only 5–30 % of all patients with cerebellar hemangioblastomas are found to have VHL. Many patients with VHL ultimately develop multiple CNS hemangioblastomas, and management of brainstem and spinal tumors can be difficult. Thus, CNS involvement remains an important cause of morbidity and mortality in VHL patients.

Fifty to 70 % of VHL patients develop renal cysts, although renal impairment from cysts is rare. However, the lifetime risk of clear cell renal cell carcinoma is greater than 70 %, and renal cell carcinoma is a major cause of death in VHL patients. Pheochromocytomas arise in up to 24 % of patients with VHL, with a mean age of 27 years at presentation (Joerger et al. 2005). These tumors may be multiple, bilateral, or extra-adrenal. Pancreatic neuroendocrine tumors develop in 5–17 % of patients with VHL, with a mean age of 36 years at presentation (Hes et al. 2001a, b). Locally aggressive endolymphatic sac tumors arising from the posterior aspect of the temporal bone and leading to hearing loss and vestibular dysfunction have also been reported in association with VHL (Kim et al. 2013).

12.6.4 Natural History and Prognosis

Patients with VHL usually present in adulthood. Initial symptoms are often visual and related to retinal angiomas with a mean age of onset of 20–40 years. Symptoms from cerebellar hemangioblastomas present later and include headache, disequilibrium, nausea, and vomiting. In a large 10-year retrospective NIH study of 160 consecutive VHL patients, many patients presented with mass effect attributable to a cyst that was far greater in size than the causative tumor (Wanebo et al. 2003). Neither tumors nor cysts spontaneously diminished in size although many untreated tumors remained the same size for several years. The tumors demonstrated a stepwise pattern of growth with enlargement followed by a plateau. Usually the mass effect caused by the cyst was responsible for symptoms. Similar findings were recently reported in a large prospective natural history study of VHL-related hemangioblastomas in 225 patients carried out by the same group (Lonser et al. 2014).

The median age of death for patients with VHL is approximately 50 years (Wilding et al. 2012). Clear cell variant renal cell carcinomas and CNS hemangioblastomas are the leading

causes of VHL-related mortality (Maher et al. 1990; Singh et al. 2001).

12.6.5 Laboratory Studies

Laboratory studies are very nonspecific. Urinary catecholamines, VMA, and HVA may be elevated in cases of pheochromocytoma, with VHL-associated pheochromocytomas associated with solitary elevations in normetanephrine (Eisenhofer et al. 2011). Hemangioblastomas may produce excess erythropoietin resulting in elevated hematocrit values. Commercial genetic testing is now available with sequencing of the VHL gene.

12.6.6 Imaging Studies

With CT head scanning, a low-density cystic mass is often present in the posterior fossa. Isodense mural nodules may enhance intensely with contrast (Fischbein et al. 2000). On MRI, brain cysts may be isointense to cerebrospinal fluid or proteinaceous (hyperintense on T1-weighted sequences) with variable hyper- or hypointensity on T2-weighted sequences (Fig. 12.6). Prominent flow voids are seen in and adjacent to solid portions of the hemangioblastoma. Conventional catheter angiography demonstrates intense tumor blush localized to the posterior fossa. The typical blood supply is from superior cerebellar, anterior inferior cerebellar, or posterior inferior cerebellar arteries but may also arise from branches of the internal and external carotid arteries. Angiography may assist with operative planning, and, if possible, embolization may reduce the tumor vascularity allowing resection with reduced blood loss. Brain MRI with thin slice sequences through the temporal bone is the diagnostic paradigm of choice for imaging endolymphatic sac tumors in VHL patients. Abdominal MRI is recommended to characterize and follow VHL-associated renal and pancreatic abnormalities, while pheochromocytomas in patients with elevated catecholamines are localized using CT/MRI in addition to MIBG and/or DOPA-PET nuclear medicine studies (Schmid et al. 2014).

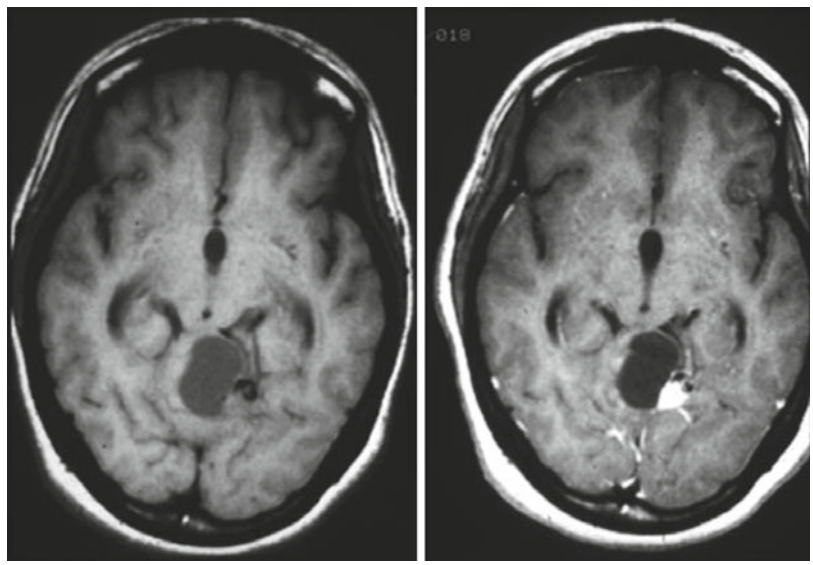

Fig. 12.6 VHL syndrome. T1-weighted images, pre- and postcontrast, demonstrating a small enhancing tumor nodule adjacent to a cyst located within the cerebellar vermis. The cyst contents are slightly hyperintense to cerebrospinal fluid

12.6.7 Treatment

To identify retinal angiomas, ophthalmologic examinations are required, and, when indicated, laser therapy and cryotherapy are effective (Hes et al. 2001a, b). Surgical removal of symptomatic lesions may also be considered. The NIH group emphasizes that the pattern of growth may be variable and saltatory growth is common (Wanebo et al. 2003; Lonser et al. 2014). Some tumors remain quiescent for many years, while others grow quickly over several months. As aforementioned, the growth of the cyst is often greater than the tumor itself and is responsible for the development of symptoms related to mass effect. In their series, asymptomatic patients rarely underwent surgery. Overall, surgical resection of cerebellar and even brainstem and spinal cord tumors was associated with acceptable morbidity and is considered first-line therapy (Capitanio et al. 2013). External beam radiation or stereotactic radiosurgery may be helpful for multiple or inaccessible lesions. One group reported radiosurgical hemangioblastoma local control rates of ~80 % at 5 years and ~50 % at 15 years (Asthagiri et al. 2010), while outcomes recently reported by an international consortium were somewhat more favorable (Kano et al. 2015). Infratentorial craniospinal radiation for patients with diffuse hemangioblastomas in the posterior fossa and spinal canal has also been described in a small pilot study, with good treatment tolerance and evidence of disease stabilization in a subset of patients (Simone et al. 2011). Antiangiogenic agents and multi-kinase inhibitors have been investigated as salvage therapies for progressive hemangioblastoma in VHL with evidence of measurable but limited benefit in a number of case reports and small trials with larger trials ongoing (Capitanio et al. 2013). Based on preliminary reports, retinal hemangioblastomas may exhibit favorable responses following administration of the anti-VEGF monoclonal antibody bevacizumab.

Renal cell carcinomas in VHL have very low metastatic potential at sizes <3 cm and may be managed with active surveillance using serial MRI until this size threshold is approached. Definitive management is primarily with nephron-sparing surgery if feasible given tumor burden, with the goal of minimizing the overall number of surgical procedures to best preserve renal function. Percutaneous CT-guided RFA may have a role in the nonsurgical treatment of smaller RCCs.

Pheochromocytomas in VHL are managed similarly to sporadic lesions, with frontline laparoscopic adrenalectomy after appropriate preoperative alpha-adrenergic blockade. It is important to exclude pheochromocytoma before performing any other surgical intervention in VHL patients due to the risk of pheochromocytoma-associated perioperative complications (Schmid et al. 2014).

Localized pancreatic neuroendocrine tumors in VHL are managed surgically. An increased risk of metastasis has been found for lesions >3 cm and a tumor doubling time of <500 days. Metastatic potential may also be increased in patients with a VHL exon 3 mutation (Blansfield et al. 2007; Corcos et al. 2008).

Multiple angiogenesis and multi-kinase inhibitors have shown efficacy in large prospective studies of metastatic clear cell renal cell carcinoma (ccRCC) in the non-VHL population. Given that pVHL mutation or loss is implicated as a central driving event in both sporadic and syndromic ccRCC, metastatic lesions in VHL patients are managed similarly to those in whom ccRCC occurs sporadically. Based on recent data, frontline agents may include one of sunitinib, pazopanib, bevacizumab plus interferon, and temsirolimus, while second-line therapies include everolimus, axitinib, and sorafenib (Sun et al. 2013; Coppin and Kollmannsberger 2011; Motzer et al. 2013). Data specific to VHL patients are more limited given the rarity of the syndrome, but a pilot trial of sunitinib in VHL patients revealed shrinkage of RCC with no overt responses in other lesion types (Jonasch et al. 2011).

Surveillance guidelines recommend screening patients with VHL annually or even biannually with MRI of the brain and spine. High-resolution

MRI scans through the temporal bones are recommended to screen for endolymphatic sac tumors. Annual fundoscopic exams are recommended starting at 6 years of age. Abdominal MRI scans, CT scans, or ultrasounds should be performed at least once per year starting at 15–18 years of age. To assess for pheochromocytoma, annual plasma and/or urine catecholamines/metanephrines should be checked (Schmid et al. 2014; Maher et al. 2011; Joerger et al. 2005).

12.7 Sturge–Weber Syndrome

12.7.1 Epidemiology

SWS, or encephalofacial angiomatosis, is a rare, sporadic neurocutaneous syndrome. The incidence is currently estimated to be 1:50,000. There is no sexual predilection and no racial bias. Although there are rare familial cases of SWS, there are no convincing data to suggest that it is a heritable condition in the majority of afflicted patients. Indeed, recent data suggest that the syndrome is associated with a postzygotic, somatic, mosaic mutation in the *GNAQ* locus (Shirley et al. 2013).

12.7.2 Genetic and Molecular Biology

Up until 2013, little was known regarding the genetic determinants of SWS. Whole-exome sequencing of DNA from normal and visibly affected tissue in three SWS patients revealed the presence of an activating mutation (p.Arg183Gln) in the *GNAQ* locus on chromosome 9q21, which encodes for a Gα-protein adaptor that mediates signaling between GPCRs and downstream effectors. The mutation was identified in affected tissue samples among 88 % (23/26) of participants with SWS and in 92 % (12/13) of samples obtained from port-wine stains (nevi flammei) in patients with no apparent SWS. The mutation was not found in six samples from control patients and in four samples of unrelated cerebrovascular malformations. It was hypothesized that severity of the resultant phenotype, from isolated port-wine stain to full SWS, depended on the timing of the mutational event during development (Shirley et al. 2013). From a pathologic perspective, malformations of embryonic vascular plexi give rise to abnormalities of the skin, leptomeninges, choroids, and cortex. Interference with vascular drainage at 5–8 weeks of gestation affects the face, eye, leptomeninges, and brain (Taly et al. 1987; Maiuri et al. 1989). Resultant angiomatosis is accompanied by poor superficial cortical venous drainage with enlarged regional transmedullary veins developing as alternate pathways. It is postulated that inefficient outflow of venous blood causes chronic hypoxia that results in brain tissue loss and dystrophic calcifications. Abnormal innervation of the affected vasculature has also been reported and has been hypothesized to potentially exacerbate cerebral ischemia during times of increased metabolic demand (Cunha e Sa et al. 1997).

12.7.3 Diagnostic Criteria and Clinical Features

Two essential features of SWS are facial cutaneous nevi flammei (commonly known as "port-wine" stains) and leptomeningeal angiomas (Table 12.7) (Sudarsanam and Ardern-Holmes 2014; Menkes and Maria 2000). The other accepted name for port-wine stain is capillary vascular malformation. Skin findings are gener-

Table 12.7 Clinical features for Sturge–Weber syndrome (Bodensteiner and Roach 1999; Menkes and Maria 2000)

Major clinical features	Additional features
Congenital facial vascular nevus	Glaucoma/buphthalmos
Focal or generalized seizures	Neurologic deterioration
Brain MRI leptomeningeal enhancement after gadolinium administration plus enlarged transmedullary veins and unilateral hypertrophy of the choroid plexus	CT head parieto-occipital calcifications arranged in parallel lines "railroad tracks"

ally noticed at birth, and seizures may present in infancy. Classic manifestations include an ipsilateral facial port-wine stain, mental retardation, contralateral hemiparesis, contralateral hemiatrophy, and contralateral homonymous hemianopsia. Other features of the syndrome include glaucoma, dental abnormalities, and skeletal lesions. Migraine-like headaches, endocrinopathies such as central hypothyroidism and growth hormone deficiency, and frequent ear infections/sinus complaints have also been associated with SWS. Although the diagnosis of SWS is seldom difficult, challenges remain in predicting functional outcome (Waelchli et al. 2014; Oakes 1992; Maria et al. 1998a, b). The facial nevi are the most obvious of the possible manifestations of SWS, although the ipsilateral leptomeningeal angioma and related MRI abnormalities are regarded as the most important component in determining prognosis. Children with widespread vascular lesions often have more seizures and greater intellectual impairment. The SWS clinical triad consists of (1) seizure disorder, (2) mental retardation, and (3) facial angiomas.

Although facial nevi are relatively common malformations, occurring in approximately 3 in 1000 births, only 15 % of infants with typical port-wine cutaneous lesions have SWS. In fact, up to 85 % of patients with typical upper hemifacial nevi are not associated with leptomeningeal angiomatosis found classically in SWS. Conversely, 13 % of patients with cerebral manifestation of SWS do not display facial nevi. There is no correlation between size of facial involvement and CNS malformations (Bodensteiner and Roach 1999). Cutaneous facial nevi are usually present at birth but may become more prominent, thicker, and darker with age. Involvement of the eyelid is associated with ipsilateral brain involvement and usually conforms to the distribution of the first division of the trigeminal nerve. The second and third divisions of the trigeminal nerve can also be involved. A recent study has challenged the notion that risk of SWS in patients with facial nevi correlates with selective trigeminal nerve branch involvement, revealing instead a stronger correlation with patterns of embryonal vascular development in the region. Specifically, facial nevi involving skin of the upper eyelid and of the forehead (defined to be above a line connecting the outer ocular canthus and the top of the ear) were associated with the highest risk of underlying SWS (Waelchli et al. 2014). These observations are consistent with the current hypothesis that SWS occurs as a result of an acquired mutation during postzygotic vascular development.

Seizures often begin in the first year of life as the initial presenting feature in 80 % of patients with SWS and are often medically refractory (Maria et al. 1998a, b). Seizures usually arise focally at first but may secondarily generalize into tonic–clonic seizures. In addition, patients experience focal neurologic deficits that develop acutely in conjunction with flurries of seizures and also as Todd's paralysis that recovers more readily. Hemiparesis occurs with or without seizures and affected extremities often grow poorly, eventually resulting in hemiatrophy. Visual field defects result from involvement of one or both occipital lobes or optic tracts with leptomeningeal angiomatosis. Hydrocephalus may occur as a result of increased venous pressure from thromboses of deep venous channels or extensive arteriovenous anastomoses.

Mental retardation is common in SWS, with IQs lower than 90 in 70 % of patients (Menkes and Maria 2000). There is some controversy in the SWS literature regarding intellectual status. One study reports that all SWS patients without seizures are mentally normal (Sujansky and Conradi 1995). A conflicting study reports that although most infants with SWS have normal neurologic function, nearly all adults with SWS are impaired, suggesting a pervasive deterioration of function regardless of seizures (Maria et al. 1998a, b). The latter conclusion was supported by the study of a Spanish Sturge–Weber cohort, where 75 % of patients had IQ scores of 85 and lower. Functional impairment was evidenced by low levels of educational attainment in all patients, including those in whom seizures were controlled (Pascual-Castroviejo et al. 2008).

Other signs and symptoms of SWS include headaches, stroke-like episodes, contralateral hemiplegia, hemisensory deficits, and contralateral homonymous hemianopsia. Ocular involvement is common and includes glaucoma and buphthalmos (enlarged ocular globe) in up to 40 % of patients. The vascular malformations of the conjunctiva, episclera, choroid, and retina predispose to abnormal intra-globe fluid dynamics.

12.7.4 Natural History and Prognosis

SWS is associated with progressive CNS disease that results in seizures as well as motor, sensory, visual, and cognitive deficits. Early development of intractable seizures associated with hemiparesis and bilateral involvement are poor prognostic signs for cognitive development and general health. Recent studies showed that early white matter volume loss measured on brain MRI is associated with poor cognitive outcome (Juhasz et al. 2007).

12.7.5 Laboratory Studies

While recent efforts have identified a somatic *GNAQ* mutation (p.R183Q) as the presumed causative event in many cases of SWS, the diagnosis remains largely clinical. Urine biomarkers of neurologic function in SWS including MMP2, MMP9, and bFGF have been explored in preliminary studies and await further validation (Sreenivasan et al. 2013).

12.7.6 Imaging Studies

Although facial nevi are the most obvious manifestations of SWS, leptomeningeal angiomas are clearly the most important determinants of ultimate patient prognosis. Leptomeningeal malformations typically involve posterior cerebral hemispheres, especially occipital lobes. Such malformations cause ischemia in adjacent brain resulting in gliosis, demyelination, parallel cortical calcifications, focal cerebral atrophy, and hemiatrophy. Other findings include absent superficial cortical veins adjacent to the malformation and enlarged ipsilateral deep venous system choroid plexi.

Head CT scans reveal gyral or "tram-track" cortical calcifications (absent in very young patients), most commonly over posterior hemispheres. There is often underlying cortical atrophy. Enlargement of the skull, diploic space, subarachnoid space, sinuses, and mastoid air cells occurs ipsilateral to port-wine stains. Contrast-enhanced scans may reveal diffuse staining of involved cerebral cortex and intense leptomeningeal enhancement if performed prior to the development of cortical calcifications (Fischbein et al. 2000).

Brain MRI scans (Fischbein et al. 2000) demonstrate ipsilateral parenchymal atrophy, compensatory skull thickening, and sinus enlargement. There is marked gadolinium enhancement in areas of leptomeningeal angiomatosis. Enlargement of the ipsilateral choroid plexus occurs secondary to angiomatosis. T2 shortening in the white matter underlies angiomatous malformations, usually seen in infants, and may be due to ischemia. In later life, areas of T2 shortening are usually secondary to calcifications. Enlargement of deep venous structures occurs ipsilateral to meningeal angiomas. Advanced MRI techniques including susceptibility-weighted imaging and magnetic resonance spectroscopy, as well as functional imaging modalities with FDG-PET are increasingly being explored to improve lesion characterization and determine prognosis in SWS (Lo et al. 2013).

12.7.7 Treatment

Unlike other neurocutaneous syndromes, SWS is not associated with heightened predisposition to CNS tumors. Treatment of facial nevi has been revolutionized by vascular-specific pulsed dye laser therapy, and a recent small trial showed further increased efficacy with addition of topical

rapamycin (Marques et al. 2015). Ophthalmologic consultation is often required for aggressive medical and surgical management of glaucoma. If intractable seizures affect neurologic development and quality of life in young patients, there is general agreement that surgical resection (lobectomy, hemispherectomy) can significantly reduce seizure frequency and improve quality of life (Kossoff et al. 2002). This usually requires removal of the involved cortex and leptomeningeal abnormality. While prospective evidence is lacking, there is increasing retrospective data that low-dose aspirin therapy may be associated with decreased stroke-like episodes and seizures in SWS (Lance et al. 2013; Bay et al. 2011; Maria et al. 1998a, b).

Conclusions

The neurocutaneous syndromes are among the most common genetic disorders observed in humans. Furthermore, this unique group of patients is at higher risk for the development of CNS neoplasms. The responsible genes have already been identified for most disorders, although the molecular pathophysiology remains unclear in many cases. Please refer to Table 12.8 for up-to-date information. For the clinical oncologist, the challenge is the decision to treat or observe. Generally, this decision is driven by the tempo and severity of the patient's clinical picture, although a clear understanding of the natural history of the disease is essential. Fortunately, most patients do not develop malignant tumors, but this information is tempered by the need for lifelong observation and follow-up.

Table 12.8 Internet sites with additional information for the phakomatoses

Neurofibromatosis	www.ctf.org
Tuberous sclerosis	www.tsalliance.org
Ataxia telangiectasia	www.atsociety.org.uk www.atcp.org
Von Hippel–Lindau	www.vhl.org
Sturge–Weber	www.sturge-weber.com

References

Agarwal R, Liebe S et al (2014) Targeted therapy for hereditary cancer syndromes: neurofibromatosis type 1, neurofibromatosis type 2, and Gorlin syndrome. Discov Med 18(101):323–330

Ambrose M, Gattia RA (2013) Pathogenesis of ataxia-telangiectasia: the next generation of ATM functions. Blood 121(20):4036–4045

Ambrose M, Goldstine JV et al (2007) Intrinsic mitochondrial dysfunction in ATM-deficient lymphoblastoid cells. Hum Mol Genet 16(18):2154–2164

Anastasaki C, Gutmann DH (2014) Neuronal NF1/RAS regulation of cyclic AMP requires atypical PKC activation. Hum Mol Genet 23(25):6712–6721

Aoki S, Barkovich AJ et al (1989) Neurofibromatosis types 1 and 2: cranial MR findings. Radiology 172(2):527–534

Asthagiri AR, Mehta GU et al (2010) Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel-Lindau disease. Neuro Oncol 12(1):80–86

Astrup J (2003) Natural history and clinical management of optic pathway glioma. Br J Neurosurg 17(4):327–335

Bakkenist CJ, Kastan MB (2003) DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature 421(6922):499–506

Balasubramaniam A, Shannon P et al (2007) Glioblastoma multiforme after stereotactic radiotherapy for acoustic neuroma: case report and review of the literature. Neuro Oncol 9(4):447–453

Balestri P, Calistri L et al (1993) Central nervous system imaging in reevaluation of patients with neurofibromatosis type 1. Childs Nerv Syst 9(8):448–451

Baser ME, Kuramoto L et al (2004) Genotype-phenotype correlations for nervous system tumors in neurofibromatosis 2: a population-based study. Am J Hum Genet 75(2):231–239

Bay MJ, Kossoff EH et al (2011) Survey of aspirin use in Sturge-Weber syndrome. J Child Neurol 26(6):692–702

Becker-Catania SG, Chen G et al (2000) Ataxia-telangiectasia: phenotype/genotype studies of ATM protein expression, mutations, and radiosensitivity. Mol Genet Metab 70(2):122–133

Benz MR, Czernin J et al (2010) Quantitative F18-fluorodeoxyglucose positron emission tomography accurately characterizes peripheral nerve sheath tumors as malignant or benign. Cancer 116(2):451–458

Berg BO (1991) Current concepts of neurocutaneous disorders. Brain Dev 13(1):9–20

Bianchi AB, Hara T et al (1994) Mutations in transcript isoforms of the neurofibromatosis 2 gene in multiple human tumour types. Nat Genet 6(2):185–192

Billiet T, Madler B et al (2014) Characterizing the microstructural basis of "unidentified bright objects" in neurofibromatosis type 1: a combined in vivo multicomponent T2 relaxation and multi-shell diffusion MRI analysis. NeuroImage: Clin 4:649–658

Bissler JJ, Kingswood JC et al (2013) Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 381(9869):817–824

Blakeley JO, Evans DG et al (2011) Consensus recommendations for current treatments and accelerating clinical trials for patients with neurofibromatosis type 2. Am J Med Genet A 158A(1):24–41

Blansfield JA, Choyke L et al (2007) Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). Surgery 142(6):814–818

Bodensteiner JB, Roach ES (1999) Sturge-Weber syndrome. Sturge-Weber Foundation, Mt Freedom

Braffman BH, Bilaniuk LT et al (1990) MR of central nervous system neoplasia of the phakomatoses. Semin Roentgenol 25(2):198–217

Cai W, Kassarjian A et al (2009) Tumor burden in patients with neurofibromatosis types 1 and 2 and schwannomatosis: determination on whole-body MR images. Radiology 250(3):665–673

Capitanio JF, Mazza E et al (2013) Mechanisms, indications and results of salvage systemic therapy for sporadic and von Hippel-Lindau related hemangioblastomas of the central nervous system. Crit Rev Oncol Hematol 86(1):69–84

Caye-Thomasen P, Baandrup L et al (2003) Immunohistochemical demonstration of vascular endothelial growth factor in vestibular schwannomas correlates to tumor growth rate. Laryngoscope 113(12):2129–2134

Chalhub EG (1976) Neurocutaneous syndromes in children. Pediatr Clin North Am 23(3):499–516

Chandra PS, Salamon N et al (2006) FDG-PET/MRI coregistration and diffusion-tensor imaging distinguish epileptogenic tubers and cortex in patients with tuberous sclerosis complex: a preliminary report. Epilepsia 47(9):1543–1549

Chaudhary MW, Al-Baradie RS (2014) Ataxia-telangiectasia: future prospects. Appl Clin Genet 7:159–167

Chen F, Kishida T et al (1995) Germline mutations in the von Hippel-Lindau disease tumor suppressor gene: correlations with phenotype. Hum Mutat 5(1):66–75

Chessa L, Leuzzi V et al (2014) Intra-erythrocyte infusion of dexamethasone reduces neurological symptoms in ataxia teleangiectasia patients: results of a phase 2 trial. Orphanet J Rare Dis 9:5:1750-1172-9-5

Chun HH, Gatti RA (2004) Ataxia-telangiectasia, an evolving phenotype. DNA Repair 3(8–9):1187–1196

Concannon P, Gatti RA (1997) Diversity of ATM gene mutations detected in patients with ataxia-telangiectasia. Hum Mutat 10(2):100–107

Cooper J, Giancotti FG (2014) Molecular insights into NF2/Merlin tumor suppressor function. FEBS Lett 588(16):2743–2752

Coppin C, Kollmannsberger C (2011) Targeted therapy for advanced renal cell cancer (RCC): a Cochrane systematic review of published randomised trials. Br J Urol Int 108(10):1556–1563

Corcos O, Couvelard A et al (2008) Endocrine pancreatic tumors in von Hippel-Lindau disease: clinical, histological, and genetic features. Pancreas 37(1):85–93

Crossey PA, Richards FM et al (1994) Identification of intragenic mutations in the von Hippel-Lindau disease tumour suppressor gene and correlation with disease phenotype. Hum Mol Genet 3(8):1303–1308

Cuccia V, Zuccaro G et al (2003) Subependymal giant cell astrocytoma in children with tuberous sclerosis. Childs Nerv System 19(4):232–243

Cunha e Sa M, Barroso CP et al (1997) Innervation pattern of malformative cortical vessels in Sturge–Weber disease: an histochemical, immunohistochemical, and ultrastructural study. Neurosurgery 41(4):872–876

Curatolo P (1996) Neurological manifestations of tuberous sclerosis complex. Childs Nerv System 12(9):515–521

Curto M, Cole BK et al (2007) Contact-dependent inhibition of EGFR signaling by Nf2/Merlin. J Cell Biol 177(5):893–903

De Vitis LR, Tedde A et al (1996a) Screening for mutations in the neurofibromatosis type 2 (NF2) gene in sporadic meningiomas. Hum Genet 97(5):632–637

De Vitis LR, Tedde A et al (1996b) Analysis of the neurofibromatosis type 2 gene in different human tumors of neuroectodermal origin. Hum Genet 97(5):638–641

De Vries PJ, Whittemore VH et al (2015) Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND checklist. Pediatr Neurol 52(1):25–35

DeBella K, Szudek J et al (2000) Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics 105(3 Pt 1):608–614

Dewan R, Pemov A et al (2015) Evidence of polyclonality in neurofibromatosis type 2-associated multilobulated vestibular schwannomas. Neuro Oncol 17(4):566–573

Diggs-Andrews KA, Gutmann DH (2013) Modeling cognitive dysfunction in neurofibromatosis-1. Trends Neurosci 36(4):237–247

Dow G, Biggs N et al (2005) Spinal tumors in neurofibromatosis type 2. Is emerging knowledge of genotype predictive of natural history? J Neurosurg Spine 2(5):574–579

Duong TA, Sdibian E et al (2011) Mortality associated with neurofibromatosis 1: a cohort study of 1895 patients in 1980–2006 in France. Orphanet J Rare Dis 6:18

Dutton JJ (1994) Gliomas of the anterior visual pathway. Surv Ophthalmol 38(5):427–452

Eaton JS, Lin ZP (2007) Ataxia-telangiectasia mutated kinase regulates ribonucleotide reductase and mitochondrial homeostasis. J Clin Invest 117(9):2723–2734

Eisenhofer G, Lenders JW et al (2011) Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma. Clin Chem 57(3):411–420

Evans DG, Baser ME et al (2005) Management of the patient and family with neurofibromatosis 2: a consensus conference statement. Br J Neurosurg 19(1):5–12

Evans DG, O'Hara C et al (2011) Mortality in neurofibromatosis 1: in North West England: an assessment of

actuarial survival in a region of the UK since 1989. Eur J Hum Genet 19(11):1187–1191
Fischbein NJ, Dillon WP et al (2000) Teaching atlas of brain imaging. Thieme, New York
Fisher MJ, Loguidice M et al (2012) Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. Neuro Oncol 14(6):790–797
Franz DN (2004) Non-neurologic manifestations of tuberous sclerosis complex. J Child Neurol 19(9):690–698
Franz DN, Belousova E et al (2013) Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 381(9861):125–132
Frew IJ, Krek W (2008) pVHL: a multipurpose adaptor protein. Sci Signal 1(24):pe30
Gallagher A, Chu-Shore CJ et al (2009) Associations between electroencephalographic and magnetic resonance imaging findings in tuberous sclerosis complex. Epilepsy Res 87(2–3):197–202
Gallagher A, Grant EP et al (2010) MRI findings reveal three different types of tubers in patients with tuberous sclerosis complex. J Neurol 257(8):1373–1381
Gnekow AK, Falkenstein F et al (2012) Long-term follow-up of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade glioma in children and adolescents of the German Speaking Society of Pediatric Oncology and Hematology. Neuro Oncol 14(10):1265–1284
Gosink EC, Chong MJ et al (1999) Ataxia telangiectasia mutated deficiency affects astrocyte growth but not radiosensitivity. Cancer Res 59(20):5294–5298
Grey PL, Moffat DA et al (1996) Factors which influence the facial nerve outcome in vestibular schwannoma surgery. Clin Otolaryngol Allied Sci 21(5):409–413
Grill J, Couanet D et al (1999) Radiation-induced cerebral vasculopathy in children with neurofibromatosis and optic pathway glioma. Ann Neurol 45(3):393–396
Guo Z, Kozlov S et al (2010) ATM activation by oxidative stress. Science 330(6003):517–521
Gururangan S, Cavazos CM et al (2002) Phase II study of carboplatin in children with progressive low-grade gliomas. J Clin Oncol 20(13):2951–2958
Habek M, Brinar VV et al (2008) Brain MRI abnormalities in ataxia-telangiectasia. Neurologist 14(3): 192–195
Hanno R, Beck R (1987) Tuberous sclerosis. Neurol Clin 5(3):351–360
Hernaiz Driever P, von Hornstein S (2010) Natural history and management of low-grade glioma in NF1 children. J Neurooncol 100(2):199–207
Herrup K (2014) ATM and the epigenetics of the neuronal genome. Mech Ageing Dev 134(10):434–439
Hervey-Jumper SL, Singla N et al (2013) Diffuse pontine lesions in children with neurofibromatosis type 1: making a case for unidentified bright objects. Pediatr Neurosurg 49(1):55–59
Hes FJ, Lips CJ et al (2001a) Molecular genetic aspects of Von Hippel-Lindau (VHL) disease and criteria for DNA analysis in subjects at risk. Neth J Med 59(5):235–243
Hes FJ, van der Luijt RB et al (2001b) Clinical management of Von Hippel-Lindau (VHL) disease. Neth J Med 59(5):225–234
Hoogeveen-Westerveld M, Ekong R et al (2012) Functional assessment of TSC1 missense variants identified in individuals with tuberous sclerosis complex. Hum Mutat 33(3):476–479. doi: 10.1002/humu.22007. Epub 2012 Jan 17
Hoogeveen-Westerveld M, Ekong R et al (2013) Functional assessment of TSC2 variants identified in individuals with tuberous sclerosis complex. Hum Mutat 34(1):167–175. doi: 10.1002/humu.22202. Epub 2012 Oct 11
Jahodova A, Krsek P et al (2014) Distinctive MRI features of the epileptogenic zone in children with tuberous sclerosis. Eur J Radiol 83(4):703–709
Jansen FE, Braams O et al (2008) Overlapping neurologic and cognitive phenotypes in patients with TSC1 or TSC2 mutations. Neurology 70(12):908–915
Jiang W, Lee BJ et al (2015) Aberrant TCRδ rearrangement underlies the T-cell lymphocytopenia and t(12;14) translocation associated with ATM deficiency. Blood 125(17):2665–2668
Joerger M, Koeberle D et al (2005) Von Hippel-Lindau disease–a rare disease important to recognize. Onkologie 28(3):159–163
Jonasch E, McCutcheon IE et al (2011) Pilot trial of sunitinib therapy in patients with von Hippel-Lindau disease. Ann Oncol 22(12):2661–2666
Jones AC, Sampson JR et al (2000) Application and evaluation of denaturing HPLC for molecular genetic analysis in tuberous sclerosis. Hum Genet 106(6):663–668
Jozwiak S, Schwartz RA et al (2000) Usefulness of diagnostic criteria of tuberous sclerosis complex in pediatric patients. J Child Neurol 15(10):652–659
Juhasz C, Lai C et al (2007) White matter volume as a major predictor of cognitive function in Sturge-Weber syndrome. Arch Neurol 64(8):1169–1174
Kalamarides M, Acosta MT et al (2012) Neurofibromatosis 2011: a report of the Children's Tumor Foundation Annual Meeting. Acta Neuropathol 123(3):369–380
Kalantari BN, Salamon N (2008) Neuroimaging of tuberous sclerosis: spectrum of pathologic findings and frontiers in imaging. AJR Am J Roentgenol 190(5):W304–W309
Kamiya M, Yamanouchi H et al (2001) Ataxia telangiectasia with vascular abnormalities in the brain parenchyma: report of an autopsy case and literature review. Pathol Int 51(4):271–276
Kano H, Shuto T et al (2015) Stereotactic radiosurgery for intracranial hemangioblastomas: a retrospective international outcome study. J Neurosurg 122(6): 1469–1478. doi: 10.3171/2014.10.JNS131602. Epub 2015 Mar 27
Karajannis MA, Ferner RE (2015) Neurofibromatosis-related tumors: emerging biology and therapies. Curr Opin Pediatr 27(1):26–33

Karajannis MA, Legault G et al (2012) Phase II trial of lapatinib in adult and pediatric patients with neurofibromatosis type II and progressive vestibular schwannomas. Neuro Oncol 14(9):1163–1170

Karajannis MA, Legault G et al (2014) Phase II study of everolimus in children and adults with neurofibromatosis type 2 and progressive vestibular schwannomas. Neuro Oncol 16(2):292–297

Kastan MB, Lim DS (2000) The many substrates and functions of ATM. Nat Rev Mol Cell Biol 1(3):179–186

Kim TS, Kawaguchi M et al (2010) The ZFHX3 (ATBF1) transcription factor induces PDGFRB, which activates ATM in the cytoplasm to protect cerebellar neurons from oxidative stress. Dis Models Mech 3(11–12):752–762

Kim HJ, Hagan M et al (2013) Surgical resection of endolymphatic sac tumors in von Hippel-Lindau disease: findings, results, and indications. Laryngoscope 132(2):477–483

Kolberg M, Holand M et al (2013) Survival meta-analyses for >1800 malignant peripheral nerve sheath tumor patients with and without neurofibromatosis type 1. Neuro Oncol 15(2):135–147

Korf BR (2000) Malignancy in neurofibromatosis type 1. Oncologist 5(6):477–485

Korf BR (2002) Clinical features and pathobiology of neurofibromatosis 1. J Child Neurol 17(8):573–577; discussion 602–604, 646–651

Kornreich L, Blaser S et al (2001) Optic pathway glioma: correlation of imaging findings with the presence of neurofibromatosis. AJNR Am J Neuroradiol 22(10):1963–1969

Kossoff EH, Buck C et al (2002) Outcomes of 32 hemispherectomies for Sturge-Weber syndrome worldwide. Neurology 59(11):1735–1738

Krueger DA, Northup H (2013) Tuberous sclerosis complex surveillance and management: recommendations of 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 49(4):255–265

Krueger DA, Care MM et al (2010) Everolimus for subependymal giant cell astrocytomas in tuberous sclerosis. N Engl J Med 363(19):1801–1811

LaFemina J, Qin LX et al (2013) Oncologic outcomes of sporadic, neurofibromatosis-associated, and radiation-induced malignant peripheral nerve sheath tumors. Ann Surg Oncol 20(1):66–72

Lamszus K, Lachenmayer L et al (2001) Molecular genetic alterations on chromosomes 11 and 22 in ependymomas. Int J Cancer 91(6):803–808

Lance EI, Sreenivasan AK et al (2013) Aspirin use in Sturge-Weber syndrome: side effects and clinical outcomes. J Child Neurol 28(2):213–218

Latif F, Tory K et al (1993) Identification of the von Hippel-Lindau disease tumor suppressor gene. Science 260(5112):1317–1320

Lavin MF (1999) ATM: the product of the gene mutated in ataxia-telangiectasia. Int J Biochem Cell Biol 31(7):735–740

Lavin MF, Concannon P et al (1999) Eighth International Workshop on Ataxia-Telangiectasia (ATW8). Cancer Res 59(15):3845–3849

Laycock-van Spyk S, Thomas N et al (2011) Neurofibromatosis type 1-associated tumours: their somatic mutation spectrum and pathogenesis. Hum Genomics 5(6):623–690

Lin AL, Gutmann DH (2013) Advances in the treatment of neurofibromatosis-associated tumours. Nat Rev Clin Oncol 10(11):616–624

Listernick R, Charrow J (2004) Neurofibromatosis-1 in childhood. Adv Dermatol 20:75–115

Listernick R, Charrow J et al (1994) Natural history of optic pathway tumors in children with neurofibromatosis type 1: a longitudinal study. J Pediatr 125(1):63–66

Listernick R, Charrow J et al (1999) Intracranial gliomas in neurofibromatosis type 1. Am J Med Genet 89(1):38–44

Listernick R, Ferner RE et al (2007) Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. Ann Neurol 61(3):189–198

Lo W, Marchuk DA et al (2013) Updates and future horizons on the understanding, diagnosis and treatment of Sturge–Weber syndrome brain involvement. Dev Med Child Neurol 54(3):214–223

Lonser RR, Butman JA et al (2014) Prospective natural history study of central nervous system hemangioblastomas in von Hippel-Lindau disease. J Neurosurg 120(5):1055–1062

Madden JR, Rush SZ et al (2014) Radiation-induced gliomas in 2 pediatric patients with neurofibromatosis type 1: case study and summary of the literature. J Pediatr Hematol Oncol 36(2):e105–e108

Maher ER, Kaelin WG Jr (1997) von Hippel–Lindau disease. Medicine 76(6):381–391

Maher ER, Yates JR et al (1990) Clinical features and natural history of von Hippel-Lindau disease. QJM: Int J Med 77(283):1151–1163

Maher ER, Neumann HP et al (2011) von Hippel-Lindau disease: a clinical and scientific review. Eur J Hum Genet 19(6):617–623

Maiuri F, Gangemi M et al (1989) Sturge–Weber disease without facial nevus. J Neurosurg Sci 33(2): 215–218

Mallory GW, Pollock BE et al (2014) Stereotactic radiosurgery for neurofibromatosis 2-associated vestibular schwannomas: toward dose optimization for tumor control and functional outcomes. Neurosurgery 74(3):292–300

Maria BL, Neufeld JA et al (1998a) High prevalence of bihemispheric structural and functional defects in Sturge-Weber syndrome. J Child Neurol 13(12):595–605

Maria BL, Neufeld JA et al (1998b) Central nervous system structure and function in Sturge-Weber syndrome: evidence of neurologic and radiologic progression. J Child Neurol 13(12):606–618

Marques L, Nunez-Cordoba JM et al (2015) Topical rapamycin combined with pulsed dye laser in the treatment of capillary vascular malformations in Sturge-Weber syndrome: phase II, randomized, double-blind, intraindividual placebo-controlled clinical trial. J Am Acad Dermatol 72(1):151–158

Mautner VF, Tatagiba M et al (1993) Neurofibromatosis 2 in the pediatric age group. Neurosurgery 33(1):92–96

Mautner VF, Tatagiba M et al (1995) Spinal tumors in patients with neurofibromatosis type 2: MR imaging study of frequency, multiplicity, and variety. AJR Am J Roentgenol 165(4):951–955

Mautner VF, Lindenau M et al (1996) The neuroimaging and clinical spectrum of neurofibromatosis 2. Neurosurgery 38(5):880–885; discussion 885–886

Maxwell PH, Weisener MS et al (1999) The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature 399(6733):271–275

Medlock MD, Madsen JR et al (1997) Optic chiasm astrocytomas of childhood. 1. Long-term follow-up. Pediatr Neurosurg 27(3):121–128

Menkes JH, Maria BL (2000) Neurocutaneous syndromes. In: Menkes JH, Sarnat HB (eds) Child neurology. Lippincott Williams & Wilkins, Philadelphia

Menor F, Marti-Bonmati L et al (1992) Neuroimaging in tuberous sclerosis: a clinicoradiological evaluation in pediatric patients. Pediatr Radiol 22(7):485–489

Menotta M, Biagotti S et al (2012) Dexamethasone partially rescues ataxia telangiectasia-mutated (ATM) deficiency in ataxia telangiectasia by promoting a shortened protein variant retaining kinase activity. J Biol Chem 287(49):41352–41363

Merchant TE, Conklin HM et al (2009) Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol 27(22):3691–3697

Messiaen LM, Callens T et al (2000) Exhaustive mutation analysis of the NF1 gene allows identification of 95% of mutations and reveals a high frequency of unusual splicing defects. Hum Mutat 15(6):541–555

Micol R, Ben Slama L et al (2011) Morbidity and mortality from ataxia-telangiectasia are associated with ATM genotype. J Allergy Clin Immunol 128(2): 382–389e1

Mitui M, Campbell C et al (2003) Independent mutational events are rare in the ATM gene: haplotype prescreening enhances mutation detection rate. Hum Mutat 22(1):43–50

Motzer RJ, Hutson TE et al (2013) Pazopanib versus sunitinib in metastatic renal cell carcinoma. N Engl J Med 369(8):722–731

Mukonoweshuro W, Griffiths PD et al (1999) Neurofibromatosis type 1: the role of neuroradiology. Neuropediatrics 30(3):111–119

Mukonoweshuro W, Wilkinson ID et al (2001) Proton MR spectroscopy of cortical tubers in adults with tuberous sclerosis complex. AJNR Am J Neuroradiol 22(10):1920–1925

Nakamura K, Fike F et al (2014) A-TWinnipeg: Pathogenesis of rare *ATM* missense mutation c.6200C>A with decreased protein expression and downstream signaling, early-onset dystonia, cancer, and life-threatening radiotoxicity. Mol Genet Genom Med 2(4):332–340

National Institutes of Health Consensus Development Conference (1988) Neurofibromatosis. Arch Neurol 45(5):575–578

Nissenkorn A, Hassin-Baer S et al (2013) Movement disorder in ataxia-telangiectasia: treatment with amantadine sulfate. J Child Neurol 28(2):155–160

Nordstrom-O'Brien M, van der Luijt RB et al (2010) Genetic analysis of von Hippel-Lindau disease. Hum Mutat 31(5):521–537

Northrup H, Krueger DA (2013) Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. International Tuberous Sclerosis Complex Consensus Group. Pediatr Neurol 49(4):243–254. doi: 10.1016/j.pediatrneurol.2013.08.001

Nunes FP, Merker VL et al (2013) Bevacizumab treatment for meningiomas in NF2: a retrospective analysis of 15 patients. PLoS One 8(3):e59941

Oakes WJ (1992) The natural history of patients with the Sturge–Weber syndrome. Pediatr Neurosurg 18(5–6):287–290

Oh KS, Hung J et al (2011) Outcomes of multidisciplinary management in pediatric low-grade gliomas. Int J Radiat Oncol Biol Phys 81(4):e481–e488

Paganini I, Chang VY et al (2015) Expanding the mutational spectrum of LZTR1 in schwannomatosis. Eur J Hum Genet 23(7):963–968. doi: 10.1038/ejhg.2014.220. Epub 2014 Oct 22

Paller AS (1987) Ataxia-telangiectasia. Neurol Clin 5(3):447–449

Parry DM, Eldridge R et al (1994) Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. Am J Med Genet 52(4):450–461

Parsa CF, Hoyt CS et al (2001) Spontaneous regression of optic gliomas: thirteen cases documented by serial neuroimaging. Arch Ophthalmol 119(4):516–529

Pascual-Castroviejo I, Pascual-Pascual SI et al (2008) Sturge-Weber syndrome. Study of 55 patients. Can J Neurol Sci 35(3):301–307

Pasmant E, Parfait B et al (2015) Neurofibromatosis type 1 molecular diagnosis: what can NGS do for you when you have a large gene with loss of function mutations? Eur J Hum Genet 23(5):596–601

Peters JM, Taquet M et al (2013) Diffusion tensor imaging and related techniques in tuberous sclerosis complex: review and future directions. Futur Neurol 8(5):583–597

Plotkin SR, Bredella MA (2012) Quantitative assessment of whole-body tumor burden in adult patients with neurofibromatosis. PLoS One 7(4):e35711

Plotkin SR, Stemmer-Rachamimov AO (2009) Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. N Engl J Med 361(4):358–367

Plotkin SR, Merkel VL et al (2012) Bevacizumab for progressive vestibular schwannoma in neurofibromatosis type 2: a retrospective review of 31 patients. Otol Neurotol 33(6):1046–1052

Plotkin SR, Merker VL et al (2014) Natural history of vestibular schwannoma growth and hearing decline in

newly diagnosed neurofibromatosis type 2 patients. Otol Neurotol 35(1):e50–e56
Pollack IF, Shultz B et al (1996) The management of brainstem gliomas in patients with neurofibromatosis 1. Neurology 46(6):1652–1660
Porter DE, Prasad V et al (2009) Survival in malignant peripheral nerve sheath tumours: a comparison between sporadic and neurofibromatosis type 1-associated tumours. Sarcoma 2009:756395
Pros E, Gomez C et al (2008) Nature and mRNA effect of 282 different NF1 point mutations: focus on splicing alterations. Hum Mutat 29(9):E173–E193
Rajaram V, Gutmann DH et al (2005) Alterations of protein 4.1 family members in ependymomas: a study of 84 cases. Mod Pathol 18(7):991–997
Ranger AM, Patel YK et al (2014) Familial syndromes associated with intracranial tumours: a review. Childs Nerv Syst 30(1):47–64
Rasmussen SA, Yang Q et al (2001) Mortality in neurofibromatosis 1: an analysis using U.S. death certificates. Am J Hum Genet 68(5):1110–1118
Richard S, David P et al (2000) Central nervous system hemangioblastomas, endolymphatic sac tumors, and von Hippel-Lindau disease. Neurosurg Rev 23(1):1–22; discussion 23–24
Rieley MB, Stevenson DA et al (2011) Variable expression of neurofibromatosis 1 in monozygotic twins. Am J Med Genet A 155A(3):478–485
Roach ES, Sparagana SP (2004) Diagnosis of tuberous sclerosis complex. J Child Neurol 19(9):643–649
Roach ES, Gomez MR et al (1998) Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 13(12):624–628
Robertson KA, Nalepa G et al (2012) Imatinib mesylate for plexiform neurofibromas in patients with neurofibromatosis type 1: a phase 2 trial. Lancet Oncol 13(12):1218–1224
Rosser T, Packer RJ (2002) Intracranial neoplasms in children with neurofibromatosis 1. J Child Neurol 17(8):630–637; discussion 646–651
Roth J, Roach ES et al (2013) Subependymal giant cell astrocytoma: diagnosis, screening and treatment. Recommendations from the International Tuberous Sclerosis Complex Consensus Conference 2012. Pediatr Neurol 49(4):439–444
Rouleau GA, Merel P et al (1993) Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. Nature 363(6429):515–521
Rovira A et al (2014) Recommendations for the radiological diagnosis and follow-up of neuropathological abnormalities associated with tuberous sclerosis complex. J Neurooncol 118(2):205–223
Rowe J, Radatz M et al (2008) Radiosurgery for type II neurofibromatosis. Prog Neurol Surg 21:176–182
Sabbagh A, Pasmant E et al (2009) Unravelling the genetic basis of variable clinical expression in neurofibromatosis 1. Hum Mol Genet 18(15):2768–2778
Sabbagh A, Pasmant E et al (2013) NF1 molecular characterization and neurofibromatosis type I genotype-phenotype correlation: the French experience. Hum Mutat 34(11):1510–1518
Sahama I, Sinclair K et al (2014a) Radiological imaging in ataxia telangiectasia: a review. Cerebellum 13(4):521–530
Sahama I, Sinclair K et al (2014b) Altered corticomotor-cerebellar integrity in young ataxia telangiectasia patients. Mov Disord 29(10):1289–1298
Saunders-Pullman R, Raymond D et al (2012) Variant ataxia-telangiectasia presenting as primary-appearing dystonia in Canadian Mennonites. Neurology 78(9):649–657
Schmid S, Gilessen S et al (2014) Management of von hippel-lindau disease: an interdisciplinary review. Oncol Res Treat 37(12):761–771
Scoles DR (2008) The merlin interacting proteins reveal multiple targets for NF2 therapy. Biochim Biophys Acta 1785(1):32–54
Selvanathan SK, Shenton A et al (2010) Further genotype-phenotype correlations in neurofibromatosis 2. Clin Genet 77(2):163–170
Sevick RJ, Barkovich AJ et al (1992) Evolution of white matter lesions in neurofibromatosis type 1: MR findings. AJR Am J Roentgenol 159(1):171–175
Shamji MF, Benoit BG (2007) Syndromic and sporadic pediatric optic pathway gliomas: review of clinical and histopathological differences and treatment implications. Neurosurg Focus 23(5):E3
Sharif S, Ferner R et al (2006) Second primary tumors in neurofibromatosis 1 patients treated for optic glioma: substantial risks after radiotherapy. J Clin Oncol 24(16):2570–2575
Sharif S, Upadhyaya M et al (2011) A molecular analysis of individuals with neurofibromatosis type 1 (NF1) and optic pathway gliomas (OPGs), and an assessment of genotype-phenotype correlations. J Med Genet 48(4):256–260
Shen C, Kaelin WG (2013) The VHL/HIF axis in clear cell renal carcinoma. Semin Cancer Biol 23(1):18–25
Shepherd CW, Stephenson JB (1992) Seizures and intellectual disability associated with tuberous sclerosis complex in the west of Scotland. Dev Med Child Neurol 34(9):766–774
Shiloh Y (2003) ATM and related protein kinases: safeguarding genome integrity. Nat Rev Cancer 3(3):155–168
Shirley MD, Tang H et al (2013) Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med 368(21):1971–1979
Simone CB II, Lonser RR et al (2011) Infratentorial craniospinal irradiation for von Hippel–Lindau: a retrospective study supporting a new treatment for patients with CNS hemangioblastomas. Neuro Oncol 13(9):1030–1036
Sims KB (2001) Von Hippel-Lindau disease: gene to bedside. Curr Opin Neurol 14(6):695–703
Singh AD, Shields CL et al (2001) von Hippel-Lindau disease. Surv Ophthalmol 46(2):117–142
Singhal S, Birch JM et al (2002) Neurofibromatosis type 1 and sporadic optic gliomas. Arch Dis Child 87(1):65–70

Sorensen SA, Mulvihill JJ et al (1986) Long-term follow-up of von Recklinghausen neurofibromatosis. Survival and malignant neoplasms. N Engl J Med 314(16):1010–1015

Sparagana SP, Roach ES (2000) Tuberous sclerosis complex. Curr Opin Neurol 13(2):115–119

Sreenivasan AK, Bachur CD et al (2013) Urine vascular biomarkers in Sturge–Weber syndrome. Vasc Med 18(3):122–128

Staples ER, McDermott EM (2008) Immunodeficiency in ataxia telangiectasia is correlated strongly with the presence of two null mutations in the ataxia telangiectasia mutated gene. Clin Exp Immunol 153(2):214–220

Suarez F, Mahlaoui N (2015) Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. J Clin Oncol 33(2):202–208

Sudarsanam A, Ardern-Holmes SL (2014) Sturge-Weber syndrome: from the past to the present. Eur J Paediatr Neurol 18(3):257–266

Sujansky E, Conradi S (1995) Sturge-Weber syndrome: age of onset of seizures and glaucoma and the prognosis for affected children. J Child Neurol 10(1):49–58

Sun M, Shariat SF et al (2013) An evidence-based guide to the selection of sequential therapies in metastatic renal cell carcinoma. Ther Adv Urol 5(2):121–128

Szudek J, Birch P et al (2000) Associations of clinical features in neurofibromatosis 1 (NF1). Genet Epidemiol 19(4):429–439

Taly AB, Nagaraja D et al (1987) Sturge–Weber–Dimitri disease without facial nevus. Neurology 37(6):1063–1064

Theeler BJ, Ellezam B et al (2014) Prolonged survival in adult neurofibromatosis type I patients with recurrent high-grade gliomas treated with bevacizumab. J Neurol 261(8):1559–1564

Thiele EA (2004) Managing epilepsy in tuberous sclerosis complex. J Child Neurol 19(9):680–686

Tsai LL, Drubach L et al (2012) [18F]-Fluorodeoxyglucose positron emission tomography in children with neurofibromatosis type 1 and plexiform neurofibromas: correlation with malignant transformation. J Neurooncol 108(3):469–475

Turgut M, Ozcan OE et al (1991) Central neurofibromatosis. Case report and review of the literature. Eur Neurol 31(4):188–192

Ullrich NJ, Raja AI et al (2007) Brainstem lesions in neurofibromatosis type 1. Neurosurgery 61(4):762–766; discussion 766–767

Upadhyaya M, Huson SM et al (2007) An absence of cutaneous neurofibromas associated with a 3-bp inframe deletion in exon 17 of the NF1 gene (c.2970-2972 delAAT): evidence of a clinically significant NF1 genotype-phenotype correlation. Am J Hum Genet 80(1):140–151

Uppal S, Coatesworth AP (2003) Neurofibromatosis type 2. Int J Clin Pract 57(8):698–703

Van Eeghen AM, Black ME et al (2012) Genotype and cognitive phenotype of patients with tuberous sclerosis complex. Eur J Hum Genet 20(5):510–515

van Engelen SJ, Krab LC et al (2008) Quantitative differentiation between healthy and disordered brain matter in patients with neurofibromatosis type I using diffusion tensor imaging. AJNR Am J Neuroradiol 29(4):816–822

van Slegtenhorst M, Verhoef S et al (1999) Mutational spectrum of the TSC1 gene in a cohort of 225 tuberous sclerosis complex patients: no evidence for genotype-phenotype correlation. J Med Genet 36(4):285–289

Verhagen MM, Abdo WF et al (2009) Clinical spectrum of ataxia-telangiectasia in adulthood. Neurology 73(6):430–437

Verhagen MM, Last JI et al (2011) Presence of ATM protein and residual kinase activity correlates with the phenotype in ataxia-telangiectasia: a genotype-phenotype study. Hum Mutat 33(3):561–571

Vortmeyer AO et al (2013) Nervous system involvement in von Hippel-Lindau disease: pathology and mechanisms. Acta Neuropathol 125(3):333–350

Waelchli R, Aylett SE et al (2014) New vascular classification of port-wine stains: improving prediction of Sturge–Weber risk. Br J Dermatol 171(4):861–867

Walker DA, Liu J et al (2013) A multi-disciplinary consensus statement concerning surgical approaches to low-grade, high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood (CPN Paris 2011) using the Delphi method. Neuro Oncol 15(4):462–468

Wanebo JE, Lonser RR et al (2003) The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. J Neurosurg 98(1):82–94

Webb DW, Fryer AE et al (1996) Morbidity associated with tuberous sclerosis: a population study. Dev Med Child Neurol 38(2):146–155

Wentworth S, Pinn M et al (2009) Clinical experience with radiation therapy in the management of neurofibromatosis-associated central nervous system tumors. Int J Radiat Oncol Biol Phys 73(1):208–213

Widemann BC, Blakeley JO et al (2013) Conclusions and future directions for the REiNS International Collaboration. Neurology 81(21 Suppl 1):S41–S44

Widemann BC, Dombi E et al (2014a) Phase 2 randomized, flexible crossover, double blinded, placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Neuro Oncol 16(5):707–718

Widemann B, Leigh JM et al (2014b) Phase I study of the MEK ½ inhibitor selumetinib (AZD6244) hydrogen sulfate in children and young adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PNs) [abstract]. J Clin Oncol 32(suppl):10018

Wilding A, Ingham SL et al (2012) Life expectancy in hereditary cancer predisposing diseases: an observational study. J Med Genet 49(4):264–269

Winterkorn EB, Pulsifer MB et al (2007) Cognitive prognosis of patients with tuberous sclerosis complex. Neurology 68(1):62–64

Modern Neuroimaging of Pediatric Brain Tumors

13

Mark D. Mamlouk, Sean O. Bryant, Soonmee Cha, and A. James Barkovich

Contents

M.D. Mamlouk, MD
Division of Neuroradiology,
Kaiser Permanente Santa Clara,
700 Lawrence Expressway, Suite 104, Santa Clara, CA 95051, USA
e-mail: mark.mamlouk@ucsf.edu

S.O. Bryant, MD
Department of Radiology, Diversified Radiology of Colorado, PC, 1746 Cole Boulevard, Suite 150, Lakewood, CO 80401, USA
e-mail: sbryant@divrad.com

S. Cha, MD
Radiology & Neurological Surgery, University of California San Francisco,
350 Parnassus Avenue, Suite 307, Box 0336,
San Francisco, CA 94143, USA
e-mail: soonmee.cha@ucsf.edu

A.J. Barkovich, MD (✉)
Departments of Radiology and Biomedical Imaging, Neurology, Pediatrics & Neurosurgery, University of California San Francisco & UCSF Benioff Children's Hospital, 505 Parnassus Avenue, Room L352,
San Francisco, CA 94143-0628, USA
e-mail: james.barkovich@ucsf.edu

13.1 Modern Neuroimaging of Pediatric CNS Tumors

Neuroimaging has been an important tool in the diagnosis and surveillance of brain tumors for more than 30 years. Although structural magnetic

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_13

resonance (MR) imaging remains the most important imaging tool for assessing CNS neoplasms, new techniques have allowed physiologic features of brain tumors and the surrounding functional brain tissue to be performed noninvasively. In this chapter, these new techniques and their applications are discussed.

13.2 MR Spectroscopy

13.2.1 Principles

Proton MR spectroscopy (MRS) is a powerful and noninvasive imaging technique that can be added to a standard MR study with only a small-time increase (Hunter and Wang 2001). MRS provides information about the activity of specific metabolites that can supplement the information obtained from routine anatomic sequences (Kim et al. 1997; Kimura et al. 2001). MRS may be useful to differentiate tumor from normal tissue, help stratify neoplasms as high- or low-grade, plan biopsies, distinguish between treatment injury and recurrent neoplasm, and separate cystic infection from cystic neoplasm (Yousem et al. 1992; Ott et al. 1993; Lazareff et al. 1999; Nelson et al. 1997a, 1999; Norfray et al. 1999; Poptani et al. 1995; Shimizu et al. 1996; Wang et al. 1996a). Routine MR imaging may lead to incorrect tumor classification in up to 40 % of cases (Ott et al. 1993).

MRS displays peaks from functional groups of numerous neurochemicals (Salibi and Brown 1998). Several of these neurochemicals are important in the analysis of patients with brain tumors, including *N*-acetylaspartate (NAA), trimethylamines (choline [Cho] and related compounds), creatine constituents (Cr), lactate (Lac), myoinositol (Myo), and amino acids (AA) (Hunter and Wang 2001; Norfray et al. 1999; Poptani et al. 1995; Birken and Oldendorf 1989; Dezortova et al. 1999; Tomoi et al. 1997; Urenjak et al. 1993).

A normal NAA peak is thought to reflect a normal number of mature, normally functioning neurons (Hunter and Wang 2001; Birken and Oldendorf 1989). NAA is synthesized in the mitochondria and is believed to be a key component in an acetyl group carrier between neuronal mitochondria and cytoplasm. It is vital in the regulation of neuronal protein synthesis and the metabolism of several neurotransmitters (Birken and Oldendorf 1989). NAA is also present in oligodendrocyte precursors (where it is metabolized to acetate (subsequently converted to acetyl CoA) and aspartate by aspartoacylase) and may be elevated or reduced in processes involving oligodendrocytes and myelin, as well as those involving neurons and axons (Urenjak et al. 1993; Tzika et al. 1997). The NAA concentration is dependent on location (it is 10 % lower in the normal cerebellum compared to cerebrum), maturity (increases as the brain develops and neurons mature), and neuronal health (decreased after injury or infiltration by neoplasm) (Wang et al. 1996a; Usenius et al. 1995).

The Cho resonance mainly comprises molecules from cell membranes, such as choline, phosphocholine, and glycerophosphorylcholine (Waldrop et al. 1998). Protons in choline molecules within intact membranes (such as those found in phosphatidylcholine), however, are immobile and do not contribute to MR signal (Norfray et al. 1999; Waldrop et al. 1998; Dowling et al. 2001). Since the Cho peak in the MR spectrum is composed of signal from these compounds during the processes of membrane synthesis and degradation (Norfray et al. 1999; Waldrop et al. 1998; Dowling et al. 2001), elevated Cho is found in neoplasms, active infection, and regions containing inflammatory cells.

The Cr peak comes from methylamine peaks of creatine and phosphocreatine – compounds that provide a high-energy phosphate buffer for adenosine triphosphate synthesis (Norfray et al. 1999). In most disorders, it is not clear what processes produce changes in Cr concentrations. Cr can be depressed in high-grade or metabolically active neoplasm, due to the overwhelming requirements of the proliferating tumor cells (Tzika et al. 1996). It can also be depleted in regions of necrosis secondary to lack of metabolic needs and cell death (Yousem et al. 1992; Tzika et al. 1997, 2001; Taylor et al. 1996).

Lactate is an end product of anaerobic glycolysis that accumulates when the glycolytic rate

exceeds lactate catabolism or overwhelms export by the blood stream (Norfray et al. 1999; Tomoi et al. 1997; Wang et al. 1995). It is a nonspecific marker seen in a variety of conditions such as tumors, necrosis, ischemia, cysts, and treatment injury (Wang et al. 1995). Increasing evidence suggests that the glycolytic pathway is an important source of energy in astrocytes (Belanger et al. 2011), which may explain why astrocytomas often are associated with increased lactate on proton MRS.

Accumulation of 2-hydroxyglutarate (2HG) has been associated with mutations in isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) in grade II and grade III gliomas. Noninvasive detection of this oncometabolite, 2HG, is now feasible using MRS, and the presence of 2HG peak on MRS has been correlated with mutations in IDH1 or IDH2 in resected tumor tissues of gliomas (Choi et al. 2012). As the MRS techniques continue to improve, detection and quantification of 2HG may become an important part of preoperative diagnosis and assessment of prognosis in patients with glioma.

13.2.2 Technique

Currently, at the University of California, San Francisco (UCSF), we obtain spectra from a large area of the brain (8×8×8 cm) and can resolve spectra from volumes of less than 1 cm^3 within that area. These data are acquired in approximately 8 min on a 3 T MRI (Nelson et al. 1999; McKnight et al. 2001; Nelson et al. 1997b). Using this technique, a small tumor focus can be identified in a large region of heterogeneous tissue. Moreover, postprocessing allows the voxel to be placed in precisely the same region of interest as in prior studies, allowing increased confidence that the tumor has been sampled in precisely the same location (Nelson et al. 1994). On MR scanners without 3D spectroscopic imaging (3D MRSI), 2D MRSI, commercially available from all major manufacturers, can be extremely useful. Two-dimensional MRSI allows coverage of a large area of tissue with small voxel size and an excellent signal-to-noise ratio (Dowling et al. 2001; Taylor et al. 1996). The only disadvantage is the necessity to acquire separate spectra for each plane sampled.

13.2.3 Application

MRS is useful in diagnosing and assessing brain tumors because tumors usually have elevated Cho levels and subnormal NAA levels compared to normal brain tissue. A Cho/NAA ratio of ≥5 is strongly suggestive of tumor. These features are also found in other conditions in which membrane turnover is increased and the number of healthy, mature neurons is decreased (e.g., immature brain, some types of dysplastic brain, and inflammation). It is important to know the normal peak ratios in the region of brain being investigated. The concentration of NAA is normally 10 % lower in the cerebellum than in cerebral white matter (Usenius et al. 1995; Wang et al. 1995). Cho concentrations in the cerebellum and pons are 70 % higher than in other areas (Usenius et al. 1995). Increased Cho in relation to NAA is even more dramatic in neonates (Tzika et al. 1996). Ratios of metabolites can also differ in different regions of the brain, even within different portions of the cerebral cortex (Wang et al. 1995). Therefore, it is critical to correlate MRS with MRI and other tests in order to avoid false positive results suggestive of tumor, when the actual process is another diagnosis (Sutton et al. 1992).

Once the diagnosis of tumor is established, MRS can be of some use in grading astrocytic neoplasms. In general, the farther the metabolite peaks vary from normal, the more likely that the tumor is aggressive (Hunter and Wang 2001). In particular, the Lac peak magnitude tends to be more elevated in more aggressive neoplasms (Girard et al. 1998). It should be noted, however, that juvenile pilocytic astrocytomas, among the most benign of brain tumors, have elevated choline and lactate, along with reduced NAA (Lazareff et al. 1999). In addition, similar grades of tumors of different histologic type may have very different spectra (e.g., a low-grade oligodendroglioma may have a very different spectrum from a low-grade astrocytoma). For these reasons, grading of neoplasms based on MRS has

focused on determining peak magnitudes and ratios in tumors of the same histologic type (Poptani et al. 1995; Shimizu et al. 1996; Tzika et al. 1996; Chang et al. 1998; Horska et al. 2001), and even in these cases, it is not entirely reliable (Kimura et al. 2001; Lazareff et al. 1999; Tzika et al. 1996, 1997; Chang et al. 1998; Barker et al. 1993; Shino et al. 1999).

Rarely, tumors have unique spectra that can help narrow the differential diagnosis from what is derived from routine MR imaging alone. For example, meningiomas and central neurocytomas exhibit an alanine peak that is typically not found in other neoplasms. In these two tumor types, it may represent a secondary marker for more aggressive histology (Kinoshita and Yokota 1997; Krishnamoorthy et al. 2007; Kugel et al. 1992; Lehnhardt et al. 2001). An elevated taurine peak has been preferentially discovered in medulloblastomas, which is not the case for astrocytomas within the posterior fossa (Chawla et al. 2007; Moreno-Torres et al. 2004). The combination of prominent Cho, Lac, and lipids peaks, and minimal NAA peaks, and basically absent myoinositol peaks has been described with atypical teratoid rhabdoid tumors (Bruggers and Moore 2014). Citrate has been observed in pediatric brain tumors, particularly diffuse intrinsic brain stem gliomas, although also in the developing brain of infants younger than 6 months (Seymour et al. 2008).

MRS can be helpful in selecting the best biopsy site in heterogeneous neoplasms (Dowling et al. 2001; Martin et al. 2001). However, for MRS to be useful in this regard, the voxel size must be small compared to the size of the neoplasm. Spectroscopic data obtained from a given volume of brain represents the average of the metabolic components of the volume. If the voxel is large or the tumor is small, the voxel might contain regions of both high and low-grade tumor, normal brain, and necrosis (Tzika et al. 1996). The resultant spectrum reflects the percentage of each component and does not reflect the nature of the tumor. For example, the MRS of a highly aggressive neoplasm with a large component of necrosis or normal brain or low-grade tumor could mimic the spectra of a low-grade neoplasm (Sijens et al. 1995; Venkatesh et al. 2001). Because spectra can also be contaminated by adjacent CSF or by fat from the calvarium or scalp (Hunter and Wang 2001; Norfray et al. 1999; Wang et al. 1996a; Sijens et al. 1995), it is imperative to use as small a voxel as possible. However, sampling many different voxels during a single exam necessitates excessively long scan times if each voxel is acquired separately. In order to reduce acquisition time, 3D MRSI can be used to sample a large volume of brain during a single acquisition, with small areas within the volume analyzed during the postprocessing step.

Although MRS can clearly distinguish abnormal from normal brain tissue, it does not always correctly differentiate a neoplasm from other disorders (Kim et al. 1997; Sutton et al. 1992; Wilken et al. 2000), particularly those with a high concentration of inflammatory cells (Venkatesh et al. 2001; Krouwer et al. 1998). There are many examples of inflammatory disorders, such as demyelinating plaques, tuberculomas, xanthogranulomas, HIV encephalitis, and HSV encephalitis, that have MRS features nearly identical to neoplasms (Venkatesh et al. 2001; Krouwer et al. 1998; Butzen et al. 2000; Shukla-Dave et al. 2001). These other processes should always be considered, particularly when the patient's history or imaging features are not consistent with a CNS tumor.

MRS can be useful in differentiating pyogenic abscess from tumor. Increased glycolysis and fermentation by bacteria produce elevated levels of lactate, acetate, and succinate, while proteolysis by enzymes produces valine, isoleucine, and leucine (Kim et al. 1997; Chang et al. 1998; Gupta et al. 2001). These compounds have protons that precess in the aliphatic region, upfield from NAA. Although elevated lactate and succinate associated with radiation necrosis makes MRS nonspecific in the posttherapy patient (Kim et al. 1997; Yeung et al. 2001), the presence of these peaks seems rather sensitive (92–100%) and specific when MRS is performed at presentation (Kim et al. 1997; Kimura et al. 2001; Shukla-Dave et al. 2001; Gupta et al. 2001; Grand et al. 1999).

Distinguishing posttherapy injury from recurrent or residual neoplasm has been difficult using anatomic imaging techniques, as the enhancement and edema seen with the two conditions can be nearly identical. This distinction is pivotal, as earlier recognition of recurrence can prolong survival

or guide future treatment (Shtern 1992). MRS can be a useful technique in making this distinction, as an injured brain produces a different spectrum than a normal brain or tumor (Kamada et al. 1997). Early radiation injury produces elevated Cho from plasma and intracellular membrane disruption, but this usually clears quickly and a normal NAA peak remains (Szigety et al. 1993). A global decrease in peak amplitudes (NAA, Cho, and Cr peaks) is consistent with treatment injury without active neoplasm (Kimura et al. 2001; Yousem et al. 1992; Ott et al. 1993; Tzika et al. 1997; Taylor et al. 1996). Recurrence is suggested by new or persistent elevation of Cho and reduction of NAA (Fig. 13.1) (Lazareff et al. 1999; Tzika et al. 1997; Sijens et al. 1995). MRS has also helped in determining survival, which can impact treatment stratification. High glutamate has been reported to be predictive

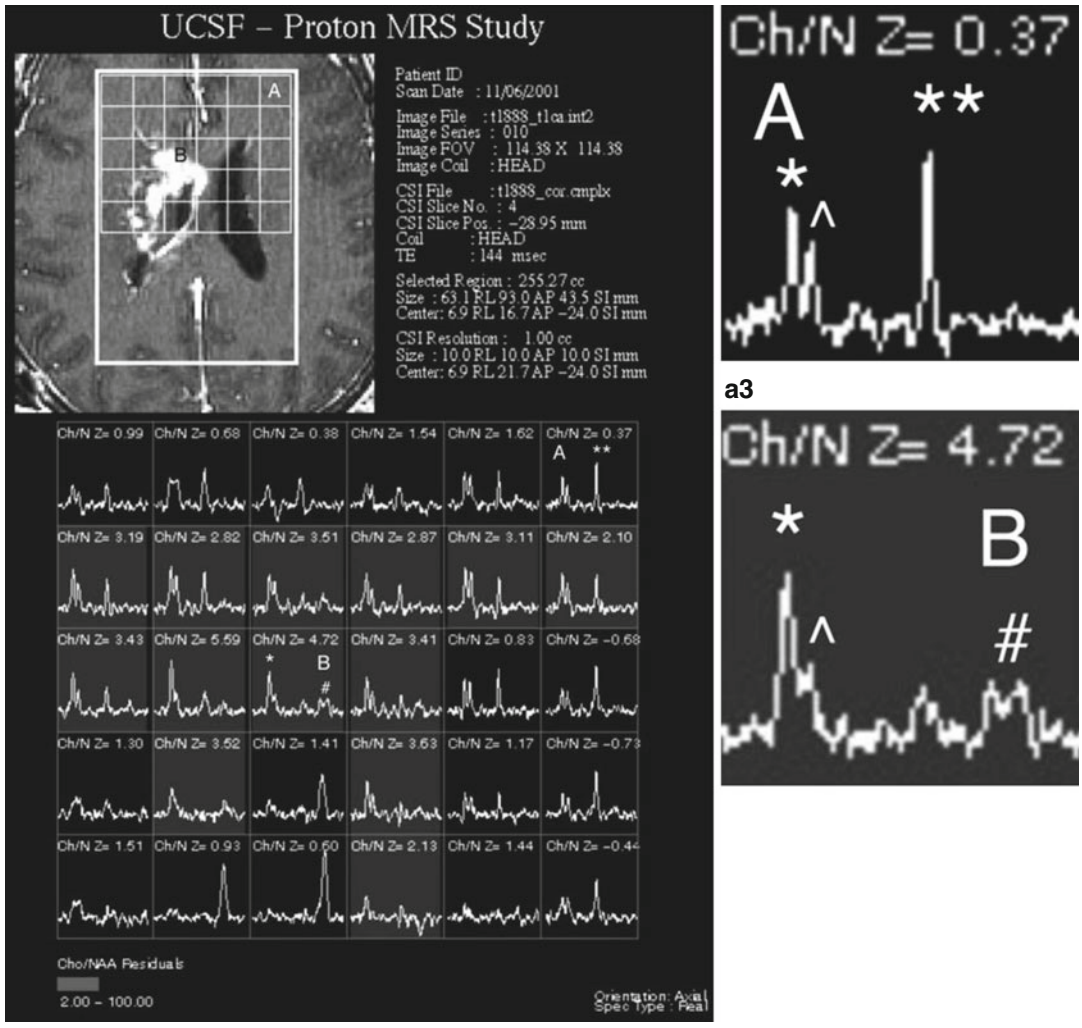

Fig. 13.1 High-grade glioma with both improved spectra and anatomic imaging after receiving radiation therapy. (**a1**–**a3**) Pretreatment 3D chemical shift imaging (CSI) transposed on T1-weighted gadolinium-enhanced axial image. Spectrum voxel labeled *A* is within normal left frontal white matter; choline (*), creatine (^), and NAA (**) peaks are normal for age and location. Spectrum voxel labeled *B* is within enhancing neoplasm; the spectrum shows elevated choline and lactate/lipid (#), with decreased NAA in the right genu. (**b1**–**b3**) Follow-up 3D CSI in the same location as image a. Choline peak (*) has decreased since the prior study, resulting in an improved *Z*-score, yet still has evidence of residual neoplasm. Spectrum voxel labeled *C* shows necrosis; all metabolites are decreased

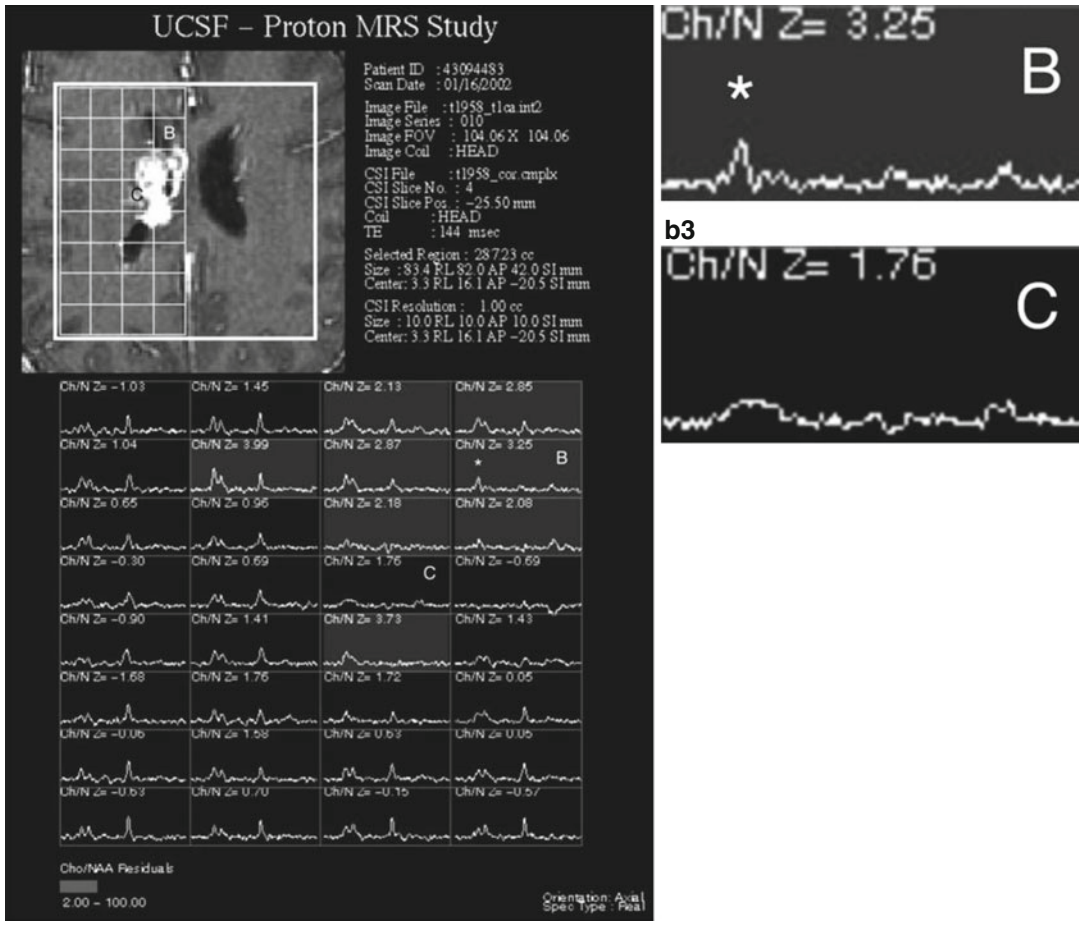

Fig. 13.1 (continued)

of poor survival in patients with medulloblastomas (Wilson et al. 2014).

There is no consensus as to how often patients should be evaluated. We believe that the most sensitive method to evaluate treatment efficacy and to screen for early recurrence or residual neoplasm is to perform serial exams, which allows comparison with a known baseline prior to treatment (Lazareff et al. 1999; Nelson et al. 1997a, 1999; Norfray et al. 1999; Vigneron et al. 2001). It is important to remember that, although combining MRS with MR imaging is more sensitive than MR imaging alone, sensitivity is not 100 %. A necrotic neoplasm with a paucity of viable tumor cells can have identical spectra to posttreatment necrosis (Taylor et al. 1996) this can only be differentiated when the Cho increases on subsequent exams. Serial follow-up studies are, therefore, essential to detect early growth of residual neoplasm.

MRS is a promising tool for assessing pediatric patients with brain tumors. In the appropriate setting, spectroscopy can improve the delineation of neoplastic brain involvement, increase specificity of diagnosis, and help discriminate posttreatment injury from residual neoplasm. Research continues to define the role of MRS in grading neoplasms and possibly predicting treatment response (Lazareff et al. 1999; Waldrop et al. 1998; Tzika et al. 2001; Girard et al. 1998; Lin et al. 1999; Negendank et al. 1996).

13.3 MR Perfusion

13.3.1 Principles

Cerebral perfusion is defined as the delivery of nutrients and oxygen, via the blood, to brain tissue per unit volume. This is typically expressed in units of milliliters per 100 g of parenchyma per minute (Cha et al. 2002). With recent advances in fast imaging techniques and computer technology, it is now possible to capture the dynamic changes in cerebral perfusion using MR imaging. Perfusion MR imaging (pMRI) provides information on cerebral hemodynamic parameters that are reflective of tissue perfusion, including relative cerebral blood volume (rCBV), cerebral blood flow (CBF), and mean transit time (MTT).

pMRI has evolved from a research tool into a clinically useful technique due to wider availability of high-performance MR gradients that allow faster imaging sequences (e.g., echo planar imaging (EPI)) and improvement in computer image processing algorithms. Quantitative analysis of perfusion parameters can now be derived from a clinically useful volume of brain using MR perfusion. This technique takes us one step closer to evaluating intracranial pathophysiology, in addition to the anatomical information gathered from conventional MR. A brief review of pMRI is presented to better understand the methodology and the basis for clinical application of MR perfusion.

13.3.2 Technique

Several methods can be used to derive perfusion parameters using MR imaging. pMRI can be performed using either exogenous (gadolinium, deuterium oxide) contrast agents or endogenous (arterial water) (Cha et al. 2002).

Dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging (DSC-pMRI) exploits the signal changes (T2* signal loss) during bolus passage of a contrast agent through the cerebral vessels (Aronen et al. 1994; Ball and Holland 2001; Cha et al. 2000a; Ludemann et al. 2000; Siegal et al. 1997; Strong et al. 1993). Using tracer kinetic principles, the signal change is converted to an integral of tissue contrast agent concentration (Peters 1998; Rosen et al. 1990; Weisskoff et al. 1994). These values are then used to generate perfusion maps of various hemodynamic parameters.

To successfully image a large volume of brain during the finite time that contrast is within the cerebral vessels, faster imaging methods are necessary. EPI fulfills this requirement, with a temporal resolution of 100 ms/slice. Several different pulse sequences can be used with EPI (e.g., spin echo, gradient echo). Spin echo images are thought to be more sensitive to signal changes from contrast agent within the intra-capillary volume (Weisskoff et al. 1994). Gradient echo images are more sensitive to medium to large vessels, and therefore greater signal drop is seen during the first pass of a contrast agent. Although more prone to susceptibility artifact, gradient echo techniques are more sensitive to small changes in blood volume. Therefore, the gradient echo technique does not require high doses of contrast agent as does spin echo to produce diagnostic images (Hunter and Wang 2001; Yeung et al. 2001; Cha et al. 2002).

Dynamic contrast-enhanced (DCE) perfusion MR imaging is another type of pMRI using gadolinium based contrast agent. In contrast to the first-pass effect of DSC-pMRI, DCE-pMRI exploits the steady-state hemodynamics of intravascular contrast agent to measure alterations in endothelial permeability, which can be used as a noninvasive marker of vascular leakiness and degree of tumor angiogenesis. DCE-pMRI is based on the acquisition of serial T1-weighted images before, during, and after contrast administration. In contrast to routine post-contrast images that reflect enhancement characteristics at a single time point, DCE perfusion depicts the wash-in, plateau, and washout contrast kinetics of the tumor (Cha 2006; Essig et al. 2013).

Arterial spin labeling (ASL) permits evaluation of CBF without the use of intravenous contrast. ASL uses arterial blood water as an endogenous tracer by inverting the magnetization of blood using radiofrequency pulses. After a brief delay to allow these "labeled" intravascular protons to flow into the brain, imaging of the brain is performed in order to see the degree of

flow of labeled protons into the cerebral hemispheres. Separate control images are also acquired in the same imaging session, and the signal difference between control and labeled images provides a measure of perfusion by arterial blood (Golay and Petersen 2006).

At our institution, ASL is performed on 1.5 T or 3 T field-strength scanners. While various methods of labeling were used in the early applications of ASL, the SNR of pseudocontinuous labeling is the method of choice for clinical applications (Zaharchuk 2012). We use a labeling period of 1,500 ms, followed by a 1,500 ms post-label delay. 3D images are obtained while suppressing background with fast spin echo stacked technique. The total image time for the ASL sequence is approximately 3–4 min.

13.3.3 Applications

DSC-pMRI, as adjunct imaging to conventional MR imaging, has several potential applications. With the wide availability and application of faster imaging hardware and software, DSC-pMRI can be incorporated into the routine evaluation of intracranial lesions. Clinical roles for DSC-pMRI include grading neoplasms, distinguishing high-grade primary neoplasm from single metastases, directing stereotactic biopsies, and distinguishing therapy-related brain injury from residual or recurrent tumor (Cha et al. 2002; Knopp et al. 1999; Law et al. 2002; Maeda et al. 1993; Tzika et al. 2002). Some advocate that DSC-pMRI may be helpful in adjusting chemotherapy dosing (Cha et al. 2000b).

Preliminary results on grading of gliomas with DSC-pMRI are promising. Although some authors using spin echo sequences have shown no statistical correlation between tumor grade and perfusion imaging, gradient echo-derived blood volumes have been more robust in distinguishing grades of glioma (Aronen et al. 1994; Ball and Holland 2001; Ludemann et al. 2000; Roberts et al. 2000a; Rosen et al. 1991; Sugahara et al. 1998).

Separating high- from low-grade gliomas by histology relies on the presence of neovascularity and necrosis (Giannini and Scheithauer 1997; Plate and Mennel 1995). DSC-pMRI is a method that can noninvasively assess tumor vascularity and is complementary to histopathology in determining the grade and malignancy potential of a neoplasm (Fig. 13.2) (Gerlowski and Jain 1986).

Histology alone may not accurately predict tumor biology or patient prognosis. DSC-pMRI correlates with the degree of tumor angiogenesis and therefore may be able to predict aggressive biology (Aronen et al. 1994). Hence, the more aggressive the tumor, the larger the rCBV, presumably due to tumor angiogenesis (Knopp et al. 1999; Sugahara et al. 1999). This technique offers a potentially powerful and noninvasive means of assessing tumor biology and serially monitoring changes in the tumor during therapy.

Most published reports using DSC-pMRI for tumor grading have studied adult patients. Sensitivity for this technique may be reduced in children since certain benign tumors, such as pilocytic astrocytoma and choroid plexus papilloma may have increased vascularity; that is, high rCBV (Ball and Holland 2001; Strong et al. 1993; Giannini and Scheithauer 1997; Plate and Mennel 1995; Keene et al. 1999). DSC-pMRI should be interpreted cautiously in heterogeneous tumors since rCBV can vary depending on the location chosen to place the region of interest. A region of interest placed in an area of necrosis or nonaggressive portion of the neoplasm could erroneously underestimate rCBV and result in undergrading of tumor. Alternatively, cortically based neoplasms that are contiguous with the brain surface vessels may be falsely given a higher grade due to a high rCBV from a region of interest placed over vessels (Sugahara et al. 2001). Larger studies are needed prior to DSC-pMRI's inclusion as a routine clinical practice for grading tumors in children.

A promising application of perfusion imaging is distinguishing treatment-induced brain injury from residual or recurrent neoplasm (Cha et al. 2000b, 2002; Siegal et al. 1997; Roberts et al. 2000a; Rosen et al. 1991; Sugahara et al. 1999). With routine MR imaging, both entities can enhance after contrast administration and are indistinguishable until growth on serial imaging

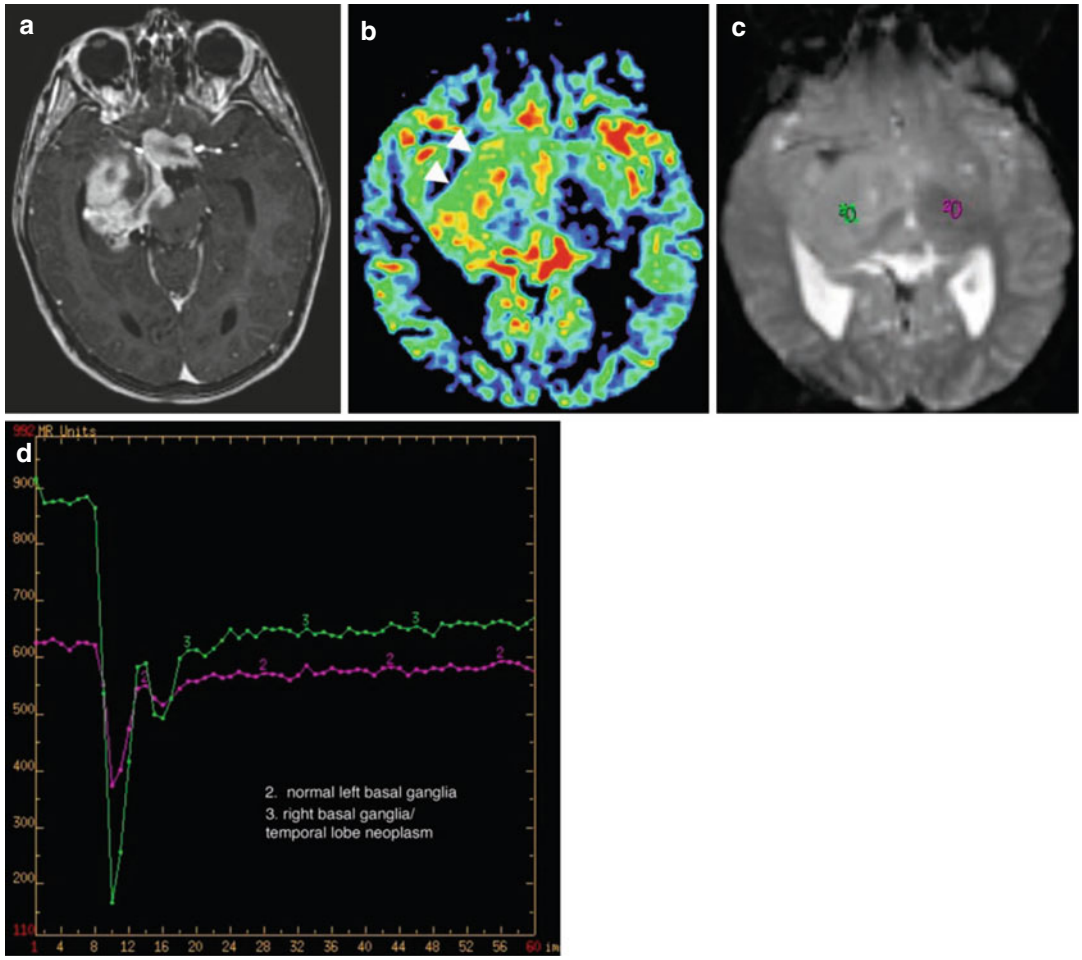

Fig. 13.2 Right medial temporal lobe and chiasmatic glioma with pMR imaging characteristics of a vascular, intra-axial neoplasm. (**a**) Axial T1-weighted gadolinium-enhanced image of the infiltrating, enhancing neoplasm. (**b**) Axial color map of the relative cerebral blood volume (CBV) showing increased CBV within the neoplasm (*white arrowheads*) relative to normal vascularity on the contralateral side. (**c**) Axial T2-weighted image shows the regions (*ovals*) that were sampled to calculate the time-signal curves (*2* normal left basal ganglia, *3* neoplasm). (**d**) Time-signal curve shows an intact blood–brain barrier (BBB) in region *2* (normal recovery of signal after the passage of the contrast bolus) but a partially disrupted BBB in region *3* (slower, incomplete recovery after the bolus due to contrast leaking through the BBB)

favors a diagnosis of neoplasm. DSC-pMRI takes advantage of the pathophysiologic differences in vascularity to separate the entities. Posttreatment brain injury, in part, is believed to be the result of endothelial damage followed by vascular thrombosis and blood–brain barrier (BBB) breakdown. This ultimately leads to hypoperfusion of the affected tissue (Chan et al. 1999). The final common pathway of delayed radiation injury is vascular thrombosis and fibrinoid necrosis, which on DSC-pMRI manifests as a decrease in rCBV when compared to normal tissue (Cha et al. 2000b, 2002). On the other hand, tumor cells require a viable blood supply for growth and spread and, therefore, increased rCBV is seen in recurrent and residual neoplasms (Ball and Holland 2001; Cha et al. 2000b; Plate and Mennel 1995). Preliminary results show that decreased signal on DSC-pMRI correlates well with treatment-induced brain injury (Ball and Holland 2001; Cha et al. 2000b; Plate and Mennel 1995).

Exceptions still exist in making this important distinction between tumor and therapy-induced brain injury. Normal or even decreased rCBV in the area of residual tumor can occur if neoplastic tissue is mixed with hypovascular necrotic tissue. Treatment-induced injury can lead to aneurysmal dilation of vessels and formation of telangiectasias that can artificially elevate the rCBV, leading to false positive results. Petechial hemorrhage or calcification in an area of residual tumor can produce susceptibility artifact that artificially reduces the rCBV, resulting in a false negative result (Sugahara et al. 2000). Further research is needed prior to standardized clinical use throughout multiple institutions.

DSC-pMRI continues to be investigated for use in guiding stereotactic biopsy of intracranial neoplasms. Usually, CT and MRI-guided biopsies of brain tumors, are directed to areas of conventional contrast enhancement. This approach, however, is prone to sampling error due to the intrinsic limitations of imaging enhancement to detect the most aggressive portion of a tumor (Cha et al. 2002; Joyce et al. 1978). In addition, limited tissue sample size can lead to erroneous grading and inadequate evaluation (Cappabianca et al. 1991; Chandrasoma et al. 1989).

Contrast enhancement on MR images reflects the areas of breakdown within the BBB (Greenwood 1991). This is often in the rim adjacent to a necrotic portion of the neoplasm. Elevated rCBV is considered to represent the areas of vascular hyperplasia in the aggressive, viable neoplasm and may not always correspond to a contrast enhancing portion (Cha et al. 2002). Using DSC-pMRI in addition to conventional anatomical images could result in reduced false negatives and errors in assessing tumor grade. Although still investigational, DSC-pMRI may be helpful in localizing the most aggressive portion of a neoplasm and serve as a complimentary tool to anatomic imaging (Aronen et al. 1994; Knopp et al. 1999; Rosen et al. 1991).

Future applications for DSC-pMRI under development include mapping dose distributions in neoplasms and following perfusion maps for therapy-outcomes research for new therapeutic agents (Cha et al. 2000b, 2002; Ludemann et al. 2000; Roberts et al. 2000a).

DCE-pMRI permits quantitative assessment of the blood–brain barrier and microvascular permeability. This can provide a more thorough assessment of brain tumor angiogenesis. Another advantage of DCE-pMRI is the high SNR that allows imaging at a higher temporal and spatial resolution.

ASL of tumors can be easily assessed qualitatively as elevated CBF will manifest as hyperintense signal relative to the remaining brain, and decreased CBF will show hypointense signal. For absolute measurements, regions of interests are placed on the tumor using postprocessing software. Comparisons can be made relative to the remaining brain or other areas within the tumor. Using the aid of conventional MRI sequences, care is taken to avoid placing regions of interest within areas of cyst, hemorrhage, or necrosis. Maximum ASL signal is recorded, in keeping with other studies in the assessment of gliomas (Knopp et al. 1999; Sugahara et al. 2001). Distinguishing high-grade and low-grade tumors has been suggested using ASL technique (Yeom et al. 2014).

The advantages of ASL include the lack of contrast requirement, high SNR, labeling efficiency, and potential for absolute CBF quantification. ASL can be repeated in cases of patient motion. In children, immature paranasal sinuses contribute to improved image quality due to less artifact (Yeom et al. 2014).

In summary, pMRI is no longer primarily a research tool, but an important diagnostic tool complementing conventional anatomical imaging. Clinical use for tumor grading, differentiating between residual neoplasm and treatment-associated injury, and assisting in therapy dosing and treatment follow-up are on the horizon. Guiding biopsies within heterogeneous tumors by perfusion imaging may reduce sampling errors and improve diagnostic accuracy.

13.3.4 Limitations

DSC-pMRI has several important constraints. Sensitivity to susceptibility artifact prevents its use in brain adjacent to the paranasal sinuses or

the skull base (Cha et al. 2002; Ball and Holland 2001; Poussaint et al. 1995). The sequence is very sensitive to patient motion, and SNR is low in comparison to anatomic MR images (Cha et al. 2002; Aronen et al. 1994; Siegal et al. 1997). Only a limited volume of brain can be covered during the time it requires a contrast bolus to pass through the intracranial vasculature. Also, a compact delivery of the bolus (through a power injector) may be difficult to attain in a patient who has limited intravenous access (Siegal et al. 1997). Furthermore, care must be taken to recognize false positives that are created by normal structures (e.g., choroid plexus and cortical veins) (Aronen et al. 1994; Sugahara et al. 1998). Additional costs may be substantial, due to the stringent hardware and software requirements to acquire and process the MR data. Access to a physicist familiar with the MR technique is also beneficial for continued support (Cha et al. 2002).

DCE-pMRI is also not without limitations, which include the complexity in image acquisition and user-dependence. The postprocessing is also challenging, as the kinetics modeling and software both require some training (Essig et al. 2013).

Limitations to ASL include sensitivity to motion and artifact from metal in the face and head region from dental/orthodontic procedures. There may also be an underestimation of CBF in regions of delayed flow such as white matter (van Gelderen et al. 2008).

13.4 Nuclear Medicine

13.4.1 Principles

The role of radionuclide CNS imaging continues to evolve. The most commonly used techniques are single photon emission computed tomography (SPECT and positron emission tomography (PET)). Areas of current study include: differentiating lesions with similar imaging appearances (e.g., lymphoma from toxoplasmosis by thallium uptake), differentiating treatment injury from residual neoplasm, grading neoplasms, localizing the most aggressive portion of the tumor prior to therapy, predicting response to therapy, and localizing eloquent cortices prior to surgery (Maria et al. 1998; Ricci et al. 1998).

The most widely practiced application is that of differentiating residual neoplasm from treatment injury. Without special techniques (such as pMRI, see earlier section), this differentiation can be extremely difficult by conventional CT and MRI (Brunelle 2000; Di Chiro et al. 1988; Valk and Dillon 1991). Both entities produce altered vasculature that can result in identical-appearing edema and enhancement. Even biopsy can lead to a false diagnosis. It is difficult to know which area of enhancement represents an aggressive margin of neoplasm or just an area of active necrosis and BBB breakdown (Poussaint et al. 1995). If cognizant of the limitations, radionuclide imaging may be very helpful to select clinical scenarios.

Both SPECT and PET, utilizing several radionuclide imaging agents, have been studied in attempts to distinguish treatment injury from neoplasm. ^{99m}Technetium, ^{201}thallium, ^{18}fluorine, and ^{11}carbon agents are the most cited (Di Chiro et al. 1988; Dadparvar et al. 2000; Go et al. 1994; Kim et al. 1992; Maria et al. 1994; Ogawa et al. 1991; Shinoura et al. 1997). ^{201}Thallium SPECT and ^{18}F-fluorodeoxyglucose (FDG) PET are currently the most utilized methods, but additional promising radionuclides are on the horizon (Chen and Silverman 2008; Hatakeyama et al. 2008; Lorberboym et al. 1997; Maria et al. 1997). The remaining discussion is limited to these agents.

13.4.2 Mechanism and Technique

The mechanism of thallium sequestration within tumor cells is unknown. The most accepted theories propose either passive uptake over a potential membrane gradient or high affinity for potassium-activated adenosine triphosphatase (Kim et al. 1992; Kaplan et al. 1987). Alteration of the BBB also contributes (Kim et al. 1992). Whatever the mechanism, thallium seems to be incorporated into neoplastic glial cells considerably more than into nonneoplastic cells. A typical dose for a ^{201}thallium brain scan is 0.03–0.05 mCi/kg, and images are obtained 5–10 min after administering the dose intravenously (O'Tuama et al. 1998).

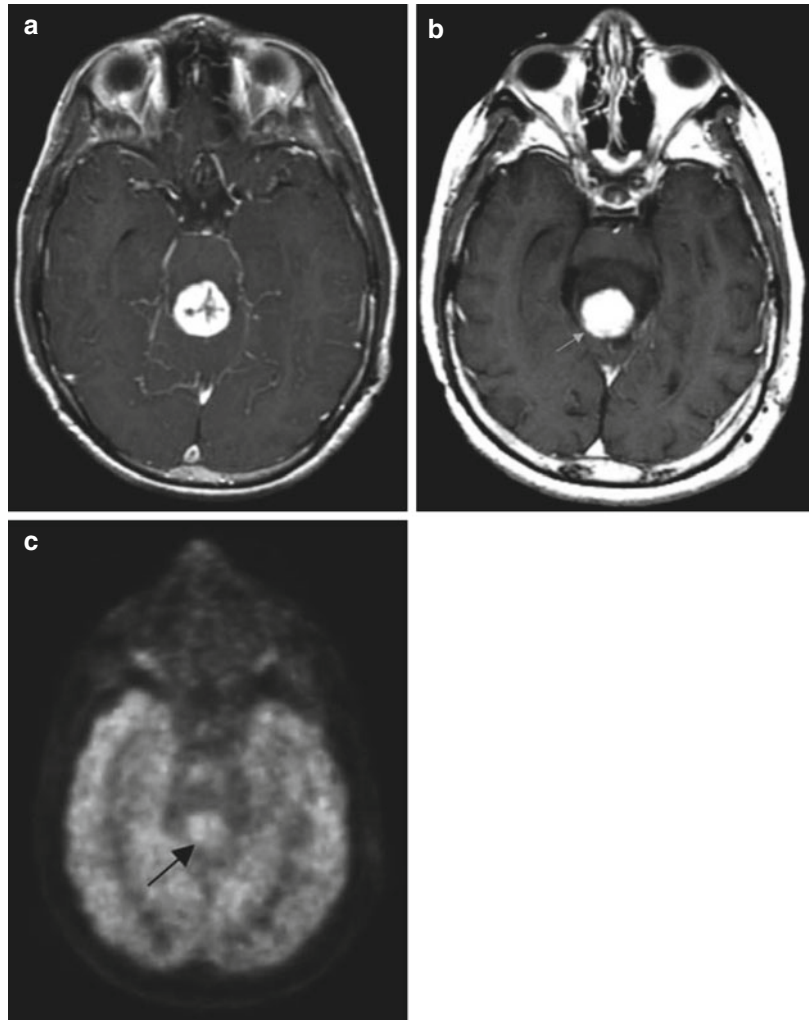

Fig. 13.3 PET imaging complimenting anatomic MR imaging in a case of tumor recurrence. (**a**) Axial T1-weighted gadolinium-enhanced image of a tectal glioma at presentation. (**b**) Axial T1-weighted gadolinium-enhanced image of the same tectal glioma (*white arrow*) after radiation treatment. The enhancing mass may represent posttreatment granulation tissue or residual neoplasm. (**c**) Axial PET image showing increased activity (*black arrow*) within the tectal mass, indicating residual active neoplasm

PET imaging for brain tumors is primarily with ^{18}FDG, a compound that has chemical properties similar to glucose and is therefore incorporated into astrocytes as an energy source. However, ^{18}FDG cannot be normally metabolized and, therefore, becomes entrapped within cells (Wang et al. 1996b). Increased ^{18}FDG within tumor cells is attributed to the increased rate of glycolysis in rapidly growing neoplasms (Shinoura et al. 1997; De Witte et al. 2000). For pediatric brain scans, 0.14 mCi/kg of ^{18}FDG is given intravenously and images are usually obtained 30 min later (Kaplan et al. 1999; Kincaid et al. 1998).

More recently, ^{18}F-fluorothymidine (^{18}FLT) and ^{11}C-thymidine (TdR) have shown promise as alternatives to ^{18}FDG for the evaluation of brain tumors in adult patients and animal models. These agents may more accurately reflect tumor-cell biology, owing to their interaction with thymidine kinase 1 (TK1), which is preferentially expressed during the S-phase of the cell cycle in proliferating cells. Intracellular phosphorylation of these agents by TK1 results in their retention within tumor cells. In addition, the near absence of proliferating cells in normal brain results in increased conspicuity of tumor from background with these agents. The higher cortical background activity of ^{18}FDG results in a relatively lower sensitivity to distinguish between normal tissue and brain tumor cells (Hatakeyama et al. 2008; Bradbury et al. 2008; Muzi et al. 2006; Ullrich et al. 2008).

O-(2-18F-fluoroethyl)-L-tyrosine (^{18}F-FET) has been recently evaluated in children and adolescents with brain tumors with promising results (Dunkl et al. 2015), although only limited data exist. ^{18}F-fluoromisoidazole is an agent sensitive to detecting hypoxia and is being studied as hypoxic regions within tumor are intrinsically more resistant to both chemotherapy and radiotherapy (Puttick et al. 2014).

13.4.3 Applications and Limitations

The usage of PET and SPECT to distinguish tumor from posttreatment injury has been studied extensively (Fig. 13.3). Both sensitivity and specificity of ^{18}FDG PET are in the range of 80–90 % (Di Chiro et al. 1988; Valk and Dillon 1991; Kim et al. 1992; Pujol et al. 1998). At least 80 % of pediatric tumors have a high affinity for thallium. It may therefore be useful to distinguish neoplasm from posttreatment granulation tissue (Maria et al. 1998; Brunelle 2000). However, the grade of the neoplasm and histologic type do not always correlate with the amount of thallium uptake (Maria et al. 1994). Pilocytic astrocytoma has a very high metabolic rate and therefore often a high radiotracer uptake, even though it is a relatively benign neoplasm.

The data for PET are calculated from lesions that are at least 5–7 mm in dimension, the lower limits of resolution for this modality. This imposes a limitation on early detection of subtle neoplastic recurrence. Furthermore, the percentage of false negatives is rather high and, as a result, many authors do not consider this method acceptable for making therapeutic (Kim et al. 1992; Ogawa et al. 1991; Barker et al. 1997; Valk et al. 1988). Other PET agents, such as FLT, TdR ^{11}C-methionine, ^{11}C.choline, and ^{11}C-tyrosine, have either had limited success in detecting neoplastic recurrence or are under active investigation (Go et al. 1994; Shinoura et al. 1997; Hatakeyama et al. 2008; Pirotte et al. 2007). The 20-min half-life of ^{11}C agents necessitates on-site production, which is an obstacle to widespread use.

Biopsy guidance by PET has been successful in the limited number of patients studied (Go et al. 1994; Pirotte et al. 2007; Massager et al. 2000). In theory, the most aggressive portion of a tumor has the highest glucose uptake and, thus, the highest ^{18}FDG uptake; thus, the PET can assist in localizing the most aggressive portion of a heterogeneous neoplasm for proper staging. However, identification of the most aggressive portion of the tumor has not been reproducible at every institution. This may be due to difficulties in coregistering the PET images to anatomic imaging (e.g., MR imaging) and, perhaps, a result of the difficulty in identifying very small regions of high-grade tumor (Maria et al. 1994, 1998). Furthermore, it can be difficult to differentiate regions of cortex (which has higher ^{18}FDG uptake compared to normal white matter) from regions of tumor recurrence without additional MR imaging.

The thymidine radionuclides do not suffer from this high background activity. Yet, analysis of uptake kinetics for thymidine tracers offers conflicting results as to their utility in assessing tumor proliferation (Muzi et al. 2006; Ullrich et al. 2008). Localizing the most aggressive portion of the tumor with thymidine agents has been most successful with suspected high-grade, untreated gliomas (Muzi et al. 2006).

Accurately predicting tumor grade by imaging is imprecise and remains an elusive goal in practice. Some authors claim that radionuclide imaging is an equivalent, or occasionally better, predictor of survival in patients with a malignant glioma compared with the prediction based on histologic grade (Valk et al. 1988). Others believe that PET is at least adequate to distinguish high- from low-grade brain neoplasms (Valk and Dillon 1991; Kincaid et al. 1998; Pirotte et al. 2007; Black et al. 1994; Provenzale et al. 1999). However, most results indicate that nuclear imaging does not grade brain neoplasms with adequate accuracy to make it useful in clinical practice (Hatakeyama et al. 2008; O'Tuama et al. 1998; De Witte et al. 2000; Muzi et al. 2006; Choi et al. 2000). For example, high-grade neoplasms, often necrotic in part, have low uptake in the necrotic regions so that when averaged with high-uptake regions, they may appear as low-grade neoplasms when calculating overall uptake. In addition,

some low-grade pediatric neoplasms, such as pilocytic astrocytomas have increased uptake, making them appear to be high-grade neoplasms.

Another potential application of radionuclides is to identify tumors that are sensitive to anti-angiogenic agents (O'Tuama et al. 1998; Valk et al. 1988). Some authors suggest using PET to localize eloquent cortices preoperatively for patients unable to tolerate MR imaging (Kaplan et al. 1999).

In general, radionuclide imaging is infrequently used for pediatric brain neoplasms at UCSF, with conventional MR imaging, perfusion imaging, and magnetic source imaging (MSI) being the imaging tools of choice. Radionuclide imaging also imposes a significant radiation dose, which is a significant issue in the pediatric population, as the effects of radiation exposure to children have a longer time to develop, with a resulting increase in its potential effects (Mettler et al. 2008). Each institution should determine the optimal tools for their patients depending upon their equipment and individual strengths.

One area of growing research is the use of combined PET-MRI via single modality scanning in the assessment of adult brain tumors (Puttick et al. 2014). PET-MRI scanners have improved temporal and spatial coregistration as opposed to scanning separately. In addition, the combined use will help validate the other modality. Our institution is currently evaluating this new modality to determine if this combined role can provide benefit.

13.5 BOLD/MSI

13.5.1 Principles

Two techniques used for locating brain activity during specific tasks are blood oxygenation level-dependent (BOLD) imaging and MSI. Many clinical applications of these techniques are under investigation, including evaluating reorganization after injury and deterioration during progressive disease, evaluation of therapies, and cortical mapping prior to neurosurgery (Roberts et al. 2000b; Vezina 1997). These techniques are well-developed in adults but are less useful in children, as they require a great deal of cooperation by the patient. Some authors have had success in children through the use of multiple training sessions. However, such training requires considerable time, personnel, and space, which are rarely available in most centers. Task-related activations, which require that the patient perform specific tasks, may be difficult or impossible in individuals with deficits such as reading disorders, mental retardation, hearing loss, and paralysis (Breier et al. 1999; Otsubo and Snead 2001; Simos et al. 1999). It is possible to perform some studies on sedated children, but it is not yet clear how much effect the sedation has on the results. Therefore, this section is based mainly on results in adults, in the hope that the difficulties in performing these studies in children will soon be overcome.

13.5.2 Mechanism of BOLD Imaging

In BOLD images, contrast is created by a local increase of oxygenated blood in activated tissue (Martin and Marcar 2001; Stippich et al. 1998). In theory, an activated group of neurons requires increased oxygenation. This increased need is fulfilled by local vasodilation, allowing more oxygenated blood to be transported to the activated cerebral cortex. The increase in blood flow more than compensates for the increased oxygen consumption, resulting in local increase in oxyhemoglobin and decrease in deoxyhemoglobin. As oxyhemoglobin is diamagnetic (does not alter the local magnetic field) and deoxyhemoglobin is paramagnetic (alters the local magnetic field and results in local signal loss), the reduced local concentration of deoxyhemoglobin results in less signal loss and increased local signal intensity (Beisteiner et al. 1995; Boxerman et al. 1995). This local signal alteration can be detected by susceptibility-weighted MR imaging sequences, if multiple acquisitions are performed.

13.5.3 Mechanism of MSI

Neuronal activation results in electrical current, which can be measured with electroencephalography. The electrical current generates magnetic flux, the magnitude of which is in the order of a few picoTeslas, a quantity that is 8 orders of magnitude smaller than that produced from the earth's magnetic field and 12 orders smaller than that produced from MR imaging (Alberstone et al. 2000; Lev and Grant 2000). When performed in a room shielded from external magnetic fields, superconducting quantum interference devices (SQUIDs) (Stippich et al. 1998; Ganslandt et al. 1999) can be used to measure and localize these minute neuromagnetic signals using small receivers placed on the scalp (Alberstone et al. 2000; Papanicolaou et al. 2001). This technique is known as magnetoencephalography (MEG). MEG signal is generated from intracellular electron flux, not local vascular changes (as seen with fMRI) (Roberts and Rowley 1997), distinguishing it from EEG, which detects extracellular currents and is therefore less precise than MEG (Alberstone et al. 2000). Superimposition of MEG data on colocalized MR images is referred to as MSI (Stippich et al. 1998).

13.5.4 Applications of BOLD and MSI

The most widely used clinical application of BOLD imaging and MSI is the localization of eloquent function in the brain for preoperative planning (Fig. 13.4) (Roberts and Rowley 1997; Disbrow et al. 1999). Both BOLD and MSI can accurately localize the primary motor cortex (Pujol et al. 1998; Roberts and Rowley 1997). Sensitivity varies from 82 to 100 %, and often depends on whether the primary motor cortex is merely displaced, or partially destroyed by the pathologic process. Both techniques can also be used for localizing the language centers prior to surgical resection of neoplasm or of the temporal lobe for epilepsy (Simos et al. 1999). BOLD may have the additional benefit over MEG of simultaneously localizing multiple areas involved in complex brain function (Roberts et al. 2000b).

The definitive test used to localize motor cortex is intraoperative cortical surface recording (Suzuki and Yasui 1992). For identification of language centers in either the right or left cerebral hemispheres, the Wada test (intracarotid amytal test) has been the standard test for many years, but BOLD techniques have similar sensitivities and are less invasive.

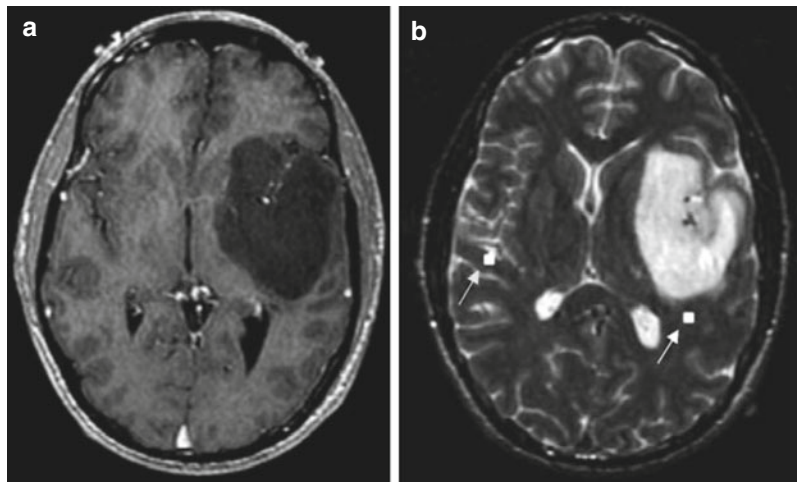

Fig. 13.4 Magnetic source imaging for preoperative surgical planning in a patient who presented with grand mal seizure and aura but without speech or motor deficits. (**a**) Axial T1-weighted gadolinium-enhanced image showing a nonenhancing left temporal lobe/basal ganglia low-grade glioma. (**b**) Axial T2-weighted image showing white squares (*arrows*) that correspond to areas of auditory stimulation with a 1,000 Hz frequency tone. The auditory cortex on the left side is displaced, but not invaded, by the neoplasm

BOLD imaging has two major advantages in comparison to intraoperative surface recording: (1) localization is obtained preoperatively, allowing prospective surgical planning, and (2) the study can be performed at the same time as the preoperative MR imaging instead of lengthening operating room time for an additional procedure. Both techniques suffer when anatomic landmarks are distorted by the tumor, as the surgeon may encounter inadequate surgical exposure of the primary motor cortex, and the navigation based on the MR image may be changed by opening of the calvarium (Cedzich et al. 1996). Anesthetic agents may also influence the sensitivity of both the intraoperative and BOLD techniques (Cedzich et al. 1996), although older children and teens can generally undergo BOLD analysis without the need for sedation. In adults, overall sensitivity of intra-operatively localized eloquent function is roughly 91–94 % (estimated by post-operative deficits), which is similar to functional imaging (Simos et al. 1999; Ganslandt et al. 1999; Szymanski et al. 2001).

The Wada test requires an invasive catheter angiogram and sedation, both with inherent risks. Hemispheric dominance can be established in the majority of cases, but more specific cortical mapping is not possible (Simos et al. 1999). MSI and BOLD are both as sensitive and provide additional information that guides surgical approach and extent of resection (Pujol et al. 1998; Alberstone et al. 2000; Ganslandt et al. 1999; Dillon and Roberts 1999). MSI localizes eloquent regions of cerebral cortex, such as the primary motor cortex, within 3–4 mm in comparison to intraoperative electrocortical stimulation (Breier et al. 1999; Szymanski et al. 2001; Wheless et al. 1999).

13.5.5 Limitations

Several pitfalls must be kept in mind when implementing these new techniques. Limitations of BOLD imaging include poor temporal resolution that can never be better than the time that is required to produce a hemodynamic response to activated neurons, roughly 2–5 s (Martin and Marcar 2001; Lev and Grant 2000; Roberts and Rowley 1997). The spatial resolution is dependent on the anatomic proximity of vessels to activated brain; high-signal contribution by sulcal veins has a marked negative effect on resolution (Roberts and Rowley 1997; Dillon and Roberts 1999; Holodny et al. 1999). Infiltration by neoplasm and edema can further distort the anatomic relationship and possibly alter the autoregulation of local vessels (Pujol et al. 1998; Dillon and Roberts 1999; Holodny et al. 1999). Motion artifact, larger caliber vessels, and inflow effects can further distort localization (Pujol et al. 1998; Beisteiner et al. 1995; Boxerman et al. 1995; Holodny et al. 1999; Field et al. 2000). Despite these shortcomings, BOLD generally localizes activated groups of neurons within 1–2 cm of their anatomic location.

MSI is hindered by susceptibility artifact from orthodontia and other ferromagnetic metals that cause overwhelming artifacts (Breier et al. 1999); BOLD imaging is also affected by such artifacts, but not as severely. The precision of labeling eloquent cortex by MEG is very good, but not perfect. Point localization is reduced by the inaccuracies of transposing data from MEG to MRI, by roughly 4 mm of dispersal (Szymanski et al. 2001). Overall error in localization is thought to be approximately 1 cm (Beisteiner et al. 1995). This is superior to other accepted techniques, including BOLD. The largest drawback of MSI is the cost and lack of availability of the necessary equipment; whereas BOLD can be performed on a clinical magnet with software upgrade, MSI requires an expensive neuromagnetometer in addition to a clinical magnet.

In summary, functional imaging has some potential for use in pediatric brain tumor patients, but a number of problems need to be overcome before these techniques will be used routinely.

13.6 Diffusion Imaging

13.6.1 Principles

Diffusion-weighted imaging (DWI) is a technique that relies on the fact that the motion of

water molecules causes decreased signal on specially acquired MR images (Mitchell 1999). Also available are special types of DWI, known as diffusion tensor imaging (DTI) and high angular resolution diffusion imaging (HARDI), which allow both the net direction and the magnitude of water motion in a voxel to be determined. These techniques have applications in the assessment of brain tumors.

13.6.2 Technique

All diffusion techniques allow the calculation of net water motion in a volume of tissue. The mean diffusivity (MD) represents the average motion of all free water molecules in a voxel during the period of the MR data acquisition (Filippi et al. 2001; Inglis et al. 1999; Poupon et al. 2000).

DTI and HARDI are based upon mathematical probability functions that calculate the precise net motion characteristics of the water protons in the voxel; in other words, they give the probability that any molecule is moving in any direction at any velocity during the time of the imaging. If all the water protons are equally free to move in all directions, the motion is said to be isotropic. If water protons move predominantly in one direction more than others (due to restricted movement in some directions or accentuated movement in others), the motion is said to be anisotropic. In the normal brain significant anisotropy is seen in the white matter. Water motion is greatest along the long axis of the axon fascicle, parallel to the axons and the axoplasmic flow. Motion along the short axis is perpendicular to the axons in the fascicle, hypothesized to be primarily impeded by the cell membrane and hydrophobic myelin sheath. The characteristics of the motion can be displayed either as images or mathematically (Filippi et al. 2001; Gauvain et al. 2001; Melhem et al. 2000; Pierpaoli et al. 1996).

Fractional anisotropy (FA) and MD are measurements derived from the diffusion tensor that have been independently studied with brain tumor imaging. FA quantifies the magnitude of diffusion directionality and is hypothesized to reflect the degree of alignment of cellular structures within fiber tracts as well as their structural integrity. MD (also called average diffusivity or apparent diffusion coefficient) is a measure of mean molecular motion that is hypothesized to be affected by cellular size and integrity. These measurements are commonly displayed as quantitative color maps overlying the brain images using commercially available software.

13.6.3 Applications

Few applications of diffusion imaging have been implemented for the routine analysis of pediatric brain tumors. DWI is less sensitive than routine sequences for assessing the extent of tumor involvement (Stadnik et al. 2001). Distinguishing between high- and low-grade primary tumors using MD values can be challenging given overlap between the tumor types (Lam et al. 2002). Nonetheless, DTI is being studied to evaluate this differentiation by evaluating the loss of anisotropy (Gauvain et al. 2001). DWI has proved useful in the assessment of posterior fossa tumors (Koral et al. 2013). DWI alone is able to distinguish juvenile pilocytic astrocytoma from medulloblastoma with high certainty, with the latter showing reduced diffusion (Jaremko et al. 2010). Another area in which diffusivity measurements have been found to be helpful is in distinguishing between ring-enhancing tumors and pyogenic abscesses. In general, cystic tumors have increased water motion compared with surrounding brain, but pyogenic abscesses have reduced water motion secondary to protein content from bacteria and inflammatory cells (Fig. 13.5) (Gauvain et al. 2001).

Diffusion characteristics can also be helpful to distinguish between cystic and solid tumors. For example, differentiation between an arachnoid and an epidermoid cyst may be difficult by conventional MR sequences or CT. CSF freely moves in an arachnoid cyst and therefore is isointense to the CSF space on DWI. An epidermoid cyst, however, is gelatinous and therefore has diffusion characteristics similar to brain tissue (Gauvain et al. 2001).

A current area of research for the use of DWI in brain tumor patients is delineating postoperative

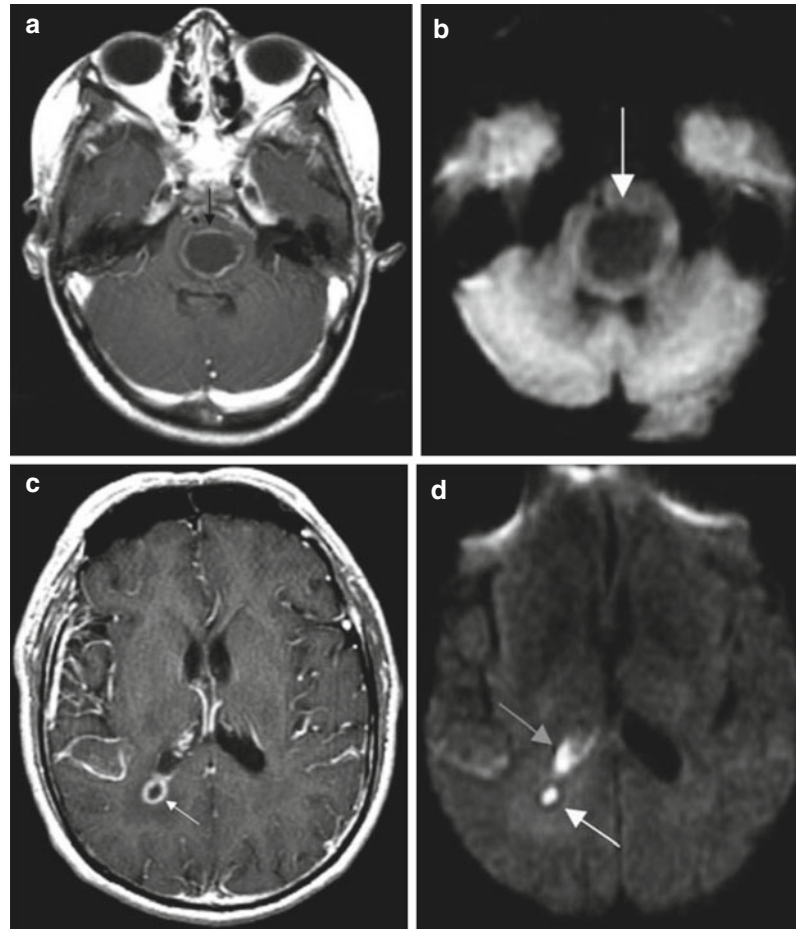

Fig. 13.5 Diffusion-weighted images used to help distinguish abscess from necrotic glioma. (**a**) Axial T1-weighted gadolinium-enhanced image showing a rim-enhancing, centrally hypointense brainstem lesion (*black arrow*). (**b**) Axial diffusion-weighted image at the same level showing increased diffusion within the central portion of the lesion (*white arrow*) consistent with a necrotic glioma. (**c**) Different patient. Axial T1-weighted gadolinium-enhanced image showing a deep right parietal ring-enhancing lesion (*white arrow*). (**d**) Axial diffusion-weighted image at the same level showing reduced diffusion within this lesion (*white arrow*) and adjacent ventricle (*gray arrow*) confirming that this was an abscess and not a neoplasm

injury (Smith et al. 2005; Tanner et al. 2000). Acutely injured tissue generally has reduced diffusion for several days to weeks after the surgery. Nodular and fingerlike areas of reduced diffusion around the surgical cavity in the first few days after tumor resection likely represent tissue injury in the region of the resection (Fig. 13.6). Such areas will generally show marked enhancement from 2 weeks to 6 months after surgery and ultimately evolve to become astrogliosis or encephalomalacia. Mistaking this area of enhancement for recurrent tumor on the early postoperative scans could lead to unnecessary treatments that could adversely affect the patient (Smith et al. 2005). Therefore, analysis of the DWI on the early postoperative MRI scans is recommended to help determine whether new enhancement on later postoperative imaging is the result of perioperative injury versus recurrent tumor.

DTI can be used to identify specific white matter tracts within the brain, a technique referred to in the literature as tractography. Tractography is helpful in localizing large bundle white matter tracts, such as the corticospinal tracts, based on anatomic characteristics (Fig. 13.7). Knowledge of the location of these tracts, which can be shifted by mass effect from the tumor, can reduce postoperative morbidity and allows for more aggressive tumor resection, which has been shown to improve long-term survival (Keles et al. 2006; Smith et al. 2008).

Clinical applications of DWI for tumor assessment within the spine are limited. The poor spatial resolution, motion of the cord during the cardiac cycle, and the susceptibility effects from surrounding osseous structures prevent robust clinical use (Saritas et al. 2008). If surgical hardware is present within the spine, DWI will be further

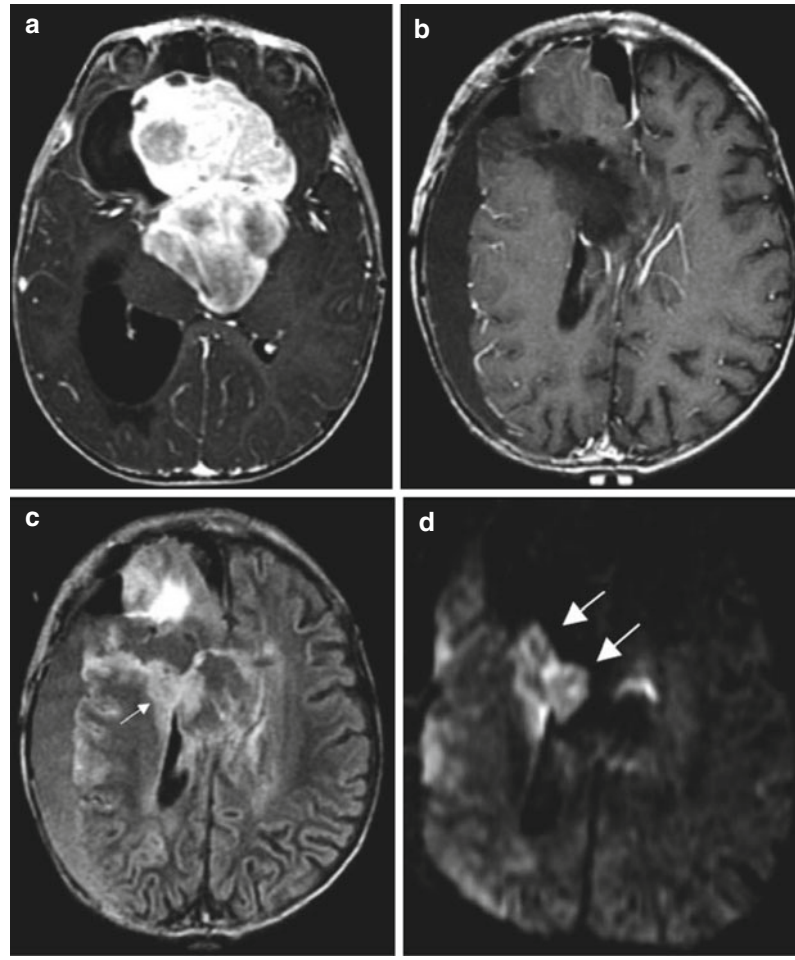

Fig. 13.6 Large chiasmatic and hypothalamic astrocytoma treated with partial surgical resection showing imaging evidence of postoperative ischemia. (**a**) Axial T1-weighted gadolinium-enhanced image shows the enhancing tumor preoperatively. (**b**) Axial T1-weighted gadolinium-enhanced image shows the postoperative resection cavity without evidence of residual enhancement. (**c**) Axial fluid attenuation inversion recovery (FLAIR) image of the resection cavity with thick posterolateral rim of high signal (*white arrow*) that may represent interstitial edema and/or injury. (**d**) Axial diffusion-weighted image at the same level shows high intensity (*arrows*), confirming that the area of increased signal on the FLAIR image was not edema, but postoperative ischemia

degraded. For these reasons, clinical applications of DWI for spinal cord tumors are infrequent. One study has described DWI to be used in conjunction with contrast-enhanced images for the assessment of spinal drop metastases (Hayes et al. 2012). Spinal DWI remains an area of active research, but with applications to neuro-oncology in the near future.

One last application of DTI and DWI is determination of prognosis. With respect to diffuse brain stem gliomas, patients with tumors displaying higher diffusivity and more isotropic diffusion tend to live longer (Chen et al. 2010), with the possible exception of optic pathway gliomas, where one study reported that higher ADC values correlated with earlier tumor progression (Yeom et al. 2013). In summary, diffusion-weighted sequences have several promising applications in pediatric brain tumor imaging that are under active investigation and will have an expanded role in the future.

13.7 Susceptibility-Weighted Imaging

13.7.1 Principles

Susceptibility weighted imaging (SWI) is a high-spatial resolution 3D gradient-echo MR technique that exploits the magnetic susceptibility differences of various tissues to yield a loss of signal. While SWI is sensitive to many compounds that distort the local magnetic field, detection of iron (primarily from blood products) and calcium are the primary roles in clinical imaging.

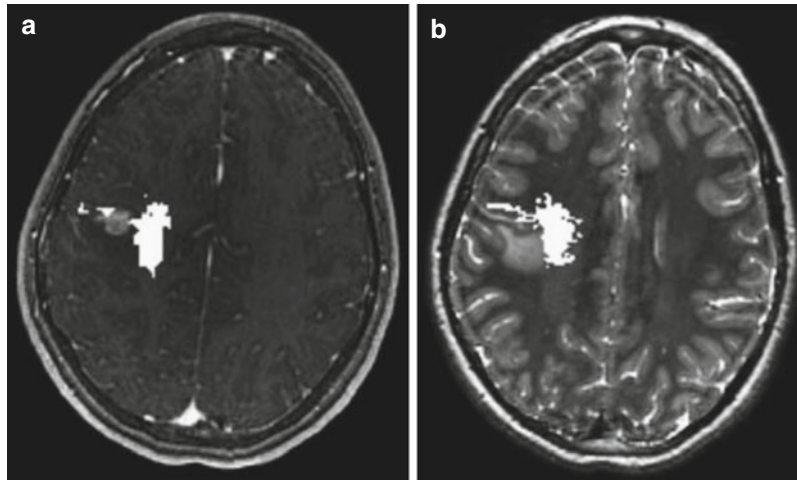

Fig. 13.7 Small ganglioglioma within the postcentral gyrus presenting with left-arm seizures. (**a**) Axial 3D Spoiled Gradient Recalled (SPGR) gadolinium-enhanced image shows the corticospinal tracts medial to the enhancing tumor by diffusion tensor imaging (DTI) fiber tracking. The fiber tracts are overlaid on the anatomic images. (**b**) Axial T2-weighted image at the same level showing a similar relationship

13.7.2 Technique

Application of a magnetic field to the brain generates an induced field that varies with the magnetic field strength and magnetic susceptibility of the materials within the field. Compounds that have paramagnetic, diamagnetic, or ferromagnetic properties interact with and alter the local magnetic field, resulting in heterogeneity of spins of local protons; as a result, the protons precess at different rates and cause signal loss, called "susceptibility artifact," that is most prominent in T2*-weighted images (Haacke et al. 2004, 2009; Tong et al. 2008). Paramagnetic compounds include deoxyhemoglobin, ferritin, and hemosiderin, while diamagnetic compounds include bone minerals and dystrophic calcifications (Schweser et al. 2010).

Compounds with susceptibility artifact will manifest on MR imaging as hypointense signal. On the routine processed images, there is no differentiation between compounds—all our hypointense. Phase imaging, which is part of the SWI data set in certain vendors, permits this differentiation, namely, blood products versus calcium, a not uncommon question in clinical imaging, especially in the absence of CT imaging. Blood products are hypointense on the phase images since deoxygenated blood is paramagnetic relative to surrounding tissue, while calcium is hyperintense since it is diamagnetic relative to surrounding tissue (Haacke et al. 2009).

13.7.3 Applications

The main application of SWI for tumor imaging is to detect hemorrhage, vascularity, and calcification characteristics that may reflect tumor grade. Calcification can be seen in lower grade tumors such as oligodendroglioma, while hemorrhage and marked vascularity may be seen in higher grade tumors, related to neoangiogenesis.

Evaluating the presence of hemorrhage has implications in management and treatment. Preoperatively, SWI can help plan the surgical approach for biopsy or resection by assessing the site of intra-tumoral hemorrhage. With regard to posttreatment analysis, hemorrhage may be seen in postoperative setting of surgery or radiosurgery. In patients that are being treated with anti-angiogenic therapy, the presence of hemorrhage on SWI may have implications in treatment course (Grabner et al. 2012). While a significant amount of hemorrhage may halt therapy, increasing SWI hypointensity within a tumor may in fact signify a better prognosis by implying less active tumor

(Lupo et al. 2013). Further research is needed to validate results.

SWI imaging is also sensitive for identifying vasculopathy resulting from radiation therapy; these lesions, usually referred to as "telangiectasias and cavernous malformations," are particularly common in children after cranial irradiation (Koike et al. 2004; Larson et al. 1998).

13.8 Improving Image Sensitivity to Analyze Small Tumors

Subtle or small neoplasms of the cortex (ganglioglioma, DNET), internal auditory canal (schwannoma in neurofibromatosis), and spinal cord (astrocytoma, ependymoma) can be missed on traditional MR sequences. There are primarily two methods to increase sensitivity to detect and characterize these neoplasms when they are small: higher resolution images obtained with a high-field-strength magnet (>4 T) or imaging with a routine strength magnet and using special coils and software (Moyher et al. 1997). In the past, use of phased array surface coils and image intensity correction algorithms increased the signal-to-noise ratio for superficial lesions beyond traditional imaging sequences. Newer multichannel coils, using parallel imaging, are now commercially available as an alternative to surface coils and provide similar sensitivity.

Magnetization transfer is a technique that allows imaging of molecules that interact with macromolecules in the brain (predominantly the components of myelin) separately from free, unbound water molecules. The major application of magnetization transfer imaging for brain tumors is to increase lesion conspicuity; by reducing the hyperintensity of white matter on T1-weighted images, enhancement becomes more conspicuous.

Conclusions

Neuroradiologic evaluation of tumors has grown to include many more techniques than anatomic imaging. Metabolic assessment, assessment of perfusion, and assessment of the function of surrounding brain can now be performed along with anatomic imaging in a single visit to the MR suite. These techniques provide useful tools to assess the character of pediatric brain tumors and their responses to therapy.

References

Alberstone CD, Skirboll SL, Benzel EC et al (2000) Magnetic source imaging and brain surgery: presurgical and intraoperative planning in 26 patients. J Neurosurg 92:79–90

Aronen HJ, Gazit IE, Louis DN et al (1994) Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings. Radiology 191:41–51

Ball WS Jr, Holland SK (2001) Perfusion imaging in the pediatric patient. Magn Reson Imaging Clin N Am 9:207–230, ix

Barker PB, Glickson JD, Bryan RN (1993) In vivo magnetic resonance spectroscopy of human brain tumors. Top Magn Reson Imaging 5:32–45

Barker FG 2nd, Chang SM, Valk PE, Pounds TR, Prados MD (1997) 18-Fluorodeoxyglucose uptake and survival of patients with suspected recurrent malignant glioma. Cancer 79:115–126

Beisteiner R, Gomiscek G, Erdler M, Teichtmeister C, Moser E, Deecke L (1995) Comparing localization of conventional functional magnetic resonance imaging and magnetoencephalography. Eur J Neurosci 7:1121–1124

Belanger M, Allaman I, Magistretti PJ (2011) Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab 14:724–738

Birken DL, Oldendorf WH (1989) N-acetyl-L-aspartic acid: a literature review of a compound prominent in 1H-NMR spectroscopic studies of brain. Neurosci Biobehav Rev 13:23–31

Black KL, Emerick T, Hoh C, Hawkins RA, Mazziotta J, Becker DP (1994) Thallium-201 SPECT and positron emission tomography equal predictors of glioma grade and recurrence. Neurol Res 16:93–96

Boxerman JL, Bandettini PA, Kwong KK et al (1995) The intravascular contribution to fMRI signal change: Monte Carlo modeling and diffusion-weighted studies in vivo. Magn Reson Med 34:4–10

Bradbury MS, Hambardzumyan D, Zanzonico PB et al (2008) Dynamic small-animal PET imaging of tumor proliferation with 3′-deoxy-3′-18F-fluorothymidine in a genetically engineered mouse model of high-grade gliomas. J Nucl Med 49:422–429

Breier JI, Simos PG, Zouridakis G et al (1999) Language dominance determined by magnetic source imaging: a comparison with the Wada procedure. Neurology 53:938–945

Bruggers CS, Moore K (2014) Magnetic resonance imaging spectroscopy in pediatric atypical teratoid rhabdoid tumors of the brain. J Pediatr Hematol Oncol 36:e341–e345

Brunelle F (2000) Noninvasive diagnosis of brain tumours in children. Childs Nerv Syst 16:731–734

Butzen J, Prost R, Chetty V et al (2000) Discrimination between neoplastic and nonneoplastic brain lesions by use of proton MR spectroscopy: the limits of accuracy with a logistic regression model. AJNR Am J Neuroradiol 21:1213–1219

Cappabianca P, Spaziante R, Caputi F et al (1991) Accuracy of the analysis of multiple small fragments of glial tumors obtained by stereotactic biopsy. Acta Cytol 35:505–511

Cedzich C, Taniguchi M, Schafer S, Schramm J (1996) Somatosensory evoked potential phase reversal and direct motor cortex stimulation during surgery in and around the central region. Neurosurgery 38:962–970

Cha S (2006) Update on brain tumor imaging: from anatomy to physiology. AJNR Am J Neuroradiol 27:475–487

Cha S, Lu S, Johnson G, Knopp EA (2000a) Dynamic susceptibility contrast MR imaging: correlation of signal intensity changes with cerebral blood volume measurements. J Magn Reson Imaging 11:114–119

Cha S, Knopp EA, Johnson G et al (2000b) Dynamic contrast-enhanced T2-weighted MR imaging of recurrent malignant gliomas treated with thalidomide and carboplatin. AJNR Am J Neuroradiol 21:881–890

Cha S, Knopp EA, Johnson G, Wetzel SG, Litt AW, Zagzag D (2002) Intracranial mass lesions: dynamic contrast-enhanced susceptibility-weighted echo-planar perfusion MR imaging. Radiology 223:11–29

Chan YL, Leung SF, King AD, Choi PH, Metreweli C (1999) Late radiation injury to the temporal lobes: morphologic evaluation at MR imaging. Radiology 213:800–807

Chandrasoma PT, Smith MM, Apuzzo ML (1989) Stereotactic biopsy in the diagnosis of brain masses: comparison of results of biopsy and resected surgical specimen. Neurosurgery 24:160–165

Chang KH, Song IC, Kim SH et al (1998) In vivo single-voxel proton MR spectroscopy in intracranial cystic masses. AJNR Am J Neuroradiol 19:401–405

Chawla A, Emmanuel JV, Seow WT, Lou J, Teo HE, Lim CC (2007) Paediatric PNET: pre-surgical MRI features. Clin Radiol 62:43–52

Chen W, Silverman DH (2008) Advances in evaluation of primary brain tumors. Semin Nucl Med 38:240–250

Chen HJ, Panigrahy A, Dhall G, Finlay JL, Nelson MD Jr, Bluml S (2010) Apparent diffusion and fractional anisotropy of diffuse intrinsic brain stem gliomas. AJNR Am J Neuroradiol 31:1879–1885

Choi JY, Kim SE, Shin HJ, Kim BT, Kim JH (2000) Brain tumor imaging with 99mTc-tetrofosmin: comparison with 201Tl, 99mTc-MIBI, and 18F-fluorodeoxyglucose. J Neurooncol 46:63–70

Choi C, Ganji SK, DeBerardinis RJ et al (2012) 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 18:624–629

Dadparvar S, Hussain R, Koffler SP, Gillan MM, Bartolic EI, Miyamoto C (2000) The role of Tc-99m HMPAO functional brain imaging in detection of cerebral radionecrosis. Cancer J 6:381–387

De Witte O, Lefranc F, Levivier M, Salmon I, Brotchi J, Goldman S (2000) FDG-PET as a prognostic factor in high-grade astrocytoma. J Neurooncol 49:157–163

Dezortova M, Hajek M, Cap F, Babis M, Tichy M, Vymazal J (1999) Comparison of MR spectroscopy and MR imaging with contrast agent in children with cerebral astrocytomas. Childs Nerv Syst 15:408–412

Di Chiro G, Oldfield E, Wright DC et al (1988) Cerebral necrosis after radiotherapy and/or intraarterial chemotherapy for brain tumors: PET and neuropathologic studies. AJR Am J Roentgenol 150:189–197

Dillon WP, Roberts T (1999) The limitations of functional MR imaging: a caveat. AJNR Am J Neuroradiol 20:536

Disbrow E, Roberts TP, Slutsky D, Krubitzer L (1999) The use of fMRI for determining the topographic organization of cortical fields in human and nonhuman primates. Brain Res 829:167–173

Dowling C, Bollen AW, Noworolski SM et al (2001) Preoperative proton MR spectroscopic imaging of brain tumors: correlation with histopathologic analysis of resection specimens. AJNR Am J Neuroradiol 22:604–612

Dunkl V, Cleff C, Stoffels G et al (2015) The usefulness of dynamic O-(2-18F-Fluoroethyl)-l-tyrosine PET in the clinical evaluation of brain tumors in children and adolescents. J Nucl Med 56:88–92

Essig M, Shiroishi MS, Nguyen TB et al (2013) Perfusion MRI: the five most frequently asked technical questions. AJR Am J Roentgenol 200:24–34

Field AS, Yen YF, Burdette JH, Elster AD (2000) False cerebral activation on BOLD functional MR images: study of low-amplitude motion weakly correlated to stimulus. AJNR Am J Neuroradiol 21:1388–1396

Filippi M, Cercignani M, Inglese M, Horsfield MA, Comi G (2001) Diffusion tensor magnetic resonance imaging in multiple sclerosis. Neurology 56:304–311

Ganslandt O, Fahlbusch R, Nimsky C et al (1999) Functional neuronavigation with magnetoencephalography: outcome in 50 patients with lesions around the motor cortex. Neurosurg Focus 6, e3

Gauvain KM, McKinstry RC, Mukherjee P et al (2001) Evaluating pediatric brain tumor cellularity with diffusion-tensor imaging. AJR Am J Roentgenol 177:449–454

Gerlowski LE, Jain RK (1986) Microvascular permeability of normal and neoplastic tissues. Microvasc Res 31:288–305

Giannini C, Scheithauer BW (1997) Classification and grading of low-grade astrocytic tumors in children. Brain Pathol 7:785–798

Girard N, Wang ZJ, Erbetta A et al (1998) Prognostic value of proton MR spectroscopy of cerebral hemisphere tumors in children. Neuroradiology 40:121–125

Go KG, Keuter EJ, Kamman RL et al (1994) Contribution of magnetic resonance spectroscopic imaging and

L-[1-11C]tyrosine positron emission tomography to localization of cerebral gliomas for biopsy. Neurosurgery 34:994–1002, discussion 1002
Golay X, Petersen ET (2006) Arterial spin labeling: benefits and pitfalls of high magnetic field. Neuroimaging Clin N Am 16:259–268, x
Grabner G, Nobauer I, Elandt K et al (2012) Longitudinal brain imaging of five malignant glioma patients treated with bevacizumab using susceptibility-weighted magnetic resonance imaging at 7 T. Magn Reson Imaging 30:139–147
Grand S, Passaro G, Ziegler A et al (1999) Necrotic tumor versus brain abscess: importance of amino acids detected at 1H MR spectroscopy – initial results. Radiology 213:785–793
Greenwood J (1991) Mechanisms of blood-brain barrier breakdown. Neuroradiology 33:95–100
Gupta RK, Vatsal DK, Husain N et al (2001) Differentiation of tuberculous from pyogenic brain abscesses with in vivo proton MR spectroscopy and magnetization transfer MR imaging. AJNR Am J Neuroradiol 22:1503–1509
Haacke EM, Xu Y, Cheng YC, Reichenbach JR (2004) Susceptibility weighted imaging (SWI). Magn Reson Med 52:612–618
Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng YC (2009) Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. AJNR Am J Neuroradiol 30:19–30
Hatakeyama T, Kawai N, Nishiyama Y et al (2008) (11) C-methionine (MET) and (18)F-fluorothymidine (FLT) PET in patients with newly diagnosed glioma. Eur J Nucl Med Mol Imaging 35:2009–2017
Hayes LL, Jones RA, Palasis S, Aguilera D, Porter DA (2012) Drop metastases to the pediatric spine revealed with diffusion-weighted MR imaging. Pediatr Radiol 42:1009–1013
Holodny AI, Schulder M, Liu WC, Maldjian JA, Kalnin AJ (1999) Decreased BOLD functional MR activation of the motor and sensory cortices adjacent to a glioblastoma multiforme: implications for image-guided neurosurgery. AJNR Am J Neuroradiol 20:609–612
Horska A, Ulug AM, Melhem ER et al (2001) Proton magnetic resonance spectroscopy of choroid plexus tumors in children. J Magn Reson Imaging 14:78–82
Hunter JV, Wang ZJ (2001) MR spectroscopy in pediatric neuroradiology. Magn Reson Imaging Clin N Am 9:165–189, ix
Inglis BA, Neubauer D, Yang L, Plant D, Mareci TH, Muir D (1999) Diffusion tensor MR imaging and comparative histology of glioma engrafted in the rat spinal cord. AJNR Am J Neuroradiol 20:713–716
Jaremko JL, Jans LB, Coleman LT, Ditchfield MR (2010) Value and limitations of diffusion-weighted imaging in grading and diagnosis of pediatric posterior fossa tumors. AJNR Am J Neuroradiol 31:1613–1616
Joyce P, Bentson J, Takahashi M, Winter J, Wilson G, Byrd S (1978) The accuracy of predicting histologic grades of supratentorial astrocytomas on the basis of computerized tomography and cerebral angiography. Neuroradiology 16:346–348
Kamada K, Houkin K, Abe H, Sawamura Y, Kashiwaba T (1997) Differentiation of cerebral radiation necrosis from tumor recurrence by proton magnetic resonance spectroscopy. Neurol Med Chir (Tokyo) 37:250–256
Kaplan WD, Takvorian T, Morris JH, Rumbaugh CL, Connolly BT, Atkins HL (1987) Thallium-201 brain tumor imaging: a comparative study with pathologic correlation. J Nucl Med 28:47–52
Kaplan AM, Bandy DJ, Manwaring KH et al (1999) Functional brain mapping using positron emission tomography scanning in preoperative neurosurgical planning for pediatric brain tumors. J Neurosurg 91:797–803
Keene DL, Hsu E, Ventureyra E (1999) Brain tumors in childhood and adolescence. Pediatr Neurol 20:198–203
Keles GE, Chang EF, Lamborn KR et al (2006) Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma. J Neurosurg 105:34–40
Kim EE, Chung SK, Haynie TP et al (1992) Differentiation of residual or recurrent tumors from post-treatment changes with F-18 FDG PET. Radiographics 12:269–279
Kim SH, Chang KH, Song IC et al (1997) Brain abscess and brain tumor: discrimination with in vivo H-1 MR spectroscopy. Radiology 204:239–245
Kimura T, Sako K, Gotoh T, Tanaka K, Tanaka T (2001) In vivo single-voxel proton MR spectroscopy in brain lesions with ring-like enhancement. NMR Biomed 14:339–349
Kincaid PK, El-Saden SM, Park SH, Goy BW (1998) Cerebral gangliogliomas: preoperative grading using FDG-PET and 201Tl-SPECT. AJNR Am J Neuroradiol 19:801–806
Kinoshita Y, Yokota A (1997) Absolute concentrations of metabolites in human brain tumors using in vitro proton magnetic resonance spectroscopy. NMR Biomed 10:2–12
Knopp EA, Cha S, Johnson G et al (1999) Glial neoplasms: dynamic contrast-enhanced T2*-weighted MR imaging. Radiology 211:791–798
Koike S, Aida N, Hata M, Fujita K, Ozawa Y, Inoue T (2004) Asymptomatic radiation-induced telangiectasia in children after cranial irradiation: frequency, latency, and dose relation. Radiology 230:93–99
Koral K, Zhang S, Gargan L et al (2013) Diffusion MRI improves the accuracy of preoperative diagnosis of common pediatric cerebellar tumors among reviewers with different experience levels. AJNR Am J Neuroradiol 34:2360–2365
Krishnamoorthy T, Radhakrishnan VV, Thomas B, Jeyadevan ER, Menon G, Nair S (2007) Alanine peak in central neurocytomas on proton MR spectroscopy. Neuroradiology 49:551–554
Krouwer HG, Kim TA, Rand SD et al (1998) Single-voxel proton MR spectroscopy of nonneoplastic brain

lesions suggestive of a neoplasm. AJNR Am J Neuroradiol 19:1695–1703
Kugel H, Heindel W, Ernestus RI, Bunke J, du Mesnil R, Friedmann G (1992) Human brain tumors: spectral patterns detected with localized H-1 MR spectroscopy. Radiology 183:701–709
Lam WW, Poon WS, Metreweli C (2002) Diffusion MR imaging in glioma: does it have any role in the pre-operation determination of grading of glioma? Clin Radiol 57:219–225
Larson JJ, Ball WS, Bove KE, Crone KR, Tew JM Jr (1998) Formation of intracerebral cavernous malformations after radiation treatment for central nervous system neoplasia in children. J Neurosurg 88:51–56
Law M, Cha S, Knopp EA, Johnson G, Arnett J, Litt AW (2002) High-grade gliomas and solitary metastases: differentiation by using perfusion and proton spectroscopic MR imaging. Radiology 222:715–721
Lazareff JA, Gupta RK, Alger J (1999) Variation of post-treatment H-MRSI choline intensity in pediatric gliomas. J Neurooncol 41:291–298
Lehnhardt FG, Rohn G, Ernestus RI, Grune M, Hoehn M (2001) 1H- and (31)P-MR spectroscopy of primary and recurrent human brain tumors in vitro: malignancy-characteristic profiles of water soluble and lipophilic spectral components. NMR Biomed 14:307–317
Lev MH, Grant PE (2000) MEG versus BOLD MR imaging: functional imaging, the next generation? AJNR Am J Neuroradiol 21:1369–1370
Lin A, Bluml S, Mamelak AN (1999) Efficacy of proton magnetic resonance spectroscopy in clinical decision making for patients with suspected malignant brain tumors. J Neurooncol 45:69–81
Lorberboym M, Mandell LR, Mosesson RE et al (1997) The role of thallium-201 uptake and retention in intracranial tumors after radiotherapy. J Nucl Med 38:223–226
Ludemann L, Hamm B, Zimmer C (2000) Pharmacokinetic analysis of glioma compartments with dynamic Gd-DTPA-enhanced magnetic resonance imaging. Magn Reson Imaging 18:1201–1214
Lupo JM, Essock-Burns E, Molinaro AM et al (2013) Using susceptibility-weighted imaging to determine response to combined anti-angiogenic, cytotoxic, and radiation therapy in patients with glioblastoma multiforme. Neuro Oncol 15:480–489
Maeda M, Itoh S, Kimura H et al (1993) Tumor vascularity in the brain: evaluation with dynamic susceptibility-contrast MR imaging. Radiology 189:233–238
Maria BL, Drane WE, Quisling RG et al (1994) Value of thallium-201 SPECT imaging in childhood brain tumors. Pediatr Neurosurg 20:11–18
Maria BL, Drane WB, Quisling RJ, Hoang KB (1997) Correlation between gadolinium-diethylenetriaminepentaacetic acid contrast enhancement and thallium-201 chloride uptake in pediatric brainstem glioma. J Child Neurol 12:341–348
Maria BL, Drane WE, Mastin ST, Jimenez LA (1998) Comparative value of thallium and glucose SPECT imaging in childhood brain tumors. Pediatr Neurol 19:351–357
Martin E, Marcar VL (2001) Functional MR imaging in pediatrics. Magn Reson Imaging Clin N Am 9:231–246, ix-x
Martin AJ, Liu H, Hall WA, Truwit CL (2001) Preliminary assessment of turbo spectroscopic imaging for targeting in brain biopsy. AJNR Am J Neuroradiol 22:959–968
Massager N, David P, Goldman S et al (2000) Combined magnetic resonance imaging- and positron emission tomography-guided stereotactic biopsy in brainstem mass lesions: diagnostic yield in a series of 30 patients. J Neurosurg 93:951–957
McKnight TR, Noworolski SM, Vigneron DB, Nelson SJ (2001) An automated technique for the quantitative assessment of 3D-MRSI data from patients with glioma. J Magn Reson Imaging 13:167–177
Melhem ER, Itoh R, Jones L, Barker PB (2000) Diffusion tensor MR imaging of the brain: effect of diffusion weighting on trace and anisotropy measurements. AJNR Am J Neuroradiol 21:1813–1820
Mettler FA Jr, Huda W, Yoshizumi TT, Mahesh M (2008) Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology 248:254–263
Mitchell DG (1999) MRI Principles. WB Saunders, Philadelphia
Moreno-Torres A, Martinez-Perez I, Baquero M et al (2004) Taurine detection by proton magnetic resonance spectroscopy in medulloblastoma: contribution to noninvasive differential diagnosis with cerebellar astrocytoma. Neurosurgery 55:824–829, discussion 829
Moyher SE, Wald LL, Nelson SJ et al (1997) High resolution T2-weighted imaging of the human brain using surface coils and an analytical reception profile correction. J Magn Reson Imaging 7:512–517
Muzi M, Spence AM, O'Sullivan F et al (2006) Kinetic analysis of 3′-deoxy-3′-18F-fluorothymidine in patients with gliomas. J Nucl Med 47:1612–1621
Negendank WG, Sauter R, Brown TR et al (1996) Proton magnetic resonance spectroscopy in patients with glial tumors: a multicenter study. J Neurosurg 84:449–458
Nelson SJ, Nalbandian AB, Proctor E, Vigneron DB (1994) Registration of images from sequential MR studies of the brain. J Magn Reson Imaging 4:877–883
Nelson SJ, Huhn S, Vigneron DB et al (1997a) Volume MRI and MRSI techniques for the quantitation of treatment response in brain tumors: presentation of a detailed case study. J Magn Reson Imaging 7:1146–1152
Nelson SJ, Vigneron DB, Star-Lack J, Kurhanewicz J (1997b) High spatial resolution and speed in MRSI. NMR Biomed 10:411–422
Nelson SJ, Vigneron DB, Dillon WP (1999) Serial evaluation of patients with brain tumors using volume MRI and 3D 1H MRSI. NMR Biomed 12:123–138
Norfray JF, Tomita T, Byrd SE, Ross BD, Berger PA, Miller RS (1999) Clinical impact of MR spectroscopy

when MR imaging is indeterminate for pediatric brain tumors. AJR Am J Roentgenol 173:119–125
Ogawa T, Kanno I, Shishido F et al (1991) Clinical value of PET with 18F-fluorodeoxyglucose and L-methyl-11C-methionine for diagnosis of recurrent brain tumor and radiation injury. Acta Radiol 32:197–202
Otsubo H, Snead OC 3rd (2001) Magnetoencephalography and magnetic source imaging in children. J Child Neurol 16:227–235
Ott D, Hennig J, Ernst T (1993) Human brain tumors: assessment with in vivo proton MR spectroscopy. Radiology 186:745–752
O'Tuama LA, Poussaint TY, Anthony DC, Treves ST (1998) Childhood brain tumor: neuroimaging correlated with disease outcome. Pediatr Neurol 19:259–262
Papanicolaou AC, Simos PG, Breier JI et al (2001) Brain plasticity for sensory and linguistic functions: a functional imaging study using magnetoencephalography with children and young adults. J Child Neurol 16:241–252
Peters AM (1998) Fundamentals of tracer kinetics for radiologists. Br J Radiol 71:1116–1129
Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996) Diffusion tensor MR imaging of the human brain. Radiology 201:637–648
Pirotte B, Acerbi F, Lubansu A, Goldman S, Brotchi J, Levivier M (2007) PET imaging in the surgical management of pediatric brain tumors. Childs Nerv Syst 23:739–751
Plate KH, Mennel HD (1995) Vascular morphology and angiogenesis in glial tumors. Exp Toxicol Pathol 47:89–94
Poptani H, Gupta RK, Roy R, Pandey R, Jain VK, Chhabra DK (1995) Characterization of intracranial mass lesions with in vivo proton MR spectroscopy. AJNR Am J Neuroradiol 16:1593–1603
Poupon C, Clark CA, Frouin V et al (2000) Regularization of diffusion-based direction maps for the tracking of brain white matter fascicles. Neuroimage 12:184–195
Poussaint TY, Siffert J, Barnes PD et al (1995) Hemorrhagic vasculopathy after treatment of central nervous system neoplasia in childhood: diagnosis and follow-up. AJNR Am J Neuroradiol 16:693–699
Provenzale JM, Arata MA, Turkington TG, McLendon RE, Coleman RE (1999) Gangliogliomas: characterization by registered positron emission tomography-MR images. AJR Am J Roentgenol 172:1103–1107
Pujol J, Conesa G, Deus J, Lopez-Obarrio L, Isamat F, Capdevila A (1998) Clinical application of functional magnetic resonance imaging in presurgical identification of the central sulcus. J Neurosurg 88:863–869
Puttick S, Bell C, Dowson N, Rose S, Fay M (2014) PET, MRI, and simultaneous PET/MRI in the development of diagnostic and therapeutic strategies for glioma. Drug Discov Today
Ricci PE, Karis JP, Heiserman JE, Fram EK, Bice AN, Drayer BP (1998) Differentiating recurrent tumor from radiation necrosis: time for re-evaluation of positron emission tomography? AJNR Am J Neuroradiol 19:407–413
Roberts TP, Rowley HA (1997) Mapping of the sensorimotor cortex: functional MR and magnetic source imaging. AJNR Am J Neuroradiol 18:871–880
Roberts HC, Roberts TP, Brasch RC, Dillon WP (2000a) Quantitative measurement of microvascular permeability in human brain tumors achieved using dynamic contrast-enhanced MR imaging: correlation with histologic grade. AJNR Am J Neuroradiol 21:891–899
Roberts TP, Disbrow EA, Roberts HC, Rowley HA (2000b) Quantification and reproducibility of tracking cortical extent of activation by use of functional MR imaging and magnetoencephalography. AJNR Am J Neuroradiol 21:1377–1387
Rosen BR, Belliveau JW, Vevea JM, Brady TJ (1990) Perfusion imaging with NMR contrast agents. Magn Reson Med 14:249–265
Rosen BR, Belliveau JW, Aronen HJ et al (1991) Susceptibility contrast imaging of cerebral blood volume: human experience. Magn Reson Med 22:293–299, discussion 300-293
Salibi N, Brown MA (1998) Clinical MR spectroscopy (first principles). Wiley-Liss, New York
Saritas EU, Cunningham CH, Lee JH, Han ET, Nishimura DG (2008) DWI of the spinal cord with reduced FOV single-shot EPI. Magn Reson Med 60:468–473
Schweser F, Deistung A, Lehr BW, Reichenbach JR (2010) Differentiation between diamagnetic and paramagnetic cerebral lesions based on magnetic susceptibility mapping. Med Phys 37:5165–5178
Seymour ZA, Panigrahy A, Finlay JL, Nelson MD Jr, Bluml S (2008) Citrate in pediatric CNS tumors? AJNR Am J Neuroradiol 29:1006–1011
Shimizu H, Kumabe T, Tominaga T et al (1996) Noninvasive evaluation of malignancy of brain tumors with proton MR spectroscopy. AJNR Am J Neuroradiol 17:737–747
Shino A, Nakasu S, Matsuda M, Handa J, Morikawa S, Inubushi T (1999) Noninvasive evaluation of the malignant potential of intracranial meningiomas performed using proton magnetic resonance spectroscopy. J Neurosurg 91:928–934
Shinoura N, Nishijima M, Hara T et al (1997) Brain tumors: detection with C-11 choline PET. Radiology 202:497–503
Shtern F (1992) Clinical experimentation in magnetic resonance spectroscopy: a perspective from the National Cancer Institute. NMR Biomed 5:325–328
Shukla-Dave A, Gupta RK, Roy R et al (2001) Prospective evaluation of in vivo proton MR spectroscopy in differentiation of similar appearing intracranial cystic lesions. Magn Reson Imaging 19:103–110
Siegal T, Rubinstein R, Tzuk-Shina T, Gomori JM (1997) Utility of relative cerebral blood volume mapping derived from perfusion magnetic resonance imaging in the routine follow up of brain tumors. J Neurosurg 86:22–27
Sijens PE, Vecht CJ, Levendag PC, van Dijk P, Oudkerk M (1995) Hydrogen magnetic resonance spectroscopy

follow-up after radiation therapy of human brain cancer. Unexpected inverse correlation between the changes in tumor choline level and post-gadolinium magnetic resonance imaging contrast. Invest Radiol 30:738–744

Simos PG, Papanicolaou AC, Breier JI et al (1999) Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping. J Neurosurg 91:787–796

Smith JS, Cha S, Mayo MC et al (2005) Serial diffusion-weighted magnetic resonance imaging in cases of glioma: distinguishing tumor recurrence from postresection injury. J Neurosurg 103:428–438

Smith JS, Chang EF, Lamborn KR et al (2008) Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 26:1338–1345

Stadnik TW, Chaskis C, Michotte A et al (2001) Diffusion-weighted MR imaging of intracerebral masses: comparison with conventional MR imaging and histologic findings. AJNR Am J Neuroradiol 22:969–976

Stippich C, Freitag P, Kassubek J et al (1998) Motor, somatosensory and auditory cortex localization by fMRI and MEG. Neuroreport 9:1953–1957

Strong JA, Hatten HP Jr, Brown MT et al (1993) Pilocytic astrocytoma: correlation between the initial imaging features and clinical aggressiveness. AJR Am J Roentgenol 161:369–372

Sugahara T, Korogi Y, Kochi M et al (1998) Correlation of MR imaging-determined cerebral blood volume maps with histologic and angiographic determination of vascularity of gliomas. AJR Am J Roentgenol 171:1479–1486

Sugahara T, Korogi Y, Shigematsu Y et al (1999) Value of dynamic susceptibility contrast magnetic resonance imaging in the evaluation of intracranial tumors. Top Magn Reson Imaging 10:114–124

Sugahara T, Korogi Y, Tomiguchi S et al (2000) Posttherapeutic intraaxial brain tumor: the value of perfusion-sensitive contrast-enhanced MR imaging for differentiating tumor recurrence from nonneoplastic contrast-enhancing tissue. AJNR Am J Neuroradiol 21:901–909

Sugahara T, Korogi Y, Kochi M, Ushio Y, Takahashi M (2001) Perfusion-sensitive MR imaging of gliomas: comparison between gradient-echo and spin-echo echo-planar imaging techniques. AJNR Am J Neuroradiol 22:1306–1315

Sutton LN, Wang Z, Gusnard D et al (1992) Proton magnetic resonance spectroscopy of pediatric brain tumors. Neurosurgery 31:195–202

Suzuki A, Yasui N (1992) Intraoperative localization of the central sulcus by cortical somatosensory evoked potentials in brain tumor. Case report. J Neurosurg 76:867–870

Szigety SK, Allen PS, Huyser-Wierenga D, Urtasun RC (1993) The effect of radiation on normal human CNS as detected by NMR spectroscopy. Int J Radiat Oncol Biol Phys 25:695–701

Szymanski MD, Perry DW, Gage NM et al (2001) Magnetic source imaging of late evoked field responses to vowels: toward an assessment of hemispheric dominance for language. J Neurosurg 94:445–453

Tanner SF, Ramenghi LA, Ridgway JP et al (2000) Quantitative comparison of intrabrain diffusion in adults and preterm and term neonates and infants. AJR Am J Roentgenol 174:1643–1649

Taylor JS, Langston JW, Reddick WE et al (1996) Clinical value of proton magnetic resonance spectroscopy for differentiating recurrent or residual brain tumor from delayed cerebral necrosis. Int J Radiat Oncol Biol Phys 36:1251–1261

Tomoi M, Kimura H, Yoshida M et al (1997) Alterations of lactate (+lipid) concentration in brain tumors with in vivo hydrogen magnetic resonance spectroscopy during radiotherapy. Invest Radiol 32:288–296

Tong KA, Ashwal S, Obenaus A, Nickerson JP, Kido D, Haacke EM (2008) Susceptibility-weighted MR imaging: a review of clinical applications in children. AJNR Am J Neuroradiol 29:9–17

Tzika AA, Vigneron DB, Dunn RS, Nelson SJ, Ball WS Jr (1996) Intracranial tumors in children: small single-voxel proton MR spectroscopy using short- and long-echo sequences. Neuroradiology 38:254–263

Tzika AA, Vajapeyam S, Barnes PD (1997) Multivoxel proton MR spectroscopy and hemodynamic MR imaging of childhood brain tumors: preliminary observations. AJNR Am J Neuroradiol 18:203–218

Tzika AA, Zurakowski D, Poussaint TY et al (2001) Proton magnetic spectroscopic imaging of the child's brain: the response of tumors to treatment. Neuroradiology 43:169–177

Tzika AA, Zarifi MK, Goumnerova L et al (2002) Neuroimaging in pediatric brain tumors: Gd-DTPA-enhanced, hemodynamic, and diffusion MR imaging compared with MR spectroscopic imaging. AJNR Am J Neuroradiol 23:322–333

Ullrich R, Backes H, Li H et al (2008) Glioma proliferation as assessed by 3′-fluoro-3′-deoxy-L-thymidine positron emission tomography in patients with newly diagnosed high-grade glioma. Clin Cancer Res 14:2049–2055

Urenjak J, Williams SR, Gadian DG, Noble M (1993) Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. J Neurosci 13:981–989

Usenius T, Usenius JP, Tenhunen M et al (1995) Radiation-induced changes in human brain metabolites as studied by 1H nuclear magnetic resonance spectroscopy in vivo. Int J Radiat Oncol Biol Phys 33:719–724

Valk PE, Dillon WP (1991) Radiation injury of the brain. AJNR Am J Neuroradiol 12:45–62

Valk PE, Budinger TF, Levin VA, Silver P, Gutin PH, Doyle WK (1988) PET of malignant cerebral tumors after interstitial brachytherapy. Demonstration of metabolic activity and correlation with clinical outcome. J Neurosurg 69:830–838

van Gelderen P, de Zwart JA, Duyn JH (2008) Pittfalls of MRI measurement of white matter perfusion based on arterial spin labeling. Magn Reson Med 59:788–795

Venkatesh SK, Gupta RK, Pal L, Husain N, Husain M (2001) Spectroscopic increase in choline signal is a nonspecific marker for differentiation of infective/inflammatory from neoplastic lesions of the brain. J Magn Reson Imaging 14:8–15

Vezina LG (1997) Diagnostic imaging in neuro-oncology. Pediatr Clin N Am 44:701–719

Vigneron D, Bollen A, McDermott M et al (2001) Three-dimensional magnetic resonance spectroscopic imaging of histologically confirmed brain tumors. Magn Reson Imaging 19:89–101

Waldrop SM, Davis PC, Padgett CA, Shapiro MB, Morris R (1998) Treatment of brain tumors in children is associated with abnormal MR spectroscopic ratios in brain tissue remote from the tumor site. AJNR Am J Neuroradiol 19:963–970

Wang Z, Sutton LN, Cnaan A et al (1995) Proton MR spectroscopy of pediatric cerebellar tumors. AJNR Am J Neuroradiol 16:1821–1833

Wang Z, Zimmerman RA, Sauter R (1996a) Proton MR spectroscopy of the brain: clinically useful information obtained in assessing CNS diseases in children. AJR Am J Roentgenol 167:191–199

Wang GJ, Volkow ND, Lau YH et al (1996b) Glucose metabolic changes in nontumoral brain tissue of patients with brain tumor following radiotherapy: a preliminary study. J Comput Assist Tomogr 20:709–714

Weisskoff RM, Zuo CS, Boxerman JL, Rosen BR (1994) Microscopic susceptibility variation and transverse relaxation: theory and experiment. Magn Reson Med 31:601–610

Wheless JW, Willmore LJ, Breier JI et al (1999) A comparison of magnetoencephalography, MRI, and V-EEG in patients evaluated for epilepsy surgery. Epilepsia 40:931–941

Wilken B, Dechent P, Herms J et al (2000) Quantitative proton magnetic resonance spectroscopy of focal brain lesions. Pediatr Neurol 23:22–31

Wilson M, Gill SK, MacPherson L, English M, Arvanitis TN, Peet AC (2014) Noninvasive detection of glutamate predicts survival in pediatric medulloblastoma. Clin Cancer Res 20:4532–4539

Yeom KW, Lober RM, Andre JB et al (2013) Prognostic role for diffusion-weighted imaging of pediatric optic pathway glioma. J Neurooncol 113:479–483

Yeom KW, Mitchell LA, Lober RM et al (2014) Arterial spin-labeled perfusion of pediatric brain tumors. AJNR Am J Neuroradiol 35:395–401

Yeung DK, Chan Y, Leung S, Poon PM, Pang C (2001) Detection of an intense resonance at 2.4 ppm in 1H MR spectra of patients with severe late-delayed, radiation-induced brain injuries. Magn Reson Med 45:994–1000

Yousem DM, Lenkinski RE, Evans S et al (1992) Proton MR spectroscopy of experimental radiation-induced white matter injury. J Comput Assist Tomogr 16:543–548

Zaharchuk G (2012) Arterial spin labeling for acute stroke: practical considerations. Trans Stroke Res 3:228–235

Current Surgical Management

14

Kurtis I. Auguste, Peter P. Sun, Corey Raffel, Mitchel S. Berger, and Nalin Gupta

Contents

14.1 Introduction

For the majority of brain tumors in children, the extent of resection is the most important factor predicting long-term outcome. This has led many neurosurgeons to be as aggressive as possible during the initial surgical procedure in an effort to achieve gross total resection (GTR; Pollack 1999). It should be recognized that GTR is not the primary goal for tumors, where sensitivity to adjuvant therapy is high (e.g., germinoma), or where there is clear extension into eloquent regions (e.g., brainstem and thalamic glioma). Fortunately, these latter groups represent a minority of pediatric brain tumors (Pollack 1994).

K.I. Auguste, MD, PhD (✉)
Departments of Neurological Surgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th St. 4th Floor, San Francisco, CA 94143-0137, USA

UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA
e-mail: kurtis.auguste@ucsf.edu

P.P. Sun, MD
Department of Neurological Surgery, UCSF Benioff Children's Hospital Oakland, 747 52nd St, Oakland, CA 94143-0137, USA
e-mail: psun@mail.cho.org

C. Raffel, MD, PhD
Department of Neurological Surgery, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th St, 4th Floor, San Francisco, CA 94143-0137, USA
e-mail: corey.raffel@ucsf.edu

M.S. Berger, MD
Department of Neurological Surgery, University of California San Francisco, 505 Parnassus Ave, Rm M779, San Francisco, CA 94143-0112, USA
e-mail: mitchel.berger@ucsf.edu

N. Gupta, MD, PhD
Division of Pediatric Neurosurgery, Departments of Neurological Surgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, San Francisco, CA, USA
e-mail: nalin.gupta@ucsf.edu

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_14

The majority of pediatric tumors are primary glial neoplasms arising within the cerebellar or cerebral hemispheres. Factors affecting the extent of resection are relation to functionally important structures, degree of infiltration, and the presence or absence of tumor dissemination at time of presentation. Although the portions of infiltrative supratentorial tumors that extend into eloquent locations (primary motor, speech cortex, basal ganglia, or major white-matter tracts such as the internal capsule) are likely to defy GTR, an argument can be offered for extending resection sufficiently to allow a change to occur in the natural history of the disease (Keles et al. 2001). Earlier, the definition of eloquent cortex relied mainly on variable anatomical maps, and resective procedures were limited by the inability to predict functional anatomy in specific patients. In the posterior fossa, GTR is limited either by involvement of the brainstem or the cranial nerves. Monitoring of virtually all cranial nerves is now possible, which greatly facilitates safe dissection of the tumor from normal structures. However, infiltration into the brainstem by malignant tumors is not amenable to surgical resection.

Progress in various technologies has allowed maps to be created for individual patients that define the actual boundaries of eloquent cortex. These advances consist of neuronavigation, coupled with high-resolution anatomic imaging noninvasive functional imaging and adaptation of brain and spinal cord mapping techniques to the pediatric population.

14.2 Technical Adjuncts for Resection of Brain Tumors

14.2.1 Ultrasound

Despite recent technological advances centered around three-dimensional navigation based on preoperative magnetic resonance imaging (MRI), a well-established and time-tested intraoperative tool is the ultrasound (Gooding et al. 1983). Intraoperative ultrasound remains a safe, nonradiative method used to determine depth, tissue consistency (solid, fluid-filled, complex, etc.), and relationship to adjacent anatomic structures. Doppler ultrasonography, in particular, is useful for determining proximity to vascular structures. Ultrasound avoids the pitfalls of initial misregistration and tissue shift during the course of tumor resection. It does not rely on static, preoperative imaging, but instead provides real-time updates regarding extent of resection (Fig. 14.1). Ultrasound lacks the image resolution of MRI, but it compensates for this shortcoming with low cost, reliability, ease of use, and shortening of operative time.

14.2.2 Neuronavigation

Conventional MRI provides the necessary detail to assess the anatomic relationships of most intracranial tumors. Several manufacturers supply systems that use a preoperative MRI scan as the basis for an intraoperative three-dimensional guidance system. In their various configurations, these are all considered neuronavigation systems. Standard MRI may be complemented by more specialized MR techniques (see Chap. 13) such as MR spectroscopy (MRS), diffusion tensor imaging (DTI), and functional MRI (fMRI), in addition to other tools such as magnetoencephalography (MEG) and conventional catheter angiography. These special MR sequences can be merged with conventional anatomic images and then used in the operating room during surgery.

Neuronavigation has impacted brain-tumor surgery in three major ways. First, surgical routes can be simulated and planned preoperatively, allowing maximum accuracy of craniotomy placements and cortical incisions. As a result, mistakes in trajectory and depth during tumor resection are prevented. Second, the shortest and safest route through brain tissue that avoids important neural and vascular structures can be determined well before the procedure. This reduces the risk of postoperative neurologic deficits, and improves assessment of risk preoperatively. Third, the use of neuronavigation improves the extent of tumor resection by providing "feedback" to augment the surgeon's perception of anatomic placement. Despite all these advantages, the major limitation of preoperative regis-

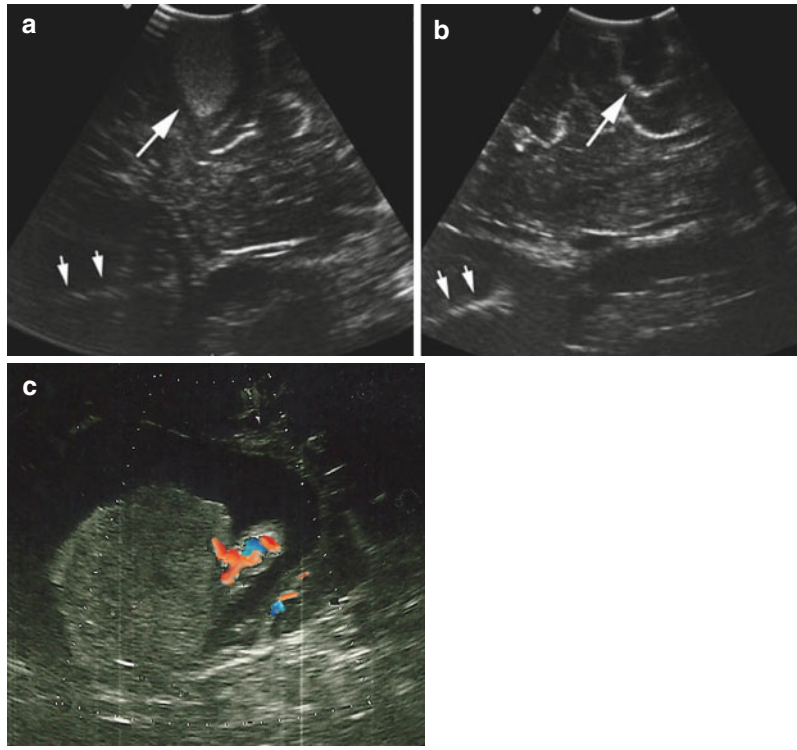

Fig. 14.1 Intraoperative ultrasound images of a 4-year-old boy with a low-grade glioma of the left frontal lobe. Preresection (**a**) and postresection (**b**) coronal plane images demonstrate the distinct echogenicity of neoplastic tissue (*large arrow*) from the surrounding brain. The midline falx cerebri is seen as an anatomic reference point (*small arrows*). (**c**) Doppler ultrasonography highlights the arterial blood supply of a choroid plexus papilloma

tered imaging data is obvious: intraoperative shifts of tissue cannot update a static set of data obtained prior to tumor resection.

The original intraoperative navigation systems used metal stereotactic frames rigidly attached to the calvarium. These were referred to as "frame-based" stereotactic devices. Target guidance relied upon anatomic coordinates as defined in anatomic atlases. Coordinates and targets could be refined modestly by imaging studies such as plain films and air ventriculograms. The inherent inaccuracy of this system is obvious, in that patient-specific data is not used to guide the actual procedure. A key advance occurred when computed tomography or MRI scans were used in conjunction with frame-based systems (e.g., Leksell, Brown-Roberts-Wells [BRW], Cosman-Roberts-Wells [CRW)]) to select targets and mathematically compute trajectories. These systems use guidance arcs that move directly over the surgical field and obstruct the surgeon if a large craniotomy is to be performed. These systems are, however, highly accurate and continue to be used widely in situations where target selection is critical such as Gamma Knife radiosurgery and functional procedures such as pallidotomy (both of which utilize refinements of the Leksell frame, Elekta AB, Stockholm).

Advances in technology with sufficient computational power to allow manipulation and calculation of three-dimensional image sets represented a major innovation in the field. This led to the creation of systems known as "frameless stereotaxy" that recreated a three-dimensional volume space by using fiducials placed on the patient's head and registered to a preoperative imaging study. This allows "real-time" intraoperative guidance and the facility to visualize the target in multiple planes (Fig. 14.2). A variety of tools, including surgical instruments, can also be registered and used as

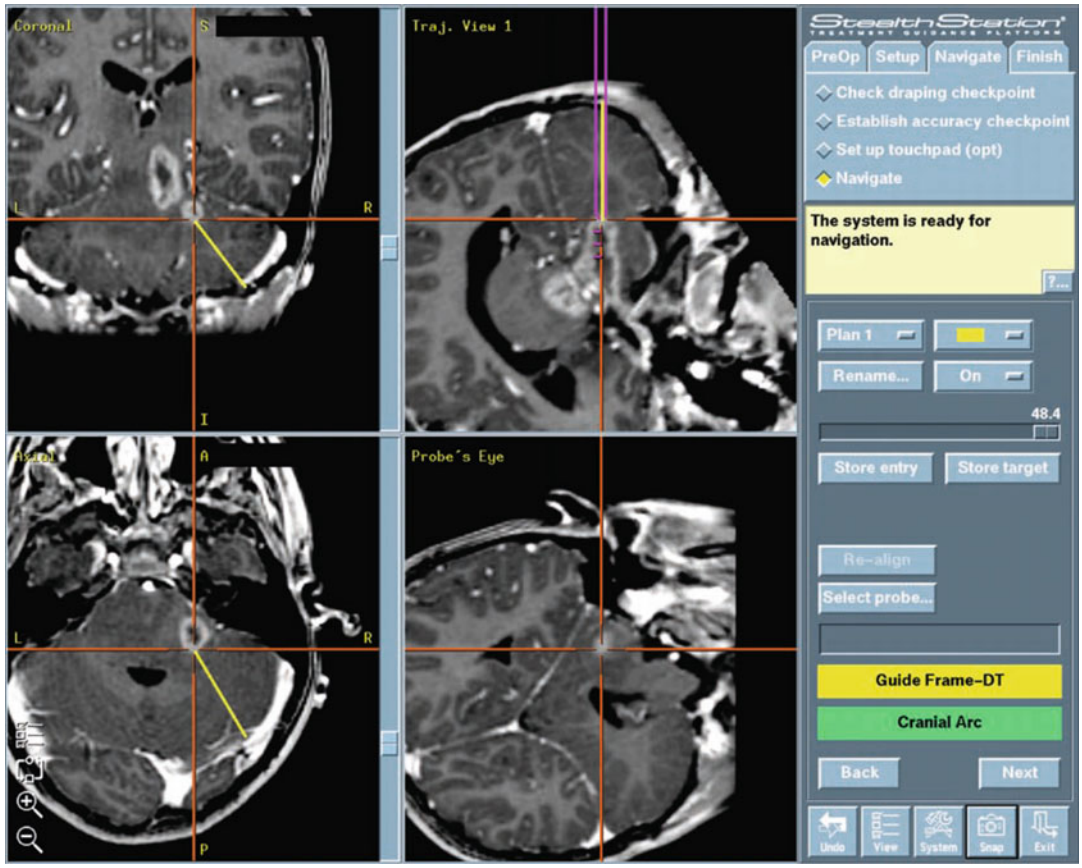

Fig. 14.2 A screen capture image from a brainstem biopsy procedure. The biopsy trajectory is shown in three planes and the tip of the biopsy needle can be tracked in real time as it enters the brain ("Probes Eye" view, *bottom right*). StealthStation is a trademark of Medtronic Corporation (Minneapolis, MN)

pointers that provide continuous updated information on a computer monitor as the tumor resection is performed. Many centers routinely use neuronavigation in all pediatric brain tumor cases. The problem of keeping scalp fiducials in place was solved by the use of surface registration of facial landmarks (Gleason et al. 1994).

Intraoperative MRI (iMRI), the next step in image-directed surgery, allows continual updating of preoperative image sets and adjustment of navigational parameters. This technique has been used to augment posterior fossa procedures (Fig. 14.3; Lam et al. 2001; Chen et al. 2007). Some reports indicate that the use of intraoperative imaging improves the extent of resection, although it is unclear whether it results in improved outcomes (Fahlbusch et al. 2000; Schneider et al. 2001; Avula et al. 2013). An intermediate step is the use of intraoperative-ultrasound-assisted navigation as a means to update imaging data (Regelsberger et al. 2000). Integration with functional information obtained from MRS, DTI, and fMRI allows intraoperative "guide-posts" for the surgeon, delineating regions amenable to resection and regions representing eloquent cortex or functional tracts (Nimsky et al. 2006; Gulati et al. 2009).

14.2.3 Functional Imaging

Several imaging technologies have been adapted to create functional maps of the brain: fMRI, diffusion weighted imaging (DWI), positron emission

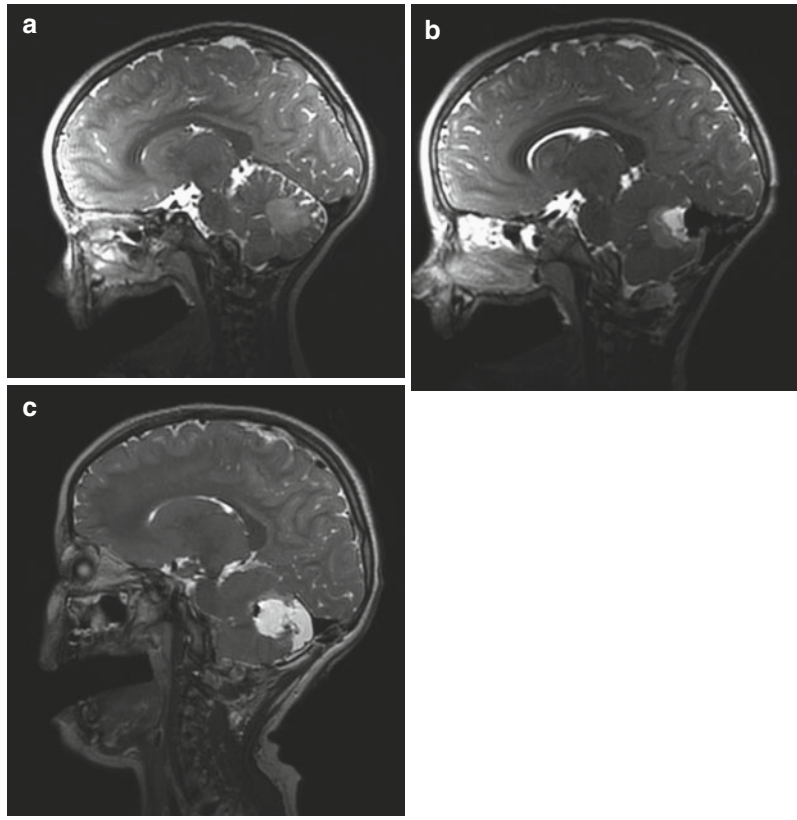

Fig. 14.3 A series of sagittal T2-weighted images from a 6-year-old girl with a grade II cerebellar astrocytoma. The first image (**a**) shows a poorly defined, cerebellar mass. After the initial resection during which the tumor margins were poorly defined, an intraoperative MR scan was done. It shows residual tumor at the base of the resection cavity (**b**). The patient was returned to the OR and a further resection was performed after which a final scan was done (**c**)

tomography (PET), and MEG. Differences that occur in blood flow between the active and inactive cortical areas are exploited by fMRI. These differences are magnified by instructing the patient to perform repetitive tasks, which may be as simple as repeatedly moving the fingers. Local increases in blood flow are then detected by specific MRI sequences. Patient cooperation is, of course, required.

DTI exploits the differences in the diffusion of water molecules depending on the local environment of those molecules (e.g., water molecules within axons vs. those in the interstitial space) (Pierpaoli et al. 1996). This information can then be extracted to create maps demonstrating the location and direction of white-matter pathways. Large white-matter pathways are particularly well-identified using these techniques (see Chap. 13, Fig. 13.7).

Preoperative use of PET was originally presented by LeBlanc and Meyer (1990) and Leblanc et al. (1992). PET relies on metabolic differences within active cortex to isolate functional areas. More recently, a variety of radiolabeled compounds such as [^{18}F] fluorodeoxyglucose (FDG), [^{11}C] L-methionine, and [^{15}O] H_2O were used by Kaplan et al. to create functional maps prior to brain tumor resection in a pediatric population (Kaplan et al. 1999). Coregistering [^{15}O] H_2O PET images with MRI allowed accurate determination of eloquent cortex prior to tumor resection. PET has also been used to select targets for biopsy within brainstem tumors (Pirotte et al. 2007).

MEG relies on the ability to detect single dipole magnetic fields created by the pooled activity of groups of neurons to define potential

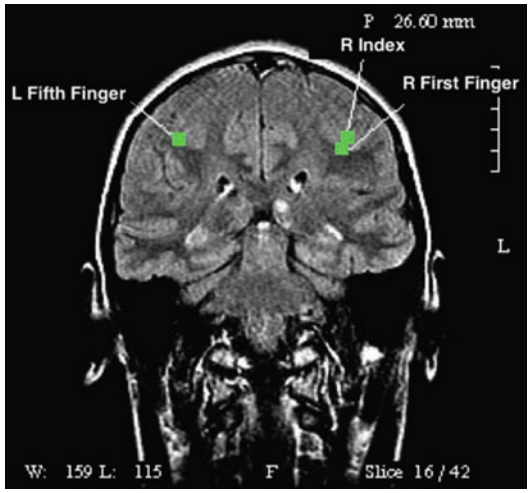

Fig. 14.4 Magnetic source imaging (MSI) of a 15-year-old boy with an infiltrative anterior insular mass (not visible in this image). *Green squares* demonstrate sensory cortex representing left fifth finger, right index finger, and right first finger. These functional maps were integrated into the neuronavigation system prior to tumor resection

areas of seizure activity (Chuang et al. 1995; Otsubo et al. 2001). Further refinement of these techniques, known as magnetic source imaging (MSI), allows the identification of functional areas of cortex and deep brain regions (Fig. 14.4). This information is especially valuable when correlated with tumor localization (Schiffbauer et al. 2001). Delineation of entire functional pathways using a combination of techniques may be possible in the near future.

14.2.4 Cortical Mapping for Supratentorial Tumors

The gold standard for functional mapping of the human brain is direct electrical stimulation of the cortex and observation of its effect upon patient-directed actions during open craniotomy (Berger and Ojemann 1992). Although pioneered in the early part of the twentieth century, continual refinements are improving the sensitivity and accuracy of these techniques. For the most part, the vast majority of mapping cases are restricted to either motor or speech mapping. The major limitations of cortical mapping in children are the relative immaturity of the central nervous (CNS) system in very young children and the inability of children to cooperate in the execution of repetitive language tasks during speech-mapping procedures.

Motor mapping as described by Penfield remains the most robust electrical technique that can be practiced in the operating room (Penfield and Boldrey 1937). Patients remain under general anesthesia and direct systematic electrical stimulation of the precentral area permits the accurate mapping of primary motor cortex. Areas of cortex responsible for specific muscle groups (e.g., face, arm, hand, leg) can be reliably identified. A bipolar electrode with 5-mm spacing is used to deliver stimuli at 60 Hz with duration of 1 ms (biphasic square wave pulse). In children less than 5 years of age, the cortex is generally less excitable by direct stimulation and motor cortex may not be clearly identified. An alternative method to detect the location of the central sulcus is by detecting a phase-reversal potential as one records over the motor and sensory cortex. Using subdural grids, mainly for the treatment of patients with epilepsy, Chitoku et al. were able to define the motor cortex in all children studied, using a variety of stimulation thresholds (Chitoku et al. 2001). Younger children responded to stimuli in the range of 8–12 mA, while older children responded to stimuli in the range of 4–6 mA.

For language mapping, a basic surgical decision point is whether a child can tolerate an "awake craniotomy" (usually above 10–12 years of age). Language mapping is entirely dependent upon patient cooperation and, therefore, is the most difficult technique to accomplish in young children. During an awake craniotomy, a handheld stimulator is used to directly inactivate the cortex, while the patient names objects presented visually. Stimulation of Broca's area, which is often adjacent to the primary motor cortex, usually leads to speech arrest although significant variability exists between individuals of different ages (Haglund et al. 1994; Ojemann et al. 2003). Current techniques of speech mapping allow accurate intraoperative localization of speech function with minimal long-term impacts upon speech function following tumor resection (Sanai et al. 2008).

In children unable to tolerate an awake craniotomy, and for whom functional localization is crucial to the success of the procedure, placement of subdural grids allows bedside cortical mapping. This requires two procedures for the patient, a substantial degree of patient cooperation, and close communication between child neurologists, psychologists, and nursing staff. Generally, this technique can be performed in children above the age of 4 years, although it is most reliable in older children. The first procedure involves a craniotomy encompassing the area of resection and placement of an implantable subdural grid containing multiple electrical contacts. The contacts on the grid are then stimulated sequentially, while the patient is led through specific language tasks such as naming, counting, and repeating. As with awake craniotomy, speech arrest during stimulation is the clue for identifying active cortex. Language paradigms have to be tailored according to the age of the patient and level of comprehension. The procedure is time-consuming and laborious, often requiring sessions over 2 or 3 days. In the patient shown in Fig. 14.5, an infiltrative tumor was noted in the left frontoparietal region. Although the patient was but 5 years old, he tolerated placement of subdural grids for several days and bedside mapping revealed the locations of the language and motor cortex allowing an extensive resection of the tumor.

14.2.5 Mapping of Seizure Foci

If seizures are particularly intractable or appear to be the dominant symptom associated with a brain

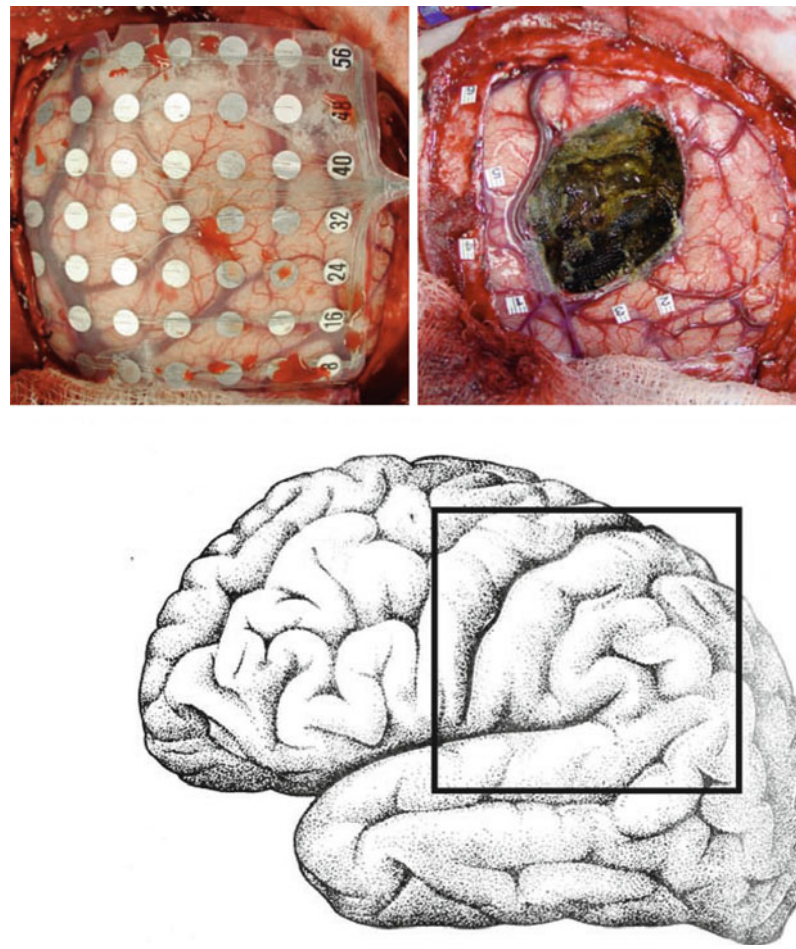

Fig. 14.5 An implanted subdural grid used to map speech and motor cortex in a 5-year-old boy with an infiltrative tumor of the left hemisphere. A 64-contact subdural grid was implanted over the area of the tumor (*left image*). Speech cortex was localized to numbers *2* and *3* during two sessions in the telemetry unit, and motor cortex to numbers *1*, *4*, *5*, and *6* (*right image*). The location of the tumor was correlated with intraoperative neuronavigation and an extensive resection was performed

tumor, the actual ictal focus may need to be identified. For most types of epilepsy associated with a definite lesion, resection of the lesion will result in seizure control in the majority of cases (Mosewich et al. 2000). In some cases, the presence of a tumor is only detected after pathologic examination of the resected tissue. In a series of surgical treatment for epilepsy, approximately 25 % of temporal lobe resections revealed a neoplasm, the majority of which were dysembryoplastic neuroepithelial tumors (DNET, see Chap. 8) (Hennessy et al. 2001).

Scalp electroencephalography is an essential first step in localization of seizure foci. This may be complemented by MEG or invasive monitoring with subdural grids and strip electrodes. Insertion of a subdural grid electrode array provides ictal and interictal information. Strip electrodes are used for recordings from mediobasal structures. In addition, recording along the hippocampus can be performed following the removal of lateral temporal cortex and entry into the temporal horn of the lateral ventricle. Strip electrodes may also be used for the orbitofrontal cortex or under the bone flap, if the cortical exposure is not adequate. The recording may either be done for short time periods intraoperatively (5–20 min) prior to resection, or for prolonged periods postoperatively in the ward in specialized monitoring units. Intravenous infusion of methohexital (Brevital 0.5–1 mg/kg) may be used to chemically induce ictal discharges if epileptiform activity is sparse. Following tumor removal, electrocorticography is always performed in patients with identifiable preresection seizure foci. Infrequent spike activity is not pursued, especially when it involves functional cortex. Resected seizure foci are identified with respect to their geographic orientation to the tumor nidus and should be submitted separately for histopathologic analysis.

14.2.6 Laser Ablation

A relatively new addition to the array of surgical techniques available for the management of CNS tumors is focused laser thermal ablation (Visualase, Medtronic Inc, Houston, TX; Carpentier et al. 2012; Hawasli et al. 2013). In comparison to open surgery, where the goals are exposure, visualization of tumor margins, and dissection of tissue planes, laser ablation therapy targets neoplastic tissue in situ through a minimally invasive approach. First, the target is identified on preoperative MR imaging. Next, a laser fiber is delivered to the target using stereotactic guidance. Surgeons have the option of using frame-based coordinates or frameless navigation to implant the laser, then confirm accurate placement with an MRI. The fibers are held in place with a small skull anchor and require a small skin incision and minimal hair removal (Fig. 14.6a). Alternatively, lasers can be delivered under direct visualization in an iMRI suite. This is most easily achieved with a skull mounted Smartframe and adjusted in real time with the guidance of Surgivision ClearPoint implantation software (MRI Interventions, Irvine, CA; Fig. 14.5b). The progress of laser therapy can then be monitored both with MR-thermography and with software that estimates the volume and extent tissue ablated (Fig. 14.6c).

14.3 Posterior Fossa Tumors

14.3.1 Surgical Principles

Posterior fossa tumors are among the most commonly encountered tumors in children and are located in the midline within the vermis, cerebellar hemisphere, and/or brainstem. Standard approaches to the posterior fossa are well developed and are described in various sources in the literature. Surgical planning is often modified by the pathology of the tumor. The three main pathologic types that occur in this location are astrocytoma, medulloblastoma, and ependymoma. Cerebellar astrocytomas are usually eccentric in location, associated with a cyst, and often cause obstructive hydrocephalus. Medulloblastomas are characteristically midline tumors occupying the vermis and in some cases extending into the cerebellar hemisphere. Ependymomas of the posterior fossa can extend into the fourth ventricle

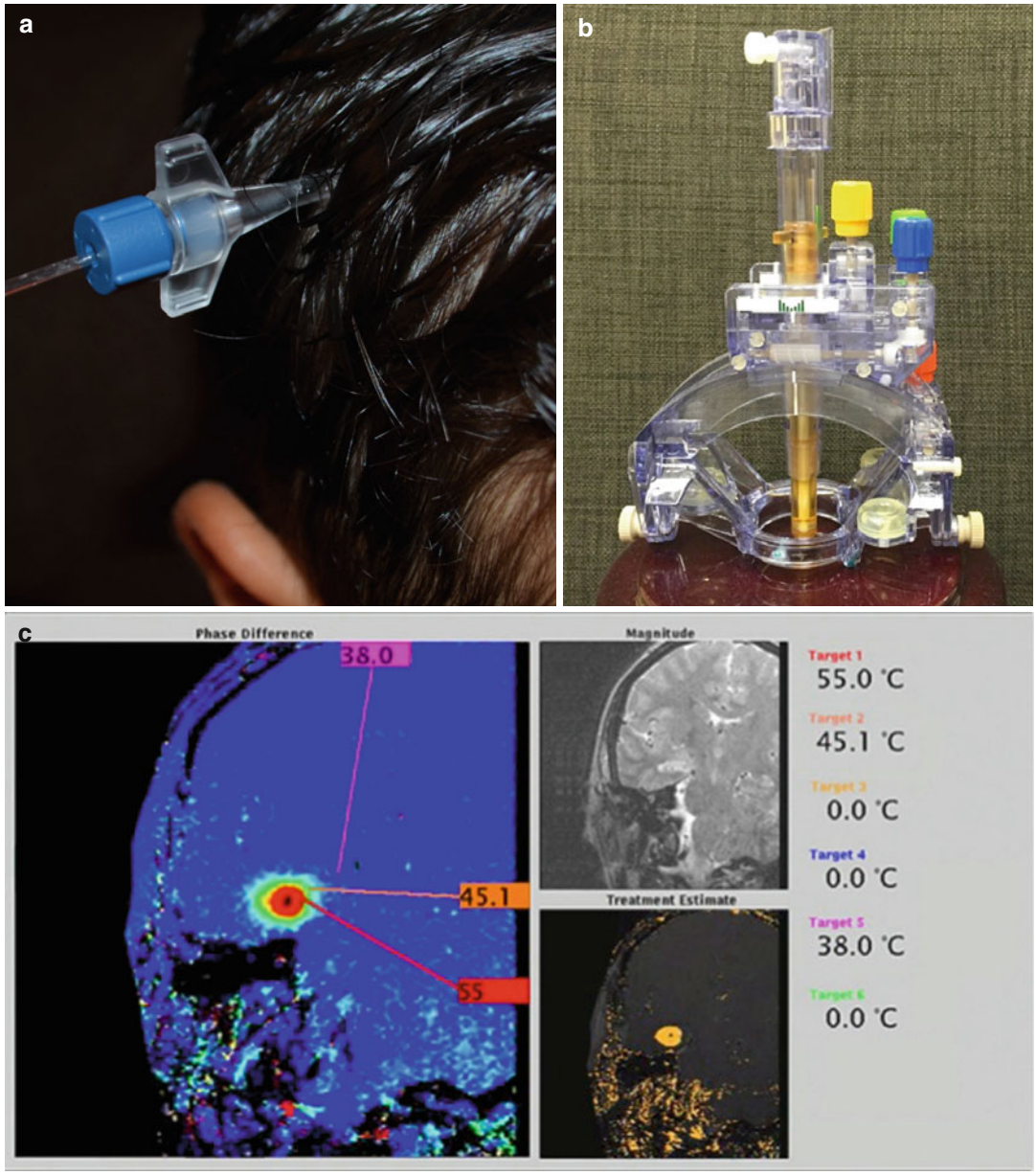

Fig. 14.6 Fixation devices for implanted laser ablation fibers. (**a**) Skull anchors for laser fixation can be placed using frame-based or frameless techniques and do not require large incisions or hair shaves. (**b**) The ClearPoint SmartFrame can be mounted above a burr-hole whose position is optimized with trajectory software. (**c**) The extent of ablation can be estimated with thermography and software that calculates tissue damage

and also may extend into the cerebellopontine angle closely associated with the cranial nerves. Both ependymoma and medulloblastoma can invade the brainstem.

For midline tumors, the standard approach is to position patients prone, with the head flexed forward. A vertical incision allows access to most of the posterior fossa. If the tumor extends anterior to the cerebellum or brainstem, the tumor must be approached from a more lateral position, often with the head turned to allow a posterolateral trajectory. In the past, most surgeons would

remove the overlying bone without replacement (craniectomy), but now, most surgeons attempt to replace the bone flap at the conclusion of the procedure (craniotomy). There is some evidence that this reduces the risk of cerebrospinal fluid (CSF) leakage and pseudomeningocele formation (Gnanalingham et al. 2002). Dural opening is followed by definition of the boundary between the tumor and the normal cerebellum. The character of the interface between tumor and brain can vary across tumor types. In general, the interface is better defined with ependymomas as compared to medulloblastomas. Cerebellar astrocytomas have a clear margin between the tumor and the adjacent brain. The large size of most pediatric tumors and the need to avoid unnecessary brain retraction results in many tumors being resected piecemeal using either standard tools (cautery and suction) or ultrasonic aspirators that use a rapidly vibrating metal tip to disintegrate tissues. Removal of the central portion of the tumor then allows reflection of the deeper tumor tissue into the operative field and subsequent removal. For deep tumors, and those related to important structures, the use of frameless stereotaxy (neuronavigation) has revolutionized intraoperative guidance and structure localization.

Finally, additional safety can be obtained by monitoring various cranial nerves such as the facial, oculomotor, and hypoglossal nerves (Grabb et al. 1997; Sekiya et al. 2000). Tumors either infiltrating the floor of the fourth ventricle or along the anterior portion of the brainstem involve cranial nerves. These nerves are sensitive to manipulation and can be difficult to identify when tumors surround them. Gradual dissection through tumor tissue requires careful identification of important structures.

14.3.2 Complications

Surgical resection of posterior fossa tumors may lead to both nonneurologic and neurologic complications (Table 14.1). Fortunately, the majority of these adverse effects are either transient or treatable, making the overall morbidity quite low. The tendency of posterior fossa tumors to occupy a midline position creates a stereotypical pattern of symptoms following surgery.

14.3.2.1 Injury to Local Structures

Symptoms include long-tract signs of weakness and sensory loss, mutism, and cranial neuropathies (Cochrane et al. 1994). Ataxia and dysmetria are usually due to retraction injury or swelling of the cerebellum and improve after several weeks and months. Injury to the vermis can cause disabling truncal ataxia, which may improve, but can be permanent, particularly if large areas of the vermis have been involved. Impaired initiation of chewing, voiding, and eye opening may present after injury to areas of the cerebellum responsible for repetitive motor movement memory. Restiform body injury may result in permanent ipsilateral limb ataxia (Rosenfeld 2000b). Patients with these deficits commonly have tumors involving the floor of the fourth ventricle, the brainstem, or cerebellar peduncles. Sometimes, removal of a hemispheric tumor creates enough intracranial shifts to affect cranial nerve VI and cause transient diplopia. Approximately one-half of those with new deficits experience complete recovery of function (Pollack et al. 1995; Ersahin 1998).

14.3.2.2 Cerebellar Mutism

Cerebellar mutism is a well-recognized complication of surgical removal of large midline posterior fossa tumors in children. Patients demonstrate

Table 14.1 Complications following surgery for cerebellar astrocytoma

Complication	Percent
Pseudomeningocele	12–24
Wound infection	2–5
Aseptic meningitis	4.5
Septic meningitis	6
Persistent hydrocephalus	10
Hematoma	
Epidural	3
Subdural	3
Operative site	1.5
Transient CN palsy	4.5
Hemiplegia	1.5
Transient mutism	1.5
Permanent neurological deficit	15

transient mutism with unimpaired consciousness, intact comprehension, and no detectable cranial nerve or motor deficits. The majority of cases will awake from surgery with intact speech function, but then develop mutism within 24–94 h (Pollack et al. 1995). In the largest series to date, the incidence was 8.5 % for all posterior fossa tumors and 12 % for vermian tumors, but did vary with histology (Catsman-Berrevoets et al. 1999). Patients with malignant tumors involving the brainstem, fourth ventricle, or vermis experienced mutism more often (20–24 %) than those with less invasive tumors (1 %) (Ersahin et al. 1996; Doxey et al. 1999; Turgut 2008).

Recovery from complete mutism begins with profoundly dysarthric and abnormal speech, usually with isolated words and phrases, progressively improving to full sentences. Most patients recover fluent speech within 4 months of surgery with an average duration of mutism lasting 6 weeks (Aguiar et al. 1995; Pollack et al. 1995; Ersahin et al. 1996). Up to 20 % of patients may have permanent dysarthria following recovery from mutism. A small case-controlled radiological review identified bilateral edema in the brachium pontis as the only factor significantly associated with mutism (Pollack et al. 1995).

14.3.2.3 Cognitive Consequences

Cerebellar lesions or injury result mainly in deficits of motor control and coordination. It is becoming clear, however, that in addition to these deficits, alterations in higher cognitive function and affect also occur (Cantelmi et al. 2008). Neuropsychological changes at 2-year follow-up in a cohort of patients having had posterior fossa surgery included visual-spatial dysfunction in 37 %, expressive language problems in 37 %, verbal memory decline in 33 %, and difficulty with affect control in 15–56 % (Levisohn et al. 2000). Irritability, impulsiveness, and disinhibition were the most common changes in affect and increased in parallel with greater involvement of the vermis. These neuropsychological consequences are often temporary, but longer-term follow-up studies indicate that neurologic and neuropsychological changes persist more frequently with injury to the dentate nuclei and inferior vermis during resection (Puget et al. 2009). School performance and IQ are also affected by cerebellar surgery, but studies are confounded by the inability to separate the emotional and psychological effects of childhood illness and stress from the surgical procedure. The majority of patients (~60 %) with benign or more indolent tumors such as cerebellar astrocytoma or histologically benign ependymoma will have normal IQ after surgery. This is in contrast to patients with medulloblastoma of whom only 10 % will have IQ >90 after treatment (Hoppe-Hirsch et al. 1995). Overall, the rate of IQ decline is determined by multiple factors such as age at time of treatment, presence or absence of hydrocephalus, use of radiotherapy, and the volume of brain that received radiation (Mulhern et al. 2004).

14.3.2.4 Hydrocephalus

Hydrocephalus is the result of a mismatch between CSF production and absorption leading to an accumulation of CSF, with characteristic symptoms and ventricular enlargement. In the setting of a posterior fossa tumor, hydrocephalus is defined as "obstructive" because the ventricular CSF pathways are blocked by a mass lesion. Children can have hydrocephalus at presentation, or it can develop acutely in the postoperative period, usually in the setting of cerebellar swelling or a hematoma accumulating in the resection cavity. Acute symptomatic hydrocephalus, either pre- or postoperative, should be treated by immediate placement of an external ventricular drain (EVD). In most patients, complete removal of the mass lesion results in resolution of the hydrocephalus. Most surgeons attempt to "wean" a patient from the EVD drain following tumor resection. Following GTR, this is usually successful, although the need for placement of a permanent CSF shunt is increased in younger children (<3 years of age) (Kumar et al. 1996).

Hydrocephalus can occur in a subacute manner following tumor resection even when GTR is achieved. These patients will usually have "communicating" hydrocephalus, as demonstrated by enlargement of the entire ventricular system. This term is probably a misnomer since the presumed site of obstruction is the arachnoid villi,

where CSF is normally absorbed back into the venous system. The presumed etiology of this type of hydrocephalus is from localized inflammation secondary to subarachnoid blood or high CSF protein leading to loss of function of the arachnoid villi. Children should be observed carefully in the first few weeks following tumor resection for symptoms suggestive of hydrocephalus.

Asymptomatic ventricular enlargement resulting from a temporary alteration of CSF dynamics requires no immediate intervention, and the patient can be followed by clinical examination and serial CT scans. Placement of a shunt is indicated if symptoms develop, a persistent pseudomeningocele is present, and/or CSF leak occurs from the wound. The rate of CSF shunting following posterior fossa surgery ranges from 10 % to 26 % of patients (Imielinski et al. 1998; Steinbok and Mutat 1999) to as high as 42 % (Gjerris et al. 1998). In the latter study of 497 patients with a posterior fossa tumor, 68 (14 %) were shunted prior to tumor resection, 94 (19 %) after tumor resection, and 43 (9 %) were treated by placement of shunt alone.

Endoscopic third ventriculostomy (ETV), or fenestration of the floor of the third ventricle to bypass the posterior fossa obstruction, is another alternative to placement of a permanent shunt. There is some evidence that ETV is successful in avoiding the placement of a permanent ventriculoperitoneal shunt in the majority of patients (Tamburrini et al. 2008). The risk of extra-neural metastasis from shunting in children with cerebellar astrocytomas is very small (Berger et al. 1991).

14.3.2.5 Pseudomeningocele

Pseudomeningocele, the formation of a CSF collection outside the confines of the subarachnoid space, has been reported in 12–24 % of patients after surgery (Abdollahzadeh et al. 1994). It occurs 1–2 weeks after the initial procedure and presents as fluctuant, occasionally tense mass under the incision. A pseudomeningocele predisposes surgical incisions to infection and dehiscence, which can then lead to more serious complications, including meningitis. The formation of a pseudomeningocele may indicate the presence of untreated hydrocephalus, a CSF fistula, or a wound infection. Most pseudomeningoceles resolve within days to weeks without intervention. Wound breakdown and hydrocephalus are indications for CSF diversion/shunting and antibiotic treatment if meningitis or other infection is suspected. Percutaneous aspiration for cell count and culture is usually not recommended as risk of infection rises with skin puncture, although it may provide temporary relief of pain from skin tension, or prevent wound dehiscence.

14.3.2.6 Other

Wound infection and breakdown are rare (2–5 %). Risk factors include poor nutritional state, formation of a CSF pseudomeningocele, poor surgical closure, wound hematoma, and premature removal of sutures. Meningitis occurs in 3–8 % of patients (Abdollahzadeh et al. 1994). Aseptic meningitis is a well-described postoperative finding after posterior fossa surgery in children. Patients complain of increasing headache 4–7 days following surgery, accompanied by fever, nuchal rigidity, and CSF pleocytosis (Rosenfeld 2000a). Organisms are not isolated and symptoms seem to correspond with steroid taper. No treatment is necessary, though bacterial meningitis must be excluded. The risk of bacterial meningitis is higher in patients with pseudomeningocele and shunts. Cervical spine instability requiring structural support is exceedingly rare, but can occur when a laminectomy extends below C1.

14.4 The Role of Second-Look Surgery

"Second-look" surgery refers to a planned second procedure to resect residual tumor prior to observation of radiographic progression. It may also be applied to situations where tissue is obtained for pathologic diagnosis in patients previously treated by adjuvant therapy. The primary procedure may have been either a biopsy or an attempt at debulking. The general utility of performing second procedures remains unclear, and few reports directly refer to its use for brain tumors. It may lead to improved rates of GTR for

a subset of patients (Khan et al. 2001), but it has not been formally examined in a randomized clinical trial. Second-look surgery must be distinguished from procedures to remove "residual" disease, which can be defined as macroscopically visible tumor remaining after what was believed to be a GTR. In clear instances of residual disease remaining after the primary resection, the patient should be returned to the operating room for removal of the residual tumor.

Residual disease may be expected, if GTR would lead to unacceptable morbidity. This is usually in the context of infiltration of eloquent areas and unresectable tissues (brainstem, cranial nerves, and vascular invasion). Interval adjuvant therapy may reduce the size of the tumor, vascularity, or may define the tumor/brain interface, ultimately facilitating the second surgical procedure (Foreman et al. 1997). A second procedure following chemotherapy has been advocated most forcefully in the treatment of intracranial germ cell tumors. Most of these tumors arise in the pineal region closely approximated to the deep cerebral veins and the brainstem. Subtotal resection is common, and adjunctive therapy is frequently used. Excluding pure germinomas, which are sensitive to either radiation or chemotherapy, malignant nongerminomatous germ cell tumors (NGGCT) pose particularly difficult management problems. Most authors recommend tissue biopsy for marker-negative tumors with pathologic diagnosis guiding further treatment. Based upon favorable responses to chemotherapy, Weiner and Finlay advocate a second-look surgery for any residual mass remaining after aggressive chemotherapy treatment (Weiner and Finlay 1999). In another analysis of malignant germ cell tumors, neoadjuvant therapy followed by surgical resection for residual disease revealed that the majority had mature teratomas (Friedman et al. 2001). Outcomes following surgery were good in five of the six patients operated on.

Conclusions

For most supra- and infratentorial brain tumors, GTR is associated with improved outcome. Cortical mapping, neuronavigation, and functional imaging can and should be utilized in children to increase the chances of a complete resection. Staged and second-look surgery may also facilitate the resection of tumors located in eloquent cortex or difficult-to-reach sites.

References

Abdollahzadeh M, Hoffman HJ, Blazer SI, Becker LE, Humphreys RP, Drake JM, Rutka JT (1994) Benign cerebellar astrocytoma in childhood: experience at the Hospital for Sick Children 1980–1992. Childs Nerv Syst 10:380–383

Aguiar PH, Plese JP, Ciquini O, Marino R (1995) Transient mutism following a posterior fossa approach to cerebellar tumors in children: a critical review of the literature. Childs Nerv Syst 11:306–310

Avula S, Pettorini B, Abernethy L, Pizer B, Williams D, Mallucci C (2013) High field strength magnetic resonance imaging in paediatric brain tumour surgery – its role in prevention of early repeat resections. Childs Nerv Syst 29:1843–1850

Berger MS, Ojemann GA (1992) Intraoperative brain mapping techniques in neuro-oncology. Stereotact Funct Neurosurg 58:153–161

Berger MS, Baumeister B, Geyer JR, Milstein J, Kanev PM, LeRoux PD (1991) The risks of metastases from shunting in children with primary central nervous system tumors. J Neurosurg 74:872–877

Cantelmi D, Schweizer TA, Cusimano MD (2008) Role of the cerebellum in the neurocognitive sequelae of treatment of tumours of the posterior fossa: an update. Lancet Oncol 9:569–576

Carpentier A, Chauvet D, Reina V, Beccaria K, Leclerq D, McNichols RJ, Gowda A, Cornu P, Delattre JY (2012) MR-guided laser-induced thermal therapy (LITT) for recurrent glioblastomas. Lasers Surg Med 44:361–368

Catsman-Berrevoets CE, Van Dongen HR, Mulder PG, Paz y Geuze D, Paquier PF, Lequin MH (1999) Tumour type and size are high risk factors for the syndrome of "cerebellar" mutism and subsequent dysarthria. J Neurol Neurosurg Psychiatry 67:755–757

Chen X, Weigel D, Ganslandt O, Fahlbusch R, Buchfelder M, Nimsky C (2007) Diffusion tensor-based fiber tracking and intraoperative neuronavigation for the resection of a brainstem cavernous angioma. Surg Neurol 68:285–291; discussion 291

Chitoku S, Otsubo H, Harada Y, Jay V, Rutka JT, Weiss SK, Abdoll M, Snead OC 3rd (2001) Extraoperative cortical stimulation of motor function in children. Pediatr Neurol 24:344–350

Chuang SH, Otsubo H, Hwang P, Orrison WW Jr, Lewine JD (1995) Pediatric magnetic source imaging. Neuroimaging Clin N Am 5:289–303

Cochrane DD, Gustavsson B, Poskitt KP, Steinbok P, Kestle JR (1994) The surgical and natural morbidity of aggressive resection for posterior fossa tumors in childhood. Pediatr Neurosurg 20:19–29

Doxey D, Bruce D, Sklar F, Swift D, Shapiro K (1999) Posterior fossa syndrome: identifiable risk factors and irreversible complications. Pediatr Neurosurg 31:131–136

Ersahin Y (1998) Transient cerebellar mutism. Childs Nerv Syst 14:687

Ersahin Y, Mutluer S, Cagli S, Duman Y (1996) Cerebellar mutism: report of seven cases and review of the literature. Neurosurgery 38:60–65; discussion 66

Fahlbusch R, Ganslandt O, Nimsky C (2000) Intraoperative imaging with open magnetic resonance imaging and neuronavigation. Childs Nerv Syst 16:829–831

Foreman NK, Love S, Gill SS, Coakham HB (1997) Secondlook surgery for incompletely resected fourth ventricle ependymomas: technical case report. Neurosurgery 40:856–860; discussion 860

Friedman JA, Lynch JJ, Buckner JC, Scheithauer BW, Raffel C (2001) Management of malignant pineal germ cell tumors with residual mature teratoma. Neurosurgery 48:518–522; discussion 522–523

Gjerris F, Agerlin N, Borgesen SE, Buhl L, Haase J, Klinken L, Mortensen AC, Olsen JH, Ovesen N, Reske-Nielsen E, Schmidt K (1998) Epidemiology and prognosis in children treated for intracranial tumours in Denmark 1960–1984. Childs Nerv Syst 14:302–311

Gleason PL, Kikinis R, Altobelli D, Wells W, Alexander E 3rd, Black PM, Jolesz F (1994) Video registration virtual reality for nonlinkage stereotactic surgery. Stereotact Funct Neurosurg 63:139–143

Gnanalingham KK, Lafuente J, Thompson D, Harkness W, Hayward R (2002) Surgical procedures for posterior fossa tumors in children: does craniotomy lead to fewer complications than craniectomy? J Neurosurg 97:821–826

Gooding GA, Edwards MS, Rabkin AE, Powers SK (1983) Intraoperative real-time ultrasound in the localization of intracranial neoplasms. Radiology 146:459–462

Grabb PA, Albright AL, Sclabassi RJ, Pollack IF (1997) Continuous intraoperative electromyographic monitoring of cranial nerves during resection of fourth ventricular tumors in children. J Neurosurg 86:1–4

Gulati S, Berntsen EM, Solheim O, Kvistad KA, Haberg A, Selbekk T, Torp SH, Unsgaard G (2009) Surgical resection of high-grade gliomas in eloquent regions guided by blood oxygenation level dependent functional magnetic resonance imaging, diffusion tensor tractography, and intraoperative 3D ultrasound. Minim Invasive Neurosurg 52:17–24

Haglund MM, Berger MS, Shamseldin M, Lettich E, Ojemann GA (1994) Cortical localization of temporal lobe language sites in patients with gliomas. Neurosurgery 34:567–576; discussion 576

Hawasli A, Begade S, Shimony JS, Miller-Thomas M, Leuthardt EC (2013) Magnetic resonance imaging-guided focused laser interstitial thermal therapy for intracranial lesions: single-institution series. Neurosurgery 73(6):1007–1017

Hennessy MJ, Elwes RD, Honavar M, Rabe-Hesketh S, Binnie CD, Polkey CE (2001) Predictors of outcome and pathological considerations in the surgical treatment of intractable epilepsy associated with temporal lobe lesions. J Neurol Neurosurg Psychiatry 70:450–458

Hoppe-Hirsch E, Brunet L, Laroussinie F, Cinalli G, Pierre-Kahn A, Renier D, Sainte-Rose C, Hirsch JF (1995) Intellectual outcome in children with malignant tumors of the posterior fossa: influence of the field of irradiation and quality of surgery. Childs Nerv Syst 11:340–345

Imielinski BL, Kloc W, Wasilewski W, Liczbik W, Puzyrewski R, Karwacki Z (1998) Posterior fossa tumors in children – indications for ventricular drainage and for V-P shunting. Childs Nerv Syst 14:227–229

Kaplan AM, Bandy DJ, Manwaring KH, Chen K, Lawson MA, Moss SD, Duncan JD, Wodrich DL, Schnur JA, Reiman EM (1999) Functional brain mapping using positron emission tomography scanning in preoperative neurosurgical planning for pediatric brain tumors. J Neurosurg 91:797–803

Keles GE, Lamborn KR, Berger MS (2001) Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. J Neurosurg 95:735–745

Khan RB, Sanford RA, Kun LE, Thompson SJ (2001) Morbidity of second-look surgery in pediatric central nervous system tumors. Pediatr Neurosurg 35:225–229

Kumar V, Phipps K, Harkness W, Hayward RD (1996) Ventriculo-peritoneal shunt requirement in children with posterior fossa tumours: an 11-year audit. Br J Neurosurg 10:467–470

Lam CH, Hall WA, Truwit CL, Liu H (2001) Intraoperative MRI-guided approaches to the pediatric posterior fossa tumors. Pediatr Neurosurg 34:295–300

Leblanc R, Meyer E (1990) Functional PET scanning in the assessment of cerebral arteriovenous malformations. Case report. J Neurosurg 73:615–619

Leblanc R, Meyer E, Bub D, Zatorre RJ, Evans AC (1992) Language localization with activation positron emission tomography scanning. Neurosurgery 31:369–373

Levisohn L, Cronin-Golomb A, Schmahmann JD (2000) Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain 123(Pt 5):1041–1050

Mosewich RK, So EL, O'Brien TJ, Cascino GD, Sharbrough FW, Marsh WR, Meyer FB, Jack CR, O'Brien PC (2000) Factors predictive of the outcome of frontal lobe epilepsy surgery. Epilepsia 41:843–849

Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE (2004) Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol 5:399–408

Nimsky C, Ganslandt O, von Keller B, Fahlbusch R (2006) Intraoperative high-field MRI: anatomical and functional imaging. Acta Neurochir Suppl 98:87–95

Ojemann SG, Berger MS, Lettich E, Ojemann GA (2003) Localization of language function in children: results of electrical stimulation mapping. J Neurosurg 98:465–470

Otsubo H, Ochi A, Elliott I, Chuang SH, Rutka JT, Jay V, Aung M, Sobel DF, Snead OC (2001) MEG predicts epileptic zone in lesional extrahippocampal epilepsy: 12 pediatric surgery cases. Epilepsia 42:1523–1530

Penfield W, Boldrey E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60:389–443

Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996) Diffusion tensor MR imaging of the human brain. Radiology 201:637–648

Pirotte BJ, Lubansu A, Massager N, Wikler D, Goldman S, Levivier M (2007) Results of positron emission tomography guidance and reassessment of the utility of and indications for stereotactic biopsy in children with infiltrative brainstem tumors. J Neurosurg 107:392–399

Pollack IF (1994) Brain tumors in children. N Engl J Med 331:1500–1507

Pollack IF (1999) The role of surgery in pediatric gliomas. J Neurooncol 42:271–288

Pollack IF, Polinko P, Albright AL, Towbin R, Fitz C (1995) Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. Neurosurgery 37:885–893

Puget S, Boddaert N, Viguier D, Kieffer V, Bulteau C, Garnett M, Callu D, Sainte-Rose C, Kalifa C, Dellatolas G, Grill J (2009) Injuries to inferior vermis and dentate nuclei predict poor neurological and neuropsychological outcome in children with malignant posterior fossa tumors. Cancer 115:1338–1347

Regelsberger J, Lohmann F, Helmke K, Westphal M (2000) Ultrasound-guided surgery of deep seated brain lesions. Eur J Ultrasound 12:115–121

Rosenfeld J (2000a) Cerebellar astrocytoma in children. In: Kaye AH, Black PM (eds) Operative neurosurgery. Churchill Livingston, New York, pp 447–463

Rosenfeld JV (2000b) Chapter 37: cerebellar astrocytoma in children. In: Kaye AH, Black PM (eds) Operative neurosurgery, vol 2. Churchill Livingstone, New York, pp 447–463

Sanai N, Mirzadeh Z, Berger MS (2008) Functional outcome after language mapping for glioma resection. N Engl J Med 358:18–27

Schiffbauer H, Ferrari P, Rowley HA, Berger MS, Roberts TP (2001) Functional activity within brain tumors: a magnetic source imaging study. Neurosurgery 49:1313–1320; discussion 1320–1321

Schneider JP, Schulz T, Schmidt F, Dietrich J, Lieberenz S, Trantakis C, Seifert V, Kellermann S, Schober R, Schaffranietz L, Laufer M, Kahn T (2001) Gross-total surgery of supratentorial low-grade gliomas under intraoperative MR guidance. AJNR Am J Neuroradiol 22:89–98

Sekiya T, Hatayama T, Shimamura N, Suzuki S (2000) Intraoperative electrophysiological monitoring of oculomotor nuclei and their intramedullary tracts during midbrain tumor surgery. Neurosurgery 47:1170–1176; discussion 1176–1177

Steinbok P, Mutat A (1999) Cerebellar astrocytoma. In: Albright AL, Pollack IF, Adelson PD (eds) Principles and practice of pediatric neurosurgery. Thieme, New York, p 1300

Tamburrini G, Pettorini BL, Massimi L, Caldarelli M, Di Rocco C (2008) Endoscopic third ventriculostomy: the best option in the treatment of persistent hydrocephalus after posterior cranial fossa tumour removal? Childs Nerv Syst 24:1405–1412

Turgut M (2008) Cerebellar mutism. J Neurosurg Pediatr 1:262

Weiner HL, Finlay JL (1999) Surgery in the management of primary intracranial germ cell tumors. Childs Nerv Syst 15:770–773

Chemotherapy

15

Theodore Nicolaides, Biljana Horn,
and Anuradha Banerjee

Contents

T. Nicolaides, MD (✉)
Division of Hematology/Oncology, Departments of Pediatrics and Neurological Surgery, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th St, 4th Floor, Box 0434, San Francisco, CA 94143, USA
e-mail: theodore.nicolaides@ucsf.edu

B. Horn, MD
Blood and Marrow Transplant Program, Department of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th Street, 4th Floor, Box 0434, San Francisco, CA 94143-0434, USA
e-mail: biljana.horn@ucsf.edu

A. Banerjee, MD
Division of Hematology/Oncology, Departments of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital, 550 16th St, 4th Floor, Box 0434, San Francisco, CA 94143, USA
e-mail: anu.banerjee@ucsf.edu

15.1 Introduction

Chemotherapy is increasingly used in the multimodal management of childhood brain tumors, with the therapeutic goals of optimizing survival and reducing radiation-related morbidity. The numerous chemotherapy treatment protocols for pediatric brain tumors reflect the extreme heterogeneity of these neoplasms. For example, in the setting of average-risk medulloblastoma

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_15

and germinoma, which have high cure rates with radiation treatment alone, chemotherapy is used to reduce radiation doses, yet maintain high cure rates. For infants with malignant brain tumors, who are particularly vulnerable to radiation-related morbidity, chemotherapy has been used to delay radiation treatment. Similarly, in the setting of unresectable, low-grade astrocytoma, chemotherapy can provide prolonged disease stabilization, perhaps allowing for delay or deferral of radiation.

While many clinical trials evaluating chemotherapy for the treatment of central nervous system (CNS) tumors are exploratory, two randomized controlled trials have shown a survival benefit from the addition of chemotherapy to radiation therapy in comparison to radiation therapy alone in children with brain tumors. Sposto et al., reporting for the Children's Cancer Group, described a randomization of patients with newly diagnosed high-grade glioma between two treatment arms: postoperative radiation treatment alone versus treatment with postoperative radiation followed by chemotherapy (Sposto et al. 1989). The chemotherapy group had 46 % 5-year event-free survival (EFS), while the radiation-only group had 18 % 5-year EFS. A large-scale, multi-institutional European trial reported improved 5-year EFS with the addition of chemotherapy to radiation therapy for average-risk medulloblastoma (74 % for radiation with chemotherapy vs. 59 % for radiation alone) (Taylor et al. 2003). Subsequent studies have demonstrated good survival when adjuvant chemotherapy is used with reduced doses of craniospinal radiation for average-risk medulloblastoma (Packer et al. 2006). In the setting of pediatric germ cell tumors, tumor response to chemotherapy may predict prognosis and may allow for reduced doses and fields of radiation as well (Khatua et al. 2010).

While most chemotherapeutic agents are initially tested in single-agent clinical trials to determine the effectiveness against a particular tumor type, combination chemotherapy regimens are in widespread use. The goal of combination therapy is to maximize therapeutic effectiveness by overcoming drug resistance, which exists in a high proportion of tumors. An optimally designed combination regimen combines agents with high response rates in single-agent trials, noncross-resistant mechanisms of action in tumor cell subpopulations, and non-overlapping toxicity profiles.

This chapter reviews important conventional chemotherapeutic agents in brain tumor management, the use of combination chemotherapy for infants with brain tumors, high-dose myeloablative chemotherapy, and new classes of therapeutic agents. Disease-specific chemotherapy regimens are discussed separately in earlier chapters.

15.2 General Principles of Chemotherapy

For most solid tumors such as CNS neoplasms, chemotherapy is considered most effective when used as an adjuvant to local control measures, specifically surgery and radiation. With the exception of CNS germ cell tumors, chemotherapy is most likely to contribute to long-term disease control when residual disease is minimal; this has been demonstrated in both medulloblastoma and high-grade glioma, where improved prognosis is clearly associated with gross-total or near-total resection followed by radiation (Sposto et al. 1989; Packer et al. 1994). Some CNS germ cell tumors are very chemotherapy responsive, and robust chemotherapy responses in bulky disease have been observed. These chemotherapy responses allow for reduced doses of radiation and allow for delayed or deferred surgical intervention (Khatua et al. 2010). While adjuvant chemotherapy is important for preventing distant metastases in extracranial solid tumors (Ortega et al. 1975; Link et al. 1986; Eilber et al. 1987), the role of chemotherapy in preventing CNS dissemination or extraneural metastasis is unclear. Neoadjuvant chemotherapy can also be used for a patient who may have unresectable or difficult-to- resect disease at diagnosis, with the hope of eliciting a tumor response that would allow improved, posttreatment resection (Rosen 1986; Trimble

et al. 1993). While this strategy is used in the management of extracranial pediatric solid tumors, its utility in CNS tumors is uncertain. Clinical trials piloting the use of focal radiotherapy with chemotherapy in infant embryonal tumors demonstrate that while relapse with dissemination still occurs, overall outcomes are improved compared to historical cohorts who were more commonly treated with radiation alone (Blaney et al. 2012; Ashley et al. 2012).

The blood–brain barrier (BBB) is an anatomic feature of the CNS consisting of specialized capillary endothelial cells that lack fenestrations and pinocytic vesicles and express specialized transport proteins. The ability of a compound to cross the BBB is restricted by molecular weight, as well as lipid solubility and pH. Small, lipid-soluble molecules at physiologic pH readily cross the BBB (Rall and Zubrod 1962), although the properties of most chemotherapeutic compounds prevent movement across the BBB. Despite this fact, the objective response of some CNS tumors to chemotherapy alone suggests that systemically administered agents are still able to reach brain tumor cells. This observation, as well as the ability of CNS tumors to enhance with gadolinium on MRI (requiring the gadolinium to cross the BBB), suggests that the BBB is physiologically disrupted in the tumor environment and that concentrations of systemically administered drugs are likely to be higher in tumors than in normal brain (Stewart 1994). Nevertheless, concerns about the role of the BBB in contributing to chemotherapy resistance have resulted in the development of various treatment strategies to overcome it, which are summarized later in this chapter.

15.3 Specific Chemotherapeutic Agents

15.3.1 Platinums

Cisplatin and carboplatin are non-cell-cycle-specific alkylating agents. The cytotoxic (free or unbound) fraction of drug acts to form a platinum–DNA adduct that produces inter- and intrastrand cross-links by alkylating the N7 position of guanine (Zwelling and Kohn 1979). When used as a single agent, cisplatin has been shown to produce disease responses in medulloblastoma, germinoma, ependymoma, and astrocytoma (Sexauer et al. 1985; Walker and Allen 1988; Bertolone et al. 1989). Used adjuvantly with CCNU and vincristine, cisplatin has been shown to improve disease-free survival in medulloblastoma (Packer et al. 1991, 1994, 2006). The toxic side effects of cisplatin are substantial, including hearing loss, nephrotoxicity, myelosuppression, nausea and vomiting, and peripheral neuropathy (Hartmann and Lipp 2003). Ototoxicity may be modestly abrogated with the cytoprotective agent amifostine in patients with average-risk medulloblastoma, but is of less benefit in patients with high-risk disease (Gurney et al. 2014).

Carboplatin, an analog of cisplatin, has similar efficacy but a different toxicity profile. While less ototoxic and nephrotoxic than cisplatin, carboplatin is more myelosuppressive. Carboplatin also has less associated peripheral neuropathy and is less emetogenic than cisplatin (Duffull and Robinson 1997). Significantly, a considerable number of patients (estimated as high as 30–40 %) develop a hypersensitivity reaction to carboplatin in some treatment regimens using weekly dosing. This is characterized mostly by skin rash and urticaria, but occasionally can be life-threatening (Lafay-Cousin et al. 2008). Single-agent treatment results in moderate tumor responses in recurrent childhood brain tumors (Walker and Allen 1988; Gaynon et al. 1990). In combination with vincristine, carboplatin has been shown to be an active agent against pediatric low-grade astrocytoma (Packer et al. 1997; Mahoney et al. 2000) and plays a role in the combination chemotherapy of infant brain tumors as well. A strategy using carboplatin in conjunction with a BBB-disrupting agent is discussed later in this chapter.

Oxaliplatin, a newer-generation platinum, is less myelosuppressive than carboplatin and appears to cause little ototoxicity or nephrotoxicity in adult clinical trials. A single-agent phase II clinical trial by the Pediatric Brain Tumor

Consortium showed that oxaliplatin was well tolerated but that it had little activity in children with recurrent medulloblastoma, primitive neuroectodermal tumor (PNET), and atypical teratoid rhabdoid tumor (AT/RT) (Fouladi et al. 2006).

15.3.2 Nitrosoureas

CCNU (lomustine) and BCNU (carmustine), the most commonly used nitrosoureas, are non-cell-cycle-specific alkylators. Both are prodrugs that spontaneously decompose into two active metabolites: an isocyanate group and a chloroethyldiazohydroxide; the chloroethyldiazohydroxide alkylates DNA, resulting in cross-linking followed by cellular instability. Nitrosoureas are small, lipophilic molecules that penetrate the BBB easily and are among the few systemically administered agents found in moderate to high concentrations in the brain (reviewed in Middleton and Margison 2003). Nitrosourea-based combination therapy resulted in a modest impact on survival in pediatric patients with high-grade astrocytoma in some trials (Sposto et al. 1989; Finlay et al. 1995; Levin et al. 2000). A retrospective analysis suggests that MGMT overexpression predicts poor outcome for patients treated with alkylator-based therapy (Pollack et al. 2006). A single-agent phase II trial of high-dose BCNU for pediatric high-grade glioma showed only modest tumor response with substantial toxicity (Bouffet et al. 1997). CCNU, in combination with vincristine, is clearly beneficial in the adjuvant, postradiation treatment of medulloblastoma and, in one study, was the rationale for reducing the neuroaxis radiation dose from 36 to 23.4 Gy, resulting in good disease-free survival in average-risk medulloblastoma patients (Packer et al. 1994). A randomized study of a nitrosourea-based adjuvant chemotherapy regimen compared to a cyclophosphamide-based regimen demonstrated equivalent efficacy, but increased toxicity in the nitrosourea-based arm (Packer et al. 2006). Nitrosourea-based therapy has also been shown to produce disease responses and prolonged stable disease in pediatric low-grade astrocytoma, when used in combination with procarbazine, 6-thioguanine, and vincristine (Prados et al. 1997). The major toxicities of nitrosoureas include nausea, myelosuppression, and, less commonly, pulmonary fibrosis and nephrotoxicity. The myelosuppression is typically delayed, seen approximately 3–5 weeks following administration of the dose, and is frequently cumulative (Balis et al. 2002). Nitrosourea use is also associated with an increased risk of secondary acute myeloid leukemia (Perry et al. 1998).

15.3.3 Cyclophosphamide and Ifosfamide

These parenterally administered prodrug members of the nitrogen mustard family of drugs are thought to have the same mechanism of activity as most classic alkylators: by forming covalent bonds with nucleophilic groups, resulting in cross-linking between DNA strands or intrastrand linking, thus impairing DNA replication (Pratt et al. 1994). These agents have produced responses and stable disease in both primary and recurrent pediatric brain tumors, including medulloblastoma, PNET, high-grade astrocytoma, and germ cell tumors. These agents are also an important part of combination chemotherapy for infants with malignant brain tumors (Friedman et al. 1986; Longee et al. 1990; Packer et al. 1999, 2006; Zeltzer et al. 1999). Toxicities are substantial, including nausea, myelosuppression, hemorrhagic cystitis, and, in the case of ifosfamide, nephrotoxicity (Balis et al. 2002) and encephalopathy (Nicolao and Giometto 2003). Impaired fertility has been reported in patients treated with these agents (Byrne et al. 1987). Secondary leukemia has recently been described in a cohort of infants with malignant brain tumors treated with high cumulative doses of cyclophosphamide and etoposide (Duffner et al. 1998; Smith et al. 1999).

15.3.4 Temozolomide

Temozolomide is a rapidly absorbed, oral prodrug that undergoes spontaneous hydrolysis to form its active metabolite, 3-methyl-(triazen-1-yl)-

imidazole-4-carboxamide (MTIC). Its mechanism of action is via the methylation of DNA, largely at the O^6 position of guanine (Newlands et al. 1997). While adult patients with glioblastoma multiforme have been shown to have some survival advantage when treated at diagnosis with radiation and temozolomide (Stupp et al. 2002; Cohen et al. 2011), the role of this agent in pediatric brain tumors has not yet been established. Responses to temozolomide have been reported in pediatric patients with recurrent high-grade astrocytoma and small series of patients with ependymoma, PNET, and germ cell tumor (Pollack et al. 1999). A large phase II study of temozolomide combination with radiation in children with diffuse pontine glioma and high-grade glioma did not demonstrate marked benefit in comparison to historical controls. Temozolomide is also active in patients with low-grade glioma treated with temozolomide as a first-line agent (Kuo et al. 2003) or as salvage therapy (Khaw et al. 2007). Combination regimens incorporating temozolomide have been piloted, and it has been shown to be tolerated in children in combination with carboplatin, CCNU, bevacizumab, and EGFR inhibitors. Temozolomide-associated toxicities include nausea, constipation, and myelosuppression (Nicholson et al. 1998; Friedman et al. 2000).

15.3.5 Etoposide

Etoposide is a semisynthetic derivative of a plant extract, podophyllotoxin. Etoposide interacts with DNA topoisomerase II, causing single- and double-stranded breaks and a cell-cycle arrest in G_2 and mitosis (Hande 1998). Despite its highly lipophilic properties, it does not cross the BBB easily due to its large size (Newton et al. 1999). Etoposide can be administered orally or parenterally. It is active against many pediatric brain tumors, including medulloblastoma, PNET, ependymoma, and germ cell tumor (Allen et al. 1985; Bouffet and Foreman 1999; Kobrinsky et al. 1999; Chamberlain 2001). It has been used in combination with cisplatin, carboplatin, ifosfamide, and cyclophosphamide with acceptable toxicity in the treatment of childhood brain tumors (Busca et al. 1997; White et al. 1998; Duffner et al. 1999; Kortmann et al. 2000). Daily oral etoposide has produced modest responses and prolonged stable disease in patients with recurrent PNET and high-grade astrocytoma (Ashley et al. 1996; Fulton et al. 1996; Chamberlain and Kormanik 1997; Needle et al. 1997).

Toxicities of etoposide include nausea and myelosuppression, as well as diarrhea and mucositis, when administered in high doses (Mathew et al. 1994; Taylor et al. 2003). High cumulative doses have been associated with an increased risk of secondary leukemia in infants with malignant brain tumors, as well as other childhood cancers (Duffner et al. 1998; Smith et al. 1999). Low-dose, orally administered etoposide, either single agent or in combination, has been reported to be tolerable and is thought to have antiangiogenic effects (Robison et al. 2014).

15.3.6 Vincristine and Vinblastine

Vincristine and vinblastine are *Vinca* plant alkaloids that bind tubulin and induce metaphase arrest in a cell cycle-specific fashion (Jordan 2002). It has limited CNS penetration and has not been rigorously evaluated as a single agent in pediatric brain tumors (Kellie et al. 2002). Nevertheless, it has shown activity in multiagent regimens and is widely used in combination treatment regimens for medulloblastoma, PNET, low-grade astrocytoma, and infant brain tumors (Packer et al. 1994, 1997; Duffner et al. 1999). Its toxicities include constipation, peripheral neuropathy, and syndrome of inappropriate diuretic hormone (SIADH) (Balis et al. 2002).

Vinblastine has a similar mechanism of action to vincristine and is effective against a variety of childhood tumors including non-Hodgkins lymphoma and histiocytosis. Vinblastine is well tolerated, and myelosuppression is the main toxicity (Balis et al. 2002). Single-agent, weekly vinblastine has efficacy in children with recurrent or refractory low-grade glioma (Bouffet et al. 2002, 2012; Lafay-Cousin et al. 2005).

15.3.7 Methotrexate

Methotrexate is an antimetabolite that exerts its antitumor activity by binding and inhibiting dihydrofolate reductase (DHFR), a key enzyme in intracellular folate homeostasis. This depletion of folate results in impaired purine and thymidylate biosynthesis and resultant cytotoxicity during the S-phase of the cell cycle (Balis et al. 2002). Methotrexate was one of the first antineoplastic agents developed and is an important part of combination chemotherapy regimens for osteosarcoma and acute lymphocytic leukemia. At high doses (>1 g/m^2), systemic methotrexate can penetrate the CNS and has shown efficacy as part of combination chemotherapy protocols for embryonal tumors (Chi et al. 2004). Methotrexate can also be given intrathecally.

High-dose methotrexate therapy is administered via a prolonged infusion and can have significant toxicity including mucositis, myelosuppression, and renal failure. Leucovorin, a folate analog, is given to patients following methotrexate infusion and preferentially rescues normal cells, thus minimizing side effects. Methotrexate therapy has been associated with leukoencephalopathy, particularly in combination with radiation therapy, and when given intrathecally (Vezmar et al. 2003). The risk of methotrexate-associated leukoencephalopathy may be reduced if it is administered prior to radiation, but not after (Kellie et al. 2005).

15.4 Combination Chemotherapy for Infant Brain Tumors

Combination chemotherapy is in widespread use for almost all types of childhood CNS tumors. Specific regimens targeted at individual tumor types are discussed in the earlier disease-specific chapters (Chaps. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12). Infants and very young children, however, are especially susceptible to complications of CNS irradiation, including neurocognitive decline, neuroendocrine deficits, and hearing loss (Miettinen et al. 1997; Siffert and Allen 2000; Mulhern et al. 2001; Packer 2002; Spoudeas et al. 2003). In order to delay or defer radiation treatment, chemotherapy has been investigated for infants and for very young patients with primary malignant brain tumors as the primary adjuvant therapy following surgery. Because malignant brain tumors in infants are rare, most infant studies include a broad range of diagnoses, often including both embryonal (e.g., medulloblastoma, PNET) and astrocytic tumors, as well as ependymoma. The largest clinical trial for infants, "Baby POG 1," conducted by the Pediatric Oncology Group (POG 8633) reported on 198 patients less than 36 months of age. The patients in this study were treated with 1 (patients 25–36 months of age) or 2 (patients 0–24 months of age) years of preradiation chemotherapy, followed by radiation therapy. Chemotherapy consisted of multiple cycles of a four-drug (cisplatin, etoposide, vincristine, and cyclophosphamide) regimen prior to radiation (Duffner et al. 1993, 1999). The overall 5-year survival for all patients was 32 %; survival for those who had gross-total resection (GTR) was 62 % compared with 31 % for patients with subtotal resection. Most of the treatment failures occurred in the first 6 months of therapy. These figures were similar when patients with medulloblastoma and ependymoma were examined independently. Significantly, the cumulative incidence of second malignancies in this cohort was 11.3 % (Duffner et al. 1993, 1998, 1999).

In another trial that demonstrated the feasibility of preradiation chemotherapy in infants, investigators attempted to achieve further gains by increasing the dose intensity of chemotherapy (Mason et al. 1998a). They used a truncated course of induction chemotherapy including vincristine, cyclophosphamide, etoposide, and cisplatin, followed by high-dose treatment with carboplatin, thiotepa, and etoposide with subsequent autologous stem cell rescue. Radiation therapy was reserved for patients with residual disease at the time of consolidation or for those with progressive disease. Sixty-two patients under the age of 6 were enrolled; the 3-year progression-free survival was 25 % (Mason et al. 1998b). Degree of resection was again found to be an important prognostic feature; 3-year overall survival for children with GTR was 59 %, in

comparison with 30 % for children who had only subtotal resection or biopsy. The proportion of patients undergoing GTR was similar between the two studies (34 % and 35 %, respectively). The high-dose chemotherapy-based regimen had substantial toxicity with a mortality rate of 8 % attributed to toxicity.

The Australian and New Zealand Children's Cancer Study Group reported on a chemotherapy-alone protocol for patients less than 36 months old using a combination of vincristine, etoposide, and cyclophosphamide for 64 weeks without radiation therapy. Forty patients were enrolled; progression-free survival was reported at 11 % (White et al. 1998). Geyer et al. reported on the CCG 921 experience in infants with PNET and malignant ependymoma who were enrolled in a randomized trial of two chemotherapy regimens ("eight drugs in one" vs. prednisone, vincristine, and lomustine), with radiation treatment at investigator discretion. Ninety-six patients were treated (only 13 were irradiated); after 3 years of follow-up, progression-free survival was 23 % (Geyer et al. 1994). Similar results were obtained in a large French Society of Pediatric Oncology Group Study of medulloblastoma in which children younger than 5 years of age were eligible for seven cycles of multiagent chemotherapy consisting of carboplatin, procarbazine, etoposide, cisplatin, cyclophosphamide, and vincristine. Patients with progression of disease or relapse received salvage high-dose chemotherapy followed by local or craniospinal radiotherapy. With this approach, 5-year progression-free survival was 29 %, 6 %, and 13 % for patients with R0M0 (no residual disease, no metastases), R1M0 (radiologic residual disease, no metastases), and RXM+ (metastases), respectively. A number of patients initially treated on this study were salvaged by high-dose chemotherapy and local radiation, and a 5-year overall survival was 73 %, 41 %, and 13 %, for patients with R0M0, R1M0, and RXM+, respectively (Grill et al. 2005). More recently, Rutkowski et al. reported on 43 infants with medulloblastoma who received adjuvant combination chemotherapy consisting of three cycles of intravenous chemotherapy (cyclophosphamide, vincristine, methotrexate, carboplatin, and etoposide) and intraventricular methotrexate. These patients avoided radiation therapy and had a 5-year progression-free survival of 83 % and 50 % for patients with GTR and partial resection, respectively. Although there were no toxic deaths associated with this regimen, 19 out of 23 patients for whom data was available were found to have leukoencephalopathy on T2-weighted magnetic resonance images. In addition, the mean IQ of treated patients was found to be significantly lower than healthy controls within the same age group, but higher than that of patients in a previous trial who had received radiotherapy (Rutkowski et al. 2005). While this study appears promising, validation is required, as the majority of patients treated with chemotherapy alone in larger-scale cooperative group studies thus far develop recurrent disease. Additionally, this study raises concerns regarding cognitive effects of chemotherapy. Nevertheless, this experience demonstrates that a subgroup of patients with medulloblastoma can be treated with surgery and chemotherapy alone.

While these preliminary results have shown the dose-intensive approach to be feasible, albeit with increased toxicity over the standard schedule, the survival benefit is unknown. There is no clear standard chemotherapy approach for infants with malignant brain tumors. One strategy currently under investigation includes a combination of chemoradiotherapy protocols. Incorporation of intrathecal mafosfamide (Blaney et al. 2005) and conformal radiation is currently under investigation by the Pediatric Brain Tumor Consortium. An alternative strategy under investigation is high-dose therapy with hematopoietic stem cell rescue.

15.5 High-Dose Chemotherapy with Hematopoietic Stem Cell Rescue

15.5.1 Rationale

Many CNS tumors fail to respond to standard-dose chemotherapy or fail to demonstrate a sustained response. Potential reasons for this failure include inherent or acquired drug resistance and poor CNS penetration of drug. High-dose,

myeloablative chemotherapy with autologous stem cell rescue is a strategy designed to maximize dose intensity and to achieve high systemic drug concentrations, which will improve drug penetration into the CNS. The initial transplant chemotherapy regimens were nitrosourea based; however, dose-limiting neurotoxicity prevented adequate dose escalation (Burger et al. 1981; Hochberg et al. 1981; Bashir et al. 1988). Contemporary regimens use alkylating agents such as thiotepa, carboplatin, melphalan, or busulfan, often in combinations with a topoisomerase inhibitor such as etoposide (Mahoney et al. 1996; Busca et al. 1997; Guruangan et al. 1998; Papadopoulos et al. 1998; Dunkel and Finlay 2002).

The two-patient groups targeted for high-dose therapy are those with recurrent disease following standard therapy (either chemotherapy or radiation) and infants with malignant brain tumors. High-dose therapy is of particular interest for infants as they typically have a poor prognosis and are especially susceptible to late effects of radiation. Multiple investigators have established the feasibility of this approach, and the initial results have been modestly encouraging.

15.5.2 Medulloblastoma

High-dose therapy for recurrent medulloblastoma has been used in a number of studies over the last two decades. Table 15.1 summarizes results of studies that utilized high-dose chemotherapy and autologous stem cell rescue in children or younger adults with recurrent medulloblastoma. Progression-free survival varied from 0 % to 61.5 %. Although direct comparison is not possible due to different inclusion criteria, conditioning regimens, and pre-transplant treatments, it appears that several factors may be related to improved outcomes following high-dose chemotherapy. Those factors include first-line therapy, as children who did not receive up-front craniospinal irradiation had better outcomes after transplant; localized relapse/progression and minimal residual disease at the time of high-dose chemotherapy; and additional use of radiation following transplant (Graham et al. 1997; Ridola et al. 2007; Shih et al. 2008). The conditioning regimen with busulfan and thiotepa, which showed good results in young children with localized relapse, deserves further evaluation (Ridola et al. 2007).

High-dose chemotherapy with peripheral stem cell rescue showed more promising results in young patients with newly diagnosed medulloblastoma, including metastatic disease, than in patients with recurrent disease.

Mason et al. evaluated high-dose chemotherapy with autologous stem cell rescue in 13 children less than 6 years of age with newly diagnosed medulloblastoma (Head Start I protocol). Patients received five cycles of induction chemotherapy with vincristine, etoposide, cisplatin, and cyclophosphamide, 3 weeks apart, followed by consolidation chemotherapy with a single myeloablative cycle of thiotepa, carboplatin, and etoposide. Irradiation was used only for residual tumor at consolidation or for progressive disease. Two-year overall survival was 62 % (95 % CI 35–89 %) with a 2-year progression-free survival of 38 % (95 % CI 11–65 %) (Mason et al. 1998b). In the follow-up study known as Head Start II, 21 children (<10 years of age) with newly diagnosed, high-risk disseminated medulloblastoma underwent induction with high-dose intravenous methotrexate in addition to the four drugs used in Head Start I protocol. Consolidation was the same as in the Head Start I study. The 3-year EFS of those high-risk patients was 49 % (95 % CI = 27–72 %), and overall survival was 60 % (95 % CI = 36–84 %) (Chi et al. 2004).

Strother et al. used full-dose craniospinal radiation (36 Gy) and posterior fossa boost, followed by four cycles of intensive chemotherapy with cisplatin, cyclophosphamide, and vincristine and stem cell rescue in 53 patients older than 3 years with newly diagnosed average- and high-risk medulloblastoma or supratentorial PNET. The 2-year progression-free survival rate was 93 % in the average-risk group and 74 % in the high-risk group (Strother et al. 2001). A similar approach was used by St. Jude Children's Research Hospital; however, they used risk-adapted craniospinal radiotherapy (23.4 Gy for average-risk disease and 36–39.6 Gy for high-risk disease) in children older than 3 years

Table 15.1 Studies of high-dose chemotherapy and autologous stem cell rescue in children with recurrent medulloblastoma

Study	Number of patients, age at transplant	Pre-transplant status	Conditioning	Posttransplant therapies	Outcome
Kalifa et al. (1992)	6, age 8 months to 16 years	All patients had residual disease	Busulfan, thiotepa	Local XRT in 2 patients	2/6 with EFS at 24 months
Mahoney et al. (1996)	8, age 2.5–15 years	95 % of patients had residual disease	Cyclophosphamide, melphalan	N/A	0 patients with EFS
Finlay et al. (1996)	9, median age 8 years (8 months to 36 years)	4 patients had bulky disease at transplant	Thiotepa, etoposide	N/A	0 patients with EFS
Graham et al. (1997)	19, age 12 months to 27 years	10/19 NED at transplant	Melphalan, cyclophosphamide in 16 patients	N/A	3/19 with EFS at >24 months posttransplant
Guruangan et al. (1998)	5, median age 2.9 years (0.7–5.9 years)	3 NED; 2 patients with minimal residual disease Did not receive pre-transplant XRT	Carboplatin, thiotepa, etoposide	Reduced-dose craniospinal XRT and local boost	3/5 with EFS at 10–30 months posttransplant
Fagioll et al. (2004)	8, median age 11 years	2/8 NED	Thiotepa, etoposide	No XRT posttransplant given	2/8 with EFS at 7 and 16 months posttransplant
Sung et al. (2007)	7, age 3–17 years	3/7 NED	3 single-transplant patients, 4 double-transplant patients[a]	No XRT posttransplant	3/7 with EFS at 9–52 months posttransplant
Ridola et al. (2007)	39 patients with localized relapse, median age 3 years (1–7 years)	9/39 NED	Busulfan, thiotepa	9 patients had second surgery posttransplant, all had posterior fossa XRT	5-year EFS = 61.5 %
Shih et al. (2008)	12, median age 6.7 years (1.1–18.8 years)	3/12 NED	Different conditioning regimens	5/12 patients received radiation as part of salvage therapy	3/12 EFS 20–56 months posttransplant
Dunkel et al. (2010)	25, median age 13.8 years (7.6–45 years), all received previous XRT	N/A	Carboplatin, thiotepa, etoposide	3/25 received XRT pre- or posttransplant	6/25 (24 %) EFS at 151 months posttransplant
Bode et al. (2014)	27, median age 12.6 years (0.4–28.8 years)	9 NED, 18 residual disease	Carboplatin, thiotepa, etoposide	Craniospinal XRT was a part of salvage therapy in children >4 years of age who have not received XRT previously	3-year EFS 10 %

[a]First transplant used cyclophosphamide and melphalan conditioning; second transplant used either carboplatin, thiotepa, and etoposide or busulfan and melphalan conditioning regimen and XRT or radiation therapy; NED, no evidence of disease

with newly diagnosed medulloblastoma, followed by four cycles of intensive chemotherapy with cisplatin, cyclophosphamide, and vincristine. Autologous stem cell infusion was used in order to maintain dose intensity in patients who received previous craniospinal radiation. The 5-year overall survival was 85 % (95 % CI = 75–94 %) in the average-risk group and 70 % (95 % CI = 54–84 %) in

the high-risk group. Five-year EFS was 83 % (95 % CI = 73–93 %) and 70 % (95 % CI = 55–85 %), respectively (Gajjar et al. 2006). COG 99703 study, conducted between 1998 and 2004, enrolled 92 infants <3 years of age with malignant brain tumors including medulloblastoma, glial tumors, and AT/RT tumors. This study used three rounds of intensive induction chemotherapy with cyclophosphamide, etoposide, vincristine, and cisplatin, followed by three rounds of high-dose chemotherapy with etoposide and thiotepa followed by autologous stem cell rescue after each round. Although the results of this study have not been published yet, the preliminary report indicates this approach to be superior to previously used five rounds of chemotherapy. This approach has become the backbone for future COG studies as well as a common clinical approach to treatment of young children <3 years of age with malignant brain tumors.

15.5.3 Gliomas

High-dose chemotherapy with autologous stem cell rescue has been studied in patients with recurrent as well as newly diagnosed high-grade gliomas. Two clinical trials using high-dose therapy following radiation for patients with diffuse pontine glioma showed no impact on survival, in comparison to historical controls (Bouffet et al. 2000). Heideman et al. treated 11 patients with newly diagnosed and recurrent high-grade astrocytoma with thiotepa and cyclophosphamide following surgery or biopsy. Radiation was given to patients who showed response or stable disease following high-dose chemotherapy. Although one complete response and two partial responses were observed, median progression-free survival remained disappointingly low at 9 months (Heideman et al. 1993). The Children's Cancer Group reported on 18 patients with recurrent malignant astrocytoma/glioblastoma multiforme treated with thiotepa and etoposide and autologous stem cell rescue, five of whom had progression-free survival ranging from 39 to 59 months (Finlay et al. 1996). A follow-up phase II pilot study conducted by the Children's Cancer Group added carmustine to thiotepa and etoposide, followed by radiation therapy for newly diagnosed glioblastoma multiforme. Although 2-year progression-free survival was promising at 46 %, accrual was closed early because of unacceptable pulmonary and neurologic toxicities (Grovas et al. 1999). In a subsequent study, 27 children <21 years of age with malignant astrocytomas were treated with myeloablative chemotherapy following initial tumor progression (Finlay et al. 2008). The conditioning regimens included thiotepa and etoposide, or thiotepa and etoposide, preceded by carmustine or carboplatin. Treatment-related death continued to be high in this group of patients (18.5 %); however, five patients (18 %) remained alive at a median of 11.1 years after transplant.

Papadakis et al. published a large series of children with newly diagnosed malignant gliomas, who were treated with high-dose carmustine, thiotepa, and etoposide and autologous bone marrow rescue. This treatment was given following surgery and local radiation. Out of 29 patients with gliomas, four died from toxicity, and three (10 %) were alive without evidence of disease or with stable disease at 64–86 months posttransplant (Papadakis et al. 2000). High-dose chemotherapy was used also in patients with newly diagnosed high-grade gliomas. Massimino et al. treated 21 pediatric patients with a combination of induction chemotherapy with cisplatin, etoposide, cyclophosphamide, and high-dose methotrexate, followed by high-dose thiotepa with stem cell rescue. The myeloablative cycle was given a second time if patients had residual disease after the first round. After high-dose chemotherapy, patients received radiation and 27 weeks of maintenance therapy with vincristine and lomustine. With this approach, at a median follow-up of 57 months, progression-free survival was 46 %, and overall survival was 43 % (Massimino et al. 2005).

Although high-dose chemotherapy may be promising in high-grade glial tumors, due to the inconsistency of results from studies published so far and reported high treatment-related mortality, use of high-dose chemotherapy with autologous stem cell rescue should be considered experimental for patients with glial tumors and used only in the context of clinical research.

15.5.4 Other Tumor Types

High-dose chemotherapy is not superior to standard chemotherapy in patients with recurrent or newly diagnosed ependymoma as confirmed in Children's Oncology Study and Head Start I–III studies (Mason et al. 1998b; Zacharoulis et al. 2007).

In a study of recurrent, noncerebellar PNETs, which included pineoblastoma ($n=8$), Broniscer et al. describe 17 patients (age 0.9–31.4 years) who were treated with high-dose chemotherapy of carboplatin and etoposide and autologous stem cell rescue. Eleven percent of patients died of toxicity. EFS was 29 % (surviving patients were followed for 40–123 months) (Broniscer et al. 2004). Sung et al. described seven patients with supratentorial PNET (three newly diagnosed and four with recurrent tumors) who were treated with a double-transplant approach using cyclophosphamide and melphalan for the first transplant and carboplatin, thiotepa, and etoposide for the second transplant. Two out of three patients with newly diagnosed PNET and one out of four with recurrent disease remained disease-free (14–31 months follow-up) (Sung et al. 2007). A number of smaller studies that included up to six patients with recurrent supratentorial PNET indicated salvage rates of approximately 25 % with high-dose chemotherapy. However, reported length of follow-up was frequently short (Kalifa et al. 1992; Mahoney et al. 1996; Busca et al. 1997; Graham et al. 1997; Fleischhack et al. 1998; Mikaeloff et al. 1998).

High-dose chemotherapy used in the first-line treatment of pineoblastoma showed quite promising results. Gururangan et al. reported on 12 patients with newly diagnosed pineoblastoma (age 0.3–43.7 years), who were treated with surgery, radiation (given to all but two patients), and high-dose chemotherapy with cyclophosphamide, melphalan, and busulfan. Four-year progression-free survival was 69 % (Gururangan et al. 2003).

Forty-three children with newly diagnosed supratentorial PNET were treated on the Head Start I and II studies using five rounds of induction followed by high-dose consolidation therapy with etoposide, carboplatin, and thiotepa. Five-year EFS was 39 % and overall survival was 49 %. Nonpineal supratentorial PNET (sPNET) patients fared significantly better than patients with pineal sPNETs. Twelve of 20 survivors never received radiation therapy (Fangusaro et al. 2008). Finally, children less than 3 years of age with sPNET were included in the CCG 99703 study, which used three rounds of induction therapy followed by three rounds of consolidation with carboplatin and thiotepa.

Similar to its use in medulloblastoma, high-dose chemotherapy has efficacy in patients with supratentorial PNET. In the studies published so far, outcomes were best when high-dose chemotherapy was used as a first-line therapy and in combination with radiation.

AT/RT is another embryonal malignant brain tumor that is typically sensitive to chemotherapy. Due to its poor prognosis in children, this tumor is often included in infant brain studies and treated with up-front high-dose chemotherapy. A report from Head Start III protocol (Zaky et al. 2014) described outcomes of 19 children younger than 3 years of age, with newly diagnosed CNS AT/RT tumors treated with five cycles of induction chemotherapy with cyclophosphamide, vincristine, etoposide, cisplatin, and high-dose methotrexate and consolidation with a single cycle of thiotepa, etoposide, and carboplatin. Eleven out of 19 children progressed early, at a median time of 4.1 months, and only four out of 19 children were without evidence of disease at 40–79 months from the diagnosis. The authors concluded that more effective approaches are required in young children with AT/RT. Similar to these findings, European data suggested that radiation therapy significantly increased the mean survival time in infants with AT/RT treated with high-dose chemotherapy and methotrexate (Seeringer et al. 2014). Thus high-dose chemotherapy with stem cell rescue is not recommended as a sole modality of treatment in young children with AT/RT (Seeringer et al. 2014). Studies of high-dose chemotherapy in CNS germ cell tumors are rare as this tumor responds well to standard chemotherapy and radiation therapy. However, if tumor recurs following both modalities, high-dose chemotherapy can be

effective. A group of Japanese investigators reported a small series of six patients with intracranial nongerminomatous germ cell tumors treated with myeloablative chemotherapy alone, all of whom survived without tumor recurrence at follow-up of 1–7 years (Tada et al. 1999). Another study described 21 patients with CNS germ cell tumors that progressed following initial chemotherapy and radiation. These patients were treated with a thiotepa-based conditioning regimen. The response was very good in patients with germinoma as 7/9 patients survived disease-free with a median follow-up of 48 months. However, in the nongerminomatous germ cell tumor category, only 33 % patients survived without disease progression (Modak et al. 2004).

Although the toxicity of stem cell transplant has significantly decreased over the last 10 years, some studies of transplant in children with brain tumors still report significant treatment-related mortality (11–19 %) (Sung et al. 2007; Dhall et al. 2008). Over the last 20 years, high-dose chemotherapy has been established as an important modality for treating recurrent, chemosensitive brain tumors as well as first-line treatment for malignant brain tumors in young children.

15.6 New Strategies

15.6.1 Radiation Sensitizers

Numerous investigational chemotherapy treatment strategies are designed to maximize the known benefit of radiation therapy in CNS tumors. Multiple potentiating effects of platinum agents on radiation have been described. Hypoxic cells (typically radiation resistant) are more sensitive to radiation following exposure to platinum agents in vitro (Skov and MacPhail 1991). Platinum agents may also have a role in preventing the development of radiation-resistant clones by inhibiting "potentially lethal damage recovery," a mechanism by which tumor cells are able to repair what would otherwise be lethal or sublethal DNA damage following radiation exposure (Wilkins et al. 1993). A phase 2 study piloting the use of daily carboplatin in combination with weekly vincristine and radiation in patients with high-risk medulloblastoma reported promising outcomes with overall and progression-free survival of 83 and 71 %, suggesting that this is a meaningful strategy (Jakacki et al. 2012). An ongoing phase 3 trial conducted by the Children's Oncology Group is investigating the role of combination carboplatin, vincristine, and radiation in comparison with vincristine and radiation alone in high-risk medulloblastoma (clinicaltrials.gov; NCT00392327).

Inhibitors of the enzyme histone deacetylase (HDAC) have also been shown to have radiation-sensitizing effects in preclinical models of malignant glioma (Chinnaiyan et al. 2008). The combination of radiation with vorinostat is currently under investigation in clinical trials for malignant glioma and diffuse pontine glioma (clinicaltrials.gov; NCT01189266).

15.6.2 Targeting Drug Resistance

Many brain tumors are resistant to conventional chemotherapeutic agents. Investigators have identified mechanisms of drug resistance amenable to pharmacologic treatment that would render tumor cells more sensitive to chemotherapy.

15.6.2.1 P-Glycoprotein Pump

The P-glycoprotein pump (PGP) is the protein product of the multidrug resistance gene (*MDR-1*), which is amplified in many resistant and refractory tumors, including glioblastoma, medulloblastoma, and ependymoma (Chou et al. 1995, 1996; von Bossanyi et al. 1997; Decleves et al. 2002). The PGP serves as an efflux pump, allowing the cell to transport specific toxins, including chemotherapeutic agents (Sikic et al. 1997). In mice, capillary endothelial cells composing the BBB have high concentrations of PGP (Schinkel et al. 1994). Cyclosporine A is a potent inhibitor of PGP and effectively sensitizes high PGP-expressing cells in vitro (Sikic et al. 1997). Clinical trials using cyclosporine A in combination with chemotherapy, largely in the setting of adult myeloid leukemia, have shown high toxicity with unclear therapeutic benefit (Chauncey

2001). A phase I clinical trial in pediatric CNS tumors consisted of intravenous cyclosporine A in combination with oral etoposide, intravenous vincristine, and radiation therapy for patients with intrinsic pontine glioma. The trial was halted early due to excessive neurotoxicity, and there was no survival advantage for the few evaluable patients (Greenberg et al. 2005).

15.6.2.2 Alkylguanine-DNA-Alkyltransferase

Alkylguanine-DNA-alkyltransferase (AGT) is a DNA repair enzyme that plays an important role in tumor resistance to alkylnitrosoureas and temozolomide. AGT reverses DNA methylation and chloroethylation (induced by chemotherapy) at the O^6 position of guanine, thus rescuing the cell from lethal injury. Many brain tumors have high levels of AGT, and these high levels are associated with poor survival in clinical trials in adults with malignant glioma (Wiestler et al. 1984; Pegg 1990; Pegg and Byers 1992; Hongeng et al. 1997). A recent trial in adult patients with malignant glioma showed that patients with methylated AGT gene promoters (and thus decreased AGT expression) had a better response to chemotherapy with the alkylating agent temozolomide (Hegi et al. 2005). Experiments in brain tumor cell lines as well as tumor xenografts have shown that depletion of AGT with O^6-benzylguanine (acting as an alternate substrate for AGT) increases tumor cell sensitivity to chemotherapy (Jaeckle et al. 1998). A phase I clinical trial in malignant glioma of O^6-benzylguanine administered preoperatively as a single agent showed reduced levels of AGT in the resected tumor, suggesting that combination treatment with O^6-benzylguanine and nitrosourea or temozolomide would increase tumor cell sensitivity (Friedman et al. 1998). A phase I clinical trial of temozolomide in combination with O^6-benzylguanine for recurrent or refractory pediatric brain tumors was recently completed through the Pediatric Brain Tumor Consortium. This study demonstrated that this regimen was well tolerated and also established modest activity, with three patients with recurrent glioma having partial responses (Broniscer et al. 2007).

15.6.2.3 PARP Inhibition

Poly (ADP-ribose) polymerases (PARPs) are enzymes with wide-ranging cellular functions, including regulation of DNA transcription, cell cycling, and DNA repair. Cancer cell resistance to DNA-damaging agents is thought to be in part related to enhanced DNA repair mediated by PARP. PARP overexpression has been observed in a number of pediatric brain tumor subtypes including DIPG and malignant glioma, leading to the hypothesis that inhibition of PARP may be a therapeutic strategy for chemotherapy-resistant tumors. The PARP inhibitor veliparib was shown to be tolerable in combination with temozolomide in patients with recurrent CNS tumors in a phase 1 study (Su et al. 2014). Although no objective responses were observed, four patients had stable disease greater than 6 months. The efficacy of this approach is under investigation in a phase 2 study of pediatric patients with diffuse pontine glioma (clinicaltrials.gov NCT01514201).

15.6.3 Molecular Targets and Signal Transduction Inhibition

The enormous expansion in the understanding of the molecular basis of oncogenesis has led to the development of a new class of agents designed to inhibit specific intracellular biochemical pathways. The majority of these agents function by inhibiting receptor tyrosine kinases, a class of cellular proteins that bind a specific ligand through their extracellular domains. Activation of the intracellular tyrosine kinase catalytic domain of the receptor after ligand binding subsequently triggers a cascade of biochemical signals. This ligand-dependent tyrosine kinase activation mediates a host of cellular properties, including proliferation, survival, and differentiation. In normal cellular homeostasis, these functions are tightly regulated. In tumors, unregulated, ligand-independent kinase phosphorylation and subsequent receptor activation is a common event and is likely a key mechanism in maintaining the malignant phenotype. Receptor tyrosine kinases known to be important in CNS tumors include

the epidermal growth factor receptor EGFR, platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR). Important downstream effector kinases are also relevant therapeutic targets. Of particular interest in pediatric tumors are drugs targeting BRAF or its downstream effector MEK, as a significant proportion of pediatric astrocytomas have aberrant signaling of this pathway related to genetic alterations in *BRAF* or *NF1*. Also of interest in pediatric astrocytoma is inhibition of mTOR, as preclinical studies demonstrate that this pathway is also activated in some tumors. The biology of these pathways are discussed in greater detail in Chap. 16.

The most notable clinical success of therapeutic molecular targeting of brain tumor is for the low-grade glioma variant subependymal giant cell astrocytoma (SEGA) in the setting of tuberous sclerosis (TS). Tuberous sclerosis is caused by genetic mutations in the *TSC1*/*TSC2* gene complex and results in a predisposition to subependymal giant cell astrocytoma. Loss of *TSC1*/*TSC2* function results in constitutive activation of mTOR signaling (Franz et al. 2012). There is strong clinical evidence demonstrating that inhibition of mTOR signaling with everolimus results in objective tumor response, and everolimus is FDA approved for the treatment of SEGA (Krueger et al. 2010). This experience provides proof of principle that CNS tumors can be treated with biologically targeted agents.

Genetic aberrations of *BRAF* are frequently observed in pediatric high-grade and low-grade gliomas that result in activation of the Ras–MAP signaling kinase pathway, an event which drives neoplastic cell behavior (see Chap. 1). Objective responses have been observed in tumors bearing a $BRAF^{V600E}$ mutation treated with the BRAF inhibitors vemurafenib and dabrafenib (Bautista et al. 2014; Shih et al. 2014; Usubalieva et al. 2015). Targeting these abnormalities with pharmacologic inhibitors of BRAF and its downstream effector MEK is currently being evaluated in clinical trials (clinicaltrials.gov NCT01748149, NCT01089101).

A subset of medulloblastoma have alterations in the sonic hedgehog (SHH) signaling pathway. Both upstream and downstream mutations in the pathway have been described in multiple genes in the pathway (Samkari et al. 2015). Aberrant signaling of one of the members of this pathway, *SMO*, can be targeted with vismodegib, and responses have been described in medulloblastoma patients treated with this agent (Robinson et al. 2015). The heterogeneous nature of the SHH pathway aberrations in medulloblastoma, however, suggests that the target tumor population who may benefit from this therapy needs to be well defined with genetic testing, as patients with activating mutation downstream of the target may not be susceptible to *SMO* inhibitors. A clinical trial of vismodegib in combination with conventional chemoradiotherapy is ongoing (clinicaltrials.gov NCT01878617).

15.6.4 Angiogenesis Inhibitors

The role of angiogenesis in supporting tumor cell proliferation and survival has been extensively investigated since the hypothesis of "angiogenesis dependency" of tumors was first proposed by Judah Folkmann (1971) and Balis et al. (2002). The angiogenesis hypothesis proposes that tumor-induced proliferation of blood vessels is necessary to support ongoing proliferation and survival. This deceptively straightforward statement must be tempered by the fact that tumor cell-induced angiogenesis appears to have multiple mechanisms, some of which are redundant. Tumor cells produce proangiogenic cytokines, including acidic and basic fibroblastic growth factor (aFGF, bFGF), angiogenin, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and interleukin-8 (IL-8). Additionally, tumor cells produce matrix metalloproteinases (MMP), which can induce breakdown in extracellular matrix, again allowing for release of proangiogenic peptides. Finally, tumor cells recruit inflammatory cells that subsequently produce proangiogenic cytokines (Bicknell and Harris 1996; Pluda 1997; Paku 1998).

A number of therapeutic agents have been shown to inhibit neovascularization in vitro and in vivo. Thalidomide, initially developed as a

sedative and subsequently found to be a potent teratogen in humans, has antiangiogenic properties (D'Amato et al. 1994). It has been shown to inhibit bFGF-induced corneal vascularization in animals (Kenyon et al. 1997). In a single-agent clinical trial of recurrent gliomas, objective response rates (partial response and stable disease) of up to 45 % were reported (Fine et al. 2000). Lenalidomide is an analog of thalidomide that has shown considerable efficacy in multiple myeloma and myelodysplasia. A phase 1 study in children demonstrated that lenalidomide was well tolerated in patients with recurrent, refractory, or progressive CNS tumors (Fine et al. 2007). Additionally, objective responses and prolonged stable disease were observed in patients with low-grade glioma (Warren et al. 2011). These findings are under further investigation in a phase 2 study of lenalidomide for children with pilocytic astrocytoma and optic pathway glioma (clincialtrials.gov NCT01553149).

The role of cyclooxygenase inhibitors as an antiangiogenic treatment strategy is also under investigation. Cyclooxygenase 2 (COX-2) induces vascular proliferation following trauma or stimulation with growth factor and is highly expressed in some human tumors, including high-grade glioma (Joki et al. 2000). Treatment of glioma cell cultures with a specific COX-2 inhibitor was found to produce diminished proliferation and invasion and increased apoptosis (Joki et al. 2000). Celecoxib is a specific inhibitor of COX-2, with a highly favorable toxicity profile. While celecoxib is not currently under investigation in large-scale pediatric clinical trials, its ease of use and low toxicity make it an appealing agent to pursue in combination with other agents.

The most successful strategy in adults thus far has been with bevacizumab, a monoclonal antibody targeting VEGF, in combination with conventional cytotoxic chemotherapy such as irinotecan (Vredenburgh et al. 2007) or temozolomide (Hofland et al. 2014). This combination is active in pediatric low-grade glioma and is reported to have similar progression-free survival to more conventional carboplatin- or nitrosourea-based regimens in a phase 2 study in tumors that had failed prior treatment (Gururangan et al. 2014). Experience with this regimen in pediatric high-grade glioma, diffuse pontine glioma, and medulloblastoma, however, has been disappointing, without an appreciable improvement in survival. Interestingly, bevacizumab may be an alternate treatment for tumor-associated edema, as transient symptomatic improvement has been observed after its use in patients with high-grade glioma. Toxicities of bevacizumab include fatigue, proteinuria, and hypertension. Less common but of concern is an increased risk of hemorrhage. Finally, the use of conventional cytotoxic agents given in low-dose, metronomic regimens is being piloted. These regimens are based on the principle that while endothelial cell proliferation appears to be sensitive to chronic but low-dose exposure, it has ample recovery time during the recovery phase of dose-intensive therapy schedules. Evidence from pilot clinical trials supports this hypothesis (Einhorn 1991; Ashley et al. 1996; Kushner et al. 1999; Klement et al. 2000). Kieran et al. described the use of metronomic chemotherapy with daily oral thalidomide and celecoxib, in addition to alternating cycles of daily oral etoposide and oral cyclophosphamide in the treatment of 20 children with recurrent or progressive cancer. The regimen was well-tolerated and prolonged progression-free survival in a number of children with CNS malignancies (Kieran et al. 2005).

15.6.5 Overcoming the Blood–Brain Barrier

The BBB is composed of tight endothelial cell junctions that exclude most large molecules and is freely permeable only to small molecules that are highly lipophilic. This barrier limits the ability of many systemically administered chemotherapeutic agents to penetrate the CNS. Radiographic evidence based on heterogeneous uptake of gadolinium on magnetic resonance imaging suggests, however, that the BBB is only partially intact in many patients with CNS tumors. Further support of tumor degradation of the BBB lies in the responsiveness of tumors to large, water-soluble molecules

such as the platinum agents. Nevertheless, resistance of CNS tumors to therapy may partially lay in the infiltrative, nonenhancing portions of tumor that presumably have an intact BBB and thus are able to escape cytotoxicity of systemically administered agents. This is supported by the propensity of many tumors to recur locally, at the infiltrating edge of the tumor. A number of strategies are under investigation with the intent to disrupt or bypass the BBB.

15.6.5.1 Blood–Brain Barrier Disruption

Mannitol was one of the first agents used to attempt disruption of the BBB. Increased osmotic pressure transiently opens the BBB, allowing entry of molecules, otherwise unable to penetrate the CNS (Neuwelt et al. 1983). Increased disease response has been reported following BBB disruption, largely in adult patients with non-AIDS CNS lymphoma (Neuwelt et al. 1981). The Children's Cancer Group reported on the only pediatric experience with this strategy, using mannitol in combination with etoposide for recurrent or refractory CNS tumors. They were unable to document a clear benefit (Kobrinsky et al. 1999).

RMP-7 is a bradykinin analog, which, on binding to specific B_2 bradykinin receptors on the surface of endothelial cells, transiently increases permeability of the BBB. While increased concentration of carboplatin when administered with this agent has been documented in animals (Dean et al. 1999), a randomized, placebo-controlled phase II trial in adults with malignant glioma showed no survival benefit from the addition of RMP-7 to carboplatin alone (Prados et al. 2003). A phase II pediatric trial was conducted by the Children's Oncology Group for patients with recurrent or refractory brain tumors (Warren et al. 2006) and did not show any activity in children with brainstem gliomas or high-grade gliomas.

15.6.5.2 Intra-arterial Delivery

Intra-arterial delivery of chemotherapy, often delivered in conjunction with mannitol, may improve delivery of drug and minimize systemic toxicity, possibly allowing for the use of lower doses delivered directly to the tumor. A number of studies have investigated the use in intra-arterial carmustine, cisplatin, and carboplatin. While modest responses have been reported, neurologic toxicities are substantial, including irreversible encephalopathy and vision loss (Bashir et al. 1988; Mahaley et al. 1989; Newton et al. 1989).

15.6.5.3 Intratumoral Drug Delivery

A variety of novel techniques to deliver drug directly to the tumor or resection cavity are under investigation. The use of carmustine-impregnated "wafers" in adults with malignant glioma has been reported. This strategy allows for the passive diffusion of high concentrations of carmustine from wafers surgically implanted in the resection cavity to surrounding tumor cells, with minimal systemic exposure. Modest improvements in survival have been shown with this intervention (Brem et al. 1995; Valtonen et al. 1997). A multi-institutional pediatric trial designed to investigate the impact of this treatment in children with recurrent high-grade glioma closed early due to poor accrual, suggesting that this strategy may have feasibility concerns in this patient population (clinicaltrials.gov NCT0004572).

Passive diffusion, however, is limited by minimal ability of the drug to penetrate beyond the margin of the tumor resection cavity. Convection-enhanced delivery (CED) is a novel delivery strategy that overcomes this barrier and allows for delivery of larger molecules. CED requires the surgical placement of catheters intra- or peritumorally, through which a therapeutic agent is infused under positive pressure (Bobo et al. 1994). This allows for a substantially larger area of the brain to be treated. Multiple agents have been tested in early-phase trials for adult patients with newly diagnosed or recurrent malignant glioma using this technique, including conventional chemotherapy drugs such as carboplatin, cell surface-targeted cytotoxin-ligand conjugates, monoclonal antibodies with or without conjugated radioisotopes (Bigner et al. 1998), antisense oligonucleotides, and liposomal vectors to deliver gene therapy. While some of these strategies have resulted in preliminary signals of efficacy, none have shown superiority over conventional treatment in a randomized setting. In addition, there are significant technical barriers associated with catheter placement (Vogelbaum and Aghi 2015).

15.6.6 Differentiation of Neoplastic Cells

Agents that induce differentiation of tumor cells, thereby suppressing neoplastic proliferation, may have a role in the management of brain tumors. Experiments in cell culture using both retinoic acid and phenylacetate show both differentiation and inhibition of proliferation of astrocytoma-derived and medulloblastoma-derived cell lines (Mukherjee and Das 1990; Rodts and Black 1994). Treatment of adult patients with malignant glioma with single-agent 13-*cis*-retinoic acid showed a modest partial response plus a stable disease rate of 46 %, with tolerable toxicity (Yung et al. 1996). A recent phase II study investigated the combination of temozolomide with 13-*cis*-retinoic acid for recurrent malignant glioma in adults. A slight improvement in a 6-month progression-free survival was observed over historical controls, suggesting that the combination is active in recurrent malignant glioma (Jaeckle et al. 2003). Another recent phase II trial used 13-*cis*-retinoic acid as maintenance therapy for adult patients with high-grade glioma after first-line multimodal therapy (Wismeth et al. 2004). This approach was well tolerated and resulted in a median survival of 74 weeks. In a randomized trial adding retinoic acid to combination therapy for high-risk neuroblastoma, patients treated with retinoic acid had better outcomes (Matthay et al. 1999). Preclinical data in medulloblastoma mouse models supports this strategy, and it is being tested in a phase 3 trial for newly diagnosed high-risk medulloblastoma patients, in which patients are randomized to receive 13-*cis*-retinoic acid after standard treatment with surgery, radiation, and chemotherapy (Spiller et al. 2008; clinicaltrials.gov NCT00392327).

15.6.7 Immunotherapy

The goal of immunologically directed antitumor therapy is to eradicate tumor cells either by stimulating host immunologic antitumor reactions or by blocking tumor-related local immunosuppression, and recent progress has been made with immunotherapy approaches in childhood leukemia and melanoma. Chimeric antigen receptor (CAR) T-cell therapy has resulted in durable remissions in CD19-positive B lineage leukemia (Lee et al. 2015). Inhibition of the T-cell antigen PD-1 along with inhibition of CTLA-4 has resulted in remarkable improvements in survival in metastatic melanoma (Larkin et al. 2015). The role of immunotherapy for CNS tumors, however, remains under investigation.

Antigen-targeted tumor vaccination is showing early promise in CNS tumors. Pollack et al. reported immunologic and radiographic responses with the use of a multiple glioma-associated antigen vaccination in combination with radiation and chemotherapy in children newly diagnosed with brainstem glioma and high-grade glioma (Pollack et al. 2014). Alternative vaccine approaches are under investigation in adults with glioblastoma. Heat shock proteins act as molecular chaperones inside cells and have been found to bind a unique "fingerprint" of peptides that are tumor specific. These HSPCCs have been found to be antigenic in human trials with a variety of tumors and function by eliciting T-cell-mediated cytotoxicity. A phase 2 study of a tumor-derived heat shock protein/protein complex (HSPPC) vaccine in adults with surgically resectable, recurrent GBM demonstrates 6-month PFS of approximately 20 %.

Dendritic cell therapy involves the collection of antigen-presenting cells followed by an ex vivo pulse with autologous tumor lysate or more specific tumor peptides. These cells are then administered intradermally or intratumorally and stimulate host cytotoxic T cells to attack the tumor. Numerous dendritic cell vaccination approaches have been tested in clinical trials. Tumor lysate-pulsed DC vaccinations have been shown to be safe, and preliminary phase 1 and phase 2 studies suggest that newly diagnosed, adult GBM patients have equivalent or improved survival compared to historical controls, and phase 3 trials of this strategy are ongoing in adults. Glioma-associated antigen-pulsed dendritic cell vaccines are also under investigation (Antonios

et al. 2015). Although relatively few immunotherapies have entered pediatric clinical trials, ongoing research in this field carries future promise.

Conclusions

While prognosis for malignant brain tumors in children has improved somewhat in the past several decades, 5-year survival for all tumors except low-grade astrocytoma remains suboptimal at 60%. The incorporation of chemotherapy into pediatric brain tumor management has allowed for advances in survival and reduction of morbidity and is now the standard of care for many childhood brain tumors. Critical to the further improvement of prognosis and long-term outcome is the continued effort of multi-institutional, cooperative group clinical trials. The largest clinical trial group conducting pediatric brain tumor trials is the National Cancer Institute (NCI)-sponsored Children's Oncology Group. The Children's Oncology Group includes the majority of pediatric cancer treatment centers in the United States and incorporates programs in Canada, Europe, and Australia. Research activities include clinical trials for the majority of newly diagnosed and recurrent brain tumors, as well as studies of new agents. The Pediatric Brain Tumor Consortium is a smaller, NCI-sponsored consortium with a mission to expedite the development of new agents' high-risk pediatric brain tumors by bringing novel agents and translational research to the pediatric brain tumor community in a multi-institutional setting. The Pacific Pediatric Neuro-oncology Consortium (http://www.pnoc.us) is another multi-institutional clinical trials group dedicated to investigation of new therapies for childhood brain tumor. Information on the Children's Oncology Group and the Pediatric Brain Tumor Consortium can be found on the World Wide Web at http://www.childrensoncologygroup.org and http://www.pbtc.org.

References

Allen JC, Bosl G, Walker R (1985) Chemotherapy trials in recurrent primary intracranial germ cell tumors. J Neurooncol 3:147–152

Antonios JP, Everson RG, Liau LM (2015) Dendritic cell immunotherapy for brain tumors. J Neurooncol 123:425–432

Ashley DM, Meier L, Kerby T, Zalduondo FM, Friedman HS, Gajjar A, Kun L, Duffner PK, Smith S, Longee D (1996) Response of recurrent medulloblastoma to low-dose oral etoposide. J Clin Oncol 14:1922–1927

Ashley DM, Merchant TE, Strother D, Zhou T, Duffner P, Burger PC, Miller DC, Lyon N, Bonner MJ, Msall M, Buxton A, Geyer R, Kun LE, Coleman L, Pollack IF (2012) Induction chemotherapy and conformal radiation therapy for very young children with nonmetastatic medulloblastoma: Children's Oncology Group study P9934. J Clin Oncol 30:3181–3186

Balis FM, Holcenberg JS, Blaney SM (2002) General principles of chemotherapy. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology. Lippincott Williams & Wilkins, Philadelphia, pp 237–308

Bashir R, Hochberg FH, Linggood RM, Hottleman K (1988) Pre-irradiation internal carotid artery BCNU in treatment of glioblastoma multiforme. J Neurosurg 68:917–919

Bautista F, Paci A, Minard-Colin V, Dufour C, Grill J, Lacroix L, Varlet P, Valteau-Couanet D, Geoerger B (2014) Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas. Pediatr Blood Cancer 61:1101–1103

Bertolone SJ, Baum ES, Krivit W, Hammond GD (1989) A phase II study of cisplatin therapy in recurrent childhood brain tumors. A report from the Childrens Cancer Study Group. J Neurooncol 7:5–11

Bicknell R, Harris AL (1996) Mechanisms and therapeutic implications of angiogenesis. Curr Opin Oncol 8:60–65

Bigner DD, Brown MT, Friedman AH, Coleman RE, Akabani G, Friedman HS, Thorstad WL, McLendon RE, Bigner SH, Zhao XG, Pegram CN, Wikstrand CJ, Herndon JE II, Vick NA, Paleologos N, Cokgor I, Provenzale JM, Zalutsky MR (1998) Iodine-131-labeled antitenascin monoclonal antibody 81C6 treatment of patients with recurrent malignant gliomas: phase I trial results. J Clin Oncol 16:2202–2212

Blaney SM, Boyett J, Friedman H, Gajjar A, Geyer R, Horowtiz M, Hunt D, Kieran M, Kun L, Packer R, Phillips P, Pollack IF, Prados M, Heideman R (2005) Phase I clinical trial of mafosfamide in infants and children aged 3 years or younger with newly diagnosed embryonal tumors: a pediatric brain tumor consortium study (PBTC-001). J Clin Oncol 23:525–531

Blaney SM, Kocak M, Gajjar A, Chintagumpala M, Merchant T, Kieran M, Pollack IF, Gururangan S, Geyer R, Phillips P, McLendon RE, Packer R, Goldman S, Banerjee A, Heideman R, Boyett JM, Kun L (2012) Pilot study of systemic and intrathecal mafosfamide followed by conformal radiation for infants with intracranial central nervous system tumors: a pediatric brain tumor consortium study (PBTC-001). J Neurooncol 109:565–571

Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH (1994) Convection-enhanced

delivery of macromolecules in the brain. Proc Natl Acad Sci U S A 91:2076–2080

Bode U, Zimmermann M, Moser O, Rutkowski M, Warmuth-Metz M, Pietsch T, Kortmann RD, Faldum A, Fleischhack G (2014) Treatment of recurrent primitive neuroectodermal tumors (PNET) in children and adolescents with high-dose chemotherapy (HDC) and stem cell support: results of the HITREZ 97 multicentre trial. J Neurooncol 120:635–642

Bouffet E, Foreman N (1999) Chemotherapy for intracranial ependymomas. Childs Nerv Syst 15: 563–570

Bouffet E, Khelfaoui F, Philip I, Biron P, Brunat-Mentigny M, Philip T (1997) High-dose carmustine for high-grade gliomas in childhood. Cancer Chemother Pharmacol 39:376–379

Bouffet E, Raquin M, Doz F, Gentet JC, Rodary C, Demeocq F, Chastagner P, Lutz P, Hartmann O, Kalifa C (2000) Radiotherapy followed by high dose busulfan and thiotepa: a prospective assessment of high dose chemotherapy in children with diffuse pontine gliomas. Cancer 88:685–692

Bouffet E, Hargrave D, Cairney E, Garre ML, Slave I, Baruchel S (2002) Weekly vinblastine for recurrent/progressive low grade gliomas [abstract]. Proceedings of the International Society of Pediatric Oncology SIOP XXXIV. Med Pediatr Oncol 39:229

Bouffet E, Jakacki R, Goldman S, Hargrave D, Hawkins C, Shroff M, Hukin J, Bartels U, Foreman N, Kellie S, Hilden J, Etzl M, Wilson B, Stephens D, Tabori U, Baruchel S (2012) Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol 30(12):1358–1363

Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G et al (1995) Placebocontrolled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. Lancet 345:1008–1012

Broniscer A, Nicolaides TP, Dunkel IJ, Gardner SL, Johnson J Jr, Allen JC, Sposto R, Finlay JL (2004) High-dose chemotherapy with autologous stem-cell rescue in the treatment of patients with recurrent noncerebellar primitive neuroectodermal tumors. Pediatr Blood Cancer 42:261–267

Broniscer A, Gururangan S, MacDonald TJ, Goldman S, Packer RJ, Stewart CF, Wallace D, Danks MK, Friedman HS, Poussaint TY, Kun LE, Boyett JM, Gajjar A (2007) Phase I trial of single-dose temozolomide and continuous administration of O^6-benzylguanine in children with brain tumors: a pediatric brain tumor consortium report. Clin Cancer Res 13:6712–6718

Burger PC, Kamenar E, Schold SC, Fay JW, Phillips GL, Herzig GP (1981) Encephalomyelopathy following high-dose BCNU therapy. Cancer 48:1318–1327

Busca A, Miniero R, Besenzon L, Cordero di Montezemolo L, Cenni M, Fagioli F, Sandri A, Vassallo E, Ricardi U, Madon E (1997) Etoposide-containing regimens with autologous bone marrow transplantation in children with malignant brain tumors. Childs Nerv Syst 13:572–577

Byrne J, Mulvihill JJ, Myers MH, Connelly RR, Naughton MD, Krauss MR, Steinhorn SC, Hassinger DD, Austin DF, Bragg K et al (1987) Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. N Engl J Med 317:1315–1321

Chamberlain MC (2001) Recurrent intracranial ependymoma in children: salvage therapy with oral etoposide. Pediatr Neurol 24:117–121

Chamberlain MC, Kormanik PA (1997) Chronic oral VP-16 for recurrent medulloblastoma. Pediatr Neurol 17:230–234

Chauncey TR (2001) Drug resistance mechanisms in acute leukemia. Curr Opin Oncol 13:21–26

Chi SN, Gardner SL, Levy AS, Knopp EA, Miller DC, Wisoff JH, Weiner HL, Finlay JL (2004) Feasibility and response to induction chemotherapy intensified with high-dose methotrexate for young children with newly diagnosed high-risk disseminated medulloblastoma. J Clin Oncol 22:4881–4887

Chinnaiyan P, Cerna D, Burgan WE, Beam K, Williams ES, Camphausen K, Tofilon PJ (2008) Postradiation sensitization of the histone deacetylase inhibitor valproic acid. Clin Cancer Res 14:5410–5415

Chou PM, Reyes-Mugica M, Barquin N, Yasuda T, Tan X, Tomita T (1995) Multidrug resistance gene expression in childhood medulloblastoma: correlation with clinical outcome and DNA ploidy in 29 patients. Pediatr Neurosurg 23:283–291; discussion 291–292

Chou PM, Barquin N, Gonzalez-Crussi F, Ridaura Sanz C, Tomita T, Reyes-Mugica M (1996) Ependymomas in children express the multidrug resistance gene: immunohistochemical and molecular biologic study. Pediatr Pathol Lab Med 16:551–561

Cohen KJ, Pollack IF, Zhou T, Buxton A, Holmes EJ, Burger PC, Brat DJ, Rosenblum MK, Hamilton RL, Lavey RS, Heideman RL (2011) Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol 13:317–323

D'Amato RJ, Loughnan MS, Flynn E, Folkman J (1994) Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci U S A 91:4082–4085

Dean RL, Emerich DF, Hasler BP, Bartus RT (1999) Cereport (RMP-7) increases carboplatin levels in brain tumors after pretreatment with dexamethasone. Neuro Oncol 1:268–274

Decleves X, Fajac A, Lehmann-Che J, Tardy M, Mercier C, Hurbain I, Laplanche JL, Bernaudin JF, Scherrmann JM (2002) Molecular and functional MDR1-Pgp and MRPs expression in human glioblastoma multiforme cell lines. Int J Cancer 98:173–180

Dhall G, Grodman H, Ji L, Sands S, Gardner S, Dunkel IJ, McCowage GB, Diez B, Allen JC, Gopalan A, Cornelius AS, Termuhlen A, Abromowitch M, Sposto R, Finlay JL (2008) Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. Pediatr Blood Cancer 50:1169–1175

Duffner PK, Horowitz ME, Krischer JP, Friedman HS, Burger PC, Cohen ME, Sanford RA, Mulhern RK, James HE, Freeman CR et al (1993) Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med 328:1725–1731

Duffner PK, Krischer JP, Horowitz ME, Cohen ME, Burger PC, Friedman HS, Kun LE (1998) Second malignancies in young children with primary brain tumors following treatment with prolonged postoperative chemotherapy and delayed irradiation: a Pediatric Oncology Group study. Ann Neurol 44:313–316

Duffner PK, Horowitz ME, Krischer JP, Burger PC, Cohen ME, Sanford RA, Friedman HS, Kun LE (1999) The treatment of malignant brain tumors in infants and very young children: an update of the Pediatric Oncology Group experience. Neuro Oncol 1:152–161

Duffull SB, Robinson BA (1997) Clinical pharmacokinetics and dose optimisation of carboplatin. Clin Pharmacokinet 33:161–183

Dunkel IJ, Finlay JL (2002) High-dose chemotherapy with autologous stem cell rescue for brain tumors. Crit Rev Oncol Hematol 41:197–204

Dunkel IJ, Gardner S, Gavin J, Goldman S, Shi W, Finlay J (2010) High-dose carboplatin, thiotepa and etoposide with autologous stem cell rescue for patients with previously irradiated medulloblastoma. Neruo Oncol 12:297–303

Eilber F, Giuliano A, Eckardt J, Patterson K, Moseley S, Goodnight J (1987) Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. J Clin Oncol 5:21–26

Einhorn LH (1991) Daily oral etoposide in the treatment of cancer. Semin Oncol 18:43–47

Fagioli F, Biasin E, Mastrodicasa L, Sandri A, Ferrero I, Berger M, Vassallo E, Madon E (2004) High-dose thiotepa and etoposide in children with poor-prognosis brain tumors. Cancer 100(10):2215–2221

Fangusaro J, Finlay J, Sposto R, Ji L, Saly M, Zacharoulis S, Asgharzadeh S, Abromowitch M, Olshefski R, Halpern S, Dubowy R, Comito M, Diez B, Kellie S, Hukin J, Rosenblum M, Dunkel I, Miller DC, Allen J, Gardner S (2008) Intensive chemotherapy followed by consolidative myeloablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) in young children with newly diagnosed supratentorial primitive neuroectodermal tumors (sPNETs): report of the Head Start I and II experience. Pediatr Blood Cancer 50:312–318

Fine HA, Figg WD, Jaeckle K, Wen PY, Kyritsis AP, Loeffler JS, Levin VA, Black PM, Kaplan R, Pluda JM, Yung WK (2000) Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. J Clin Oncol 18:708–715

Fine HA, Kim L, Albert PS, Duic JP, Ma H, Zhang W, Tohnya T, Figg WD, Royce C (2007) A phase I trial of lenalidomide in patients with recurrent primary central nervous system tumors. Clin Cancer Res 13:7101–7106

Finlay JL, Boyett JM, Yates AJ, Wisoff JH, Milstein JM, Geyer JR, Bertolone SJ, McGuire P, Cherlow JM, Tefft M et al (1995) Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. Childrens Cancer Group. J Clin Oncol 13:112–123

Finlay JL, Goldman S, Wong MC, Cairo M, Garvin J, August C, Cohen BH, Stanley P, Zimmerman RA, Bostrom B, Geyer JR, Harris RE, Sanders J, Yates AJ, Boyett JM, Packer RJ (1996) Pilot study of high-dose thiotepa and etoposide with autologous bone marrow rescue in children and young adults with recurrent CNS tumors. The Children's Cancer Group. J Clin Oncol 14:2495–2503

Finlay J, Dhall G, Boyett J, Dunkel I, Gardner S, Goldman S, Yates A, Rosenblum M, Stanley P, Zimmerman R, Wallace D, Pollack I, Packer R (2008) Myeloablative chemotherapy with autologous bone marrow rescue in children and adolescents with recurrent malignant astrocytoma: outcome compared with conventional chemotherapy: a report from the Children's Oncology Group. Pediatr Blood Cancer 51:806–811

Fleischhack G, Popping K, Hasan C, Utsch B, Juttner J, Bode U (1998) High dose chemotherapy with thiotepa, carboplatin, VP16 and autologous stem cell transplantation in treatment of malignant brain tumors with poor prognosis. Results of a mono-center pilot study. Klin Padiatr 210:248–255

Folkman J (1971) Tumor angiogenesis: therapeutic implications. N Engl J Med 285:1182–1186

Fouladi M, Blaney SM, Poussaint TY, Freeman BB 3rd, McLendon R, Fuller C, Adesina AM, Hancock ML, Danks MK, Stewart C, Boyett JM, Gajjar A (2006) Phase II study of oxaliplatin in children with recurrent or refractory medulloblastoma, supratentorial primitive neuroectodermal tumors, and atypical teratoid rhabdoid tumors: a pediatric brain tumor consortium study. Cancer 107:2291–2297

Friedman HS, Mahaley MS Jr, Schold SC Jr, Vick NA, Falletta JM, Bullard DE, D'Souza BJ, Khandekar JD, Lew S, Oakes WJ et al (1986) Efficacy of vincristine and cyclophosphamide in the therapy of recurrent medulloblastoma. Neurosurgery 18:335–340

Friedman HS, Kokkinakis DM, Pluda J, Friedman AH, Cokgor I, Haglund MM, Ashley DM, Rich J, Dolan ME, Pegg AE, Moschel RC, McLendon RE, Kerby T, Herndon JE, Bigner DD, Schold SC Jr (1998) Phase I trial of O^6-benzylguanine for patients undergoing surgery for malignant glioma. J Clin Oncol 16:3570–3575

Friedman HS, Kerby T, Calvert H (2000) Temozolomide and treatment of malignant glioma. Clin Cancer Res 6:2585–2597

Fulton D, Urtasun R, Forsyth P (1996) Phase II study of prolonged oral therapy with etoposide (VP16) for patients with recurrent malignant glioma. J Neurooncol 27:149–155

Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, Woo S, Wheeler G, Ahern V, Krasin MJ, Fouladi M, Broniscer A, Krance R, Hale GA,

Stewart CF, Dauser R, Sanford RA, Fuller C, Lau C, Boyett JM, Wallace D, Gilbertson RJ (2006) Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. Lancet Oncol 7:813–820

Gaynon PS, Ettinger LJ, Baum ES, Siegel SE, Krailo MD, Hammond GD (1990) Carboplatin in childhood brain tumors. A Children's Cancer Study Group Phase II trial. Cancer 66:2465–2469

Geyer JR, Zeltzer PM, Boyett JM, Rorke LB, Stanley P, Albright AL, Wisoff JH, Milstein JM, Allen JC, Finlay JL et al (1994) Survival of infants with primitive neuroectodermal tumors or malignant ependymomas of the CNS treated with eight drugs in 1 day: a report from the Childrens Cancer Group. J Clin Oncol 12:1607–1615

Graff JR, McNulty AM, Hanna KR, Konicek BW, Lynch RL, Bailey SN, Banks C, Capen A, Goode R, Lewis JE, Sams L, Huss KL, Campbell RM, Iversen PW, Neubauer BL, Brown TJ, Musib L, Geeganage S, Thornton D (2005) The protein kinase Cbeta-selective inhibitor, Enzastaurin (LY317615. HCl), suppresses signaling through the AKT pathway, induces apoptosis, and suppresses growth of human colon cancer and glioblastoma xenografts. Cancer Res 65:7462–7469

Graham ML, Herndon JE 2nd, Casey JR, Chaffee S, Ciocci GH, Krischer JP, Kurtzberg J, Laughlin MJ, Longee DC, Olson JF, Paleologus N, Pennington CN, Friedman HS (1997) High-dose chemotherapy with autologous stem-cell rescue in patients with recurrent and high-risk pediatric brain tumors. J Clin Oncol 15:1814–1823

Greenberg ML, Fisher PG, Freeman C, Korones DN, Bernstein M, Friedman H, Blaney S, Hershon L, Zhou T, Chen Z, Kretschmar C (2005) Etoposide, vincristine, and cyclosporin A with standard-dose radiation therapy in newly diagnosed diffuse intrinsic brainstem gliomas: a pediatric oncology group phase I study. Pediatr Blood Cancer 45:644–648

Grill J, Sainte-Rose C, Jouvet A, Gentet JC, Lejars O, Frappaz D, Doz F, Rialland X, Pichon F, Bertozzi AI, Chastagner P, Couanet D, Habrand JL, Raquin MA, Le Deley MC, Kalifa C (2005) Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. Lancet Oncol 6:573–580

Grovas AC, Boyett JM, Lindsley K, Rosenblum M, Yates AJ, Finlay JL (1999) Regimen-related toxicity of myeloablative chemotherapy with BCNU, thiotepa, and etoposide followed by autologous stem cell rescue for children with newly diagnosed glioblastoma multiforme: report from the Children's Cancer Group. Med Pediatr Oncol 33:83–87

Gurney JG, Bass JK, Onar-Thomas A, Huang J, Chintagumpala M, Bouffet E, Hassall T, Gururangan S, Heath JA, Kellie S, Cohn R, Fisher MJ, Panandiker AP, Merchant TE, Srinivasan A, Wetmore C, Qaddoumi I, Stewart CF, Armstrong GT, Broniscer A, Gajjar A (2014) Evaluation of amifostine for protection against cisplatin-induced serious hearing loss in children treated for average-risk or high-risk medulloblastoma. Neuro Oncol 16:848–855

Gururangan S, McLaughlin C, Quinn J, Rich J, Reardon D, Halperin EC, Herndon J 2nd, Fuchs H, George T, Provenzale J, Watral M, McLendon RE, Friedman A, Friedman HS, Kurtzberg J, Vredenbergh J, Martin PL (2003) High-dose chemotherapy with autologous stem-cell rescue in children and adults with newly diagnosed pineoblastomas. J Clin Oncol 21:2187–2191

Gururangan S, Fangusaro J, Poussaint TY, McLendon RE, Onar-Thomas A, Wu S, Packer RJ, Banerjee A, Gilbertson RJ, Fahey F, Vajapeyam S, Jakacki R, Gajjar A, Goldman S, Pollack IF, Friedman HS, Boyett JM, Fouladi M, Kun LE (2014) Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas – a Pediatric Brain Tumor Consortium study. Neuro Oncol 16:310–317

Hande KR (1998) Etoposide: four decades of development of a topoisomerase II inhibitor. Eur J Cancer 34:1514–1521

Hartmann JT, Lipp HP (2003) Toxicity of platinum compounds. Exp Opin Pharmacother 4:889–901

Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352:997–1003

Heideman RL, Douglass EC, Krance RA, Fontanesi J, Langston JA, Sanford RA, Kovnar EH, Ochs J, Kuttesch J, Jenkins JJ et al (1993) High-dose chemotherapy and autologous bone marrow rescue followed by interstitial and external-beam radiotherapy in newly diagnosed pediatric malignant gliomas. J Clin Oncol 11:1458–1465

Hochberg FH, Parker LM, Takvorian T, Canellos GP, Zervas NT (1981) High-dose BCNU with autologous bone marrow rescue for recurrent glioblastoma multiforme. J Neurosurg 54:455–460

Hofland KF, Hansen S, Sorensen M, Engelholm S, Schultz HP, Muhic A, Grunnet K, Ask A, Costa JC, Kristiansen C, Thomsen C, Poulsen HS, Lassen U (2014) Neoadjuvant bevacizumab and irinotecan versus bevacizumab and temozolomide followed by concomitant chemoradiotherapy in newly diagnosed glioblastoma multiforme: a randomized phase II study. Acta Oncol 53:939–944

Hongeng S, Brent TP, Sanford RA, Li H, Kun LE, Heideman RL (1997) O^6-Methylguanine-DNA methyltransferase protein levels in pediatric brain tumors. Clin Cancer Res 3:2459–2463

Jaeckle KA, Eyre HJ, Townsend JJ, Schulman S, Knudson HM, Belanich M, Yarosh DB, Bearman SI, Giroux DJ, Schold SC (1998) Correlation of tumor O^6 methylguanine-DNA methyltransferase levels with survival of malignant astrocytoma patients treated with

bis-chloroethylnitrosourea: a Southwest Oncology Group study. J Clin Oncol 16:3310–3315

Jaeckle KA, Hess KR, Yung WK, Greenberg H, Fine H, Schiff D, Pollack IF, Kuhn J, Fink K, Mehta M, Cloughesy T, Nicholas MK, Chang S, Prados M (2003) Phase II evaluation of temozolomide and 13-cis-retinoic acid for the treatment of recurrent and progressive malignant glioma: a North American Brain Tumor Consortium study. J Clin Oncol 21:2305–2311

Jakacki RI, Burger PC, Zhou T, Holmes EJ, Kocak M, Onar A, Goldwein J, Mehta M, Packer RJ, Tarbell N, Fitz C, Vezina G, Hilden J, Pollack IF (2012) Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. J Clin Oncol 30:2648–2653

Joki T, Heese O, Nikas DC, Bello L, Zhang J, Kraeft SK, Seyfried NT, Abe T, Chen LB, Carroll RS, Black PM (2000) Expression of cyclooxygenase 2 (COX-2) in human glioma and in vitro inhibition by a specific COX-2 inhibitor, NS-398. Cancer Res 60:4926–4931

Jordan MA (2002) Mechanism of action of antitumor drugs that interact with microtubules and tubulin. Current Medicinal Chemistry. Anti Cancer Agents 2:1–17

Kalifa C, Hartmann O, Demeocq F, Vassal G, Couanet D, Terrier-Lacombe MJ, Valteau D, Brugieres L, Lemerle J (1992) Highdose busulfan and thiotepa with autologous bone marrow transplantation in childhood malignant brain tumors: a phase II study. Bone Marrow Transplant 9:227–233

Kellie SJ, Barbaric D, Koopmans P, Earl J, Carr DJ, de Graaf SS (2002) Cerebrospinal fluid concentrations of vincristine after bolus intravenous dosing: a surrogate marker of brain penetration. Cancer 94:1815–1820

Kellie SJ, Chaku J, Lockwood LR, O'Regan P, Waters KD, Wong CK (2005) Late magnetic resonance imaging features of leukoencephalopathy in children with central nervous system tumours following high-dose methotrexate and neuraxis radiation therapy. Eur J Cancer 41:1588–1596

Kenyon BM, Browne F, D'Amato RJ (1997) Effects of thalidomide and related metabolites in a mouse corneal model of neovascularization. Exp Eye Res 64:971–978

Khatua S, Dhall G, O'Neil S, Jubran R, Villablanca JG, Marachelian A, Nastia A, Lavey R, Olch AJ, Gonzalez I et al (2010) Treatment of primary CNS germinomatous germ cell tumors with chemotherapy prior to reduced dose whole ventricular and local boost irradiation. Pediatr Blood Cancer 2010(55):42–46

Khaw SL, Coleman LT, Downie PA, Heath JA, Ashley DM (2007) Temozolomide in pediatric low-grade glioma. Pediatr Blood Cancer 49:808–811

Kieran MW, Turner CD, Rubin JB, Chi SN, Zimmerman MA, Chordas C, Klement G, Laforme A, Gordon A, Thomas A, Neuberg D, Browder T, Folkman J (2005) A feasibility trial of antiangiogenic (metronomic) chemotherapy in pediatric patients with recurrent or progressive cancer. J Pediatr Hematol Oncol 27:573–581

Klement G, Baruchel S, Rak J, Man S, Clark K, Hicklin DJ, Bohlen P, Kerbel RS (2000) Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity. J Clin Inv 105:R15–R24

Kobrinsky NL, Packer RJ, Boyett JM, Stanley P, Shiminski-Maher T, Allen JC, Garvin JH, Stewart DJ, Finlay JL (1999) Etoposide with or without mannitol for the treatment of recurrent or primarily unresponsive brain tumors: a Children's Cancer Group Study, CCG-9881. J Neurooncol 45:47–54

Kortmann RD, Kuhl J, Timmermann B, Mittler U, Urban C, Budach V, Richter E, Willich N, Flentje M, Berthold F, Slavc I, Wolff J, Meisner C, Wiestler O, Sorensen N, Warmuth-Metz M, Bamberg M (2000) Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91. Int J Radiat Oncol Biol Phys 46:269–279

Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, Wilson KA, Byars A, Sahmoud T, Franz DN (2010) Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med 363:1801–1811

Kuo DJ, Weiner HL, Wisoff J, Miller DC, Knopp EA, Finlay JL (2003) Temozolomide is active in childhood, progressive, unresectable, low-grade gliomas. J Pediatr Hematol Oncol 25:372–378

Kushner BH, Kramer K, Cheung NK (1999) Oral etoposide for refractory and relapsed neuroblastoma. J Clin Oncol 17:3221–3225

Lafay-Cousin L, Holm S, Qaddoumi I, Nicolin G, Bartels U, Tabori U, Huang A, Bouffet E (2005) Weekly vinblastine in pediatric low-grade glioma patients with carboplatin allergic reaction. Cancer 103: 2636–2642

Lafay-Cousin L, Sung L, Carret AS, Hukin J, Wilson B, Johnston DL, Zelcer S, Silva M, Odame I, Mpofu C, Strother D, Bouffet E (2008) Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. Cancer 112:892–899

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373:23–34

Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, Fry TJ, Orentas R, Sabatino M, Shah NN, Steinberg SM, Stroncek D, Tschernia N, Yuan C, Zhang H, Zhang L, Rosenberg SA, Wayne AS, Mackall CL (2015) T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic

leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 385:517–528
Levin VA, Lamborn K, Wara W, Davis R, Edwards M, Rabbitt J, Malec M, Prados MD (2000) Phase II study of 6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine chemotherapy with radiotherapy for treating malignant glioma in children. Neuro Oncol 2:22–28
Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, Pritchard J, Malpas JS, Baker AR, Kirkpatrick JA et al (1986) The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 314:1600–1606
Longee DC, Friedman HS, Albright RE Jr, Burger PC, Oakes WJ, Moore JO, Schold SC Jr (1990) Treatment of patients with recurrent gliomas with cyclophosphamide and vincristine. J Neurosurg 72:583–588
Mahaley MS Jr, Hipp SW, Dropcho EJ, Bertsch L, Cush S, Tirey T, Gillespie GY (1989) Intracarotid cisplatin chemotherapy for recurrent gliomas. J Neurosurg 70:371–378
Mahoney DH Jr, Strother D, Camitta B, Bowen T, Ghim T, Pick T, Wall D, Yu L, Shuster JJ, Friedman H (1996) High-dose melphalan and cyclophosphamide with autologous bone marrow rescue for recurrent/progressive malignant brain tumors in children: a pilot pediatric oncology group study. J Clin Oncol 14:382–388
Mahoney DH Jr, Cohen ME, Friedman HS, Kepner JL, Gemer L, Langston JW, James HE, Duffner PK, Kun LE (2000) Carboplatin is effective therapy for young children with progressive optic pathway tumors: a Pediatric Oncology Group phase II study. Neuro Oncol 2:213–220
Mason WP, Goldman S, Yates AJ, Boyett J, Li H, Finlay JL (1998a) Survival following intensive chemotherapy with bone marrow reconstitution for children with recurrent intracranial ependymoma–a report of the Children's Cancer Group. J Neurooncol 37:135–143
Mason WP, Grovas A, Halpern S, Dunkel IJ, Garvin J, Heller G, Rosenblum M, Gardner S, Lyden D, Sands S, Puccetti D, Lindsley K, Merchant TE, O'Malley B, Bayer L, Petriccione MM, Allen J, Finlay JL (1998b) Intensive chemotherapy and bone marrow rescue for young children with newly diagnosed malignant brain tumors. J Clin Oncol 16:210–221
Massimino M, Gandola L, Luksch R, Spreafico F, Riva D, Solero C, Giangaspero F, Locatelli F, Podda M, Bozzi F, Pignoli E, Collini P, Cefalo G, Zecca M, Casanova M, Ferrari A, Terenziani M, Meazza C, Polastri D, Scaramuzza D, Ravagnani F, Fossati-Bellani F (2005) Sequential chemotherapy, highdose thiotepa, circulating progenitor cell rescue, and radiotherapy for childhood high-grade glioma. Neuro Oncol 7:41–48
Mathew P, Ribeiro RC, Sonnichsen D, Relling M, Pratt C, Mahmoud H, Bowman L, Meyer W, Avery L, Crist W (1994) Phase I study of oral etoposide in children with refractory solid tumors. J Clin Oncol 12:1452–1457
Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, Swift P, Shimada H, Black CT, Brodeur GM, Gerbing RB, Reynolds CP (1999) Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Child Cancer Group N Engl J Med 341:1165–1173
Middleton MR, Margison GP (2003) Improvement of chemotherapy efficacy by inactivation of a DNA-repair pathway. Lancet Oncol 4:37–44
Miettinen S, Laurikainen E, Johansson R, Minn H, Laurell G, Salmi TT (1997) Radiotherapy enhanced ototoxicity of cisplatin in children. Acta Otolaryngol Suppl 529:90–94
Mikaeloff Y, Raquin MA, Lellouch-Tubiana A, Terrier-Lacombe MJ, Zerah M, Bulteau C, Habrand JL, Kalifa C (1998) Primitive cerebral neuroectodermal tumors excluding medulloblastomas: a retrospective study of 30 cases. Pediatr Neurosurg 29:170–177
Modak S, Gardner S, Dunkel IJ, Balmaceda C, Rosenblum MK, Miller DC, Halpern S, Finlay JL (2004) Thiotepa-based high-dose chemotherapy with autologous stem-cell rescue in patients with recurrent or progressive CNS germ cell tumors. J Clin Oncol 22:1934–1943
Mukherjee P, Das SK (1990) Antiproliferative action of retinoic acid in cultured human brain tumour cells Gl-As-14(S). Cancer Lett 52:83–89
Mulhern RK, Palmer SL, Reddick WE, Glass JO, Kun LE, Taylor J, Langston J, Gajjar A (2001) Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. J Clin Oncol 19:472–479
Needle MN, Molloy PT, Geyer JR, Herman-Liu A, Belasco JB, Goldwein JW, Sutton L, Phillips PC (1997) Phase II study of daily oral etoposide in children with recurrent brain tumors and other solid tumors. Med Pediatr Oncol 29:28–32
Neuwelt EA, Diehl JT, Vu LH, Hill SA, Michael AJ, Frenkel EP (1981) Monitoring of methotrexate delivery in patients with malignant brain tumors after osmotic blood–brain barrier disruption. Ann Intern Med 94:449–454
Neuwelt EA, Specht HD, Howieson J, Haines JE, Bennett MJ, Hill SA, Frenkel EP (1983) Osmotic blood–brain barrier modification: clinical documentation by enhanced CT scanning and/or radionuclide brain scanning. AJR Am J Roentgenol 141:829–835
Newlands ES, Stevens MF, Wedge SR, Wheelhouse RT, Brock C (1997) Temozolomide: a review of its discovery, chemical properties, pre-clinical development and clinical trials. Cancer Treat Rev 23:35–61
Newton HB, Page MA, Junck L, Greenberg HS (1989) Intraarterial cisplatin for the treatment of malignant gliomas. J Neurooncol 7:39–45
Newton HB, Turowski RC, Stroup TJ, McCoy LK (1999) Clinical presentation, diagnosis, and pharmacotherapy of patients with primary brain tumors. Ann Pharmacother 33:816–832
Nicholson HS, Krailo M, Ames MM, Seibel NL, Reid JM, Liu-Mares W, Vezina LG, Ettinger AG, Reaman GH (1998) Phase I study of temozolomide in children and

adolescents with recurrent solid tumors: a report from the Children's Cancer Group. J Clin Oncol 16: 3037–3043

Nicolao P, Giometto B (2003) Neurological toxicity of ifosfamide. Oncology 65(Suppl 2):11–16

Ortega JA, Rivard GE, Isaacs H, Hittle RE, Hays DM, Pike MC, Karon MR (1975) The influence of chemotherapy on the prognosis of rhabdomyosarcoma. Med Pediatr Oncol 1:227–234

Packer RJ (2002) Radiation-induced neurocognitive decline: the risks and benefits of reducing the amount of wholebrain irradiation. Curr Neurol Neurosci Rep 2:131–133

Packer RJ, Sutton LN, Goldwein JW, Perilongo G, Bunin G, Ryan J, Cohen BH, D'Angio G, Kramer ED, Zimmerman RA et al (1991) Improved survival with the use of adjuvant chemotherapy in the treatment of medulloblastoma. J Neurosurg 74:433–440

Packer RJ, Sutton LN, Elterman R, Lange B, Goldwein J, Nicholson HS, Mulne L, Boyett J, D'Angio G, Wechsler-Jentzsch K et al (1994) Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. J Neurosurg 81:690–698

Packer RJ, Ater J, Allen J, Phillips P, Geyer R, Nicholson HS, Jakacki R, Kurczynski E, Needle M, Finlay J, Reaman G, Boyett JM (1997) Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive lowgrade gliomas. J Neurosurg 86:747–754

Packer RJ, Goldwein J, Nicholson HS, Vezina LG, Allen JC, Ris MD, Muraszko K, Rorke LB, Wara WM, Cohen BH, Boyett JM (1999) Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group Study. J Clin Oncol 17:2127–2136

Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL, Bayer L, LaFond D, Donahue BR, Marymont MH et al (2006) Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 24:4202–4208

Paku S (1998) Current concepts of tumor-induced angiogenesis. Pathol Oncol Res 4:62–75

Papadakis V, Dunkel IJ, Cramer LD, Kramer E, Papadopoulos E, Goldman S, Packer RJ, Willoughby M, Baker D, Garvin J, Strandjord S, Coccia P, Kaplan AM, Klemperer M, Finlay JL (2000) High-dose carmustine, thiotepa and etoposide followed by autologous bone marrow rescue for the treatment of high risk central nervous system tumors. Bone Marrow Transplant 26:153–160

Papadopoulos KP, Garvin JH, Fetell M, Vahdat LT, Garrett TJ, Savage DG, Balmaceda C, Bruce J, Sisti M, Isaacson S, De LaPaz R, Hawks R, Bagiella E, Antman KH, Hesdorffer CS (1998) High-dose thiotepa and etoposide-based regimens with autologous hematopoietic support for high-risk or recurrent CNS tumors in children and adults. Bone Marrow Transplant 22:661–667

Pegg AE (1990) Mammalian O^6-alkylguanine-DNA alkyltransferase: regulation and importance in response to alkylating carcinogenic and therapeutic agents. Cancer Res 50:6119–6129

Pegg AE, Byers TL (1992) Repair of DNA containing O^6-alkylguanine. FASEB J 6:2302–2310

Perry JR, Brown MT, Gockerman JP (1998) Acute leukemia following treatment of malignant glioma. J Neurooncol 40:39–46

Pluda JM (1997) Tumor-associated angiogenesis: mechanisms, clinical implications, and therapeutic strategies. Semin Oncol 24:203–218

Pollack IF, Boyett JM, Finlay JL (1999) Chemotherapy for high-grade gliomas of childhood. Childs Nerv Syst 15:529–544

Pollack IF, Hamilton RL, Sobol RW, Burnham J, Yates AJ, Holmes EJ, Zhou T, Finlay JL (2006) O^6-methylguanine-DNA methyltransferase expression strongly correlates with outcome in childhood malignant gliomas: results from the CCG-945 Cohort. J Clin Oncol 24:3431–3437

Pollack IF, Jakacki RI, Butterfield LH, Hamilton RL, Panigrahy A, Potter DM, Connelly AK, Dibridge SA, Whiteside TL, Okada H (2014) Antigen-specific immune responses and clinical outcome after vaccination with glioma-associated antigen peptides and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in children with newly diagnosed malignant brainstem and nonbrainstem gliomas. J Clin Oncol 32:2050–2058

Prados MD, Edwards MS, Rabbitt J, Lamborn K, Davis RL, Levin VA (1997) Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. J Neurooncol 32: 235–241

Prados MD, Schold SJS, Fine HA, Jaeckle K, Hochberg F, Mechtler L, Fetell MR, Phuphanich S, Feun L, Janus TJ, Ford K, Graney W (2003) A randomized, double-blind, placebocontrolled, phase 2 study of RMP-7 in combination with carboplatin administered intravenously for the treatment of recurrent malignant glioma. Neuro Oncol 5:96–103

Pratt WB, Ruddon RW, Ensminger WD, Maybaum J (1994) The anticancer drugs. Oxford University Press, New York

Rall DP, Zubrod CG (1962) Mechanisms of drug absorption and excretion passage of drugs in and out of the central nervous system. Annu Rev Pharmacol 2:109–128

Ridola V, Grill J, Doz F, Gentet JC, Frappaz D, Raquin MA, Habrand JL, Sainte-Rose C, Valteau-Couanet D, Kalifa C (2007) High-dose chemotherapy with autologous stem cell rescue followed by posterior fossa irradiation for local medulloblastoma recurrence or progression after conventional chemotherapy. Cancer 110:156–163

Robinson GW, Orr BA, Wu G, Gururangan S, Lin T, Qaddoumi I, Packer RJ, Goldman S, Prados MD, Desjardins A, Chintagumpala M, Takebe N, Kaste SC, Rusch M, Allen SJ, Onar-Thomas A, Stewart CF,

Fouladi M, Boyett JM, Gilbertson RJ, Curran T, Ellison DW, Gajjar A (2015) Vismodegib exerts targeted efficacy against recurrent sonic Hedgehog-Subgroup medulloblastoma: results from phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032. J Clin Oncol 33: 2646–2654

Robison NJ, Campigotto F, Chi SN, Manley PE, Turner CD, Zimmerman MA, Chordas CA, Werger AM, Allen JC, Goldman S, Rubin JB, Isakoff MS, Pan WJ, Khatib ZA, Comito MA, Bendel AE, Pietrantonio JB, Kondrat L, Hubbs SM, Neuberg DS, Kieran MW (2014) A phase II trial of a multi-agent oral antiangiogenic (metronomic) regimen in children with recurrent or progressive cancer. Pediatr Blood Cancer 61:636–642

Rodts GE Jr, Black KL (1994) Trans retinoic acid inhibits in vivo tumour growth of C6 glioma in rats: effect negatively influenced by nerve growth factor. Neurol Res 16:184–186

Rosen G (1986) Neoadjuvant chemotherapy for osteogenic sarcoma: a model for the treatment of other highly malignant neoplasms. Recent Results Cancer Res 103:148–157

Rutkowski S, Bode U, Deinlein F, Ottensmeier H, Warmuth-Metz M, Soerensen N, Graf N, Emser A, Pietsch T, Wolff JE, Kortmann RD, Kuehl J (2005) Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med 352:978–986

Samkari A, White J, Packer R (2015) SHH inhibitors for the treatment of medulloblastoma. Expert Rev Neurother 15:763–770

Schinkel AH, Smit JJ, van Tellingen O, Beijnen JH, Wagenaar E, van Deemter L, Mol CA, van der Valk MA, Robanus-Maandag EC, te Riele HP et al (1994) Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood–brain barrier and to increased sensitivity to drugs. Cell 77:491–502

Seeringer A, Bartelheim K, Kerl K, Hasselblatt M, Leuschner I, Rutkowski S, Timmermann B, Kortmann RD, Koscielniak E, Schneppenheim R, Warmuth-Metz M, Gerβ J, Siebert R, Graf N, Boos J, Frühwald MC (2014) Feasibility of intensive multimodal therapy in infants affected by rhabdoid tumors – experience of the EU-RHAB registry. Klin Padiatr 226:143–148

Sexauer CL, Khan A, Burger PC, Krischer JP, van Eys J, Vats T, Ragab AH (1985) Cisplatin in recurrent pediatric brain tumors. A POG Phase II study. A Pediatric Oncology Group Study. Cancer 56:1497–1501

Shih CS, Hale GA, Gronewold L, Tong X, Laningham FH, Gilger EA, Srivastava DK, Kun LE, Gajjar A, Fouladi M (2008) High-dose chemotherapy with autologous stem cell rescue for children with recurrent malignant brain tumors. Cancer 112:1345–1353

Shih KC, Shastry M, Williams JT, Jelsma PF, Abram SR, Ayyanar K, Burris HA 3rd, Infante JR (2014) Successful treatment with dabrafenib (GSK2118436) in a patient with ganglioglioma. J Clin Oncol 32:e98–e100

Siffert J, Allen JC (2000) Late effects of therapy of thalamic and hypothalamic tumors in childhood: vascular, neurobehavioral and neoplastic. Pediatr Neurosurg 33:105–111

Sikic BI, Fisher GA, Lum BL, Halsey J, Beketic-Oreskovic L, Chen G (1997) Modulation and prevention of multidrug resistance by inhibitors of P-glycoprotein. Cancer Chemother Pharmacol 40(Suppl):S13–S19

Skov K, MacPhail S (1991) Interaction of platinum drugs with clinically relevant x-ray doses in mammalian cells: a comparison of cisplatin, carboplatin, iproplatin, and tetraplatin. Int J Radiat Oncol Biol Phys 20:221–225

Smith MA, Rubinstein L, Anderson JR, Arthur D, Catalano PJ, Freidlin B, Heyn R, Khayat A, Krailo M, Land VJ, Miser J, Shuster J, Vena D (1999) Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. J Clin Oncol 17:569–577

Spiller SE, Ditzler SH, Pullar BJ, Olson JM (2008) Response of preclinical medulloblastoma models to combination therapy with 13-cis retinoic acid and suberoylanilide hydroxamic acid (SAHA). J Neurooncol 87:133–141

Sposto R, Ertel IJ, Jenkin RD, Boesel CP, Venes JL, Ortega JA, Evans AE, Wara W, Hammond D (1989) The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Childrens Cancer Study Group. J Neurooncol 7:165–177

Spoudeas HA, Charmandari E, Brook CG (2003) Hypothalamo-pituitary-adrenal axis integrity after cranial irradiation for childhood posterior fossa tumours. Med Pediatr Oncol 40:224–229

Stewart DJ (1994) A critique of the role of the blood–brain barrier in the chemotherapy of human brain tumors. J Neurooncol 20:121–139

Strother D, Ashley D, Kellie SJ, Patel A, Jones-Wallace D, Thompson S, Heideman R, Benaim E, Krance R, Bowman L, Gajjar A (2001) Feasibility of four consecutive high-dose chemotherapy cycles with stem-cell rescue for patients with newly diagnosed medulloblastoma or supratentorial primitive neuroectodermal tumor after craniospinal radiotherapy: results of a collaborative study. J Clin Oncol 19:2696–2704

Stupp R, Dietrich PY, Ostermann Kraljevic S, Pica A, Maillard I, Maeder P, Meuli R, Janzer R, Pizzolato G, Miralbell R, Porchet F, Regli L, de Tribolet N, Mirimanoff RO, Leyvraz S (2002) Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol 20:1375–1382

Su JM, Thompson P, Adesina A, Li XN, Kilburn L, Onar-Thomas A, Kocak M, Chyla B, McKeegan E, Warren KE, Goldman S, Pollack IF, Fouladi M, Chen A, Giranda V, Boyett J, Kun L, Blaney SM (2014) A phase I trial of veliparib (ABT-888) and temozolomide in children with recurrent CNS tumors: a pediatric brain tumor consortium report. Neuro Oncol 16:1661–1668

Sung KW, Yoo KH, Cho EJ, Koo HH, Lim do H, Shin HJ, Ahn SD, Ra YS, Choi ES, Ghim TT (2007)

High-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk or relapsed medulloblastoma or supratentorial primitive neuroectodermal tumor. Pediatr Blood Cancer 48:408–415

Tada T, Takizawa T, Nakazato F, Kobayashi S, Koike K, Oguchi M, Ishii E, Amano Y (1999) Treatment of intracranial nongerminomatous germ-cell tumor by high-dose chemotherapy and autologous stem-cell rescue. J Neurooncol 44:71–76

Taylor RE, Bailey CC, Robinson K, Weston CL, Ellison D, Ironside J, Lucraft H, Gilbertson R, Tait DM, Walker DA, Pizer BL, Imeson J, Lashford LS (2003) Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: the International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. J Clin Oncol 21:1581–1591

Trimble EL, Ungerleider RS, Abrams JA, Kaplan RS, Feigal EG, Smith MA, Carter CL, Friedman MA (1993) Neoadjuvant therapy in cancer treatment. Cancer 72:3515–3524

Usubalieva A, Pierson CR, Kavran CA, Huntoon K, Kryvenko ON, Mayer TG, Zhao W, Rock J, Ammirati M, Puduvalli VK, Lehman NL (2015) Primary meningeal pleomorphic xanthoastrocytoma with anaplastic features: a report of 2 cases, one with BRAF(V600E) mutation and clinical response to the BRAF inhibitor dabrafenib. J Neuropathol Exp Neurol 74(10):960–969

Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, Unsgaard G, Kuurne T (1997) Interstitial chemotherapy with carmustine-loaded polymers for highgrade gliomas: a randomized double-blind study. Neurosurgery 41:44–48; discussion 48–49

Vezmar S, Becker A, Bode U, Jaehde U (2003) Biochemical and clinical aspects of methotrexate neurotoxicity. Chemotherapy 49:92–104

Vogelbaum MA, Aghi MK (2015) Convection-enhanced delivery for the treatment of glioblastoma. Neuro Oncol 17(Suppl 2):ii3–ii8

von Bossanyi P, Diete S, Dietzmann K, Warich-Kirches M, Kirches E (1997) Immunohistochemical expression of P-glycoprotein and glutathione S-transferases in cerebral gliomas and response to chemotherapy. Acta Neuropathol 94:605–611

Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Sampson J, Wagner M, Bailey L, Bigner DD, Friedman AH, Friedman HS (2007) Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 25:4722–4729

Walker RW, Allen JC (1988) Cisplatin in the treatment of recurrent childhood primary brain tumors. J Clin Oncol 6:62–66

Warren K, Jakacki R, Widemann B, Aikin A, Libucha M, Packer R, Vezina G, Reaman G, Shaw D, Krailo M, Osborne C, Cehelsky J, Caldwell D, Stanwood J, Steinberg SM, Balis FM (2006) Phase II trial of intravenous lobradimil and carboplatin in childhood brain tumors: a report from the Children's Oncology Group. Cancer Chemother Pharmacol 58:343–347

Warren KE, Goldman S, Pollack IF, Fangusaro J, Schaiquevich P, Stewart CF, Wallace D, Blaney SM, Packer R, Macdonald T, Jakacki R, Boyett JM, Kun LE (2011) Phase I trial of lenalidomide in pediatric patients with recurrent, refractory, or progressive primary CNS tumors: Pediatric Brain Tumor Consortium study PBTC-018. J Clin Oncol 29(3):324–329

White L, Kellie S, Gray E, Toogood I, Waters K, Lockwood L, Macfarlane S, Johnston H (1998) Postoperative chemotherapy in children less than 4 years of age with malignant brain tumors: promising initial response to a VETOPEC-based regimen. A Study of the Australian and New Zealand Children's Cancer Study Group (ANZCCSG). J Pediatr Hematol Oncol 20:125–130

Wiestler O, Kleihues P, Pegg AE (1984) O^6-alkylguanine-DNA alkyltransferase activity in human brain and brain tumors. Carcinogenesis 5:121–124

Wilkins DE, Heller DP, Raaphorst GP (1993) Inhibition of potentially lethal damage recovery by cisplatin in a brain tumor cell line. Anticancer Res 13:2137–2142

Wismeth C, Hau P, Fabel K, Baumgart U, Hirschmann B, Koch H, Jauch T, Grauer O, Drechsel L, Brawanski A, Bogdahn U, Steinbrecher A (2004) Maintenance therapy with 13-cis retinoid acid in high-grade glioma at complete response after first-line multimodal therapy–a phase-II study. J Neurooncol 68:79–86

Yung WK, Kyritsis AP, Gleason MJ, Levin VA (1996) Treatment of recurrent malignant gliomas with high-dose 13-cisretinoic acid. Clin Cancer Res 2:1931–1935

Zacharoulis S, Levy A, Chi SN, Gardner S, Rosenblum M, Miller DC, Dunkel I, Diez B, Sposto R, Ji L, Asgharzadeh S, Hukin J, Belasco J, Dubowy R, Kellie S, Termuhlen A, Finlay J (2007) Outcome for young children newly diagnosed with ependymoma, treated with intensive induction chemotherapy followed by myeloablative chemotherapy and autologous stem cell rescue. Pediatr Blood Cancer 49:34–40

Zaky W, Dhall G, Ji L, Haley K, Allen J, Atlas M, Bertolone S, Cornelius A, Gardner S, Patel R, Pradhan K, Shen V, Thompson S, Torkildson J, Sposto R, Finlay J (2014) Intensive induction chemotherapy followed by myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for young children newly-diagnosed with central nervous system atypical teratoid/rhabdoid tumors: the Head Start III experience. Pediatr Blood Cancer 61:95–101

Zeltzer PM, Boyett JM, Finlay JL, Albright AL, Rorke LB, Milstein JM, Allen JC, Stevens KR, Stanley P, Li H, Wisoff JH, Geyer JR, McGuire-Cullen P, Stehbens JA, Shurin SB, Packer RJ (1999) Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. J Clin Oncol 17:832–845

Zwelling LA, Kohn KW (1979) Mechanism of action of cisdichlorodiammineplatinum(II). Cancer Treat Rep 63:1439–1444

Advances in Radiation Therapy

16

Mekhail Anwar, Sean M. McBride,
and Daphne A. Haas-Kogan

Contents

M. Anwar, MD, PhD (✉)
Department of Radiation Oncology, University of California San Francisco,
1825 4th Street, Room M2260, San Francisco, CA 94158, USA
e-mail: mekhail.anwar@ucsf.edu

S.M. McBride, MD, MPH
Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center,
1275 York Ave, New York, NY 10065, USA
e-mail: mcbrides@mskcc.org

D.A. Haas-Kogan, MD
Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston Children's Hospital, 450 Brookline Ave. D1622, Boston, MA 02215-5418, USA
e-mail: dhaas-kogan@lroc.harvard.edu

16.1 Introduction

Recent developments in radiation therapy have largely centered on the improvement in delivering radiation to a highly conformal target with high precision. The increased use of stereotactic body radiotherapy (SBRT) has also introduced another dimension of treatment, potentially replacing surgery in select situations to aggressive treatment of oligometastatic disease to invoking a systemic response using immunomodulators. Simultaneously, advances in systemic

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_16

therapy ranging from traditional chemotherapy regimens to targeted biologics, and more recently immune modulators, are rapidly affecting the field of radiation oncology. These advances rely on a synergy between significant improvements in radiation delivery, driven by image guidances and more conformal delivery or radiation, and a greater understanding of tumor biology. This chapter will focus on an understanding of advances in these areas and future directions for pediatric brain tumors levering these innovations.

16.2 Radiobiology

Understanding the radiobiology of tumors, and the normal tissues surrounding then, is essential to understanding what modality of radiation to use; higher dose per fraction, such as SBRT, results in ablation of all targeted tissue, while conventionally fractionated radiation (CF-RT) has a selective preference for tumor over normal tissues. The results of this mean that for tumors with diffuse invasion into normal tissues, or abut critical structures, CF-RT is often used, while tumors well circumscribed and identified on imaging can be selectively targeted with SBRT.

The biologic effects of ionizing radiation primarily result from the formation of double-strand breaks in cellular DNA (Hall 2000). Although most radiation-induced single-strand DNA breaks are efficiently repaired, double-strand breaks cause irreparable damage, resulting in mitotic cell death. Photon radiation (X-ray or gamma ray) can cause damage by direct interaction with the DNA molecule or indirectly by the formation of free radicals that then interact chemically with DNA leading to double-strand breaks. Oxygen then "fixes" the DNA damage, preventing its repair, resulting in cell death. This process makes the oxygen content of tumors important, and poorly oxygenated tissues are two to three times more resistant to radiation than normally oxygenated tissues. The hypoxic tumor microenvironment therefore poses a challenge to the effectiveness of radiation and can be especially exacerbated in the postoperative setting.

New methods of developing charged particle irradiation leverage the unique properties of these particles to improve both the biological effectiveness and dosimetry of radiation therapy. Charged particles such as helium, carbon, or neon predominantly cause damage by direct interactions and therefore do not depend on oxygenation as much as photons. Furthermore, the properties of these particles lend themselves to having a Bragg peak, whereby the majority of the particle energy is deposited at the end of its path, resulting in a steep dose falloff, enabling the exit dose of the particle beam to be significantly attenuated compared to photon irradiation. These properties lend themselves well to targets where an entry beam is needed, but the exit dose associated with high-energy photons can cause toxicity, such as craniospinal irradiation in pediatric patients. High-energy neutrons, although not charged, also interact with the nucleus of an atom, resulting in the creation of densely ionizing recoil protons, alpha particles, and nuclear fragments.

16.3 Intensity-Modulated Radiation Therapy (IMRT)

Analogous to the selectivity of targeted molecular agents, radiotherapy's selectivity stems not only from its radiobiological properties (preferentially damaging cells with disrupted DNA repair pathways, characteristic of tumor cells) but also from the ability to spatially map radiation to specific target areas. In order to achieve maximal dose at the tumor, while limiting the high-dose region outside the target area, multiple different beams are aimed at the target area, each entering the patient from a different angle. The radiation distribution can be further shaped by modulating the shape of each beam using leaves called multileaf collimators or MLCs. Intensity-modulated radiotherapy (IMRT) utilizes these features to combine multiple beam angles and shapes that allow multiple beam angles to precisely sculpt the radiation dose delivered (Purdy 1999; Webb 2000). The putative clinical advantage of IMRT resides in its demonstrated ability to improve dose conformity and spare normal tissue.

Prospective trials designed to demonstrate survival benefit have yet to be conducted; however, there is recent evidence that, at least for the treatment of medulloblastomas, IMRT significantly reduces auditory toxicity (Huang et al. 2002).

IMRT can either be "forward planned" (Verhey 1999) in which each beam shape and angle is manually entered to derive the optimal dose distribution, or as is more commonly done with complex shapes, IMRT can be "inverse planned." Inverse planning relies on mathematically optimizing the beam shapes and angles based on the desired dosimetry.

Methods of increasing the conformality have recently been implemented in commercially available linear accelerators. These methods consist of VMAT (volumetric modulated arc therapy), tomotherapy, and "4-π" therapy (Dong et al. 2013; Rwigema et al. 2015). The common theme across these newer techniques is the increase in the number of angles with which to delivery radiotherapy, resulting in increased conformality. Arc therapy relies on a gantry that is constantly rotating around the patient while the beam shape is modulated, dramatically increasing the number of beam angles from the standard "step and shoot" technique. Tomotherapy applies the same principle of a rotating beam to achieve high conformality and adds a moving table that slides the patient past the gantry (similar to a CT scanner), enabling radiation to be given to a much longer field. This has made it very useful in delivering craniospinal irradiation, since there is no need for matching fields, eliminating potential cold spots. Taking the notion of "more angles equals higher conformality" one step further, the 4-π technique utilizes noncoplanar beams to increase the number of angles with which to delivery radiotherapy. Appropriately, the name "4-π" comes from the solid angle subtended by an entire sphere.

Using these techniques can result in dramatic dose gradients, allowing high doses to tumor, with rapid dose falloff (Verhey 1999). These techniques can allow precise shaping of radiation to a complex structure. Illustrating this is a radiation plan for whole ventricular radiation in a 21-year-old female with history of grade 3 pineal parenchymal tumor of intermediate differentiation (PPTID) after gross total resection (GTR) (Fig. 16.1). The MRI sequences are co-registered to the planning CT to outline the target area as well as critical structures, like the optic chiasm. Because of rapid falloff of dose, immobilization systems for IMRT are of particular importance to avoid underdosing the target or delivering a high dose to a neighboring critical structure. Another issue that must be noted when using IMRT is integral dose, as low entrance and exit dose are associated with each beam angle, resulting in a low dose given to a large volume of tissue. Also, because of the beam modulation with IMRT, the total number of monitor units delivered to the patient is higher than with conventional treatments.

In the use of any of these conformal therapies, it is important to consider the relevant anatomical features. Particularly in the use of inverse planning, if an area is not contoured as tumor, it will likely receive suboptimal dose. Areas of subclinical disease must also be taken into account. Only through careful consideration of anatomy and dose can IMRT be safely applied. Once can achieve sparing of inner structures with IMRT, as compared to 3DCRT, without compromise of the dose delivered to the target volume (Fig. 16.2).

While IMRT has many advantages, there are also disadvantages that should be noted when selecting the treatment modality. With IMRT, the total radiation needed to deliver the plan (i.e., the monitor units) is increased since much of the beam is blocked by MLCs resulting in additional scatter and leakage. Furthermore, with increased beam angles, a larger volume of low dose, or integral dose, is delivered. A study found that, in high-grade gliomas, IMRT actually decreased integral dose by 7–10% relative to 3DCRT (Hermanto et al. 2007). Furthermore, IMRT results in an inhomogeneous dose over within the treated volume, with hot spots reaching doses of 10–15% above the prescription dose. Although these hot spots typically fall within the tumor volume, the significance of having regions of extremely high dose is unclear.

To address patient immobilization and daily positioning, some centers use image-guided

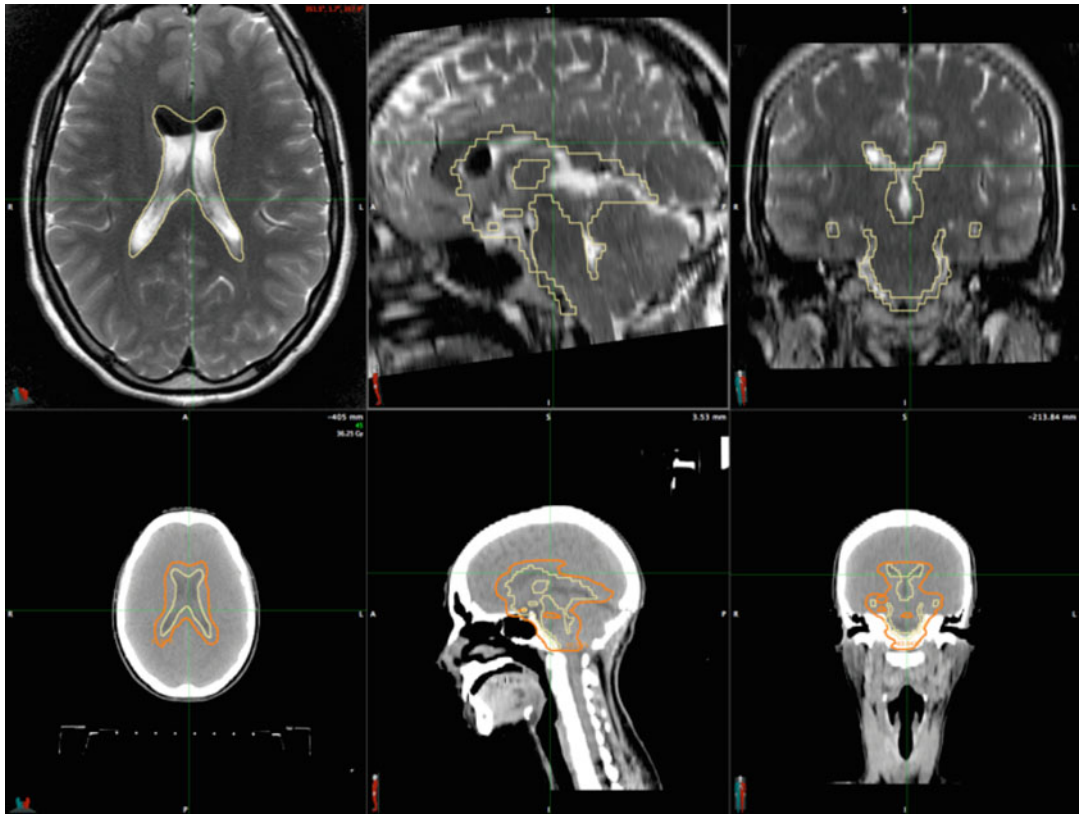

Fig. 16.1 A 21-year-old female with history of grade 3 pineal parenchymal tumor of intermediate differentiation (PPTID) status post gross total resection (GTR) receiving adjuvant whole ventricular radiation therapy. *Top row*: MRI images (axial, sagittal, coronal) corresponding to the planning CT scan (*bottom row*). The whole ventricular volume is outlined in *yellow* and the prescribed radiation dose in *orange* (Courtesy of Dr. Steve Braunstein, Department of Radiation Oncology, UCSF)

techniques. These new approaches allow the radiation oncologist to confirm the tumor location every day. One of the most exciting techniques to minimize tumor and patient movement is the use of a CT image of the patient using the "cone-beam" technique that generates an image of the tumor and all surrounding normal structures using the same linear accelerator with which the patient is being treated. Newer machines are commonly incorporating kilovoltage cone-beam imaging, providing images comparable in quality to clinical CT scans, and facilitating accurate image registration. Appropriate adjustments can then be made daily to ensure that the tumor is receiving the prescribed dose of radiation, and normal tissues are receiving doses within their tolerance range.

The emerging concept of image-guided motion management is standard in the radiation oncology community. Motion management techniques primarily center on accounting for respiratory motion. Abdominal compression devices are used to limit the range of motion associated with breathing. Respiratory gating is used to trigger the radiation beam when the target is within a specified window.

16.3.1 Immobilization and Imaging

The initial step of the planning process is patient immobilization, to ensure reliable reproduction of the radiation delivery each day. This position may be different for each patient and depends on the specific location, shape and size of the tumor,

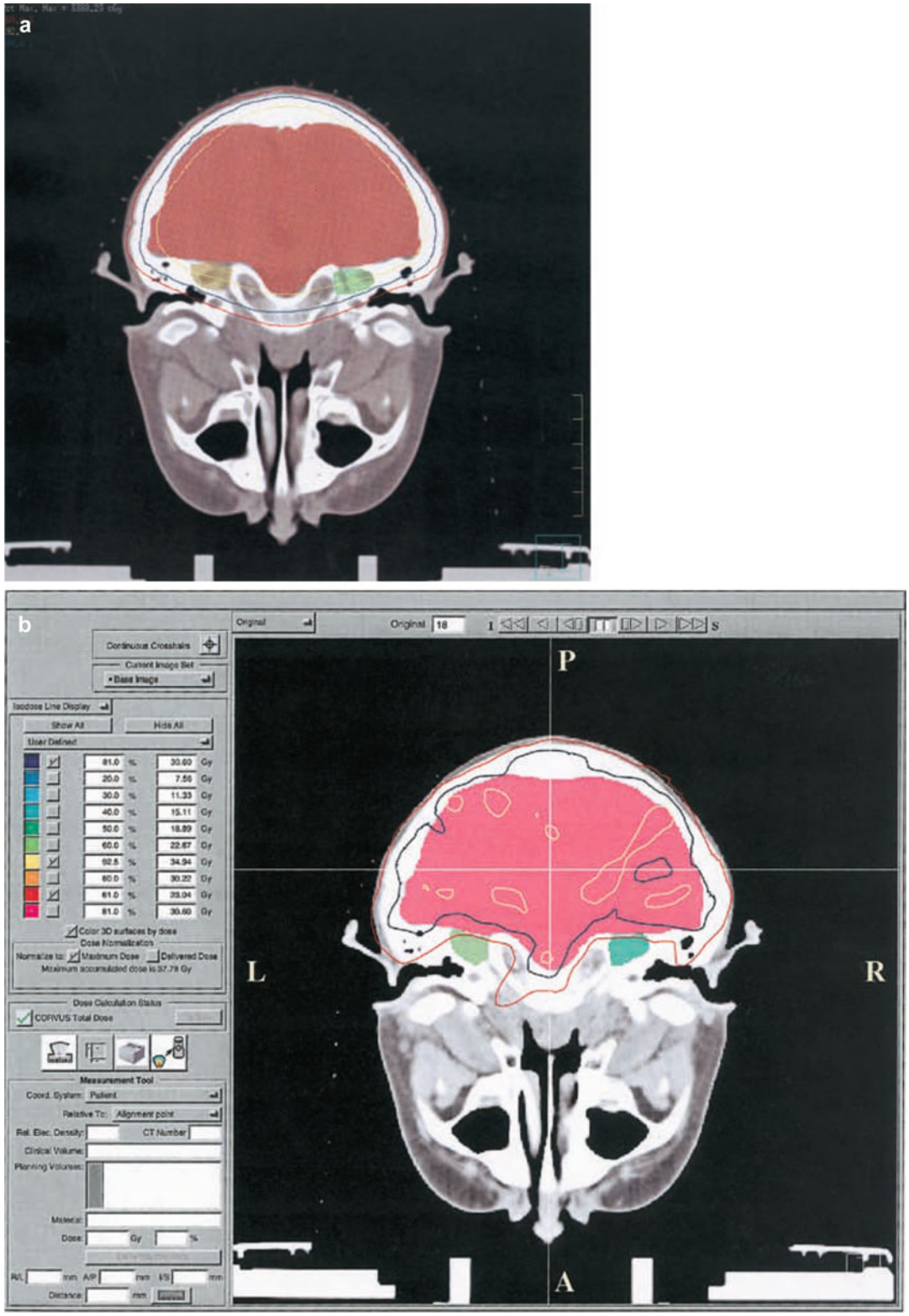

Fig. 16.2 Comparison of axial sections planned with either three-dimensional conformal radiation therapy (3DCRT) (**a**) or intensity-modulated radiation therapy (IMRT) (**b**), demonstrating the sparing of inner structures achieved with IMRT without compromising the dose delivered to the target volume

and areas at risk for suspected microscopic disease. A variety of customizable immobilization devices are available, including thermoplastic face masks, alpha cradles, and vacuum bags. It is important to note that as the planned course of radiation therapy becomes increasingly conformal and high dose per fraction (often exceeding the tolerance of neighboring critical structures), the importance of reliable and reproducible immobilization becomes critical. Once the patient has been optimally and reproducibly positioned, localization marks are placed on the skin. With the patient in the treatment position, CT images of the area of interest are obtained. These data are then transferred to the planning system, at which point the clinician can define target volumes as well as critical structures. While some well-defined structures can be contoured automatically, most structures must be defined manually. A pretreatment CT scan is generally used for treatment planning, although other imaging modalities such as MRI and PET/CT scans can be co-registered with the CT data.

16.3.2 Target Definition and Planning

The CT images are analyzed jointly by radiation oncologists, by diagnostic radiologists, and occasionally by other treating physicians such as medical oncologists and surgeons. The treatment volume is dictated by the natural history of the tumor. Gross tumor volume (GTV) is defined by physical exam and imaging studies and encompasses the macroscopic extent of the tumor. Clinical target volume (CTV) contains both the GTV and areas at risk for microscopic spread of disease. The planning target volume (PTV) is defined as the CTV surrounded by adequate margin to account for variation in patient position, organ motion, and other movement (Purdy 1999; Hall 2000).

Once target volumes and critical structures are defined, beam geometry and weighting are defined, and dose distribution is calculated (Purdy 1999). As discussed earlier, this can be done using either forward planning where the beam directions and energies are designated by the planner (Fig. 16.3) or inverse planning whereby an optimization algorithm determines the optimal arrangement of beams to deliver dose to the target while respecting the prescribed normal tissue constraints.

Plans are then evaluated by viewing isodose curves on serial images of a CT scan (Fig. 16.4a–c), as well as by the generation of dose–volume histograms (DVHs; Fig. 16.5). DVHs can be generated for a tumor volume or other organ of interest, allowing the clinician to evaluate the dose delivered to the total volume. DVHs typically graph percent volume of a given tissue on the *Y*-axis and dose on the *X*-axis. This allows a clinician to visualize what percentage of a defined structure is receiving a given dose. These data allow plans to be modified as needed to either increase dose delivered to tumor or decrease dose to a nearby critical structure. Dose constraints are often given prescribing a volume of an organ that cannot exceed a certain dose. For example, a common constraint for normal lung tissue is V20 Gy <20 % which means that the volume receiving 20 Gy should be less than 20 %.

16.3.3 Treatment Verification and Delivery

Treatment verification for IMRT plans is often done using patient-specific QA (quality assurance). This involves delivering the dose to a phantom, embedded with dosimeters, and ensuring that the received radiation agrees with the planned radiation dose. For 3D plans, DRRs corresponding to the planned radiation fields are generated. These DRRs typically display field shapes and tumor volumes, as well as standard radiographic information, such as anatomy.

During the first day of treatment, before the first radiation dose is delivered, the patient position confirmed using a cone-beam CT. For patients undergoing radiation with 3D planning, all the beam angles are confirmed using X-rays from the beam's eye view, called portal films. These films can be done with conventional portal films or with the use of an electronic portal-imaging device (EPID). Because there is no development time (as there is with conventional

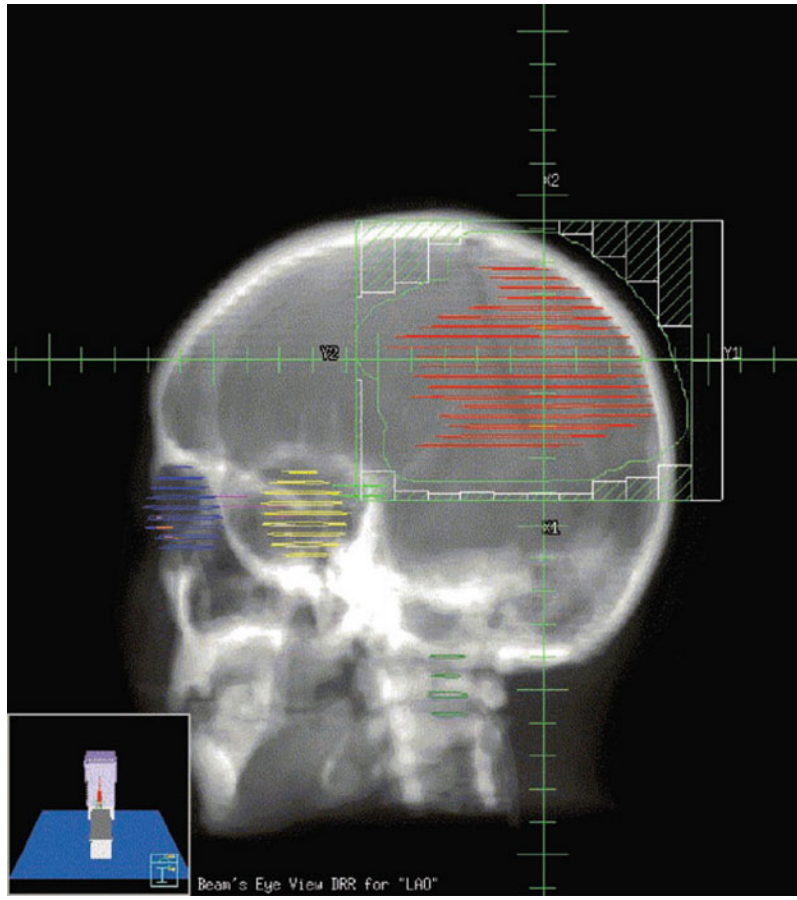

Fig. 16.3 Beam's eye view (BEV) of a left anterior oblique field in a patient with a supratentorial primitive neuroectodermal tumor (PNET). BEV allows the visualization of the relationship of tumor volumes to those of critical normal tissues, as if looking from the origin of the beam. This allows beam angles and beam shaping to be selected more intelligently. Once an initial plan has been developed, the resulting dose distributions are calculated and evaluated by the clinician. The plan can then be altered to improve on initial results, if necessary. The beam directions as well as their relative weights and shapes are modified to finally optimize the 3DCRT plan (Courtesy of Clayton Akazawa, Department of Radiation Oncology, UCSF)

portal images), the use of an EPID can significantly shorten the time needed to take portal images of complex multifield plans.

16.4 New Technical Approaches

16.4.1 Charged Particle Therapy (Proton Therapy)

Although proton radiation has similar inherent biological effectiveness as conventional radiation, its charged nature lends it a physical characteristic whereby the dose falls off rapidly (after penetrating a specified distance which is a function of the energy of the particle), often referred to as the "Bragg peak" (Yang 1999). For reference, the dose proximal to the Bragg peak is roughly 30 % of Bragg peak, while the dose afterward is almost zero (Mitin and Zietman 2014). This feature allows the exit dose to be significantly reduced sparing critical structures. It is conventionally accepted that proton beam therapy is superior to standard radiotherapy for skull-base chondrosarcomas and chordomas, but its effectiveness compared to radiosurgery or conformal radiotherapy has yet to be demonstrated in randomized clinical trials. It is often used in

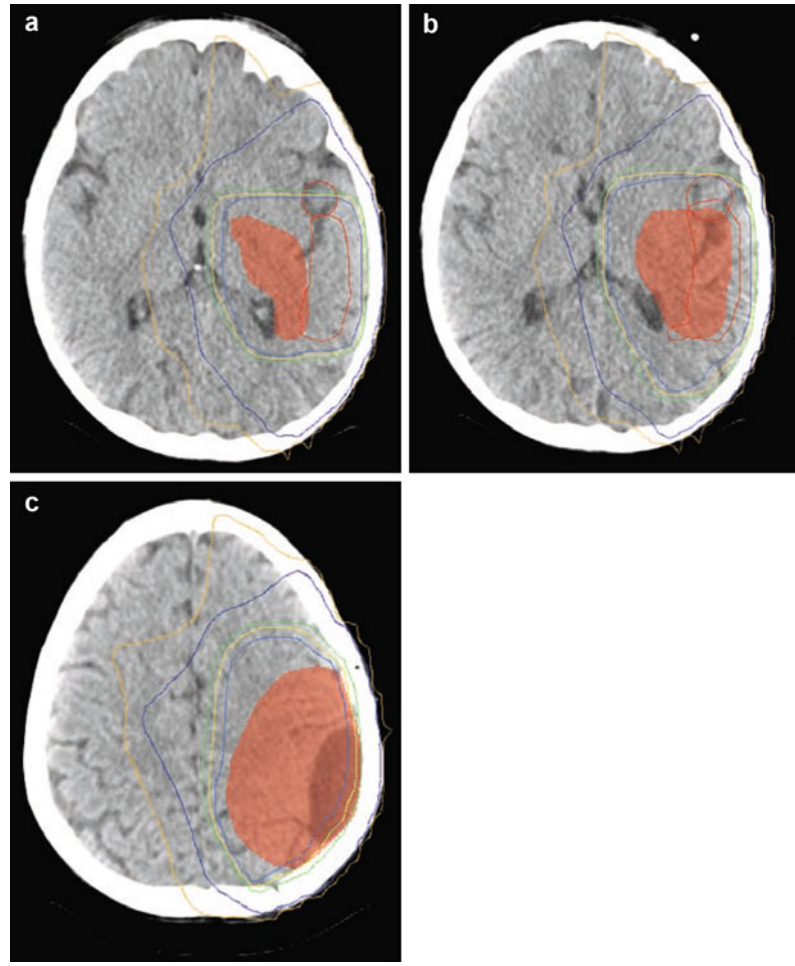

Fig. 16.4 (**a**–**c**) Isodose curves of a three-dimensional conformal plan on serial axial slices in a patient with a supratentorial primitive neuroectodermal tumor (PNET). *Red line* depicts the 99 % isodose line, *light blue* represents 95 %, *yellow* depicts 93 %, *green* depicts 90 %, *blue* depicts 60 %, and *gold* depicts 50 % (Courtesy of Clayton Akazawa, Department of Radiation Oncology, UCSF)

posterior fossa tumors as well as craniospinal irradiation, where the target structure is close to the surface of the patient.

The physical advantages of proton beam radiotherapy must be weighed against proton beam contamination by neutrons that may contribute significantly to risks of second malignancies, particularly in children. Additionally, the maturity of radiotherapy planning in protons lags behind photons, often requiring larger margins for proton therapy. A recent review notes an average of 3.5 % + 1 mm for the uncertainty margin when planning with protons (Mitin and Zietman 2014). Improvements in planning software and delivery of protons, particularly with pencil-beam scanners, may allow reduction of the PTV margins as these techonlogies mature.

Despite the lack of Class 1 evidence, retrospective studies do exist to support the use of proton-based radiotherapy in specific subtypes of pediatric intracranial lesions. Macdonald et al. found that in pediatric ependymomas, local control, progression-free survival, and overall survival rates were comparable to those published in the literature for photon radiotherapy. As anticipated, traditional proton therapy and intensity-modulated proton therapy (IMPT) resulted in greater sparing of normal tissue compared to photon-based IMRT (MacDonald et al. 2008). Using a model designed to predict neurocognitive dysfunction after radiation therapy, Merchant et al. concluded that the reduction in lower-dose volumes and mean dose afforded by proton therapy might reduce the incidence of

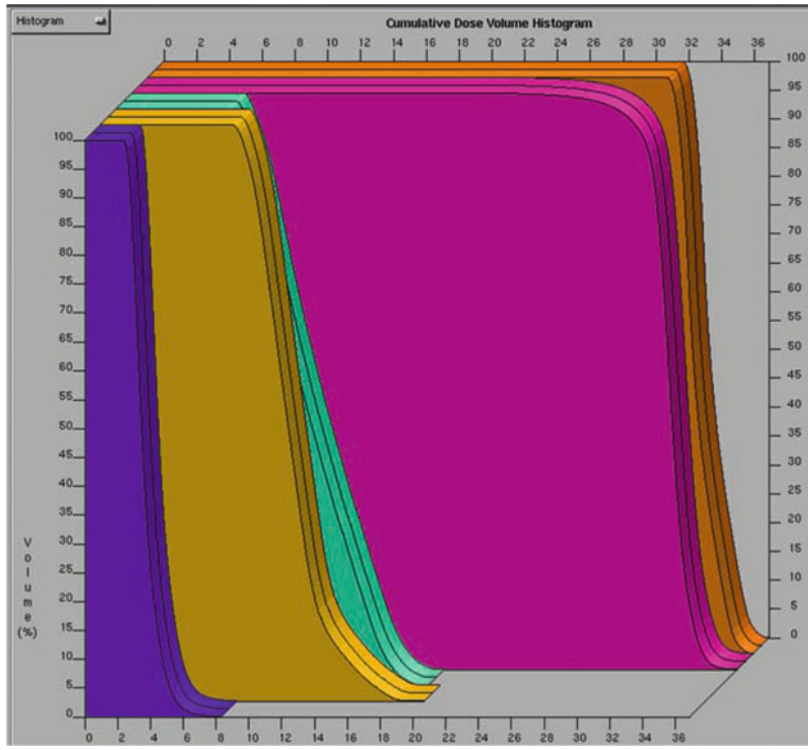

Fig. 16.5 A dose–volume histogram for an intensity-modulated radiation therapy (IMRT) plan in a patient with a medulloblastoma. Clinical target volume (CTV) is depicted in *orange*, planning target volume (PTV) in *pink*, left ear in *light blue*, right ear in *orange*, and optic chiasm in *dark blue* (Courtesy of Pam Akazawa, Department of Radiation Oncology, UCSF)

late-term sequelae in children with medulloblastomas, craniopharyngiomas, and optic pathway gliomas (Merchant et al. 2008). Specifically, they found that small, critical, and normal structures such as the cochlea and hypothalamus, which were anatomically separated from the PTV, received substantially less radiation using protons compared with photons. Proton radiotherapy would therefore be expected to reduce the risks of endocrine deficits and hearing loss. In addition, protons lowered the low (0–20 Gy) and intermediate (20–40 Gy) doses to the cerebrum in patients receiving focal radiation. Using longitudinal models of radiation dose–cognitive effects, the data indicated that proton radiotherapy would mitigate intelligence quotient (IQ) loss.

The benefit of proton beam radiotherapy in children is well exemplified by its use for craniospinal irradiation. Comparisons of proton beam, conventional 3D radiation, and IMRT for treatment of the posterior fossa and spinal column suggest superior sparing of normal structures by protons. In particular, protons are likely to mitigate long-term toxicities related to hearing, endocrine, and cardiac functions. For example, 90 % of the cochlea received 101.2 % of posterior fossa boost dose with conventional radiation techniques, 33.4 % with IMRT, and only 2.4 % with protons. Similarly, 50 % of the heart received 72.2 %, 29.5 %, and 0.5 % of the posterior fossa boost dose for conventional X-ray therapy, IMRT, and proton beam therapy, respectively (St. Clair et al. 2004). Comparable reductions in normal tissue doses have been documented in other pediatric disease sites (Lee et al. 2005), such as retinoblastoma and sarcoma.

Recent publications highlight potentially higher toxicities observed after treatment with protons than with photons, and one must

acknowledge persistent uncertainties related to proton dose deposition and biological effects. A study examining imaging changes following proton- or photon-based (IMRT) radiotherapy demonstrated more imaging changes following proton-based radiation compared to photon-based IMRT. Furthermore, only proton-treated patients experienced grade 3 or 4 changes and had persistent symptoms, including one grade 5 toxicity related to radiation necrosis documented at autopsy (Gunther et al. 2015). A similar study assessing brainstem toxicity following proton radiotherapy for pediatric brain or skull-base tumors reported a 2-year cumulative incidence of grade 3 or higher brainstem toxicity of 2.1 % ± 0.9 %, with one grade 5 toxicity (Indelicato et al. 2014).

To help assess the proper role of proton beam radiotherapy, the American Society for Radiation Oncology (ASTRO) published the findings of a task force in 2012 (Allen et al. 2012), noting that "In pediatric CNS malignancies PBT appears superior to photon approaches but more data is needed. In large ocular melanomas and chordomas, we believe that there is evidence for a benefit of PBT over photon approaches." Building on the biological principle of proton therapy, whereby a charged particle with mass can deposit its energy in a small, defined range within the body, carbon therapy is also being explored. Due to the significant cost, it is being investigated only in a few centers in the world.

16.4.2 Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) typically involves the delivery of a single large fraction of radiation therapy at the time of open surgery (Willett 2001). Radiation is most commonly given to the resection cavity using electrons. Depth of dose is controlled by choice of electron energy and use of bolus. Falloff is rapid beyond the effective range of the selected electron energy. There is little data regarding either the efficacy or the side effect profile of IORT in the treatment of primary pediatric CNS lesions. However, a recent Phase I study using the Photon Radiosurgery System found that IORT to a dose of 10 Gy prescribed to 2-mm depth was feasible and safe; the authors cautioned though that, when dose was maintained but depth increased to 5 mm, side effect, namely, radiation necrosis, increased (Kalapurakal et al. 2006).

16.4.3 Temporary or Permanent Brachytherapy

Interstitial brachytherapy, which involves the placement of radiation sources either directly in tissues or into catheters placed within tissue, allows for the delivery of high doses of radiation to a tumor region. The fundamental difference between brachytherapy and external beam radiation therapy is twofold: (1) the radioactive particle is often an electron in brachytherapy (as opposed to a photon), and (2) the dose falloff is related to geometry and goes as the inverse of the distance squared, since the source is very close to the target (Hall 2000). Both of these features give a sharp dose falloff, allowing highly conformal radiotherapy to be delivered, but, likely, all surgical procedures are highly dependent on operator experience.

Temporary brachytherapy typically entails the implantation of catheters in the tumor or tumor bed, using a variety of radioactive sources, including radium and cesium. In current practice, an ^{192}I source is frequently used, utilizing a robotic remote afterloading system to minimize dose to medical personnel. Permanent brachytherapy implants utilized seeds placed into the tumor cavity, and remain in the cavity, and commonly used sources are ^{125}I and ^{103}Pd.

A retrospective study reported a large series of pediatric brain tumors treated with ^{125}I brachytherapy (Sneed et al. 1996). Twenty-eight children were treated with temporary, high-activity ^{125}I brachytherapy for recurrent or persistent supratentorial, unifocal, well-circumscribed tumors less than 6 cm in diameter that had previously received external beam radiation therapy. Exclusion criteria included tumors with diffuse margins, corpus callosum involvement, or subependymal spread. The most useful result from this

study is the documentation of acute and late toxicities. Outcome data, however, are less reliable, given the variety of brain tumors included in the analysis. No Grade III or IV acute or late toxicities occurred. However, 22 patients (79 % of 28 total patients) required at least one reoperation following brachytherapy, and 17 of these 22 patients had evidence of necrosis in the resected specimen.

In an effort to reduce the incidence of radiation necrosis, an additional retrospective pediatric study looked at permanent low-activity ^{125}I seed implants for primary pediatric CNS lesions. Six patients with recurrent disease were enrolled, five of whom had received prior EBRT, and all of whom had reoperations after recurrence; only two patients had local failures at the first site of recurrence, leading the authors to conclude that low-activity permanent ^{125}I seed implants can help to provide good local control while diminishing the risk of significant treatment-related morbidity (Rostomily et al. 2001).

16.4.4 Stereotactic Radiosurgery (SBS) and Stereotactic Radiotherapy (SRT)

The primary difference with SRS and SRT over conventionally fractionated approaches is that the goal is to ablate the target region (analogous to surgical excision). This requires several factors: (1) excellent imaging capable of precisely delineating the tumor volume and neighboring critical structures for accurate targeting, (2) immobilization and intrafraction imaging to ensure stability of the target, and (3) motion management strategies to target moving tumors (i.e., lung and liver). Conceptually, SRS and SBRT consist of multiple beams of radiation, all converging at the designated target volume. The large number of noncoplanar beams allows increased conformality over the limited number of angles that a standard linear accelerator is capable of, translating into a sharper dose falloff outside of the target region. CyberKnife radiotherapy can be used to achieve high conformality to the tumor, while only a low dose is given to the surrounding brain tissue. In this example shown in Fig. 16.6, the green line represents 23 % of the dose, where the red represents the prescription isodose line (70 %).

There are several instruments capable of providing SBRT, and most new linear accelerators have this capability. The first instrument used for SRS was the Gamma Knife® with 201 collimated beams of cobalt-60 radiation. In this modality, a patient's head is physically immobilized to the table and a single or multidose ($\leq\leq 5$) regiment of focused radiation to a small intracranial target. Frequently, sensitive normal structures lie near the target volume. Rapid falloff of radiation dose outside the target spares adjacent normal tissues and maintains a safe, acceptable level of irradiation. The value of SRS has been demonstrated by many retrospective studies, which include a variety of benign and malignant brain tumors (Kondziolka et al. 2000).

Radiosurgery use in pediatric populations is less frequent; however, retrospective case series have proven its feasibility. One of the few outcome studies retrospectively examined a population of 90 pediatric patients, the majority of whom were diagnosed with medulloblastoma, anaplastic astrocytoma, glioblastoma, or primitive neuroectodermal tumor (PNET). In some patients, SRS was used as an initial treatment, while in others it was implemented at the time of recurrence. The study confirmed the safety of SRS in pediatric patients, with a minimal side effect profile; there was an apparent reduction in local failure at the site of first recurrence compared to historical controls, and efficacy was increased when SRS was used as initial management rather than as salvage. The authors concluded that, in cases where residual or recurrent tumor is focally unresectable, an SRS boost might be beneficial (Hodgson et al. 2001).

Stereotactic radiotherapy (SRT) uses a noninvasive immobilization device and fractionates dose. The number of fractions is typically five or less, but this is an arbitrary definition based on US billing codes. Again, the literature is lacking in randomized controlled trials, but a prospective trial studied the effect of SRT in 50 pediatric patients with low-grade astrocytomas, including optic pathway gliomas. All the children were

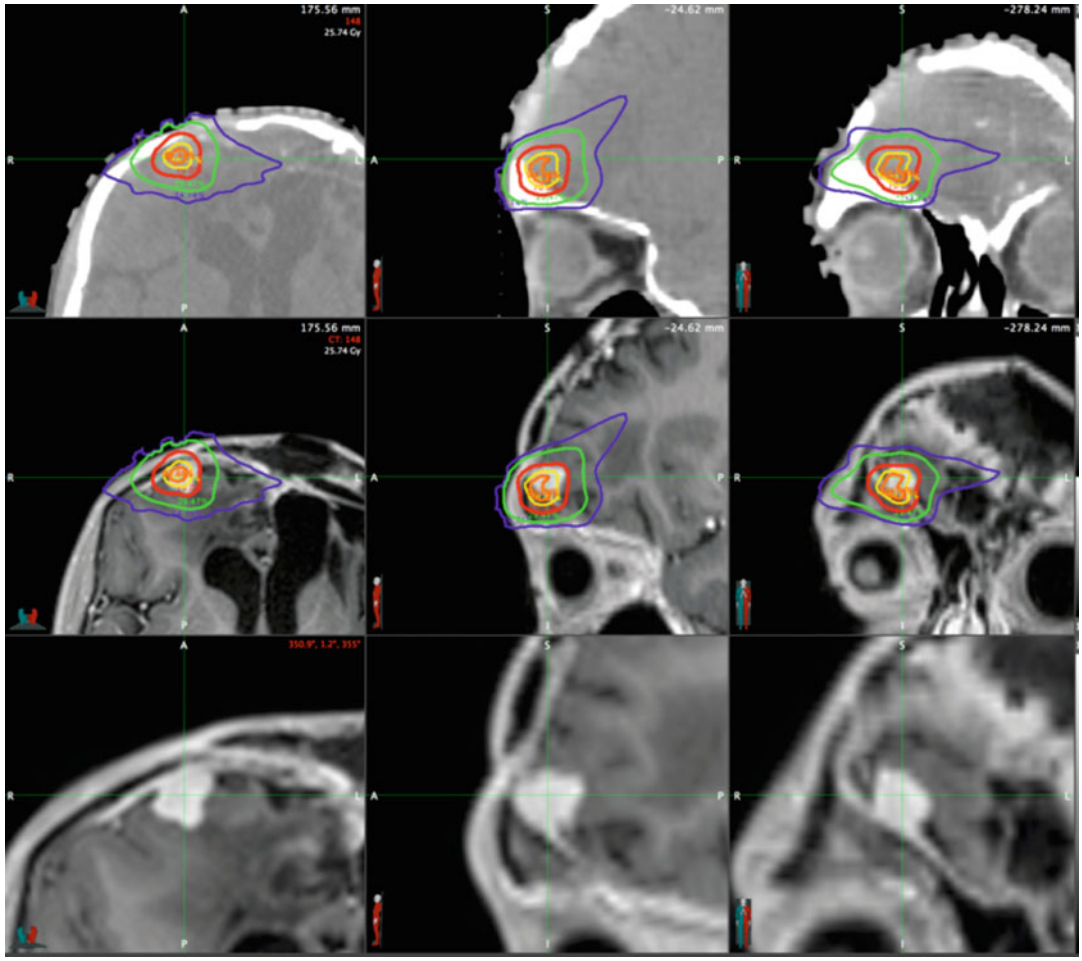

Fig. 16.6 SBRT used to treat a 16-year-old male with history of malignant neuroglial tumor with numerous recurrences, following multiple resections, chemotherapy trials, and multiple radiation treatments including SBRT to two lesions in the RUL and extensive radiation to the brain with a single fraction of SBRT via CyberKnife to a *left frontal* recurrence with 19 Gy in 1 fraction to the 70 % isodose line (*red isodose curve*). The *top panel* contains the planning CT scan, the *middle panel* has the MRI (post-gadolinium volume) with dosimetry overlaid, and the bottom shows the zoomed in tumor volume without isodose lines (Courtesy Dr. Jean Nakamura, UC San Francisco, Department of Radiation Oncology)

treated with SRT for progression following either surgery or chemotherapy. The total dose delivered was 52.2 Gy in 1.8 Gy daily fractions. Overall survival was 97.8 % at 5 years and 82 % at 8 years. Because tight margins were used in the hope of reducing late sequelae, there was some concern over marginal failures, but none were observed within a median follow-up of 6.9 years. The excellent local control observed supports the use of SRT for small, localized, low-grade CNS lesions (Marcus et al. 2005).

16.4.5 Neutron Beam Therapy

Neutrons, a particle with mass but no charge, deposit their dose more densely than conventional photon radiation, and the increased relative biological effect results in greater cell death. In addition, hypoxic cells exhibit less resistance to neutron radiation than to conventional photon radiation. Although clinical trials of neutron beam therapy in the treatment of malignant gliomas have resulted in a higher rate of tumor

control than treatment with photons, no improvement in survival was demonstrated, likely due to increased necrosis associated with neutron therapy (Battermann 1980; Catteral et al. 1980; Griffin et al. 1983; Laramore et al. 1988). In a randomized study examining the optimal dose of neutrons for a limited-volume neutron boost combined with photon whole-brain radiotherapy, no beneficial combination was documented (Laramore et al. 1988).

16.4.6 Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT) was first proposed in 1936, but has yet to make significant clinical inroads and is included here for completeness. A stable isotope of boron, ^{10}B, is administered to patients in a pharmacologic preparation and accumulates in tumor cells. Normal and tumor tissues are then irradiated by broad-beam, low-energy thermal or epithermal neutron irradiation. The ^{10}B nuclei have a high probability of thermal neutron capture that results in nuclear fission. High LET particles are created with a range of only one cell diameter, killing only the cells in the immediate vicinity of the boron compound.

The clinical utility of BNCT depends on developing new ^{10}B-containing compounds that accumulate more selectively within tumor cells and achieve higher concentrations in these cells than within blood, scalp, and normal brain tissues (Diaz et al. 2000). The major compound used in clinical trials to date, *p*-boronophenylalanine (BPA), produces ^{10}B concentrations 3.5-fold higher in tumor and 1.5-fold higher in scalp than in blood (Chadha et al. 1998). Recent preclinical research in a rat model used a boronated monoclonal antibody (L8A4) directed against EGFRvIII, a mutant form of the EGF receptor. The authors found a statistically significant increase in overall survival when compared to intravenous BPA; the combination of intravenous BPA and boronated L8A4 proved still more potent, leading to an increase in overall survival greater than that achieved with either therapy alone (Yang et al. 2008).

16.5 Toxicity of Radiation Therapy

A wide range of potential toxicities complicates the implementation of radiation therapy in the treatment of tumors of the craniospinal axis. These toxicities can be severe and debilitating, particularly in pediatric patients (Donahue 1992; Syndikus et al. 1994; Kalapurakal and Thomas 1997). Care should be taken to minimize these effects. Treatment of intracranial tumors can result in damage to the eye, ear, brain, and hypothalamic–pituitary axis, as well as impairment of normal growth. Treatment of the spine can result in growth deficits and damage to the spinal cord. Specific potential acute side effects of radiation to the central nervous system include epilation, skin reactions, otitis, hematopoietic depression, and somnolence. Specific late toxicities of radiation include radionecrosis, myelopathy, leukoencephalopathy, vascular injury, neuropsychologic sequelae, endocrine dysfunction, bone and tooth abnormalities, ocular complications, ototoxicity, and induction of second primary tumors (Donahue 1992; Syndikus et al. 1994; Kalapurakal and Thomas 1997). Table 16.1 delineates the radiation doses associated with late toxicities that may result from radiation therapy to the CNS.

Table 16.1 Late toxicities of CNS irradiation

		Threshold dose (Gy)
Structure	Late effect	Conventional fractionation
Spinal cord	Chronic progressive myelitis	45
Brain	Radiation necrosis	60
	Intellectual deficits	12–18
Eye		
Lens	Cataract formation	8
Retina	Radiation retinopathy	45
Optic nerve	Optic neuritis	50
Inner ear	Sensorineural hearing loss	40–50

16.5.1 Spinal Cord

Although rare, severe damage to the spinal cord can result following radiation therapy, with transection of the cord at the affected level being the most severe potential consequence. This usually takes the form of a chronic progressive myelitis. Wara et al. reported a 1 % incidence of spinal cord damage at 42 Gy and a 5 % incidence at 45 Gy. A number of reports have indicated that tolerance of the cervical spinal cord to radiation toxicity is somewhat higher than 45 Gy in adults (Wara et al. 1975). However, it is unclear what the cervical spinal cord tolerance is in pediatric patients. Radiation to the spinal cord can also result in Lhermitte's syndrome, which is characterized by tingling, numbness, and a sensation of electric shock. Symptoms are often present only with neck flexion. Lhermitte's syndrome is typically self-limiting, presenting within the first 1–3 months following radiation, and having an average duration of 3–4 months. Craniospinal radiation can result in decreased truncal, or sitting, height. This is due to decreased growth of the vertebral bodies following radiation therapy and becomes clinically evident at doses greater than 20 Gy.

16.5.2 Brain

Acute reactions during radiation therapy, thought to result from disruption of the blood–brain barrier, are uncommon. However, there are reports of edema following single conventional fractions (Kramer and Lee 1974). Clinically, apparent acute changes are more common with hypofractionated doses, such as those used in radiosurgery (Loeffler et al. 1990). Steroids can be administered to address edema.

Subacute reactions are more common and are thought to be due to transient demyelination (Boldrey and Sheline 1966). These effects typically occur within the first few months following radiation and usually resolve within 6–9 months. Delayed, transitory clinical manifestations of radiation, including somnolence syndrome, are seen in a large number of patients receiving prophylactic craniospinal radiation along with intrathecal chemotherapy for acute lymphoblastic lymphoma (ALL) (Littman et al. 1984). Severe subacute effects such as rapidly progressive ataxia are rare and are generally associated with fractions larger than 2.0 Gy and total doses larger than 50 Gy (Lampert and Alegria 1964).

The late effects of radiation are primarily due to radiation necrosis. Symptoms are related to the neuroanatomical location of necrosis (sensory, motor, speech/receptive deficits, seizures) and may also be caused by increased intracranial pressure. Focal necrosis is uncommon with doses below 60 Gy given with conventional fractionation (Halperin and Burger 1985). As the number of survivors of childhood cancers increases, it is becoming apparent that those who received cranial irradiation are at increased risk for the later development of primary CNS neoplasms. A recent retrospective case-control study looking at survivors of childhood cancer found an increase in the incidence of glioma (OR = 6.78, 95 % CI = 1.54–29.7) and meningioma (OR = 9.94, 95 % CI = 2.17–45.6), with most of the excess risk attributable to radiation exposure (Neglia et al. 2006). These children were treated between 1970 and 1986, before the advent of IMRT. There is some concern that IMRT, because of increased radiation leakage and integral dose, may further increase the incidence of secondary neoplasms (Hall 2006); however, mechanisms do exist to mitigate scattering and leakage. Finally, in addition to secondary CNS neoplasms, children that receive cranial irradiation are also at elevated risk for stroke and cerebrovascular accidents (Bowers et al. 2006).

With large-volume radiation therapy, diffuse white matter changes can be seen. Clinically, these can result in lassitude, personality change, or neurocognitive deficits. Multiple studies have examined the effect of whole-brain radiation therapy on intellect in patients treated for leukemia. Radiation-associated depression in IQ has been noted by a number of authors (Rowland et al. 1984; Copeland et al. 1985). Halberg et al. compared three groups of patients. The first group received 18 Gy (1.8 Gy per fraction) of cranial irradiation, while the second received

24 Gy of cranial irradiation. The third group consisted of other oncology patients who did not receive cranial irradiation. Lower IQ scores were noted in the group receiving 24 Gy (Halberg et al. 1992). High-dose methotrexate and female sex appear to increase risk of intellectual deficits (Waber et al. 1992). The effects of cranial irradiation are also more severe in younger children. Intellectual deficits resulting from radiation most commonly result in difficulty acquiring new knowledge, decreased processing speed, and memory deficits (most frequently short-term memory) (Mulhern et al. 1992).

Children irradiated for primary brain tumors have also shown intellectual deficits. Effects of radiation are more difficult to evaluate in this setting, as most of these patients have also had surgical resection. However, similar to patients with ALL, younger age appears to result in a higher rate of neurocognitive deficits. Larger fields and higher doses also appear to cause higher rates of toxicity.

Attempts to avoid the cognitive sequelae of cranial irradiation tend to involve the sparing of certain critical structures. Because adult patients who receive whole-brain radiation therapy are at increased risk for dementia, attempts have been made to develop plans, using conformal technology that spare critical memory structures such as the hippocampus (Gutierrez et al. 2007). Additional effort has focused on creating conformal plans that spare the neural stem cell compartments (subventricular and subgranular zones) in the hope of further mitigating neurologic impairment secondary to radiation (Barani et al. 2007).

Finally, alternative modalities of radiation have the potential to lessen neurocognitive toxicities. Merchant et al. compared models of photon radiation to those of proton radiation and predicted the relationship of each to cognitive function in children treated for brain tumors (Merchant et al. 2008). These investigators utilized models of radiation dose–cognitive effects developed from patients with four types of childhood brain tumors chosen for their characteristic location, volume, and radiation dosimetry. These included optic pathway glioma, infratentorial ependymoma, craniopharyngioma, and standard-risk medulloblastoma. They found that, compared to photon-based radiation plans, proton beam radiotherapy delivers smaller doses to critical normal structures that were not adjacent to the tumor volume, specifically the cochlea and hypothalamus. Furthermore, protons resulted in a smaller proportion of normal supratentorial brain receiving low- and intermediate-dose radiation. Thus, superior dose distributions of proton beam radiotherapy were likely to translate into less radiation-induced cognitive dysfunction in children with optic pathway glioma, infratentorial ependymoma, craniopharyngioma, and standard-risk medulloblastoma.

16.5.3 Eye

The lens of the eye is exquisitely sensitive to radiation. Radiation-induced cataracts are caused by damage to the germinal zone at the equator of the lens. Initially, this results in a central opacity that progresses to an opaque cortex. The threshold for radiation damage is 8 Gy in a single fraction or 10–15 Gy in fractionated doses. More rapid cataract formation is associated with higher doses of radiation. Radiation-induced retinopathy appears to have a threshold of 46 Gy at conventional fractionation (1.8–2.0 Gy per fraction), but is rare below doses of 50–60 Gy. Retinopathy is typically seen beginning from 6 months to 3 years following radiation. It is characterized by macular edema, nonperfusion, and neovascularization. The optic nerves and chiasm are also at risk for damage from radiation. Damage to the optic nerve is characterized by a pale optic disk, abnormal papillary response, and visual deficits. Damage to the optic nerve or chiasm is potentially blinding. The threshold for this damage is 50 Gy. Every effort should be made to keep these structures below their tolerated doses (Emami et al. 1991).

16.5.4 Ear

Radiation-induced sensorineural hearing loss is dose dependent and is more severe in younger patients. Hearing loss can result from doses greater than 40–50 Gy, usually developing within

6–12 months of treatment (Grau et al. 1991; Grau and Overgaard 1996). High-frequency hearing loss is seen in 25–50 % of patients who received greater than 50–60 Gy to inner ear structures (Anteunis et al. 1994). Hearing loss is typically attributed to radiation changes induced in the cochlea and vasculature. Ototoxicity related to cis-platinum chemotherapy is well documented (Schell et al. 1989). Cranial irradiation prior to or concurrent with cis-platinum chemotherapy enhances ototoxicity (Schell et al. 1989; Walker et al. 1989). Chronic otitis can also develop following radiation therapy, due to obstruction of the Eustachian canal.

16.5.5 Endocrine

Whole cranial irradiation or focal radiation that includes the hypothalamic–pituitary axis can result in neuroendocrine abnormalities. The neuroendocrine complications that can result from radiation therapy are summarized in Table 16.2. Growth hormone (GH) production appears to be the most prone to disruption by radiation therapy. GH deficiency worsens over time and may follow radiation doses as low as 12 Gy (Merchant et al. 2002). This appears to be a result of decreased GH-releasing hormone (GHRH) in the hypothalamus, as GH deficiency is seen in patients undergoing hypothalamic radiation with pituitary sparing. Clinically, GH deficiency can result in short stature, bone loss, and metabolic abnormalities. Treatment with synthetic GH can allow children to maintain their expected growth percentile, despite irradiation.

Table 16.2 Endocrine abnormalities resulting from radiation to the hypothalamus and pituitary gland

Hormone abnormality	Threshold dose (Gy)
Growth hormone deficit	18–25
ACTH deficit	40
TRH/TSH deficit	40
Precocious puberty	20
LH/FSH deficit	40
Hyperprolactinemia	40

Other endocrine deficiencies, including decreased thyroid-stimulating hormone, adrenocorticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), appear to have a higher threshold. These effects are typically seen following doses greater than 40 Gy. It is important that children treated for tumors in the region of the hypothalamic–pituitary axis be followed closely for endocrine abnormalities, so that timely replacement therapy can be initiated.

16.5.6 Hypofractionated Dose Tolerances

As hypofractionated dose regimens become more ubiquitous, different dose constraints are required. Published references such as TG101 (Benedict et al. 2010) give constraints commonly used in adults and should be used with caution when applying to pediatric malignancies.

16.6 Molecular Targets for Radiosensitization

16.6.1 Molecular Targeting and Radiosensitization

Inhibitors of cell signaling hold the promise not only of single-agent activity but also of combined activity with more traditional cytotoxic therapies. Such cytotoxic treatment include chemotherapy and radiation, and, indeed, in vitro and in vivo models of cancer demonstrate that treatment with signaling inhibitors augments tumor response to radiation (Jones et al. 2001). The promising combinatorial activity of targeted agents and radiotherapy has provided the preclinical rationale for multimodality trials. Molecular mechanisms implicated in radiosensitization associated with signaling inhibitors include effects on cell proliferation, survival, migration, invasion, angiogenesis, and DNA repair. The precise molecular mechanisms, however, remain elusive.

The strongest data for radiosensitization exist for agents that block EGFR signaling. EGFR overexpression correlates with resistance to radiation in vitro and in vivo (Wollman et al. 1994; Sheridan et al. 1997; Miyaguchi et al. 1998; Pillai et al. 1998). EGFR overexpression correlates with radiographically measured radiation response of human GBM in vivo (Barker et al. 2001). In a model of human squamous cell carcinoma cells grown in mice, administration of cetuximab together with radiation resulted in complete regression of established xenograft tumors (Huang et al. 1999; Milas et al. 2000). Impressive efficacy of concurrent cetuximab and radiation has also been documented in intracranial tumors of human glioma cells grown as xenografts in athymic mice. Small-molecule inhibitors of EGFR, such as gefitinib and CI-1033, similarly sensitize human malignancies to radiation in cell lines in vitro and in animal models of human malignancies in vivo (Mendelsohn and Baselga 2000). Mechanisms for this sensitization by EGFR inhibitors inevitably vary, but may include elimination of cancer stem cells, modification of signal transduction, inhibition of DNA repair, and improved oxygenation (Baumann et al. 2007). These studies establish the rationale for current clinical trials examining concurrent administration of gefitinib or erlotinib and radiation in the treatment of adult and pediatric gliomas.

Similarly, FTIs reverse the radiation resistance of cell lines containing mutant Ras without affecting the radiosensitivity of cells expressing wild-type Ras (Jones et al. 2001). A critical unanswered question is whether FTIs will also preferentially radiosensitize cells with aberrant signaling cascades that rely on Ras as an intermediary. Direct evidence is lacking for radiosensitization by signaling inhibitors that target other RTKs such as PDGF and VEGF receptors. However, indirectly blocking VEGF signaling with antiangiogenic drugs augments the cytotoxic effects of radiation in vivo (Gorski et al. 1999). In vivo experiments have also shown that anti-VEGF therapy may, by normalizing tumor vasculature, improve oxygenation and thus heighten radiation sensitivity.

Mammalian target of rapamycin (mTOR) is a key downstream component of the phosphoinositide 3-kinase (PI3K)/Akt pathway (Fan and Weiss 2006). In GBM patients, PTEN mutation (occurring in approximately 30–40 % of cases) results in constitutive activation of the Akt pathway. It has therefore been hypothesized that inhibition of downstream effectors in this pathway might prove beneficial in the treatment of gliomas; preclinical models bore this out, with data suggesting that PTEN-deficient tumors were sensitive to extant mTOR inhibitors. A Phase II trial of the mTOR inhibitor temsirolimus showed a measurable radiographic response in 36 % of patients, with an accompanying increase in time to progression (Galanis et al. 2005). More recently, attention has focused on trials involving synergistic multidrug therapy. Results of a Phase II trial using the EGFR tyrosine kinase inhibitor gefitinib and the mTOR inhibitor everolimus in unselected patients with recurrent GBM showed a response rate of 26 %. Despite this, there was no concomitant increase in progression-free or overall survival compared to historical controls (Nyugen et al. 2006). The eventual hope is that selection of patients based upon the biological characteristics of their individual tumors will result in improvements in clinical response.

Unfortunately, most targeted agents, including those delineated above, have failed to show convincing and consistent activity against most pediatric central nervous system tumors. Notable exceptions are agents that target the Ras/Raf/MAPK kinase pathway. Preclinical models of $BRAF^{V600E}$-mutated gliomas have shown that combination treatment with radiation and $BRAF^{V600E}$ inhibitors leads to prolonged survival compared to monotherapy. These translational studies will inform the next generation of clinical trials of $BRAF^{V600E}$ inhibitors and radiation in patients with $BRAF^{V600E}$-mutated brain tumors and metastases. At least one of these studies is underway under the umbrella of the Pacific Pediatric Neuro-Oncology Consortium (PNOC, http://www.pnoc.us). This Phase 1 study will establish the safety and pharmacokinetic characteristics of vemurafenib in children with recurrent or refractory gliomas containing the BRAF

V600E mutation. If the dose-limiting toxicities of vemurafenib in this trial are not prohibitive to its administration in children, then a possible next step will be to provide combination treatment of vemurafenib with concurrent external beam radiation in children with BRAF V600E-mutated high-grade gliomas or recurrent BRAF V600E-mutated low-grade gliomas.

16.6.2 P53 Tumor Suppressor Protein

P53 regulates apoptosis, proliferation, differentiation, angiogenesis, and cell–matrix interactions in a tissue-specific manner and is mutated in over 50% of human cancers. For example, in vitro irradiation of hematologic malignancies, such as leukemia and lymphoma, produces rapid p53-dependent apoptosis. A clinical corollary of this laboratory observation is that radiation treatment of hematologic malignancies produces a rapid and durable response. Similarly, in many pediatric tissues, apoptosis plays a key role during organogenesis, and pediatric solid tumors, such as Wilms' tumor and neuroblastoma, exhibit significant apoptosis and excellent cure rates when treated with radiation. In contrast, in many adult solid tumors such as astrocytoma, apoptosis plays a minor role, and the balance of p53-mediated functions tilts toward proliferation and differentiation.

Although in glial neoplasms, the role of p53 inactivation in mediating radiation resistance remains unclear (Nozaki et al. 1999), enhanced radiosensitivity of glioma cells occurs after reconstitution of p53 function (Lang et al. 1999). Two main approaches have been utilized to restore wild-type p53 function and overcome resistance to radiation: gene therapy and pharmacologic molecules that confer wild-type function on mutant forms of p53. Many impediments to gene therapy have arisen, including inefficient delivery and detrimental immune responses. Pharmacologic agents that impinge on p53 functions hold greater promise for translational clinical practice. Some mutated forms of p53 are amenable to treatment with either synthetic peptides or monoclonal antibodies that can restore wild-type p53 function.

16.7 Immunotherapy

A recent advance in oncology, and of particular interest to radiation oncologists, is the approach of immunotherapy coupled with radiation to elicit a systemic immune response. The basic premise is that at baseline, tumor cells express antigens that can be targeted by the immune system, but that this mechanism is suppressed by several methods, and that eventually tumor cells escape immune surveillance. The goal of immunotherapy is to restore this balance and, if possible, leverage the immune system to actively attack the existing tumor cells.

Vaccines have been increasingly employed in cancer therapy and leverage exposure of the immune system to antigens on the tumor cells. Interestingly, vaccines have not had a track record of significantly reducing tumor burden, but have been shown to increase overall survival in specific cases. This has led to the hypothesis that vaccines help to restore the immune system balance, but obstacles still remain in having the immune system actively destroy existing tumor foci (Kalabasi et al. 2013).

There has been significant interest in using radiation to potentiate the immune response. Chakraborty et al. explored (Chakraborty et al. 2003, 2004) the effects of radiation on upregulation of Fas, which in turn sensitizes them to the cell killing of cytotoxic T lymphocytes (CTLs). The combination of irradiation and CTL resulted in more effective antitumor responses. In related work, the same group showed that local irradiation, combined with vaccine therapy, resulted in significant tumor infiltration with T lymphocytes and led to a significantly greater tumor response than either radiation or vaccine alone.

Radiation therapy has also been linked to the abscopal effect, whereby local radiation therapy on one area of the body leads to tumor regression outside the radiation field. The notion is that tumor antigen is released during cell death that is induced by radiotherapy (either via apoptosis or autophagy). The associated cytokine increases have also been linked to tumor systemic tumor responses.

To further unlock the potential of the immune system to combat cancer, checkpoint inhibitors

have recently been developed. These enhance the immune system's ability to attack cancer cells, working synergistically with radiation, as radiation can increase the intra-tumoral T-cell repertoire. Two checkpoint inhibitors are of current clinical interest: anti-CTLA-4 and anti-PD-1/PD-L1. CTLA-4 helps maintain tolerance to self-antigens by reducing or inactivating T-cell response. Programmed death 1 (PD-1), is an inhibitory receptor on the surface of T cells that is thought to have a role in preventing autoimmune disease. Two main ligands, PD-L1 and PD-L2, bind to this receptor to inhibit T-cell function.

To illustrate the role of these checkpoint inhibitors, a recent study (Twyman-Saint et al. 2015) combined both anti-CTLA-4 and anti-PD-1 inhibitors. They found that in patients who progressed on an anti-CTLA-4 agent with radiation, there was upregulation of PD-L1 on melanoma cells, mitigating the effector of the checkpoint inhibitor. By using a combination of anti-PD-1/PD-L1 and anti-CTLA-4 with radiation in animal models, they were able to overcome this mechanism of resistance and increase overall survival.

To date, no investigations specific to pediatric CNS tumors have been published; however, a provocative investigation of adult glioblastomas has been reported by Zeng and colleagues (2013). The combination of anti-PD-1 therapy and radiation improved survival compared with either modality alone: median survival was 25 days in the control arm, and long-term survival of mice with this GBM model was observed only after combination treatment. Anti-PD-1 therapy and radiation also resulted in increased tumor infiltration by cytotoxic T cells and less infiltration by regulatory T cells compared with monotherapy.

These agents are the subject of multiple ongoing clinical trials in radiation oncology and have elicited significant excitement about their potential. Further study will help define the optimal patient, and tumor types, for this novel treatment.

Conclusions

Radiation is a key therapeutic modality in the treatment of brain tumors and plays a role in the multimodality approach to virtually every pediatric CNS malignancy. Efforts to increase the efficacy of radiation using IMRT, high-LET particles, BNCT, radiation modifiers, and altered fractionation have contributed to enhanced cure rates for pediatric patients. Nevertheless, great opportunities exist in improving prognosis for children with brain tumors while reducing long-term side effects of treatment. Novel pharmacologic agents, such as signaling inhibitors and immunotherapy, hold great promise for scientific and clinical breakthroughs.

References

Allen AM, Pawlicki T, Dong L, Fourkal E, Buyyounouski M, Cengel K, Plastaras J, Bucci MK, Yock TI, Bonilla L, Price R, Harris EE, Konski AA (2012) An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. Radiother Oncol 103:8–11

Anteunis LJ, Wanders SL, Hendriks JJ, Langendijk JA, Manni JJ, de Jong JM (1994) A prospective longitudinal study on radiation-induced hearing loss. Am J Surg 168:408–411

Barani IJ, Cuttino LW, Benedict SH, Todor D, Bump EA, Wu Y, Chung TD, Broaddus WC, Lin PS (2007) Neural stem cell preserving external-beam radiotherapy of central nervous system malignancies. Int J Radiat Oncol Biol Phys 68:978–985

Barker FG 2nd, Simmons ML, Chang SM, Prados MD, Larson DA, Sneed PK, Wara WM, Berger MS, Chen P, Israel MA, Aldape KD (2001) EGFR overexpression and radiation response in glioblastoma multiforme. Int J Radiat Oncol Biol Phys 51:410–418

Battermann JJ (1980) Fast neutron therapy for advanced tumors. Int J Radiat Oncol Biol Phys 6:333–335

Baumann M, Krause M, Dikomey E, Dittmann K, Dorr W, Kasten-Pisula U, Rodemann HP (2007) EGFR-targeted anti-cancer drugs in radiotherapy: preclinical evaluation of mechanisms. Radiother Oncol 83:238–248

Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, Keall P, Lovelock M, Meeks S, Papiez L, Purdie T, Sadagopan R, Schell MC, Salter B, Schlesinger DJ, Shiu AS, Solberg T, Song DY, Stieber V, Timmerman R, Tomé WA, Verellen D, Wang L, Yin FF (2010) Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 37:4078–4101

Boldrey E, Sheline G (1966) Delayed transitory clinical manifestations after radiation treatment of intracranial tumors. Acta Radiol: Ther Phys Biol 5:5–10

Bowers DC, Liu Y, Leisenring W, McNeil E, Stovall M, Gurney JG, Robison LL, Packer RJ, Oeffinger KC (2006) Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report

from the Childhood Cancer Survivor Study. J Clin Oncol 24:5277–5282

Catteral M, Bloom HJG, Ash DV, Walsh L, Richardson A, Uttley D, Gowing NFC, Lewis P, Chaucer B (1980) Fast neutrons compared with megavoltage x-rays in the treatment of patients with supratentorial glioblastoma: a controlled pilot study. Int J Radiat Oncol Biol Phys 6:261–266

Chadha M, Capala J, Coderre JA, Elowitz EH, Iwai J-I, Joel DD, Liu HB, Wielopolski L, Chanana AD (1998) Boron neutron-capture therapy (BNCT) for glioblastoma multiforme (GBM) using the epithermal neutron beam at the Brookhaven National Laboratory. Int J Radiat Oncol Biol Phys 40:829–834

Chakraborty M, Abrams SI, Camphausen K, Liu K, Scott T, Coleman CN, Hodge JW (2003) Irradiation of tumor cells up-regulates Fas and enhances CTL lytic activity and CTL adoptive immunotherapy. J Immunol 170:6338–6347

Chakraborty M, Abrams SI, Coleman CN, Camphausen K, Schlom J, Hodge JW (2004) External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated T-cell killing. Cancer Res 64:4328–4337

Copeland DR, Fletcher JM, Pfefferbaum-Levine B, Jaffe N, Ried H, Maor M (1985) Neuropsychological sequelae of childhood cancer in long-term survivors. Pediatrics 75:745–753

Diaz AZ, Coderre JA, Chanana AD, Ma R (2000) Boron neutron capture therapy for malignant gliomas. Ann Med 32:81–85

Donahue B (1992) Short- and long-term complications of radiation therapy for pediatric brain tumors. Pediatr Neurosurg 18:207–217

Dong P, Lee P, Ruan D, Long T, Romeijn E, Yang Y et al (2013) 4π non-coplanar liver SBRT: a novel delivery technique. Int J Radiat Oncol Biol Phys 85(5):1360–1366

Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M (1991) Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21:109–122

Fan QW, Weiss WA (2006) Isoform specific inhibitors of PI3 kinase in glioma. Cell Cycle 5:2301–2305

Galanis E, Buckner JC, Maurer MJ, Kreisberg JI, Ballman K, Boni J, Peralba JM, Jenkins RB, Dakhil SR, Morton RF, Jaeckle KA, Scheithauer BW, Dancey J, Hidalgo M, Walsh DJ (2005) Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study. J Clin Oncol 23:5294–5304

Gorski DH, Beckett MA, Jaskowiak NT, Calvin DP, Mauceri HJ, Salloum RM, Seetharam S, Koons A, Hari DM, Kufe DW, Weichselbaum RR (1999) Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. Cancer Res 59:3374–3378

Grau C, Overgaard J (1996) Postirradiation sensorineural hearing loss: a common but ignored late radiation complication. Int J Radiat Oncol Biol Phys 36:515–517

Grau C, Moller K, Overgaard M, Overgaard J, Elbrond O (1991) Sensori-neural hearing loss in patients treated with irradiation for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 21:723–728

Griffin TW, Davis R, Laramore G (1983) Fast neutron radiation therapy for glioblastoma multiforme–results of an RTOG study. Am J Clin Oncol 6:661–667

Gunther JR, Sato M, Chintagumpala M, Ketonen L, Jones JY, Allen PK, Paulino AC, Okcu MF, Su JM, Weinberg J, Boehling NS, Khatua S, Adesina A, Dauser R, Whitehead WE, Mahajan A (2015) Imaging changes in pediatric intracranial ependymoma patients treated with proton beam radiation therapy compared to intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 93:54–63

Gutierrez AN, Westerly DC, Tome WA, Jaradat HA, Mackie TR, Bentzen SM, Khuntia D, Mehta MP (2007) Whole brain radiotherapy with hippocampal avoidance and simultaneously integrated brain metastases boost: a planning study. Int J Radiat Oncol Biol Phys 69:589–597

Halberg FE, Kramer JH, Moore IM, Wara WM, Matthay KK, Ablin AR (1992) Prophylactic cranial irradiation dose effects on late cognitive function in children treated for acute lymphoblastic leukemia. Int J Radiat Oncol Biol Phys 22:13–16

Hall EJ (2000) Radiobiology for the radiologist. Lippincott Williams & Wilkins, Philadelphia

Hall EJ (2006) Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys 65:1–7

Halperin EC, Burger PC (1985) Conventional external beam radiotherapy for central nervous system malignancies. Neurol Clin 3:867–882

Hermanto U, Frija EK, Lii MJ, Chang EL, Mahajan A, Woo SY (2007) Intensity-modulated radiotherapy (IMRT) and conventional three-dimensional conformal radiotherapy for high-grade gliomas: does IMRT increase the integral dose to normal brain? Int J Radiat Oncol Biol Phys 67:1135–1144

Hodgson DC, Goumnerova LC, Loeffler JS, Dutton S, Black PM, Alexander E 3rd, Xu R, Kooy H, Silver B, Tarbell NJ (2001) Radiosurgery in the management of pediatric brain tumors. Int J Radiat Oncol Biol Phys 50:929–935

Huang SM, Bock JM, Harari PM (1999) Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. Cancer Res 59:1935–1940

Huang E, Teh BS, Strother DR, Davis QG, Chiu JK, Lu HH, Carpenter LS, Mai WY, Chintagumpala MM, South M, Grant WH 3rd, Butler EB, Woo SY (2002) Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys 52:599–605

Indelicato DJ, Flampouri S, Rotondo RL, Bradley JA, Morris CG, Aldana PR, Sandler E, Mendenhall NP (2014) Incidence and dosimetric parameters of pediat-

ric brainstem toxicity following proton therapy. Acta Oncol 53:1298–1304
Jones HA, Hahn SM, Bernhard E, McKenna WG (2001) Ras inhibitors and radiation therapy. Semin Radiat Oncol 11:328–337
Kalapurakal JA, Thomas PR (1997) Pediatric radiotherapy. An overview. Radiol Clin N Am 35:1265–1280
Kalapurakal JA, Goldman S, Stellpflug W, Curran J, Sathiaseelan V, Marymont MH, Tomita T (2006) Phase I study of intraoperative radiotherapy with photon radiosurgery system in children with recurrent brain tumors: preliminary report of first dose level (10 Gy). Int J Radiat Oncol Biol Phys 65:800–808
Kalbasi A et al (2013) Radiation and immunotherapy: a synergistic combination. J Clin Invest 123(7):2756
Kondziolka D, Flickinger JC, Lunsford LD (2000) Stereotactic radiosurgery and radiation therapy. In: Bernstein M, Berger MS (eds) Neuro-oncology: the essentials. Thieme, New York, pp 183–197
Kramer S, Lee KF (1974) Complications of radiation therapy: the central nervous system. Semin Roentgenol 9:75–83
Lampert H, Alegria A (1964) Treatment of post-poliomyelitis paralysis of long duration. Acta Neurol Latinoam 10:160–171
Lang FF, Yung WK, Sawaya R, Tofilon PJ (1999) Adenovirus-mediated p53 gene therapy for human gliomas. Neurosurgery 45:1093–1104
Laramore GE, Diener-West M, Griffin TW, Nelson JS, Griem ML, Thomas FJ, Hendrickson FR, Griffin BR, Myrianthopoulos LC, Saxton J (1988) Randomized neutron dose searching study for malignant gliomas of the brain: results of an RTOG study. Int J Radiat Oncol Biol Phys 14:1093–1102
Lee CT, Bilton SD, Famiglietti RM, Riley BA, Mahajan A, Chang EL, Maor MH, Woo SY, Cox JD, Smith AR (2005) Treatment planning with protons for pediatric retinoblastoma, medulloblastoma, and pelvic sarcoma: how do protons compare with other conformal techniques? Int J Radiat Oncol Biol Phys 63:362–372
Littman P, Rosenstock J, Gale G, Krisch RE, Meadows A, Sather H, Coccia P, DeCamargo B (1984) The somnolence syndrome in leukemic children following reduced daily dose fractions of cranial radiation. Int J Radiat Oncol Biol Phys 10:1851–1853
Loeffler JS, Siddon RL, Wen PY, Nedzi LA, Alexander E 3rd (1990) Stereotactic radiosurgery of the brain using a standard linear accelerator: a study of early and late effects. Radiother Oncol 17:311–321
MacDonald SM, Safai S, Trofimov A, Wolfgang J, Fullerton B, Yeap BY, Bortfeld T, Tarbell NJ, Yock T (2008) Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. Int J Radiat Oncol Biol Phys 71:979–986
Marcus KJ, Goumnerova L, Billett AL, Lavally B, Scott RM, Bishop K, Xu R, Young Poussaint T, Kieran M, Kooy H, Pomeroy SL, Tarbell NJ (2005) Stereotactic radiotherapy for localized low-grade gliomas in children: final results of a prospective trial. Int J Radiat Oncol Biol Phys 61:374–379
Mendelsohn J, Baselga J (2000) The EGF receptor family as targets for cancer therapy. Oncogene 19:6550–6565
Merchant TE, Goloubeva O, Pritchard DL, Gaber MW, Xiong X, Danish RK, Lustig RH (2002) Radiation dose-volume effects on growth hormone secretion. Int J Radiat Oncol Biol Phys 52:1264–1270
Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U (2008) Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatr Blood Cancer 51:110–117
Milas L, Mason K, Hunter N, Petersen S, Yamakawa M, Ang K, Mendelsohn J, Fan Z (2000) In vivo enhancement of tumor radioresponse by C225 antiepidermal growth factor receptor antibody. Clin Cancer Res 6:701–708
Mitin T, Zietman AL (2014) Promise and pitfalls of heavy-particle therapy. J Clin Oncol 32:2855–2863
Miyaguchi M, Takeuchi T, Morimoto K, Kubo T (1998) Correlation of epidermal growth factor receptor and radiosensitivity in human maxillary carcinoma cell lines. Acta Otolaryngol 118:428–431
Mulhern RK, Ochs J, Fairclough D (1992) Deterioration of intellect among children surviving leukemia: IQ test changes modify estimates of treatment toxicity. J Consult Clin Psychol 60:477–480
Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, Hammond S, Yasui Y, Kasper CE, Mertens AC, Donaldson SS, Meadows AT, Inskip PD (2006) New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 98:1528–1537
Nozaki M, Tada M, Kobayashi H, Zhang CL, Sawamura Y, Abe H, Ishii N, Van Meir EG (1999) Roles of the functional loss of p53 and other genes in astrocytoma tumorigenesis and progression. Neuro-Oncology 1:124–137
Nyugen TD, Lassman AB, Lis E, Rosen N, Shaffer DR, Scher HI, DeAngelis LM, Abrey LE (2006) A pilot study to assess the tolerability and efficacy of RAD-001 (everolimus) with gefitinib in patients with recurrent glioblastoma multiforme (GBM). J Clin Oncol 24:1507, 2006 ASCO Annual Meeting Proceedings Part I
Pillai MR, Jayaprakash PG, Nair MK (1998) Tumour-proliferative fraction and growth factor expression as markers of tumour response to radiotherapy in cancer of the uterine cervix. J Cancer Res Clin Oncol 124:456–461
Purdy JA (1999) 3D treatment planning and intensity modulated radiation therapy. Oncology 13:155–168
Rostomily RC, Halligan J, Geyer R, Stelzer K, Lindsley K, Berger MS (2001) Permanent low-activity (125)I seed placement for the treatment of pediatric brain tumors: preliminary experience. Pediatr Neurosurg 34:198–205
Rowland JH, Glidewell OJ, Sibley RF, Holland JC, Tull R, Berman A, Brecher ML, Harris M, Glicksman AS,

Forman E et al (1984) Effects of different forms of central nervous system prophylaxis on neuropsychologic function in childhood leukemia. J Clin Oncol 2:1327–1335

Rwigema JC, Nguyen D, Heron DE, Chen AM, Lee P, Wang PC, Vargo JA, Low DA, Huq MS, Tenn S, Steinberg ML, Kupelian P, Sheng K (2015) 4π noncoplanar stereotactic body radiation therapy for head-and-neck cancer: potential to improve tumor control and late toxicity. Int J Radiat Oncol Biol Phys 91(2):401–409

Schell MJ, McHaney VA, Green AA, Kun LE, Hayes FA, Horowitz M, Meyer WH (1989) Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. J Clin Oncol 7:754–760

Sheridan MT, O'Dwyer T, Seymour CB, Mothersill CE (1997) Potential indicators of radiosensitivity in squamous cell carcinoma of the head and neck. Radiat Oncol Investig 5:180–186

Sneed PK, Russo C, Scharfen CO, Prados MD, Malec MK, Larson DA, Lamborn KR, Lamb SA, Voss B, Weaver KA, Phillips TL, Gutin PH, Wara WM, Edwards MS (1996) Long-term follow-up after high-activity 125I brachytherapy for pediatric brain tumors. Pediatr Neurosurg 24:314–322

St Clair WH, Adams JA, Bues M, Fullerton BC, La Shell S, Kooy HM, Loeffler JS, Tarbell NJ (2004) Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys 58:727–734

Syndikus I, Tait D, Ashley S, Jannoun L (1994) Long-term follow-up of young children with brain tumors after irradiation. Int J Radiat Oncol Biol Phys 30:781–787

Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, Benci JL, Xu B, Dada H, Odorizzi PM, Herati RS, Mansfield KD, Patsch D, Amaravadi RK, Schuchter LM, Ishwaran H, Mick R, Pryma DA, Xu X, Feldman MD, Gangadhar TC, Hahn SM, Wherry EJ, Vonderheide RH, Minn AJ (2015) Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 520:373–377

Verhey LJ (1999) Comparison of three-dimensional conformal radiation therapy and intensity-modulated radiation therapy systems. Semin Radiat Oncol 9:78–98

Waber DP, Tarbell NJ, Kahn CM, Gelber RD, Sallan SE (1992) The relationship of sex and treatment modality to neuropsychologic outcome in childhood acute lymphoblastic leukemia. J Clin Oncol 10:810–817

Walker DA, Pillow J, Waters KD, Keir E (1989) Enhanced cis-platinum ototoxicity in children with brain tumours who have received simultaneous or prior cranial irradiation. Med Pediatr Oncol 17:48–52

Wara WM, Phillips TL, Sheline GE, Schwade JG (1975) Radiation tolerance of the spinal cord. Cancer 35:1558–1562

Webb S (2000) Advances in three-dimensional conformal radiation therapy physics with intensity modulation. Lancet Oncol 1:30–36

Willett CG (2001) Intraoperative radiation therapy. Int J Clin Oncol 6:209–214

Wollman R, Yahalom J, Maxy R, Pinto J, Fuks Z (1994) Effect of epidermal growth factor on the growth and radiation sensitivity of human breast cancer cells in vitro. Int J Radiat Oncol Biol Phys 30:91–98

Yang TC (1999) Proton radiobiology and uncertainties. Radiat Meas 30:383–392

Yang W, Wu G, Barth RF, Swindall MR, Bandyopadhyaya AK, Tjarks W, Tordoff K, Moeschberger M, Sferra TJ, Binns PJ, Riley KJ, Ciesielski MJ, Fenstermaker RA, Wikstrand CJ (2008) Molecular targeting and treatment of composite EGFR and EGFRvIII-positive gliomas using boronated monoclonal antibodies. Clin Cancer Res 14:883–891

Zeng J M.D., See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, Durham N, Meyer C, Harris TJ, Albesiano E, Pradilla G, Ford E Ph.D., Wong J Ph.D., Hammers HJ, Mathios D, Tyler B, Brem H, Tran PT, Pardoll D, Drake CG, Lim M (2013) Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. Int J Radiat Oncol Biol Phys 86:343–349

Late Effects of Treatment and Palliative Care

17

Eric Chang, Robert Goldsby, Sabine Mueller, and Anu Banerjee

Contents

E. Chang, MD
Department of Radiation Oncology,
University of California Los Angeles,
200 UCLA Medical Plaza, Suite B265, Los Angeles,
CA 90095-6951, USA
e-mail: eric.chang@cshs.org

R. Goldsby, MD • A. Banerjee, MD (✉)
Division of Hematology/Oncology, Departments of Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital,
550 16th St, 4th Floor, Box 0434, San Francisco,
CA 94143, USA
e-mail: goldsbyr@ucsf.edu; anu.banerjee@ucsf.edu

S. Mueller, MD, PhD, MAS
Departments of Neurology, Neurosurgery and Pediatrics, University of California San Francisco & UCSF Benioff Children's Hospital,
625 Nelson Rising Lane, Room 402C, Sandler Neuroscience Building, San Francisco,
CA 94158, USA
e-mail: sabine.mueller@ucsf.edu

17.1 Introduction

Identifying late effects of treatment and integrating palliative care when appropriate are increasingly recognized as important elements of childhood tumor management. Patients with CNS tumors are at a high risk for mortality, and survivors have high morbidity rates related to the late effects of treatment. While intensified therapy has improved average 5-year survival in patients with pediatric brain tumors to 73% (Ostrom et al. 2014) from less than 60% in 1975–1979 (Linabery and Ross 2008), it has also increased the long-term consequences. Survivors may develop a spectrum of late effects ranging from subtle memory loss and cosmetic anomalies

N. Gupta et al. (eds.), *Pediatric CNS Tumors*, Pediatric Oncology,
DOI 10.1007/978-3-319-30789-3_17

to severe neurological disabilities and recurrent neoplasms. While seemingly quite different, both palliative and late-effects care focus on improving quality of life for patients and need to be integrated into the overall care plan.

17.2 Late Effects

Late effects of cancer treatment are defined as toxicities that manifest after therapy, influenced by growth, development, and aging. Treatment-related complications include secondary malignancies, organ-system dysfunction, psychosocial difficulties, cognitive disabilities, and death. Characterization of late effects associated with novel therapies will become increasingly important as these therapies are integrated into pediatric brain tumor management.

17.2.1 Mortality

Patients treated for CNS malignancies are at risk for late mortality. The Childhood Cancer Survivor Study (CCSS) is a large cohort study of childhood cancer survivors treated from 1970 through 1986 that included newly diagnosed patients who survived at least 5 years after cancer diagnosis. This cohort of patients has been used to examine late effects of pediatric oncology treatment, including the risk of late mortality (Mertens et al. 2008). Survivors had higher mortality rates compared to age-adjusted survival rates for the US population. The cumulative mortality for the survivors of childhood cancer was 6.5 % at 10 years from diagnosis, 11.9 % at 20 years, and 18.1 % at 30 years. The CNS tumor survivors had the worst overall survival with a cumulative mortality rate of 13.5 % at 15 years from diagnosis, 17.1 % at 20 years, 21.5 % at 25 years, and 25.8 % at 30 years (Armstrong et al. 2009a; Fig. 17.1). The risk for death from disease recurrence was greatest in the time period of 5–9 years after initial diagnosis. As the risk of death due to primary malignancy decreases with increasing time from diagnosis, the rising mortality rates 20–30 years following diagnosis imply that other causes for late mortality become more important with time. Recurrence and/or progressive disease accounted for the majority of deaths (61 %), followed by death due to subsequent neoplasms (9 %), cardiac disease (3 %), and pulmonary disease (3 %).

17.2.2 Secondary Malignancy

Chemotherapy-associated hematopoietic second malignancies typically occur within the first decade after treatment of the primary malignancy. Solid tumor secondary malignancies are usually radiation related and occur late, even several decades after initial therapy. In a study using CCSS data to assess secondary malignancies in all pediatric cancer survivors, the cumulative incidence of secondary malignant neoplasms was 7.9 % at 30 years from diagnosis (Friedman et al. 2010). Among survivors of pediatric CNS tumors, the incidence of either a benign or malignant secondary neoplasm was 10.7 % at 25 years from diagnosis (Armstrong 2010). Notably, there is no plateau of risk over time. Radiation is a major risk factor for the development of secondary malignancy, with the cumulative incidence of a subsequent CNS neoplasm of 7.1 % at 25-year follow-up in patients who received radiation versus 1.0 % in those who did not (Armstrong et al. 2009a). Additionally, multiple studies have identified a dose-response relationship between radiation dose received and the development of subsequent neoplasms (Armstrong 2010). The delayed nature of secondary malignant neoplasms associated with radiation therapy may lead to early underestimation of risk (Schiff and Wen 2006). The most common radiation-associated brain tumors are meningiomas, followed by gliomas and sarcomas (Behin and Delattre 2002). The CNS secondary malignancies occurred in survivors of other malignancies more often than in survivors of a CNS primary cancer. In all survivors of childhood cancer, the significant risk factors for a secondary malignant neoplasm adjusted for therapeutic radiation exposure included female sex and young age at diagnosis.

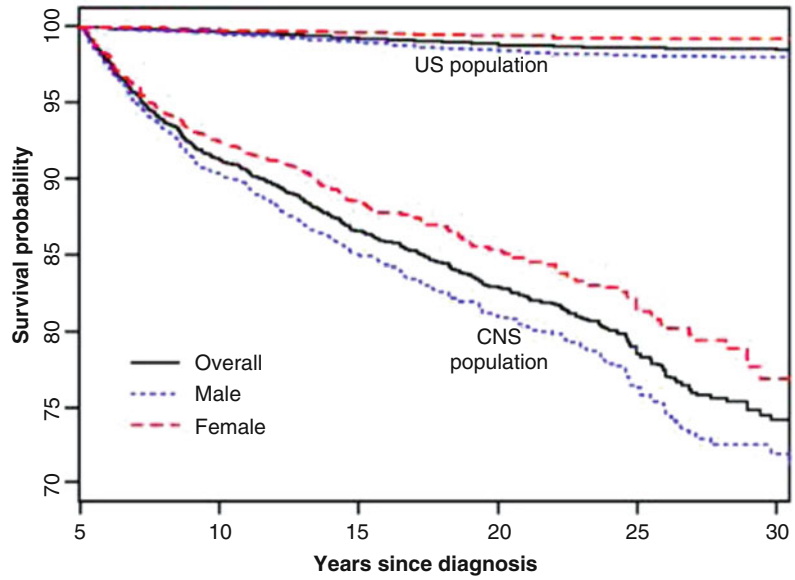

Fig. 17.1 CNS tumor all-cause and sex-specific mortality rate compared with age-adjusted US population (Armstrong et al. 2009a) (Reprinted with permission ©2009 Oxford University Press, all rights reserved)

17.2.3 General Late Effects

In addition to the increased risk of secondary cancer and death, survivors of childhood CNS malignancies are at risk for morbidity related to injury from the tumor itself and long-term effects of radiation, surgery, and chemotherapy (Butler et al. 1994; Packer and Mehta 2002; Nathan et al. 2007; Turner et al. 2009). The CNS tumor survivors have among the highest morbidity rates of all pediatric cancer survivors (Hays et al. 1992; Foreman et al. 1999).

Pediatric cancer survivors treated with radiotherapy alone (55 %) have an increased risk of late adverse events when compared to patients treated with chemotherapy (15 %) or surgery (25 %) alone (Geenen et al. 2007). The CNS injury from radiation and chemotherapy is primarily due to cortical and subcortical white-matter changes, including glial-cell damage, and demyelination (Nathan et al. 2007). Radiation injury to CNS microvasculature results in hypoxia, as well as impairment of normal neurogenesis and synaptic plasticity (Tofilon and Fike 2000; Schiff and Wen 2006). Survivors of pediatric CNS tumors who received radiation therapy show decreased white-matter volume compared to those who did not (Reddick et al. 2000; Rueckriegel et al. 2010).

Oeffinger used the CCSS database to assess chronic health conditions in pediatric cancer survivors. His analysis found that survivors were 3.3 times as likely as their siblings to have a chronic health condition. The CNS tumor survivors were among the survivors at highest risk for a grade 3 or 4 chronic health conditions using the Common Terminology Criteria for Adverse Events, Version 3 (Fig. 17.2). Female survivors of any cancer were found to be at greater risk for any, a grade 3 or higher, and multiple chronic medical conditions (Oeffinger et al. 2006). For all diagnoses, the cumulative incidence of chronic health conditions continued to slowly increase over time, even beyond the fourth decade of life (Armstrong et al. 2014).

The CCSS examined general health outcomes among 9,535 childhood cancer survivors. The CNS tumor survivors reported increased adverse outcomes in general health, functional status, and activity status and were twice as likely to have at least one negatively affected domain when compared to other pediatric cancer survivors (Hudson et al. 2003). The most commonly affected medical domains for CNS tumor survivors include neurologic, neurocognitive, neuropsychological, endocrine, and other organ dysfunctions (Table 17.1).

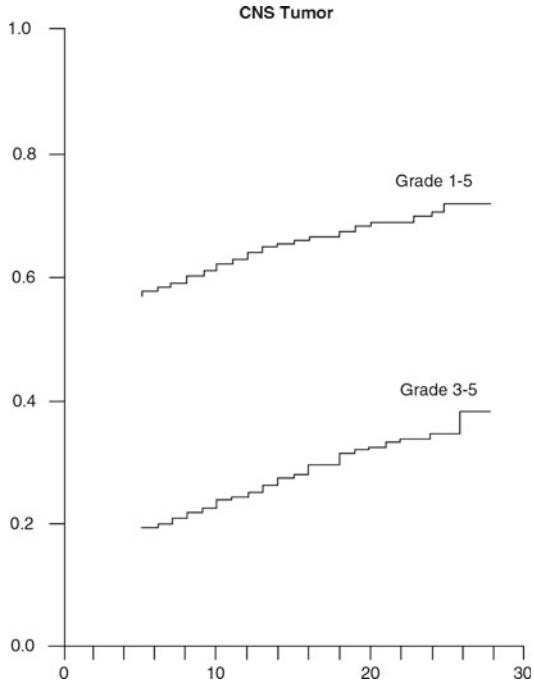

Fig. 17.2 In 1,322 adult survivors of pediatric CNS tumors, the incidence of chronic health conditions continues to increase over time (Oeffinger et al. 2006) (Copyright 2006 Massachusetts Medical Society. All rights reserved)

17.2.4 Neurologic

Multiple studies have analyzed questionnaire data from CCSS primary CNS tumor patients to assess long-term neurologic and neurosensory deficits (Packer et al. 2003; Armstrong et al. 2009a). When compared to siblings, survivors are at a significant increased risk for late onset of legal blindness, cataracts, and double vision. Twelve percent of patients report hearing impairment with a statistically significant relationship to posterior fossa irradiation greater than 50 Gy (Packer et al. 2003) and a dose-dependent increase in risk with doses above 32 Gy (Merchant et al. 2004). Children with primitive neuroectodermal tumors (PNET) are at higher risk for developing hearing deficits than other CNS tumor survivors. Focal neurologic dysfunction is common, with 49 % of patients reporting coordination problems and 26 % reporting a motor control problem. Seizure disorder is reported in 25 % of patients, and 6.5 % of this group reported the first seizure five or more years after initial diagnosis (Packer et al. 2003). Seizures, hand-eye coordination problems, and hemiplegia have been associated with supratentorial tumors, while ataxia and balance have been associated with infratentorial tumors (Lannering et al. 1990). Chronic progressive radiation myelopathy can occur following spinal radiation (Schiff and Wen 2006). Fatigue has been shown to be associated in pediatric cancer survivors with a poor health-related quality of life (Meeske et al. 2007) as well as poor neurocognitive function (Clanton et al. 2011). However, there are conflicting reports on the impact of cancer therapy on long-term fatigue (Zebrack and Chesler 2002; Langeveld et al. 2003; Mulrooney et al. 2008). In a study of 176 childhood cancer survivors, including 19 CNS tumor patients, all study enrollees reported ongoing fatigue on a quality-of-life questionnaire (Zebrack and Chesler 2002). Conflicting with this outcome, a report of 416 pediatric cancer survivors, which included 30 CNS tumor survivors, found no evidence of excess fatigue in brain tumor survivors or pediatric cancer survivors overall (Langeveld et al. 2003). Analysis of the CCSS cohort indicated significantly increased scores on standardized measures of fatigue among survivors of pediatric CNS tumors compared to the sibling group, though with questionable clinical significance (Mulrooney et al. 2008). Chronic pain has also been reported as a late effect in 19–33 % of pediatric brain tumor survivors in a series of 52 and 44 patients, respectively (Barr et al. 1999; Foreman et al. 1999), though in a study of the CCSS cohort, pediatric CNS tumor survivors had a lower risk of reporting pain conditions compared with the sibling group (Lu et al. 2011).

17.2.5 Neurocognitive

Neurocognitive dysfunction can be a debilitating consequence and a predominant late effect of cancer therapy. Between 40 % and 100 % of pediatric CNS tumor survivors report neurocognitive problems (Moleski 2000; Oeffinger et al. 2008). Severity and probability of neurocognitive deficits

Table 17.1 Chronic health conditions in pediatric CNS tumor survivors

Organ system	Chronic health condition
Neurological	Paralysis
	Seizure
	Fatigue
	Chronic pain
	Spasticity
	Ataxia
	Dysarthria
Ocular	Diplopia
	Cataracts
	Visual loss
	Dry eyes
Auditory	Tinnitus
	Hearing loss
Neurocognitive	Learning deficits
	Executive function (planning and organization)
	Sustained attention
	Memory
	Processing speed
	Visual-motor integration
	Diminished IQ
	Behavioral change
Neuropsychiatric	Social withdrawal
	Depression
	Anxiety
	Posttraumatic stress
Endocrine	Gonadal dysfunction, gonadotropin deficiency, infertility
	Metabolic syndromes, obesity
	Growth hormone deficiency
	Precious puberty
	Hyperprolactinemia
	Central hypothyroidism
	Central adrenal insufficiency
Pulmonary	Pulmonary fibrosis
	Interstitial pneumonitis
	Restrictive lung disease
	Obstructive lung disease
Gastrointestinal	Dysphagia
	Esophageal stricture
	Bowel obstruction
	Chronic enterocolitis
	Fistula
	Strictures
	Hepatic dysfunction
Cardiovascular	Congestive heart failure
	Cardiomyopathy
	Pericarditis
	Pericardial fibrosis
	Valvular disease
	Myocardial infarction
	Arrhythmia
	Atherosclerotic heart disease
	Stroke
	Vasculopathy
Renal	Impaired function
Musculoskeletal	Osteopenia
	Osteonecrosis
Dermatologic	Alopecia
	Scarring
Dental	Tooth/root agenesis
	Root thinning/shortening
	Enamel dysplasia
	Dental caries

are related to age at diagnosis and treatment, female gender, dose and volume of radiation given, dose and type of chemotherapy, hydrocephalus, and tumor type, size, and location (Packer et al. 1989; Radcliffe et al. 1992; Ris et al. 2001; Oeffinger et al. 2008; Ellenberg et al. 2009; Duffner 2010). Socioeconomic status has also been identified as a risk factor in some studies (Nathan et al. 2007). It is essential to monitor at-risk patients over time as a nonlinear decline in intellectual function is often seen. Although earlier-learned information is typically retained, the ability to acquire new information at the same rate as one's peers is impaired (Mabbott et al. 2005). Children who have received brain irradiation may have cognitive dysfunction years after treatment that is independent of the number of school days missed due to therapy (Oberfield et al. 1986; Radcliffe et al. 1992; Ris et al. 2001; Padovani et al. 2012).

The most common neurocognitive impairments are problems with attention and concentration, processing speed and visual perceptual skills, executive function, and memory (Mulhern et al. 1998; Moleski 2000; Oeffinger et al. 2008). Deficits in full-scale intelligence quotient, verbal

intelligence quotient, performance intelligence quotient, nonverbal memory, and somatosensory functioning have also been reported. Intelligence quotient scores have been shown to decrease as much as 15–25 points from baseline (Nathan et al. 2007). This decline increases in severity with increasing time from treatment (Askins and Moore 2008). The CCSS reported that 18% of 18–24-year-old brain tumor survivors had not completed high school. In addition, brain tumor survivors often required special education services, with use increasing based on younger age at diagnosis. About 70% of brain tumor survivors diagnosed before the age of 6 required special education services in school, compared with 24% in those diagnosed after age 15 (Mitby et al. 2003). Multiple studies have examined the role of pharmacological stimulants in improving neurocognitive function in pediatric CNS tumor survivors (Castellino et al. 2012; Smithson et al. 2013). A recent review identified four original trials that demonstrated improved attention, processing speed, and cognitive flexibility in pediatric CNS tumor survivors treated with methylphenidate (Smithson et al. 2013). Additionally, trials evaluating the effects of acetylcholinesterase inhibitor donepezil and dopaminergic CNS stimulant modafinil on neurocognitive function in childhood brain tumor survivors are ongoing.

17.2.6 Neuropsychology

Neuropsychological effects of brain tumor therapy include general behavioral problems, maladjustment, depressive symptoms, and poor self-concept (Carpentieri et al. 2003). Some more severe psychiatric complications include emotional dysfunction and psychosis. Seventeen percent of CCSS survivors have depressive, somatic, or anxious symptoms (Hudson et al. 2003), with a subset of these survivors reporting persistently elevated distress symptoms (Brinkman et al. 2013). Nine percent report functional impairment and/or clinical distress consistent with a diagnosis of post-traumatic stress disorder (Stuber et al. 2010). Specifically, cerebellar damage has been associated with neuropsychological and psychiatric problems (Steinlin et al. 2003). There is some evidence to suggest that survivors of CNS tumors are at increased risk of hospitalization for psychiatric disorders (Ross et al. 2003). Within the CCSS cohort, CNS tumor survivors reported the highest prevalence of suicidal ideation compared with other pediatric tumor survivors and controls (Recklitis et al. 2010). While previous analyses have not indicated an increased risk of suicide mortality in pediatric tumor survivors compared with the general population (Mertens et al. 2008; Armstrong et al. 2009b), suicidal ideation has been associated with increased all-cause mortality in survivors of childhood cancer (Brinkman et al. 2014).

17.2.7 Psychosocial

Using CCSS self-reported employment history, Pang and colleagues examined survivor employment status. Of the cancer survivors, 5.6% had never been employed compared to 1.2% of the sibling group. The CNS tumor survivors had the highest risk of having never been employed (odds ratio [OR] = 9.9), although all survivors were at increased risk (OR = 3.7). Within the group of CNS tumor survivors, risk for unemployment by treatment modality was also evaluated: surgery alone (OR = 3.7), radiotherapy and surgery (OR = 11.8), and chemotherapy, radiotherapy, and surgery (OR = 10.7) (Pang et al. 2008). Survivors are additionally employed in lower-skill jobs than siblings (Kirchhoff et al. 2011). Survivors of CNS tumors are less likely than siblings to be married, have an income of greater than $20,000, and graduate from college (Armstrong et al. 2009a). Though survivors of other pediatric tumors report high levels of current and predicted life satisfaction, brain tumor survivors predict lower levels of life satisfaction 5 years into the future compared with sibling controls (Zeltzer et al. 2008).

17.2.8 Endocrine

Endocrine dysfunction is common in CNS tumor survivors. Children with suprasellar brain tumors have a high incidence of hormonal dysfunction

(Ogilvy-Stuart et al. 1991; Sklar and Constine 1995). Patients who have received high-dose irradiation to the hypothalamic region can develop delayed-onset hormonal deficiency (Oberfield et al. 1986; Ogilvy-Stuart et al. 1991; Sklar and Constine 1995). Specific endocrinopathies include hypothyroidism, growth hormone deficiency, precocious puberty and/or gonadotropin deficiency, adrenocorticotropic hormone deficiency, panhypopituitarism, and diabetes insipidus (Rutter and Rose 2007; Nandagopal et al. 2008). Overall, patients treated with surgery alone manifest much lower rates of endocrine abnormalities than patients who also received radiation and/or chemotherapy (Gurney et al. 2003a). Young age at diagnosis increases risk of hypothalamic-pituitary axis dysfunction (Gleeson and Shalet 2004) (Gurney et al. 2003b).

Growth hormone deficiency is the most common endocrinopathy in pediatric CNS tumor survivors (Muirhead et al. 2002; Gurney et al. 2003a; Nandagopal et al. 2008). Livesey's series of 144 CNS tumor survivors showed laboratory evidence of growth hormone deficiency in 97 % of the survivors at a median follow-up time of 9.6 years (Livesey et al. 1990). Risk factors for growth hormone dysfunction include increased radiation dose, fewer radiation fractions, and younger age at diagnosis (Darzy and Shalet 2009). Cranial radiation doses as low as 18 Gy can affect the growth hormone axis (Brownstein et al. 2004). Growth hormone deficiency in children results in growth failure and short stature. Recent studies have also demonstrated that growth hormone deficiency can have effects on adults including abnormal body composition, reduced lean body mass, increased abdominal adiposity, reduced strength and exercise capacity, impaired psychological well-being, depressed mood, reduced vitality and energy, emotional lability, impaired self-control, anxiety, and increased social isolation (Carroll et al. 2000). Investigations have shown no increased risk for disease recurrence in CNS tumor survivors treated with growth hormone therapy (Moshang et al. 1996; Sklar et al. 2002). Initial reports assessing the CCSS cohort indicated a small increase in the overall risk for subsequent neoplasms in survivors treated with growth hormone (Sklar et al. 2002), though this risk diminished with longer duration of follow-up (Ergun-Longmire et al. 2006) and was not found when analysis was limited to CNS subsequent neoplasms (Patterson et al. 2014).

Central thyroid dysfunction in addition to growth hormone dysfunction can cause obesity syndrome due to the compounded effects on linear growth, in addition to the effects of hypothyroidism. These hormonal imbalances likely contribute to the increased incidence of obesity in female survivors of pediatric brain tumors. Abnormal thyroid function may also contribute to learning disabilities in this population (Anderson 2003). Gonadal dysfunction often occurs later than other endocrinopathies in pediatric CNS tumor survivors and may not be detected until puberty or early adulthood. Gonadal dysfunction includes a wide range of abnormalities from precocious or delayed puberty to infertility. Livesey found that following spinal radiation, 35 % of females had ovarian dysfunction, while only 3 % of males had testicular dysfunction (Livesey et al. 1990). The use of alkylating agents increases the risk of gonadal failure. The use of vinblastine, cytarabine, or cisplatin has also been associated with infertility (Thomson et al. 2002). Panhypopituitarism is usually only diagnosed in patients who have received greater than 40 Gy of cranial radiation. Central adrenal deficiency may present as failure to thrive, anorexia, dehydration, hypoglycemia, decreased weight gain, and hypotension. Hyperprolactinemia often manifests as galactorrhea and menstrual abnormalities.

17.2.9 Cardiovascular and Cerebrovascular

The vascular system can be affected by CNS tumor treatments as the result of damage to both the CNS vasculature and the heart itself. In an evaluation of 1,607 CNS tumor survivors, 18 % of patients reported problems, including primary arrhythmia, stroke, blood clots, and angina-like symptoms (Gurney et al. 2003a).

Spinal irradiation may contribute to cardiac injury (Jakacki et al. 1993). In the CCSS cohort, pediatric brain tumor survivors were 6.1 times more likely to experience myocardial infarction than sibling controls (Mulrooney et al. 2009). Metabolic dysfunction as a result of treatment-related endocrinopathies and limitations on physical activity may further exacerbate the risk of cardiovascular disease. Stroke is an important late effect in childhood CNS tumor survivors and may contribute to neurologic and neurocognitive disability. In the CCSS cohort, pediatric CNS tumor survivors demonstrated an increased risk of stroke as compared with sibling controls, by as much as a 30-fold (Bowers et al. 2006; Mueller et al. 2013). The underlying pathology is thought to be a radiation-induced vasculopathy, with cranial radiation increasing risk of stroke in a dose-dependent manner. Other common cranial vasculopathies following cranial radiation in children include moyamoya disease, cavernous malformations, and cerebral microhemorrhages (Ullrich et al. 2007; Lupo et al. 2012; Gastelum et al. 2014).

17.2.10 Other

Pediatric brain tumor survivors in the CCSS cohort demonstrated increased rates of pulmonary fibrosis, chest wall abnormalities, chronic cough, and need for supplemental oxygen as compared with sibling controls (Huang et al. 2014). Pulmonary disease following treatment is often linked to the use of nitrosoureas in this patient population. Cranial radiation is associated with low bone mineral density in brain tumor survivors. Methotrexate and steroids used in treatment may also contribute to this problem (Nandagopal et al. 2008).

17.2.11 Patient Factors

17.2.11.1 Age

Children less than 3 years of age at the time of therapy are thought to be at greatest risk for late effects due to their immature stage of brain development. These patients almost universally require special education services and are unlikely to live independently as adults (Nathan et al. 2007). Many CNS tumor treatment protocols have attempted to postpone and reduce cranial radiation as well as explore more targeted radiotherapy methodologies in young children, with a potential reduction in late effects (Sands et al. 2010; Saha et al. 2014).

17.2.11.2 Site

There is controversy over the role that tumor location plays in outcome (Mulhern et al. 1992; Ater et al. 1996; Steinlin et al. 2003). Multiple studies have demonstrated that supratentorial tumors confer worse morbidity than infratentorial tumors (Ellenberg et al. 1987; Lannering et al. 1990). Tumors in the cerebral hemispheres can cause problems with performance intelligence quotient, academic achievement, memory, motor skills, and attention. Posterior fossa tumors are associated with memory and motor deficits (Ater et al. 1996). Tumors that involve the hypothalamic and parasellar region are related to growth hormone deficiency. Children treated with surgery alone for benign cerebellar lesions showed deficits in attention, memory, processing speed, and visual-constructive copying (Steinlin et al. 2003). Late effects associated with particular tumor locations are shown in Table 17.2 (Ellenberg et al. 1987; Lannering et al. 1990; Livesey et al. 1990; Mostow et al. 1991; Constine et al. 1993; Syndikus et al. 1994; Ilveskoski et al. 1997; Foreman et al. 1999).

17.2.11.3 Genetics

Variation in patient response to treatment and neurocognitive outcomes may also depend on genetic polymorphisms. Currently, enzymes that effect chemotherapy metabolism and clearance are under investigation, including glutathione *S*-transferase and enzymes involved in folate metabolism. Signaling pathways known to be dysregulated in solid/brain tumors such as ErbB1-4, mTOR, IGF-IR, and PTCH1 are under investigation as future targets for therapy. In addition, identification of molecular markers predictive of outcome, survival, and treatment response may allow more patient-specific treatment plans in the

Table 17.2 Central nervous system tumor locations and associated late effects

Region	Histology (percentage of primary CNS tumors)	Important associated late effects
Supratentorial	Low-grade astrocytoma (15–20 %), high-grade astrocytoma (8–12 %), other glioma (5–10 %)	Poor cognitive function, poor manual dexterity, emotional difficulties, seizures, poorer overall quality of life
Hypothalamic/parasellar	Craniopharyngioma (6–10 %), optic pathway glioma (4–8 %)	Growth hormone deficiency with hypothyroidism and hypogonadism
Infratentorial	Primitive neural ectodermal tumor, cerebellar astrocytoma (12–15 %), high-grade pontine glioma (5–10 %), ependymoma (4–8 %)	Ataxia, primary thyroid dysfunction, ovarian dysfunction

Anderson et al. (2001). Copyright 2001 American Cancer Society. This material is reproduced with the permission of Wiley-Liss, Inc., a subsidiary of Wiley

future with the aim of cure and minimal late effects. In particular, radiogenomic studies have attempted to identify genetic variants underlying individual sensitivity to radiation in an effort to optimize radiotherapy for children genetically susceptible to neurotoxicity.

17.2.12 Treatment Factors

17.2.12.1 Radiation

The most common delayed toxicity of radiation therapy is cognitive impairment (Schiff and Wen 2006). The risk of neurocognitive late effects increases with the cumulative cranial radiation therapy dose given (Mulhern et al. 1998; Grill et al. 1999; Ris et al. 2001). Larger individual radiation fractions and larger fields of radiation also increase the risk of neurocognitive sequelae. A Pediatric Oncology Group study compared radiation doses and outcomes in medulloblastoma patients and found a decrease in neuropsychiatric toxicity in patients treated with 23.4 Gy instead of 36 Gy (Packer and Mehta 2002). Furthermore, a retrospective review of medulloblastoma patients indicated stable cognitive outcomes at 5-year follow-up in patients treated with lower dose craniospinal radiation and reduced volume tumor bed boost versus progressive decline in IQ in patients receiving standard craniospinal radiation or full volume posterior fossa boost (Moxon-Emre et al. 2014). An ongoing Children's Oncology Group study sets out to prospectively measure cognitive changes in patients enrolled on therapeutic trials for medulloblastoma and CNS germinoma; both of these therapeutic trials are examining the feasibility of reduced doses of radiation in young, good risk medulloblastoma patients or chemotherapy sensitive germ cell tumors. The CNS tumor survivors who are treated with cranial radiation have greater deficits in neurocognitive functioning than those who do not receive cranial radiation. Neuropathologic changes following whole-brain radiation include leukoencephalopathy, mineralizing microangiopathy, subacute necrotizing leukomyelopathy, and intracerebral calcifications, commonly with subsequent cerebral atrophy and microcephaly.

17.2.12.2 Chemotherapy

Methotrexate, corticosteroids, carmustine, cisplatin, and cytarabine hydrochloride can be associated with long-term neurocognitive dysfunction. The most common neurocognitive effects of chemotherapy alone include deficits in visual processing, visual-motor functioning, and attention/executive functioning (Anderson and Kunin-Batson 2009). Methotrexate can cause a syndrome termed methotrexate leukoencephalopathy, most common in patients who have had treatment with both intravenous and intrathecal methotrexate therapy, in addition to whole-brain radiation therapy (Pizzo et al. 1979). Methotrexate has also has been shown to increase the effect of cranial

radiation on the neurocognitive function (Waber et al. 1995; Moe and Holen 2000; Moleski 2000). Chemotherapy may have synergistic toxicity when given in combination with radiation therapy due to radiation-induced increase in blood-brain barrier permeability (Schiff and Wen 2006).

17.2.12.3 Surgery

A study of 28 children who were treated for medulloblastoma showed that neurologic deficits, meningitis, shunt infections, or the need for repeat surgery increased the risk of late neurocognitive deficits (Kao et al. 1994). In addition to neurocognitive affect, cerebellar dysfunction, spastic paresis, vision loss, epilepsy, and cranial nerve palsy may occur (Sønderkaer et al. 2003). Posterior fossa syndrome, characterized by loss of speech following surgery, is often present following midline posterior fossa tumor resection. Previously thought to be a transient phenomenon, posterior fossa syndrome has been associated with long-term neurologic and neurocognitive deficits (Turner et al. 2009).

17.2.13 Recommendations for Late Effects Care

In order to provide appropriate care for pediatric CNS tumor survivors, a plan for follow-up screening, surveillance, and prevention based on the individual's cancer and treatment history as well as family history, lifestyle behaviors, and comorbid conditions should be established and communicated to the patient as well as their primary-care provider. Multiple studies have shown significant deficits in survivors' knowledge regarding their diagnosis, completed treatment, and cancer-related health risks (Byrne et al. 1989; Hudson et al. 2002; Kadan-Lottick et al. 2002) as well as limited adherence with cancer screening guidelines (Nathan et al. 2010). It is essential that patients receive a summary of their treatment and appropriate recommendations for follow-up. Risk-stratified, lifelong medical monitoring can improve quality of life through early detection and intervention. Physicians also play a key role in encouraging health-promoting behaviors and prevention strategies. In order to properly address the neuropsychological deficits in CNS tumor survivors, a comprehensive neuropsychological assessment upon entry to a late-effects or follow-up clinic is necessary, regardless of patient or family report of deficits. For providers of late-effects or follow-up care for CNS tumor survivors, it is important to consider that many insurance companies may not provide coverage for neuropsychological testing (Oeffinger et al. 2008).

There is controversy regarding the optimal setting for pediatric cancer survivor follow-up. Some pediatric cancer survivors may have minimal risk for late effects and could receive follow-up by a local primary-care physician with guidance and support from a pediatric oncology treatment group. Pediatric brain tumor survivors, however, are at high risk for a large variety of significant late effects and would be best served by continued follow-up through adulthood at a multidisciplinary late-effects clinic at a center that provides pediatric oncology care. The Children's Oncology Group is a group of over 240 institutions that has developed "Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young-Adult Cancer," available at www.survivorshipguidelines.org.

17.3 Palliative Care

Cancer is the leading disease-related cause of death in children aged 5–14 years (Murphy et al. 2013). The CNS malignancies are the second most common type of cancer diagnosed in children (Howlader et al. 2014). Surveillance, Epidemiology, and End Results (SEER) registry data show 5-year relative survival rate of brain and other nervous system malignancies in children aged 0–19 from 2004 to 2010 to be 74 % (Howlader et al. 2014). These mortality data define the important role of pediatric palliative care in the management of pediatric CNS malignancies.

The World Health Organization defines palliative care for children as an active and total approach to care, embracing physical, emotional, social, and spiritual elements (Waldman and

Wolfe 2013). This approach focuses on enhancing patient's quality of life and support for family by managing distressing symptoms and providing respite and care through treatment, death, and bereavement. Care can be provided in multiple locations including the hospital, a hospice facility, or within the child's home. The family-centered approach requires a multidisciplinary team. Optimally, palliative care is not separate from curative care and should be integrated into the overall care plan from the point of initial diagnosis for patients with a life-threatening illness, but instead is increasingly incorporated into treatment planning as prognosis for cure becomes less likely (Fig. 17.3). Ideally, the need for palliative care should be based on the prognostic uncertainty inherent to a cancer diagnosis rather than likelihood of survival.

Concerns regarding growth and development uniquely separate pediatric palliative care from adult palliative care. Developmental differences among infants, children, and adolescents must be considered when designing and implementing a pediatric palliative-care program. In addition, pediatric palliative care encounters different obstacles than adult palliative care (Korones

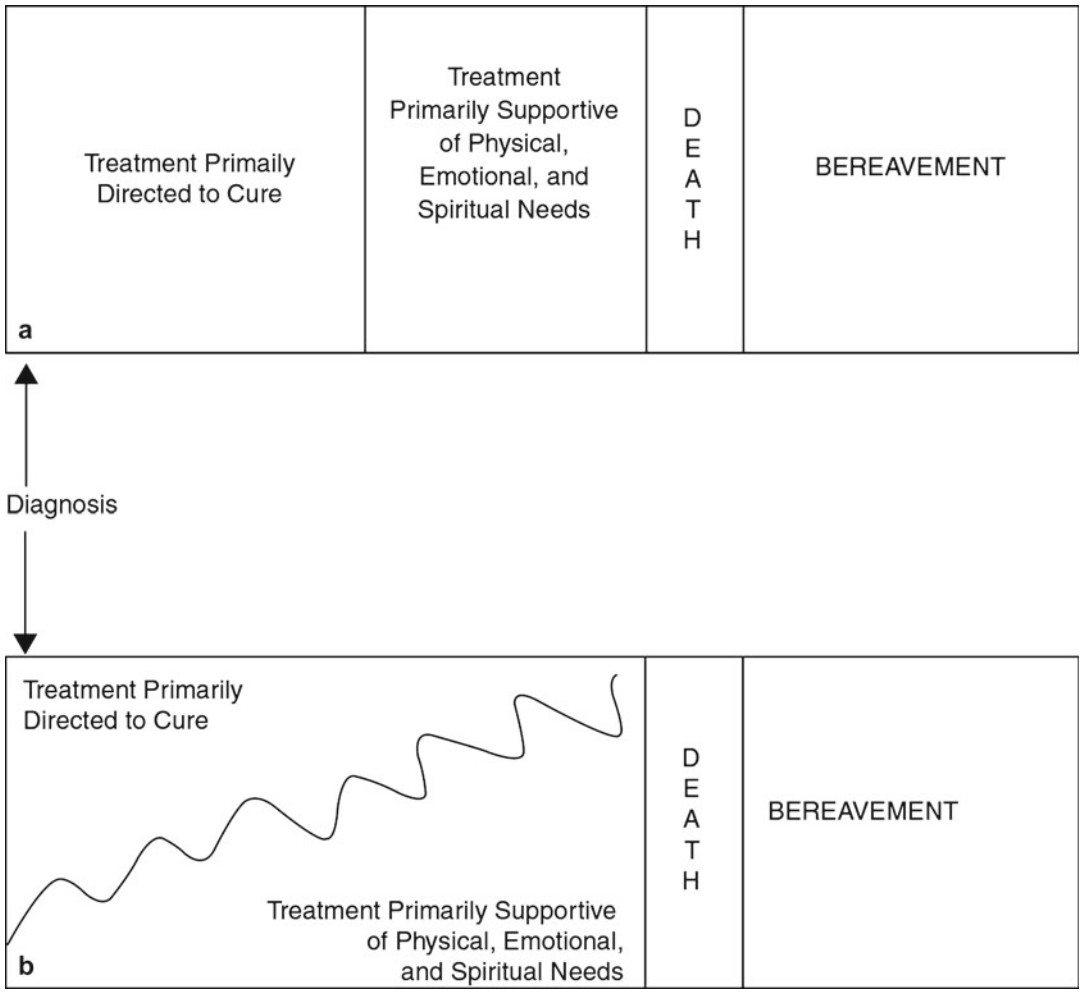

Fig. 17.3 Models for incorporating palliative care. (**a**) Palliative care is introduced only after treatment directed to cure is completed. (**b**) Palliative care is introduced early on during treatment directed to cure and begins to comprise a larger component of care over time (Sahler et al. 2000) (Reproduced with permission from Pediatrics, ©2000 by the AAP)

2007). Overall, only 25 % of childhood deaths are from a complex chronic medical condition and therefore suitable for involvement of a pediatric palliative-care team. When combined with the overall lower mortality rate in children, this creates a relatively small population of pediatric patients compared to the adult population utilizing palliative-care services. On average, a general pediatrician in North America cares for less than three children who die per year. Limited experience contributes to physician discomfort when providing pediatric palliative care (Kolarik et al. 2006).

The Medicare hospice benefit is primarily targeted for adults and requires patients to forgo curative or life-prolonging therapy. Pediatric palliative care strives to integrate curative and palliative care in combination, and thus, this reimbursement approach often directly conflicts with care plans. Typically, pediatric care does not require a do-not-resuscitate order or prognosis for short-term survival. Under the US Affordable Care Act, children under the age of 21 eligible for Medicaid or the Children's Health Insurance Program and diagnosed with a life-limiting illness may receive all services related to the treatment of that illness; this includes palliative-care and hospice-care services provided concurrently with other disease-related treatments (Waldman and Wolfe 2013). Pediatric providers and families often choose to continue supportive measures such as blood transfusions and supplemental feeding with the goal of contributing to the overall well-being of the child (Sirkia et al. 1997).

Inadequate training is another barrier to providing good palliative care. In a survey of medical staff, 49–54 % of attending physicians and residents responded that they felt inexperienced in providing pain management for dying patients (Contro et al. 2004). Multiple studies have documented a lack of pediatric palliative-care education during medical school and residency (Flint and Weidner 2012). Pediatric patients have unique medical and psychosocial needs that adult-trained palliative-care providers may feel unequipped to address. Limited clinical and community resources for hospice, homecare, and pediatric end-of-life services further complicate efforts to maximize quality of care outside of the hospital.

Many paradigms have been developed to conceptualize how and when medical treatment transitions from curative care to palliative care. In a treatment model where palliative care is considered only when curative treatment is abandoned, the patient may suffer unnecessarily as interventions to improve quality of life and comfort are deferred. An abrupt shift from curative to palliative care can be emotionally difficult for the patient, family, and medical team, creating barriers to providing the many beneficial aspects of palliative care (Fig. 17.3a). This model may also foster a feeling of abandonment in the patient and his or her family when the transition is made. Wolfe et al. documented that pain related to end-of-life was more common and severe in patients whose primary physicians were not involved in end-of-life care (Wolfe et al. 2000). Some treatment models include palliative care as an early component of overall medical care, regardless of whether the provider anticipates cure, chronic disease, or death (Fig. 17.3b). The transition to a primarily palliative-care model is made slowly and gradually allowing appropriate consideration of comfort and quality of life without forcing the patient, family, and medical care providers to discontinue curative efforts (Sahler et al. 2000). Earlier initiation of palliative care may improve symptom management and quality of life as well as benefit the bereavement process (Klick and Hauer 2010).

17.3.1 Developmental Stage

Pediatric palliative-care providers must always consider the age and developmental stage of each patient in care decisions. The role of the child in discussions and medical decision-making is an obvious example, but developmental stage must also be considered in pain assessment, techniques for communication, and conversations about death and dying. Communication appropriate to the child's developmental stage can improve

understanding of disease, reduce anxiety, and promote involvement in care and decision-making.

A child's ability to understand death evolves as they mature. In addition, each child is unique and a discussion of death and dying must be directed to match understanding at the time of communication. A general knowledge of children's developmental understanding of death by age can be helpful in approaching these challenging conversations (Table 17.3). Generally, children over 14 years old are considered to have the ability to reason as well as the competent adult. However, children as young as 9 may be able to convey reasonable preferences with regards to treatment that allow them to participate in treatment-related decision-making. Children and adolescents with chronic disease can have advanced comprehension of death for their chronological age (Poltorak and Glazer 2006).

Table 17.3 Understanding of death based on age

Age (years)	Understanding of death	Interventions
0–2	Death is interpreted as separation or abandonment, no cognitive understanding of death	Consistency, physical comfort, familiar people and objects
3–6	Death is interpreted as reversible or temporary, often seen as a punishment, magical thinking: wishes can come true	Minimize separation from family, clarify that illness is not a punishment
7–12	Gradual awareness of irreversibility and finality, specific death of self or loved one difficult to understand, interest in physiology and details of death, concrete reasoning: can see cause and effect relationships	Be truthful, allow to maintain usual activities as much as possible, allow participation in decision-making
>12	Death is irreversible, universal, and inevitable, all people and self die: usually see self death in far future, abstract and philosophical reasoning	Promote independence, allow expression of emotions, maintain access to peers, be truthful, allow participation in decision-making

Initially, some parents express the desire to exclude their children from conversations regarding their diagnosis, prognosis, and treatment plans in order to protect them. Respect for these fears and concerns enables a relationship of trust between the medical provider and family. Once this trust is established, the provider can more effectively communicate the importance of providing the child with honest, developmentally appropriate information, as well as a genuine willingness to listen to questions. This can help alleviate the anxiety that the child may be experiencing and provide a safe environment for discussion of the child's own fears and concerns. In a study of 429 parents who had a child that died of cancer, none of the parents who had discussed death with their child had regrets (Kreicbergs et al. 2004). Of the parents who did not discuss death with their child, 27 % did have regrets. Many parents prefer to inform the child themselves of new information. The physician and medical team can be of great help by providing communication techniques as well as being available for support and to answer questions. Children may have significant anxiety and depression when faced with end-of-life issues. Play therapy is an excellent tool to elicit these feelings. Often, giving voice to these concerns is a significant first step in treating the child's anxiety and/or depression. For patients who require additional intervention, combined counseling and medical therapy with antidepressants and anxiolytics can be beneficial.

17.3.2 Communication

Innovative efforts to define communication as a skill, institute formal education in communication during physician training, and develop tools to help physicians improve their communication skills, all emphasize the essential role that communication plays in the patient-provider relationship. Effective and compassionate communication is paramount when conveying bad news and addressing end-of-life issues. In order to address the unique needs of each patient and family, the palliative-care team must establish ongoing open

communication. This also allows improved support for each family's religious customs and cultural needs.

A survey of 228 pediatric oncologists was completed in 1998 by the American Society of Clinical Oncology (ASCO) (Hilden et al. 2001). Providing education focusing on communication skills when discussing the transition from curative to palliative care with pediatric patients and their families was found to need improvement. More recent surveys indicate little progress, with 75 % of pediatric oncologists indicating no formal training in end-of-life issues (Fowler et al. 2006). Families of 44 children who received palliative care reported confusing, inadequate, ineffective, and insensitive communication from the treatment team (Contro et al. 2004). Another study showed that physicians recognize that a child no longer has a realistic chance of cure well before the parents do (Wolfe et al. 2000). These findings indicate a need for improved provider communication.

To address the shortcomings of physician communication in this field, it is essential to acknowledge that sharing bad news and discussion of difficult issues is not an innate, but a learned skill (Korones 2007). Multistep communication tools can aid physician education in this arena. Von Gunten, Ferris, and Emanuel developed a seven-step communication tool to provide clinicians with a formal approach to structuring conversations with families (von Gunten et al. 2000). In this model, the physician should begin (Step 1) by preparing for the discussion by confirming medical facts of the case, designating an appropriate time and location for the conversation, and ensuring that everyone in the family who would like to be present can attend. Next (Step 2), the physician should clarify what the patient and family understand about the current medical situation of the patient using open-ended questions to elicit the active involvement of the family and patient in the conversation. Step 3 aims to identify the developmentally appropriate manner in which the patient and family would like to handle new information. Step 4 focuses on delivery of information in a clear and sensitive manner followed by time for questions. In Step 5, the physician responds to the emotional reactions of the patient, parents, and others present. Next (Step 6), the physician begins to establish goals for care and treatment priorities. Finally (Step 7), the group establishes a plan. These steps may seem intuitive, but a study analyzing 398 clinic conversations between 51 adult oncologists and 270 patients found that the doctors responded to empathic opportunities only 22 % of the time (Pollak et al. 2007). Role-play and standardized patient interactions provide safe and effective teaching environments to build and improve communication skills.

Although a do-not-resuscitate order is not a requirement for palliative-care team involvement, there is often a point in the child's care when this issue should be addressed. Providers often wait until respiratory or cardiac arrest is a significant possibility before initiating do-not-resuscitate discussions because of the emotionally charged nature of the discussion. Discussion of wishes regarding resuscitation earlier in the clinical course, in a calm and non-acute setting, has many advantages, allowing the provider to shift the emphasis to maximizing quality of life and avoiding interventions with low likelihood of benefit but high likelihood of suffering. The parents should understand that a do-not-resuscitate (DNR) decision can be changed at any time and does not bar other life-sustaining or curative measures. Tools such as the "Voicing My Choices" document may help facilitate patient participation in advance care planning (Wiener et al. 2012).

Siblings of patients are often inadvertently neglected during treatment and throughout the pediatric palliative-care process. While some may exhibit positive responses, such as increased maturity and empathy (Waldman and Wolfe 2013), a subset of these children may be at increased risk for multiple problems including school issues, negative interpersonal relationships with their parents, and other psychological and social problems. To assure that sibling needs are appropriately met, the Society of Paediatric Oncology (SIOP) working committee on psychosocial issues in pediatric oncology generated a report with general principles and specific treat-

ment phase guidelines (Spinetta et al. 1999). Siblings should be involved early to avoid feelings of isolation and abandonment. Parents should be encouraged and supported to have open and honest conversations with siblings on a regular basis in a developmentally appropriate manner. Evading the truth can create feelings of fear, isolation, guilt, and resentment. Families should be provided information support groups and other resources for their children.

17.3.3 Team Approach

The multidisciplinary team involving physicians, nurses, social workers, psychologists, child-life specialists, clergy, and family members must also communicate well to optimize patient care. In family meetings, each member of the medical team plays an important role to ensure effective and thorough conveyance of information. Patients and their families should be considered as team members and instructed on how to participate. A study of 95 pediatric oncology patients including 25 brain tumor patients demonstrated that most pediatric oncology patients who die of progressive disease die at home (Klopfenstein et al. 2001). Continued communication between the care providers in the home and the hospital-based providers can be challenging.

17.3.4 Pain and Symptom Management

One of the primary goals of pediatric palliative care is to ensure the highest quality of life for the patient. Pediatric cancer patients often have poorly controlled symptoms and ongoing suffering. Wolfe and colleagues found that pain, fatigue, and dyspnea were the most frequent symptoms during end-of-life care as reported by 103 parents of pediatric oncology patients (Fig. 17.4) (Wolfe et al. 2000). Patients with CNS tumors may additionally experience headaches, vomiting, decreased level of consciousness, and increased oral secretions at end of life due to the location of their malignancy (Foster et al. 2010).

17.3.4.1 Pain

Pain is often not recognized or appropriately treated in children. Wolfe's study of symptom management in children dying of cancer found that only 27 % of patients received successful pain treatment (Wolfe et al. 2000), with a more recent study indicating that 47 % of patients still reported "a great deal" or "a lot" of suffering from pain in the last month of life (Wolfe et al. 2008). Yet, a survey of 632 practicing pediatric oncologists found that 86 % of providers reported proficiency in end-of-life pain management (Fowler et al. 2006). There is clearly a disconnect between provider and parent perceptions of pain management. Using basic guidelines for pain management in children can help physicians to recognize and assess pain (Hain et al. 2004). The tool used to assess pain in a child must be appropriate to the child's developmental level. Although not all children are capable of self-report, it is the gold standard for pain measurement. In order to ensure accurate pain reports from children, the provider needs to establish a relationship of trust with the child by promptly and effectively responding to pain reports. The physician must also prevent and treat adverse effects of medical interventions. Use of developmentally appropriate language for pain (e.g., *hurt*, *owie*, *boo-boo*) can improve communication. Pain changes over time and therefore must be assessed regularly.

Assessing response to pain treatment is also essential for effective management. In a chronically or critically ill child, physiological indicators including pulse and blood pressure may not accurately represent pain. Behavioral indicators may also be inaccurate in this patient population. Lastly, a child that is playing or sleeping may still have pain. Some tools to assess pain in children are body charts, face scales, numeric scales, color tools, visual analog scales, and behavior observation (Goldman 1998). Cognitively impaired patients may be unable to communicate effectively and thus caregiver input becomes an important tool for pain assessment (Klick and Hauer 2010).

The World Health Organization has created a four-step analgesic pain ladder to guide pain

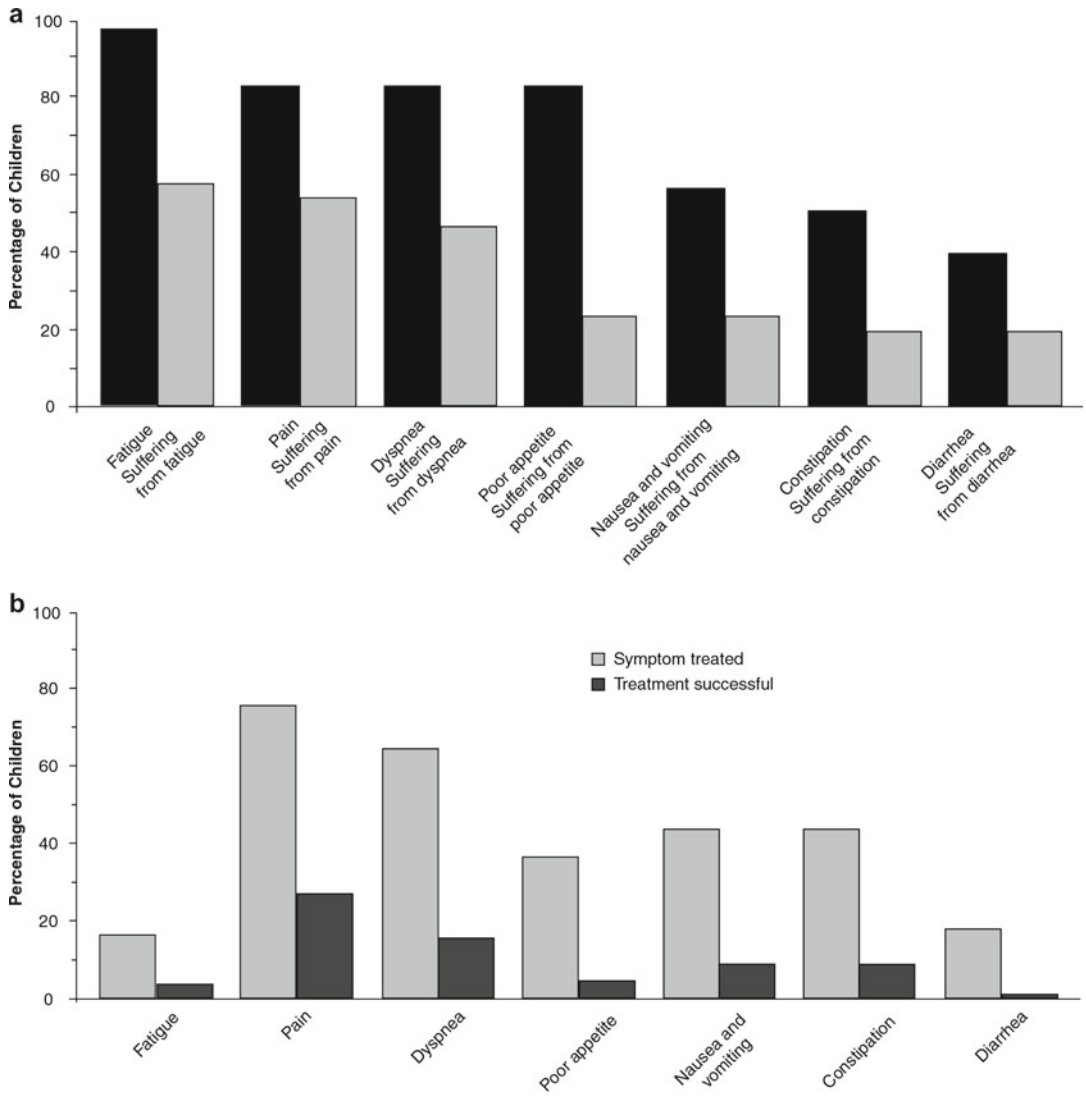

Fig. 17.4 Symptoms in the final month of life of 103 pediatric cancer patients. (**a**) Percentage of patients with a specific symptom who had "a great deal" or "a lot" of suffering as a result of that symptom by parental report. (**b**) Percentage of children with a specific symptom that was treated, and where treatment was categorized as "successful" as opposed to "somewhat successful" or "not successful" by parental report (Wolfe et al. 2000) (Copyright 2000 Massachusetts Medical Society. All rights reserved)

management. For children who have moderate to severe pain, opioids are the primary pharmaceutical agent used for treatment (Korones 2007). However, there are some barriers to appropriate opioid dosing in pediatric palliative care. Often parents and even physicians are concerned about the risk of opioid addiction. When used for treatment of pain, this is quite rare. Concerns regarding possible drug overdose or respiratory depression can interfere with appropriate medication dosing and pain relief. In children greater than 3 months of age, the incidence of opioid-induced respiratory depression is similar to the adult rate of 0.9 % (Sahler et al. 2000). There is no maximal dose for opioid medications. It is appropriate to continue dose escalation until

there are either intolerable side effects or no improvement in analgesia.

Other medications are also used for treatment of specific types of pain. Neuropathic pain is treated using gabapentin, amitriptyline, or nortriptyline. Somatic pain in bone and soft tissues is often effectively reduced by nonsteroidal anti-inflammatory drugs and glucocorticoids. For uncontrolled pain, a pain service consultation is available at many institutions and can provide the patient access to pain control techniques including nerve blocks. Alternative pain reduction techniques can also be employed, including hypnosis, distraction, biofeedback, massage, guided imagery, acupuncture and acupressure, and play.

17.3.4.2 Seizure and Other Neurologic Symptoms

Pediatric CNS tumor patients are at significant risk for seizures. They can be quite distressing to both the family and child and should be appropriately managed in consultation with a pediatric neurologist (Wusthoff et al. 2007). Daily antiepileptic drugs are often initiated. The medical team should also consider and plan for the possibility of status epilepticus. Families can administer rectal diazepam gel and other antiepileptic medicines if prolonged seizures occur outside the medical setting.

Agitation is often referred to as terminal restlessness and manifests as increased arousal with or without delirium. Some nonpharmaceutical methods of easing this agitation include familiar objects and reminders of orientation such as a clock or calendar. Pharmaceutical agents may be required. Some of the drug classes used for this purpose include benzodiazepines, neuroleptics, adrenergic agonists and antagonists, and, in more severe cases, barbiturates (Wusthoff et al. 2007).

Spasticity is defined as an increase in resistance to passive muscle stretch that is velocity dependent. When severe, it can cause significant pain and complicate changing and positioning of the child. Physical therapy, positioning, and specific medical equipment can be used prior to initiation of medication. Some of the more commonly used agents are baclofen, α-adrenergic agonists, benzodiazepines, and dantrolene (Wusthoff et al. 2007).

17.3.4.3 Nutrition

Many families feel that continuing to provide nourishment for their child is essential. The primary goal should be comfort and enjoyment and risks of aspiration with oral feeding should be discussed with families and patients as developmentally appropriate. If nausea and vomiting from increased intracranial pressure or ongoing treatment are impairing a child's ability to eat and drink, appropriate pharmaceutical management should be initiated.

While some children and their families choose to spend the end of the child's life in the hospital, others prefer to be in their home. Efforts should be made to support the family in whatever they choose. In the past few years, more pediatric home health nursing and hospice services have provided the support families need at home. In this setting, pharmacologic therapy with antidepressants and anxiolytics can be beneficial.

It is important to address what can be expected during the actual physical process of dying with families and patients. Some general issues to include in this discussion are that in the days prior to death, a child may have periods of confusion, restlessness, and agitation as well as deep sleep and lethargy. Oral intake and urine and stool output often decrease significantly. Some children may talk about death, heaven, and other related topics. In the time immediately preceding death, the child's skin may become cool. Breathing patterns may vary with gasping sounds and rattling sounds. These are not known to be uncomfortable or indicative of pain for the child, but can be quite distressing for observers. Having a health-care provider available to listen for heart rate and pronounce death is important for many families. Many parents request that nasogastric tubes, intravenous catheters, and other medical equipment be removed. The time after death can be an opportunity to cut locks of hair or create handprints for some families as well. Families should be encouraged to spend as much time as they would like with their child after they have died.

17.4 Ethical Considerations of Clinical Trials and Consent

Participation in clinical trials is an important option available to many pediatric brain tumor patients. Preservation of the patient's and the family's right to autonomy and self-determination in medical decision-making is integral to good end-of-life care. Three specific areas to consider are the patient's role in decision-making, best interests, and determination of the course of care (Sahler et al. 2000). Often there are new chemotherapy protocols or Phase I or II experimental drug trials available to patients with progressive or relapsed disease. The physician must balance the hope offered by these treatment options with realistic expectations of long-term outcome (Levy 2005). Phase I trials are generally defined as the first stage of testing in human subjects to test safety, tolerability, pharmacokinetics, and pharmacodynamics of a drug. They can also include assessment of new combinations or dosing schedules of FDA-approved drugs (Horstmann et al. 2005). The estimated number of patients who can expect to have disease response is variable, based on the exact study design, but is estimated to be 4–6 % for single-agent investigational trials (Kurzrock and Benjamin 2005). The physician must be aware that communication about the risks and benefits to participation may be affected by the "therapeutic misconception," or the belief that the purpose of the research is to benefit the individual patient. The primary benefit is to future patients. Phase II trials are designed to test the effects of the drug on a specific disease and learn more about the effects of the drug on the human body. The highest dose tolerated in the Phase I trial is the dose administered, and although a few patients can show disease response, again the primary benefit is to future patients. Palliative chemotherapy is often an alternative option that should be discussed especially if the selected agent is well tolerated and easy to administer. The physician is responsible for clarifying that palliative chemotherapy aims to improve the quality of life, not eliminate the disease, and the likelihood of benefit may be unpredictable.

17.5 Bereavement

The time following a child's death is very difficult for the surviving family members and is a significant stressor (Wheeler 2001). Parents who report having not worked through their grief are at increased risk for long-term physical and psychological morbidity (Lannen et al. 2008). The abrupt departure from the medical environment can cause additional feelings of loss and sorrow. Many families appreciate continued communication with members of the medical team. Other families desire privacy, and the needs of each family must be determined and respected individually. Support groups can be very helpful to grieving family members. A palliative-care team should provide ongoing support and assessment to the family after a child's death. Bereavement counseling may be offered, if needed. The needs of the medical team are often neglected in discussions of grief and sadness after the death of a child. Often a debriefing session can be helpful and allow providers to mourn the loss of a child.

References

Anderson DM, Rennie KM, Ziegler RS, Neglia JP, Robison LR, Gurney JG (2001) Medical and neurocognitive late effects among survivors of childhood central nervous system tumors. Cancer 92:2709–2719

Anderson FS, Kunin-Batson AS (2009) Neurocognitive late effects of chemotherapy in children: the past 10 years of research on brain structure and function. Pediatr Blood Cancer 52:159–164

Anderson NE (2003) Late complications in childhood central nervous system tumour survivors. Curr Opin Neurol 16:677–683

Armstrong GT, Liu Q, Yasui Y, Huang S, Ness KK, Leisenring W, Hudson MM, Donaldson SS, King AA, Stovall M, Krull KR, Robison LL, Packer RJ (2009a) Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst 101:946–958

Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, Mertens AC (2009b) Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol 27:2328–2338

Armstrong GT (2010) Long-term survivors of childhood central nervous system malignancies: the experience

of the Childhood Cancer Survivor Study. Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc 14:298–303

Armstrong GT, Kawashima T, Leisenring W, Stratton K, Stovall M, Hudson MM, Sklar CA, Robison LL, Oeffinger KC (2014) Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. J Clin Oncol 32:1218–1227

Askins MA, Moore BD (2008) Preventing neurocognitive late effects in childhood cancer survivors. J Child Neurol 23:1160–1171

Ater JL, Moore BD III, Francis DJ, Castillo R, Slopis J, Copeland DR (1996) Correlation of medical and neurosurgical events with neuropsychological status in children at diagnosis of astrocytoma: utilization of a neurological severity score. J Child Neurol 11:462–469

Barr RD, Simpson T, Whitton A, Rush B, Furlong W, Feeny DH (1999) Health-related quality of life in survivors of tumours of the central nervous system in childhood–a preference-based approach to measurement in a cross-sectional study. Eur J Cancer 35:248–255

Behin A, Delattre JY (2002) Neurological sequelae of radiation therapy on the nervous system. In: Schiff D, Wen PY (eds) Cancer neurology in clinical practice. Humana, Totowa, pp 173–191

Bowers DC, Liu Y, Leisenring W, McNeil E, Stovall M, Gurney JG, Robison LL, Packer RJ, Oeffinger KC (2006) Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. J Clin Oncol 24:5277–5282

Brinkman TM, Zhu L, Zeltzer LK, Recklitis CJ, Kimberg C, Zhang N, Muriel AC, Stovall M, Srivastava DK, Robison LL, Krull KR (2013) Longitudinal patterns of psychological distress in adult survivors of childhood cancer. Br J Cancer 109:1373–1381

Brinkman TM, Zhang N, Recklitis CJ, Kimberg C, Zeltzer LK, Muriel AC, Stovall M, Srivastava DK, Sklar CA, Robison LL, Krull KR (2014) Suicide ideation and associated mortality in adult survivors of childhood cancer. Cancer 120:271–277

Brownstein CM, Mertens AC, Mitby PA, Stovall M, Qin J, Heller G, Robison LL, Sklar CA (2004) Factors that affect final height and change in height standard deviation scores in survivors of childhood cancer treated with growth hormone: a report from the childhood cancer survivor study. J Clin Endocrinol Metab 89:4422–4427

Butler RW, Hill JM, Steinherz PG, Meyers PA, Finlay JL (1994) Neuropsychologic effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. J Clin Oncol 12:2621–2629

Byrne J, Lewis S, Halamek L, Connelly RR, Mulvihill JJ (1989) Childhood cancer survivors' knowledge of their diagnosis and treatment. Ann Intern Med 110:400–403

Carpentieri SC, Meyer EA, Delaney BL, Victoria ML, Gannon BK, Doyle JM, Kieran MW (2003) Psychosocial and behavioral functioning among pediatric brain tumor survivors. J Neurooncol 63:279–287

Carroll PV, Christ ER, Sonksen PH (2000) Growth hormone replacement in adults with growth hormone deficiency: assessment of current knowledge. Trends Endocrinol Metab 11:231–238

Castellino SM, Tooze JA, Flowers L, Hill DF, McMullen KP, Shaw EG, Parsons SK (2012) Toxicity and efficacy of the acetylcholinesterase (AChe) inhibitor donepezil in childhood brain tumor survivors: a pilot study. Pediatr Blood Cancer 59:540–547

Clanton NR, Klosky JL, Li C, Jain N, Srivastava DK, Mulrooney D, Zeltzer L, Stovall M, Robison LL, Krull KR (2011) Fatigue, vitality, sleep, and neurocognitive functioning in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 117:2559–2568

Constine LS, Woolf PD, Cann D, Mick G, McCormick K, Raubertas RF, Rubin P (1993) Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 328:87–94

Contro NA, Larson J, Scofield S, Sourkes B, Cohen HJ (2004) Hospital staff and family perspectives regarding quality of pediatric palliative care. Pediatrics 114:1248–1252

Darzy KH, Shalet SM (2009) Hypopituitarism following radiotherapy revisited. Endocr Dev 15:1–24

Duffner PK (2010) Risk factors for cognitive decline in children treated for brain tumors. Eur J Paediatr Neurol 14:106–115

Ellenberg L, McComb JG, Siegel SE, Stowe S (1987) Factors affecting intellectual outcome in pediatric brain tumor patients. Neurosurgery 21:638–644

Ellenberg L, Liu Q, Gioia G, Yasui Y, Packer RJ, Mertens A, Donaldson SS, Stovall M, Kadan-Lottick N, Armstrong G, Robison LL, Zeltzer LK (2009) Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the Childhood Cancer Survivor Study. Neuropsychology 23:705–717

Ergun-Longmire B, Mertens AC, Mitby P, Qin J, Heller G, Shi W, Yasui Y, Robison LL, Sklar CA (2006) Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. J Clin Endocrinol Metab 91:3494–3498

Flint H, Weidner N (2012) Crossing the chasm: understanding modern practice and application of pediatric palliative care. Int Anesthesiol Clin 50:96–108

Foreman NK, Faestel PM, Pearson J, Disabato J, Poole M, Wilkening G, Arenson EB, Greffe B, Thorne R (1999) Health status in 52 long-term survivors of pediatric brain tumors. J Neurooncol 41:47–53

Foster TL, Lafond DA, Reggio C, Hinds PS (2010) Pediatric palliative care in childhood cancer nursing: from diagnosis to cure or end of life. Semin Oncol Nurs 26:205–221

Fowler K, Poehling K, Billheimer D, Hamilton R, Wu H, Mulder J, Frangoul H (2006) Hospice referral practices

for children with cancer: a survey of pediatric oncologists. J Clin Oncol 24:1099–1104
Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL, Neglia JP (2010) Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 102:1083–1095
Gastelum E, Sear K, Hills N, Roddy E, Randazzo D, Chettout N, Hess C, Cotter J, Haas-Kogan DA, Fullerton H, Mueller S (2015) Rates and characteristics of radiographically detected intracerebral cavernous malformations after cranial radiation therapy in pediatric cancer patients. J Child Neurol 30(7):842–849, published online
Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, Jaspers MW, Koning CC, Olden-burger F, Langeveld NE, Hart AA, Bakker PJ, Caron HN, van Leeuwen FE (2007) Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 297:2705–2715
Gleeson HK, Shalet SM (2004) The impact of cancer therapy on the endocrine system in survivors of childhood brain tumours. Endocr Relat Cancer 11:589–602
Goldman A (1998) ABC of palliative care. Special problems of children. BMJ 316:49–52
Grill J, Renaux VK, Bulteau C, Viguier D, Levy-Piebois C, Sainte-Rose C, Dellatolas G, Raquin MA, Jambaque I, Kalifa C (1999) Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes. Int J Radiat Oncol Biol Phys 45:137–145
Gurney JG, Kadan-Lottick NS, Packer RJ, Neglia JP, Sklar CA, Punyko JA, Stovall M, Yasui Y, Nicholson HS, Wolden S, McNeil DE, Mertens AC, Robison LL (2003a) Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer 97:663–673
Gurney JG, Ness KK, Stovall M, Wolden S, Punyko JA, Neglia JP, Mertens AC, Packer RJ, Robison LL, Sklar CA (2003b) Final height and body mass index among adult survivors of childhood brain cancer: childhood cancer survivor study. J Clin Endocrinol Metabol 88:4731–4739
Hain R, Weinstein S, Oleske J, Orloff S, Cohn S (2004) Holistic management of symptoms. In: Carter BS, Levetown M (eds) Palliative care for infants, children and adolescents: a practical handbook. Johns Hopkins University Press, Baltimore, pp 163–195
Hays DM, Landsverk J, Sallan SE, Hewett KD, Patenaude AF, Schoonover D, Zilber SL, Ruccione K, Siegel SE (1992) Educational, occupational, and insurance status of childhood cancer survivors in their fourth and fifth decades of life. J Clin Oncol 10:1397–1406
Hilden JM, Emanuel EJ, Fairclough DL, Link MP, Foley KM, Clarridge BC, Schnipper LE, Mayer RJ (2001) Attitudes and practices among pediatric oncologists regarding end-of-life care: results of the 1998 American Society of Clinical Oncology survey. J Clin Oncol 19:205–212
Horstmann E, McCabe MS, Grochow L, Yamamoto S, Rubinstein L, Budd T, Shoemaker D, Emanuel EJ, Grady C (2005) Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engla J Med 352:895–904
Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (2014) SEER cancer statistics review, 1975-2011. National Cancer Institute, Bethesda
Huang TT, Chen Y, Dietz AC, Yasui Y, Donaldson SS, Stokes DC, Stovall M, Leisenring WM, Sklar CA, Diller LR, Mertens AC, Armstrong GT, Green DM, Robison LL, Ness KK (2014) Pulmonary outcomes in survivors of childhood central nervous system malignancies: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer 61:319–325
Hudson MM, Tyc VL, Srivastava DK, Gattuso J, Quargnenti A, Crom DB, Hinds P (2002) Multicomponent behavioral intervention to promote health protective behaviors in childhood cancer survivors: the protect study. Med Pediatr Oncol 39:2–11; discussion 2
Hudson MM, Mertens AC, Yasui Y, Hobbie W, Chen H, Gurney JG, Yeazel M, Recklitis CJ, Marina N, Robison LR, Oeffinger KC (2003) Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. JAMA 290:1583–1592
Ilveskoski I, Pihko H, Sankila R, Lanning M, Perkkio M, Aarimaa T, Makipernaa A, Saarinen UM (1997) Improving outcome of malignant brain tumours in very young children: a population-based study in Finland during 1975–93. Acta Paediatr 86:724–729
Jakacki RI, Goldwein JW, Larsen RL, Barber G, Silber JH (1993) Cardiac dysfunction following spinal irradiation during childhood. J Clin Oncol 11:1033–1038
Kadan-Lottick NS, Robison LL, Gurney JG, Neglia JP, Yasui Y, Hayashi R, Hudson M, Greenberg M, Mertens AC (2002) Childhood cancer survivors' knowledge about their past diagnosis and treatment: Childhood Cancer Survivor Study. JAMA 287:1832–1839
Kao GD, Goldwein JW, Schultz DJ, Radcliffe J, Sutton L, Lange B (1994) The impact of perioperative factors on subsequent intelligence quotient deficits in children treated for medulloblastoma/posterior fossa primitive neuroectodermal tumors. Cancer 74:965–971
Kirchhoff AC, Krull KR, Ness KK, Park ER, Oeffinger KC, Hudson MM, Stovall M, Robison LL, Wickizer T, Leisenring W (2011) Occupational outcomes of adult childhood cancer survivors: a report from the childhood cancer survivor study. Cancer 117:3033–3044
Klick JC, Hauer J (2010) Pediatric palliative care. Curr Probl Pediatr Adolesc Health Care 40:120–151
Klopfenstein KJ, Hutchison C, Clark C, Young D, Ruymann FB (2001) Variables influencing end-of-life care in children and adolescents with cancer. J Pediatr Hematol Oncol 23:481–486

Kolarik RC, Walker G, Arnold RM (2006) Pediatric resident education in palliative care: a needs assessment. Pediatrics 117:1949–1954

Korones DN (2007) Pediatric palliative care. Pediatr Rev 28:e46–e56

Kreicbergs U, Valdimarsdottir U, Onelov E, Henter JI, Steineck G (2004) Talking about death with children who have severe malignant disease. N Engl J Med 351:1175–1186

Kurzrock R, Benjamin RS (2005) Risks and benefits of phase 1 oncology trials, revisited. N Engl J Med 352:930–932

Langeveld NE, Grootenhuis MA, Voute PA, de Haan RJ, van den Bos C (2003) No excess fatigue in young adult survivors of childhood cancer. Eur J Cancer 39:204–214

Lannen PK, Wolfe J, Prigerson HG, Onelov E, Kreicbergs UC (2008) Unresolved grief in a national sample of bereaved parents: impaired mental and physical health 4 to 9 years later. J Clin Oncol 26:5870–5876

Lannering B, Marky I, Lundberg A, Olsson E (1990) Long-term sequelae after pediatric brain tumors: their effect on disability and quality of life. Med Pediatr Oncol 18:304–310

Levy AS (2005) Brain tumors in children: evaluation and management. Curr Probl Pediatr Adolesc Health Care 35:230–245

Linabery AM, Ross JA (2008) Childhood and adolescent cancer survival in the US by race and ethnicity for the diagnostic period 1975-1999. Cancer 113:2575–2596

Livesey EA, Hindmarsh PC, Brook CG, Whitton AC, Bloom HJ, Tobias JS, Godlee JN, Britton J (1990) Endocrine disorders following treatment of childhood brain tumours. Br J Cancer 61:622–625

Lu Q, Krull KR, Leisenring W, Owen JE, Kawashima T, Tsao JC, Zebrack B, Mertens A, Armstrong GT, Stovall M, Robison LL, Zeltzer LK (2011) Pain in long-term adult survivors of childhood cancers and their siblings: a report from the Childhood Cancer Survivor Study. Pain 152:2616–2624

Lupo JM, Chuang CF, Chang SM, Barani IJ, Jimenez B, Hess CP, Nelson SJ (2012) 7-Tesla susceptibility-weighted imaging to assess the effects of radiotherapy on normal-appearing brain in patients with glioma. Int J Radiat Oncol Biol Phys 82:e493–e500

Mabbott DJ, Spiegler BJ, Greenberg ML, Rutka JT, Hyder DJ, Bouffet E (2005) Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. J Clin Oncol 23:2256–2263

Meeske KA, Patel SK, Palmer SN, Nelson MB, Parow AM (2007) Factors associated with health-related quality of life in pediatric cancer survivors. Pediatr Blood Cancer 49:298–305

Merchant TE, Gould CJ, Xiong X, Robbins N, Zhu J, Pritchard DL, Khan R, Heideman RL, Krasin MJ, Kun LE (2004) Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. Int J Radiat Oncol Biol Phys 58:1194–1207

Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, Robison LL, Yasui Y (2008) Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 100:1368–1379

Mitby PA, Robison LL, Whitton JA, Zevon MA, Gibbs IC, Tersak JM, Meadows AT, Stovall M, Zeltzer LK, Mertens AC, Childhood Cancer Survivor Study Steering Committee (2003) Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 97:1115–1126

Moe PJ, Holen A (2000) High-dose methotrexate in childhood all. Pediatr Hematol Oncol 17:615–622

Moleski M (2000) Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. Arch Clin Neuropsychol 15:603–630

Moshang T Jr, Rundle AC, Graves DA, Nickas J, Johanson A, Meadows A (1996) Brain tumor recurrence in children treated with growth hormone: the National Cooperative Growth Study experience. J Pediatr 128:S4–S7

Mostow EN, Byrne J, Connelly RR, Mulvihill JJ (1991) Quality of life in long-term survivors of CNS tumors of childhood and adolescence. J Clin Oncol 9:592–599

Moxon-Emre I, Bouffet E, Taylor MD, Laperriere N, Scantlebury N, Law N, Spiegler BJ, Malkin D, Janzen L, Mabbott D (2014) Impact of craniospinal dose, boost volume, and neurologic complications on intellectual outcome in patients with medulloblastoma. J Clin Oncol 32:1760–1768

Mueller S, Fullerton HJ, Stratton K, Leisenring W, Weathers RE, Stovall M, Armstrong GT, Goldsby RE, Packer RJ, Sklar CA, Bowers DC, Robison LL, Krull KR (2013) Radiation, atherosclerotic risk factors, and stroke risk in survivors of pediatric cancer: a report from the Childhood Cancer Survivor Study. Int J Radiat Oncol Biol Phys 86:649–655

Muirhead SE, Hsu E, Grimard L, Keene D (2002) Endocrine complications of pediatric brain tumors: case series and literature review. Pediatr Neurol 27:165–170

Mulhern RK, Hancock J, Fairclough D, Kun L (1992) Neuropsychological status of children treated for brain tumors: a critical review and integrative analysis. Med Pediatr Oncol 20:181–191

Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE (1998) Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. J Clin Oncol 16:1723–1728

Mulrooney DA, Ness KK, Neglia JP, Whitton JA, Green DM, Zeltzer LK, Robison LL, Mertens AC (2008) Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the childhood cancer survivor study (CCSS). Sleep 31:271–281

Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar

CA, Robison LL, Leisenring WM (2009) Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. Br Med J 339:b4606

Murphy SL, Xu J, Kochanek KD (2013) Deaths: final data for 2010. Natl Vital Stat Rep 61:1–118

Nandagopal R, Laverdiere C, Mulrooney D, Hudson MM, Meacham L (2008) Endocrine late effects of childhood cancer therapy: a report from the Children's Oncology Group. Horm Res 69:65–74

Nathan PC, Patel SK, Dilley K, Goldsby R, Harvey J, Jacobsen C, Kadan-Lottick N, McKinley K, Millham AK, Moore I, Okcu MF, Woodman CL, Brouwers P, Armstrong FD (2007) Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer: a report from the Children's Oncology Group. Arch Pediatr Adolesc Med 161:798–806

Nathan PC, Ness KK, Mahoney MC, Li Z, Hudson MM, Ford JS, Landier W, Stovall M, Armstrong GT, Henderson TO, Robison LL, Oeffinger KC (2010) Screening and surveillance for second malignant neoplasms in adult survivors of childhood cancer: a report from the childhood cancer survivor study. Ann Intern Med 153:442–451

Oberfield SE, Allen JC, Pollack J, New MI, Levine LS (1986) Long-term endocrine sequelae after treatment of medullo-blastoma: prospective study of growth and thyroid function. J Pediatr 108:219–223

Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL (2006) Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355:1572–1582

Oeffinger KC, Nathan PC, Kremer LC (2008) Challenges after curative treatment for childhood cancer and long-term follow up of survivors. Pediatr Clin North Am 55:251–273, xiii

Ogilvy-Stuart AL, Shalet SM, Gattamaneni HR (1991) Thyroid function after treatment of brain tumors in children. J Pediatr 119:733–737

Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y, Dowling J, Wolinsky Y, Kruchko C, Barnholtz-Sloan J (2014) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. Neuro Oncol 16:iv1–v63

Packer RJ, Mehta M (2002) Neurocognitive sequelae of cancer treatment. Neurology 59:8–10

Packer RJ, Sutton LN, Atkins TE, Radcliffe J, Bunin GR, D'Angio G, Siegel KR, Schut L (1989) A prospective study of cognitive function in children receiving whole-brain radiotherapy and chemotherapy: 2-year results. J Neurosurg 70:707–713

Packer RJ, Gurney JG, Punyko JA, Donaldson SS, Inskip PD, Stovall M, Yasui Y, Mertens AC, Sklar CA, Nicholson HS, Zeltzer LK, Neglia JP, Robison LL (2003) Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. J Clin Oncol 21:3255–3261

Padovani L, André N, Constine LS, Muracciole X (2012) Neurocognitive function after radiotherapy for paediatric brain tumours. Nat Rev Neurol 8:578–588

Pang JW, Friedman DL, Whitton JA, Stovall M, Mertens AC, Robison LL, Weiss NS (2008) Employment status among adult survivors in the Childhood Cancer Survivor Study. Pediatr Blood Cancer 50:104–110

Patterson BC, Chen Y, Sklar CA, Neglia J, Yasui Y, Mertens A, Armstrong GT, Meadows A, Stovall M, Robison LL, Meacham LR (2014) Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report from the childhood cancer survivor study. J Clin Endocrinol Metab 99:2030–2037

Pizzo PA, Poplack DG, Bleyer WA (1979) Neurotoxicities of current leukemia therapy. Am Jo Pediatr Hematol Oncol 1:127–140

Pollak KI, Arnold RM, Jeffreys AS, Alexander SC, Olsen MK, Abernethy AP, Sugg Skinner C, Rodriguez KL, Tulsky JA (2007) Oncologist communication about emotion during visits with patients with advanced cancer. J Clin Oncol 25:5748–5752

Poltorak DY, Glazer JP (2006) The development of children's understanding of death: cognitive and psychodynamic considerations. Child Adolesc Psychiatr Clin N Am 15:567–573

Radcliffe J, Packer RJ, Atkins TE, Bunin GR, Schut L, Goldwein JW, Sutton LN (1992) Three- and four-year cognitive outcome in children with noncortical brain tumors treated with whole-brain radiotherapy. Ann Neurol 32:551–554

Recklitis CJ, Diller LR, Li X, Najita J, Robison LL, Zeltzer L (2010) Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 28:655–661

Reddick WE, Russell JM, Glass JO, Xiong X, Mulhern RK, Langston JW, Merchant TE, Kun LE, Gajjar A (2000) Subtle white matter volume differences in children treated for medulloblastoma with conventional or reduced dose craniospinal irradiation. Magn Reson Imaging 18:787–793

Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett JM (2001) Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. J Clin Oncol 19:3470–3476

Ross L, Johansen C, Dalton SO, Mellemkjaer L, Thomassen LH, Mortensen PB, Olsen JH (2003) Psychiatric hospitalizations among survivors of cancer in childhood or adolescence. N Engl J Med 349:650–657

Rueckriegel SM, Driever PH, Blankenburg F, Lüdemann L, Henze G, Bruhn H (2010) Differences in supratentorial damage of white matter in pediatric survivors of posterior fossa tumors with and without adjuvant treatment as detected by magnetic resonance diffusion tensor imaging. Int J Radiat Oncol Biol Phys 76:859–866

Rutter MM, Rose SR (2007) Long-term endocrine sequelae of childhood cancer. Curr Opin Pediatr 19:480–487

Saha A, Salley CG, Saigal P, Rolnitzky L, Goldberg J, Scott S, Olshefski R, Hukin J, Sands SA, Finlay J, Gardner SL (2014) Late effects in survivors of childhood CNS tumors treated on Head Start I and II protocols. Pediatr Blood Cancer 61:1644–1652

Sahler OJ, Frager G, Levetown M, Cohn FG, Lipson MA (2000) Medical education about end-of-life care in the pediatric setting: principles, challenges, and opportunities. Pediatrics 105:575–584

Sands SA, Oberg JA, Gardner SL, Whiteley JA, Glade-Bender JL, Finlay JL (2010) Neuropsychological functioning of children treated with intensive chemotherapy followed by myeloablative consolidation chemotherapy and autologous hematopoietic cell rescue for newly diagnosed CNS tumors: an analysis of the Head Start II survivors. Pediatr Blood Cancer 54:429–436

Schiff D, Wen P (2006) Central nervous system toxicity from cancer therapies. Hematol Oncol Clin North Am 20:1377–1398

Sirkia K, Saarinen UM, Ahlgren B, Hovi L (1997) Terminal care of the child with cancer at home. Acta Paediatr 86:1125–1130

Sklar CA, Constine LS (1995) Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 31:1113–1121

Sklar CA, Mertens AC, Mitby P, Occhiogrosso G, Qin J, Heller G, Yasui Y, Robison LL (2002) Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 87:3136–3141

Smithson EF, Phillips R, Harvey DW, Morrall MC (2013) The use of stimulant medication to improve neurocognitive and learning outcomes in children diagnosed with brain tumours: a systematic review. Eur J Cancer 49:3029–3040

Sønderkaer S, Schmiegelow M, Carstensen H, Nielsen LB, Müller J, Schmiegelow K (2003) Long-term neurological outcome of childhood brain tumors treated by surgery only. J Clin Oncol 21:1347–1351

Spinetta JJ, Jankovic M, Eden T, Green D, Martins AG, Wandzura C, Wilbur J, Masera G (1999) Guidelines for assistance to siblings of children with cancer: report of the SIOP Working Committee on Psychosocial Issues in Pediatric Oncology. Med Pediatr Oncol 33:395–398

Steinlin M, Imfeld S, Zulauf P, Boltshauser E, Lovblad KO, Ridolfi Luthy A, Perrig W, Kaufmann F (2003) Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. Brain 126:1998–2008

Stuber ML, Meeske KA, Krull KR, Leisenring W, Stratton K, Kazak AE, Huber M, Zebrack B, Uijtdehaage SH, Mertens AC, Robison LL, Zeltzer LK (2010) Prevalence and predictors of posttraumatic stress disorder in adult survivors of childhood cancer. Pediatrics 125:e1124–e1134

Syndikus I, Tait D, Ashley S, Jannoun L (1994) Long-term follow-up of young children with brain tumors after irradiation. Int J Radiat Oncol Biol Phys 30:781–787

Thomson AB, Critchley HO, Kelnar CJ, Wallace WH (2002) Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. Best Pract Res Clin Endocrinol Metab 16:311–334

Tofilon PJ, Fike JR (2000) The radioresponse of the central nervous system: a dynamic process. Radiat Res 153:357–370

Turner CD, Rey-Casserly C, Liptak CC, Chordas C (2009) Late effects of therapy for pediatric brain tumor survivors. J Child Neurol 24:1455–1463

Ullrich NJ, Robertson R, Kinnamon DD, Scott RM, Kieran MW, Turner CD, Chi SN, Goumnerova L, Proctor M, Tarbell NJ, Marcus KJ, Pomeroy SL (2007) Moyamoya following cranial irradiation for primary brain tumors in children. Neurology 68:932–938

von Gunten CF, Ferris FD, Emanuel LL (2000) The patient-physician relationship. Ensuring competency in end-of-life care: communication and relational skills. JAMA 284:3051–3057

Waber DP, Tarbell NJ, Fairclough D, Atmore K, Castro R, Isquith P, Lussier F, Romero I, Carpenter PJ, Schiller M et al (1995) Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: cranial radiation requires an accomplice. J Clin Oncol 13:2490–2496

Waldman E, Wolfe J (2013) Palliative care for children with cancer. Nat Rev Clin Oncol 10:100–107

Wheeler I (2001) Parental bereavement: the crisis of meaning. Death Stud 25:51–66

Wiener L, Zadeh S, Battles H, Baird K, Ballard E, Osherow J, Pao M (2012) Allowing adolescents and young adults to plan their end-of-life care. Pediatrics 130:897–905

Wolfe J, Grier HE, Klar N, Levin SB, Ellenbogen JM, Salem-Schatz S, Emanuel EJ, Weeks JC (2000) Symptoms and suffering at the end of life in children with cancer. N Engl J Med 342:326–333

Wolfe J, Hammel JF, Edwards KE, Duncan J, Comeau M, Breyer J, Aldridge SA, Grier HE, Berde C, Dussel V, Weeks JC (2008) Easing of suffering in children with cancer at the end of life: is care changing? J Clin Oncol 26:1717–1723

Wusthoff CJ, Shellhaas RA, Licht DJ (2007) Management of common neurologic symptoms in pediatric palliative care: seizures, agitation, and spasticity. Pediatr Clin North Am 54:709–733, xi

Zebrack BJ, Chesler MA (2002) Quality of life in childhood cancer survivors. Psychooncology 11: 132–141

Zeltzer LK, Lu Q, Leisenring W, Tsao JC, Recklitis C, Armstrong G, Mertens AC, Robison LL, Ness KK (2008) Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev 17:435–446