Radiation Oncology for Pediatric CNS Tumors

Anita Mahajan
Arnold Paulino
Editors

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Preface

In the United States, brain tumors account for 20% of new cancer cases and 30% of cancer deaths in children. Currently, 70–75% of central nervous system (CNS) patients younger than 19 years will survive. Radiation therapy has been and will continue to be a critical component of the multidisciplinary approach required in the care of children with CNS tumors. Gone are the days when radiation therapy or "radiodiagnosis" was used for germinoma or similarly simple "hockey stick" fields to treat the craniospinal axis. Continued advances in technology and understanding of diagnosis, imaging, and radiotherapy influence management of patients. This book integrates these advances specifically in the radiation therapy management of pediatric neuro-oncology.

The book is organized into four segments: (1) basic principles, (2) disease-specific sections, (3) radiotherapy practice, and (4) radiotherapy toxicity and management. The basic principles cover the epidemiology of brain tumors as well as the various disciplines aside from radiotherapy which are important in the management of CNS tumors. Individual disease-specific sites cover embryonal, glial, germ cell, and other tumor types and are discussed next. Treatment techniques used in radiotherapy practice for children including the use of anesthesia, craniospinal irradiation, proton therapy, and hypofractionated radiotherapy are discussed. Finally, various toxicities that relate to vision, hearing, endocrine, and cognitive function are discussed in radiotherapy toxicity and management.

We have been fortunate to have contributing authors who are experts in the field of pediatric radiation oncology. While many authors are from the United States, there is a representation from countries such as Germany, France, United Kingdom, Ireland, Japan, South Korea, Canada, and Brazil.

We hope this book will provide information and guidance to the pediatric oncology community as a whole and serve as a resource and educational tool to the radiation oncology community. We hope that this book provides a solid foundation as we continue to improve our understanding of pediatric CNS tumors.

Rochester, USA — Anita Mahajan
Houston, USA — Arnold Paulino

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Part I

Basic Principles

Epidemiology of Childhood Brain Tumors

1

Philip J. Lupo, Surya P. Rednam, and Murali Chintagumpala

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Abstract

Childhood brain tumors are the most common form of pediatric solid tumors. Significant improvements over the decades in the treatment of brain tumors in children have improved outcomes but mortality and morbidity are still high. Pediatric brain tumors are clinically and biologically distinct from those that occur in adults. Our understanding of risk factors in childhood brain tumors remains limited to several exposures of the head and neck to ionizing radiation and well-described hereditary cancer predisposition syndromes. In this chapter, we review the descriptive and analytic epidemiology of childhood brain tumors, including a discussion of the roles of radiation exposure, established predisposing syndromes, and other suspected risk factors.

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1.1 Introduction

Brain tumors are the leading cause of cancer death in individuals 0–19 years of age in the USA and Canada (Curtin et al. 2016). Furthermore, brain tumors are a significant source of cancer-related morbidity in infants and children. Given the relative frequency of childhood brain tumors and their suboptimal outcome with therapy, it is important to identify their etiologies. Epidemiologic studies help in this endeavor in two ways. Descriptive studies reveal the incidence of brain tumors, and their associated mortality and survival rates with respect to histologic subtype and demographic characteristics. Analytic studies compare the risk of brain tumors in people with and without certain characteristics (cohort studies) or compare the histories of people with and without brain tumors (case-control studies) to identify and assess a wide range of possible risk factors, including exposures to radiation and hereditary cancer predisposition syndromes. In addition to epidemiologic analyses, progress in the molecular classification of these tumors could provide greater insight into the role of tumor genetics in disease progression and sensitivity to radiation treatment and chemotherapy. The hope is that knowledge from epidemiologic and tumor biology studies will lead to improved assessment of pediatric brain tumor risk, development of appropriate approaches to early tumor identification, and eventually individualized prevention and treatment strategies.

1.2 Descriptive Epidemiology

There are more than 100 different histological subtypes of brain tumors, and the incidence of each subtype varies with several factors including age, geography, sex, and race/ethnicity. For instance, childhood brain tumor incidence varies by country from 1.12 to 5.14 cases per 100,000 persons (Table 1.1) (Johnson et al. 2014). Overall, childhood brain tumors are more common in males, although this can vary by histologic subtype. In the USA, non-Hispanic whites and Asian-Pacific Islanders have a higher incidence when compared to Hispanics or non-Hispanic blacks. However, it should be noted that differences in incidence and survival may be related to differences in case ascertainment methodology among cancer registries. Furthermore, cancer registries differ on ascertainment of benign brain tumors. For example, in the USA, registration of nonmalignant tumors was not required by law prior to 2004. However, across registries, the standard approach is to include both benign and malignant brain tumors and other central nervous system (CNS) tumors in all statistics. Therefore information on specific histologic subtypes and all comparison statistics must be interpreted with these potential limitations in mind.

1.2.1 Glioma

Gliomas arise from glial cells and overall are the most common category of childhood brain tumor (Bauchet et al. 2009). Incidence (Table 1.1) and survival (Table 1.2) vary significantly depending on location and histologic subtype. The most common type of glioma in children is pilocytic astrocytoma.

Table 1.1 Incidence of selected childhood brain tumors per 100,000 persons by histology and region

Histologic subtype	Region and reference	Years	Incidence rate (95% CI)
All brain tumors	Europe (Peris-Bonet et al. 2006)	1988–1997	2.99
	United States (Ostrom et al. 2013)	2006–2010	5.26 (5.19–5.33)
	Japan (Makino et al. 2010)	1989–2008	3.61
	Kuwait (Katchy et al. 2013)	1995–2011	1.12
	Denmark, Finland, Norway, and Sweden (Schmidt et al. 2011)	1985–2006	4.20
Pilocytic astrocytoma	United States (Ostrom et al. 2013)	2006–2010	0.90 (0.87–0.93)
	England (Arora et al. 2009)	1995–2003	0.75
Astrocytoma	Europe (Peris-Bonet et al. 2006)	1988–1997	1.18
	Japan (Makino et al. 2010)	1989–2008	1.32
	Denmark, Finland, Norway, and Sweden (Schmidt et al. 2011)	1985–2006	1.79
Ependymoma	Europe (Peris-Bonet et al. 2006)	1988–1997	0.34
	United States (Ostrom et al. 2013)	2006–2010	0.28 (0.26–0.30)
	Japan (Makino et al. 2010)	1989–2008	0.15
	Denmark, Finland, Norway, and Sweden (Schmidt et al. 2011)	1985–2006	0.42
	England (Arora et al. 2009)	1995–2003	0.25
Embryonal tumors	United States (Ostrom et al. 2013)	2006–2010	0.80 (0.77–0.84)
	Denmark, Finland, Norway, and Sweden (Schmidt et al. 2011)	1985–2006	0.73
	England (Arora et al. 2009)	1995–2003	0.28
PNET	Austria (Woehrer et al. 2010)	1996–2006	0.21 (0.15–0.30)
	England (Arora et al. 2009)	1995–2003	0.08
Medulloblastoma	Japan (Makino et al. 2010)	1989–2008	0.37
	Austria (Woehrer et al. 2010)	1996–2006	0.58 (0.16–0.71)
	England (Arora et al. 2009)	1995–2003	0.20
ATRT	Austria (Woehrer et al. 2010)	1996–2006	0.14
	United States (Ostrom et al. 2013)	2006–2010	0.11 (0.10–0.12)

1.2.1.1 Pilocytic Astrocytoma

Pilocytic astrocytoma (World Health Organization [WHO] grade I) is the most common childhood brain tumor, representing approximately 17% of all CNS tumors in children (Ostrom et al. 2013). The incidence of these tumors ranges from 0.7 to 0.9 cases per 100,000 persons (Table 1.1). While these tumors are

Table 1.2 Five-year survival of selected childhood brain tumors by histology and region

Histologic subtype	Region and reference	Years	5-year survival (95% CI)
All brain tumors	Europe (Peris-Bonet et al. 2006)	1988–1997	91.0 (60.0–62.0)
	United States (Ostrom et al. 2013)	2006–2010	72.3 (71.2–73.3)
	Sweden (Lannering et al. 2009)	1984–2005	76.0
Ependymoma	Europe (Peris-Bonet et al. 2006)	1988–1997	53.0 (49.0–57.0)
	United States (Ostrom et al. 2013)	1995–2010	72.2 (67.9–76.1)
	Sweden (Lannering et al. 2009)	1984–2005	72.0
Astrocytoma	Europe (Peris-Bonet et al. 2006)	1988–1997	75.0 (73.0–76.0)
	Sweden (Lannering et al. 2009)	1984–2005	84.0
Pilocytic astrocytoma	United States (Ostrom et al. 2013)	2006–2010	97.2 (96.3–98.0)
Embryonal tumors	United States (Ostrom et al. 2013)	1995–2010	62.1 (59.6–64.5)
PNET	Europe (Peris-Bonet et al. 2006)	1988–1997	49.0 (46.0–51.0)
	United States (Ostrom et al. 2013)	1995–2010	49.5 (45.3–53.6)
	Sweden (Lannering et al. 2009)	1984–2005	47.0
Medulloblastoma	United States (Ostrom et al. 2013)	1995–2010	71.1 (68.5–73.5)
	Sweden (Lannering et al. 2009)	1984–2005	63.0
ATRT	United States (Ostrom et al. 2013)	1995–2010	28.0 (20.7–35.7)

low grade, rarely they may progress to higher-grade malignancies (Fisher et al. 2008; Stokland et al. 2010). Overall 5-year survival is high at 97% (Table 1.2) (Ostrom et al. 2013).

1.2.1.2 High-Grade Glioma

High-grade gliomas represent 7–11% of childhood brain tumors. The most common high-grade gliomas are anaplastic astrocytoma and glioblastoma. Overall, high-grade gliomas (WHO grade III and IV) are less common, with incidence rates of 0.08 for anaplastic astrocytoma and 0.14 for glioblastoma (Ostrom et al. 2013). These tumors have a very poor 5-year survival, which is often <30% (Johnson et al. 2014).

1.2.1.3 Brain Stem Gliomas

Brain stem tumors represent approximately 10% of childhood brain tumors which vary widely by biology, natural history, and outcomes. The most common of these tumors is diffuse intrinsic pontine glioma (DIPG) (Freeman and Farmer 1998). Survival for those diagnosed with DIPG is very poor, with >90% of cases dying within 2 years of presentation (Hargrave et al. 2006). These tumors are rarely biopsied, instead diagnosed by imaging, and as a result, their true incidence from cancer registry datasets is difficult to assess (Hargrave et al. 2006).

1.2.2 Embryonal Tumors

Embryonal tumors are believed to arise from disrupted embryonic cells remaining in the CNS after birth. There are three major embryonal tumor types with distinct differences in age at diagnosis and survival: medulloblastoma, primitive neuroectodermal tumor, and atypical teratoid/rhabdoid tumor (Louis et al. 2007).

1.2.2.1 Medulloblastoma

Medulloblastomas are the most common embryonal brain tumors, with an annual incidence ranging from 0.20 to 0.58 cases per 100,000 persons. Recent data suggest 1-year survival is 52%, 90%, and 92% for children aged 0–1, 1–9, and 10–19 years, respectively (Smoll 2012). Molecular analysis has identified four distinct medulloblastoma subtypes that correlate strongly with survival (Rutkowski et al. 2010). No population-based studies of subtype-specific survival have been reported, but in an international meta-analysis children with WNT tumors had a 95% 10-year overall survival. Children with sonic hedgehog (SHH), group 3, and group 4 tumors had 51%, 50%, and 32% 10-year survival, respectively (Kool et al. 2012).

1.2.2.2 Primitive Neuroectodermal Tumor (PNET)

PNET represents the second most common form of embryonal brain tumor. Average annual incidence rates for PNET range from 0.08 to 0.21 cases per 100,000 persons. PNET survival appears to improve with increasing age of diagnosis. For instance, 1-year survival is 31%, 88%, and 95% for children aged 0–1, 1–9, and 10–19 years, respectively (Smoll 2012). Given that PNETs and medulloblastoma share a similar histology, the 1993 WHO criteria specified a categorization based on location. Specifically, those tumors that are supratentorial are considered PNETs, whereas those that are infratentorial are considered to be medulloblastoma. Classification continues to evolve. PNET is no longer considered to be one disease. In fact, there are several subtypes and the correct classification remains challenging (Pfister et al. 2010).

1.2.2.3 Atypical Teratoid/Rhabdoid Tumor (AT/RT)

AT/RT is a rare embryonal CNS tumor that most commonly occurs in children <3 years of age. The annual incidence ranges from 0.07 to 0.14 per 100,000 persons (Johnson et al. 2014; Woehrer et al. 2010). Prognosis is generally poor, though survival increases with age (Hilden et al. 2004; Lafay-Cousin et al. 2012; von Hoff et al. 2011;

Woehrer et al. 2010). Overall, median survival is usually between 6 and 18 months (Athale et al. 2009; Lafay-Cousin et al. 2012; Lee et al. 2012; von Hoff et al. 2011). This tumor is typically more common among males (Heck et al. 2013; Lafay-Cousin et al. 2012) and among non-Hispanic whites (Bishop et al. 2012). A systematic diagnostic approach for AT/RT was not common until 2005; prior to that these tumors were frequently misclassified, mostly as medulloblastoma or PNET (Woehrer et al. 2010).

1.2.3 Other Brain Tumors

1.2.3.1 Choroid Plexus Carcinoma

Choroid plexus carcinomas constitute a very small percentage of childhood brain tumors (1–4%). Most of these tumors (70%) occur during the first year of life, and 5-year survival can be <30% (Johnson et al. 2014).

1.2.3.2 Ependymoma

Ependymomas constitute approximately 10% of all brain tumors in children. Over 90% of these tumors are intracranial. The highest incidence occurs within the first 7 years of life and the overall 5-year relative survival rate is 82% (Johnson et al. 2014). Additionally, males appear to be more likely to develop ependymoma compared to females (Johnson et al. 2014).

1.2.3.3 Craniopharyngioma

While craniopharyngiomas account for between 6 and 9% of all brain tumors in children, these tumors rarely occur in infants. In fact, the peak incidence during childhood is between 8 and 10 years of age. A recent assessment using data from the Surveillance, Epidemiology and End Results (SEER) Program indicated that 1-year survival rates were >90%. However, up to 75% of these children have significant complications including hypothalamic obesity (Hoffmann et al. 2015).

1.2.3.4 Germ Cell Tumors

Germ cell tumors are a mixed grouping of brain tumors classified on the basis of histological and immunohistochemical features. The WHO recognizes multiple different types of germ cell tumors, ranging from pure germinomas, mature teratomas to variety of highly aggressive nongerminomatous germ cell tumors. The incidence of these tumors is relatively low at 0.051 per 100,000 but varies by geography (e.g., the incidence is higher in some Asian countries compared to the USA) (de Robles et al. 2014c).

1.3 Analytic Epidemiology

1.3.1 Environmental Risk Factors

1.3.1.1 Radiation Exposure

High-dose radiation to the head and neck for treatment of cancer or other conditions is an established risk factor for childhood brain tumors (Kleinerman 2006). Cranial radiation therapy for acute lymphoblastic leukemia is associated with a particularly

high risk for developing (Ohgaki and Kleihues 2005) brain tumors (gliomas, PNETs) in children who received prophylactic CNS irradiation (usually a cumulative dose of 25 Gy, which is no longer part of contemporary therapy). Additionally, childhood exposure to low-dose ionizing radiation for tinea capitis has been associated with benign meningiomas and malignant brain tumors (Sadetzki et al. 2005). The latency between radiation therapy and subsequent brain tumor development has been estimated at 7–9 years with a higher risk for children diagnosed earlier in life (Ohgaki and Kleihues 2005). It has also been broadly accepted for several decades that in utero diagnostic radiation exposure is associated with a small to moderate dose-dependent increase in childhood cancer risk, including brain tumors (Streffer et al. 2003).

Ionizing Radiation

A study using data from the Childhood Cancer Survivor Study reported that children who received radiation therapy for their first primary CNS tumor were 7 times more likely to develop a subsequent CNS tumor (Neglia et al. 2006). The evidence regarding diagnostic X-ray exposure and childhood brain tumor risk is not well established. For example, in one study, while those who were exposed to diagnostic X-ray as neonates were 2 times more likely to develop a childhood brain tumor, this association was not statistically significant (Mellemkjaer et al. 2006). A Swedish study of individuals born between 1975 and 1984 examined the association between prenatal abdominal radiation exposures and childhood brain tumors. While there was not an increased risk overall, exposed individuals were twice as likely to develop a PNET (Stalberg et al. 2007). In a recently conducted study in the USA, maternally reported postnatal exposures to diagnostic X-rays were not associated with childhood medulloblastoma or PNET (Khan et al. 2010).

Nonionizing Radiation

Sources of nonionizing radiation that have been studied for their role in childhood brain tumor risk include radio frequency/microwave (e.g., cell phones, AM and FM radio, televisions, microwaves) and extremely low-frequency magnetic fields (e.g., power lines and electrical wiring). These exposures have been classified as possibly carcinogenic by the International Agency for Cancer Research (International Agency for Cancer Research 2014). However, epidemiologic studies have shown few significant positive associations between nonionizing radiation exposure and childhood brain tumors (Johnson et al. 2014).

1.3.1.2 Other Environmental Risk Factors

While there have been several epidemiologic studies of childhood brain tumors, few risk factors have been confirmed and established. Additionally, very few of these have led to prevention strategies. A recent review concluded that the strongest evidence for childhood brain tumor risk factors was for hereditary cancer predisposition syndromes and therapeutic ionizing radiation (Johnson et al. 2014). While some risk factors including parental age, birth defects, and pesticides have suggestive evidence, other factors including maternal medications and parental

occupational exposure during pregnancy have only weak or insufficient evidence (Johnson et al. 2014).

1.3.2 Genetic Factors

1.3.2.1 Hereditary Cancer Predisposition Syndromes

Up to 10% of pediatric cancers occur in the context of a set of well-described hereditary cancer predisposition syndromes (HCPSs) (Strahm and Malkin 2006). Individuals affected by these rare conditions are at greatly increased risk of developing malignancies at levels 10–100 fold above those seen in the general population. Several clues may raise suspicion for the presence of one of these conditions. An individual may have a specific tumor (or subtype) which is commonly associated with genetic susceptibility (e.g., optic pathway glioma with Neurofibromatosis Type 1) (Listernick et al. 2007). A tumor may occur at a significantly younger age than seen in the general population (e.g., childhood meningioma and Neurofibromatosis Type 2) (Evans et al. 1999, 2005; Thuijs et al. 2012). Family history, clinical features, certain laboratory values, or imaging abnormalities may indicate the presence of HCPS. Multiple primary tumors may occur in the same individual. A comprehensive family history may also trigger a genetic evaluation either due to a relative who has been diagnosed with a hereditary cancer predisposition syndrome or suggestive clinical history evident in the pedigree.

HCPSs are associated with increased risk of pediatric brain tumors (Table 1.3) may be categorized by their pattern of inheritance: autosomal dominant or autosomal recessive. The autosomal dominant syndromes can be further subdivided into neurocutaneous disorders, familial colon cancer syndromes involving elevated risks of brain tumors (i.e., Turcot Syndrome), and conditions exclusively having oncologic features. The autosomal recessive syndromes associated with increased childhood brain tumor susceptibility share impaired DNA repair as their underlying defect. Select examples for each of these syndrome groupings will be presented (extended listing in Table 1.3).

Neurocutaneous Disorders

Neurofibromatosis Type 1 (NF1 gene) occurs in approximately 1 in 2500–3000 people and is associated with both neoplastic and nonneoplastic features including multiple café-au-lait spots, axillary and inguinal freckling, cutaneous neurofibromas, and iris Lisch nodules (Hirbe and Gutmann 2014). Approximately 15–20% of affected individuals develop optic pathway gliomas (OPGs) (Fisher et al. 2012). When OPGs progress, usually in children less than 6 years of age, significant visual impairment may occur (approximately 1 in 3 with OPGs). There is also a significant risk of developing gliomas at other sites, predominantly low-grade. Radiation is considered the definitive therapy for non-NF1 OPGs, especially in the older child when the risk for significant neurocognitive effects is less. However, it is typically avoided in NF1 due to the risk for secondary malignancies and radiation-induced vasculopathy (Listernick et al. 2007).

Table 1.3 Hereditary cancer predisposition syndromes associated pediatric brain tumors

Syndrome	Select clinical features	Brain tumors
Autosomal dominant		
Neurocutaneous disorders		
Neurofibromatosis Type 1 (Fisher et al. 2012; Hirbe and Gutmann 2014; Listernick et al. 2007)	Dermatologic: Café-au-lait macules, axillary and inguinal freckling, neurofibromas Other: Lisch nodules and vasculopathy	Optic pathway glioma Other low-grade glioma
Neurofibromatosis Type 2 (Baser et al. 2000; Lloyd and Evans 2013)	Dermatologic: Café-au-lait macules (few) Ophthalmologic: Posterior subcapsular lens opacity, epiretinal membrane	Bilateral vestibular schwannomas Other schwannomas Meningioma Ependymoma
Tuberous Sclerosis Complex (Northrup and Krueger 2013)	Neurologic: Seizures, cortical tubers, subependymal nodules Dermatologic: Facial angiofibromas, hypomelanotic macules, shagreen patches Other: Renal angiomyolipoma, cardiac rhabdomyoma, retinal hamartoma	Subependymal giant cell astrocytoma (SEGA)
Von Hippel–Lindau Disease (Lonser et al. 2014; Maher et al. 2011)	Oncologic: Pheochromocytoma, renal cell carcinoma, tumors and cysts of abdominal visceral organs Other: Retinal angiomas	Cerebellar hemangioblastoma Spinal hemangioblastoma
Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome) (Amlashi et al. 2003; Cowan et al. 1997; Evans et al. 2010; Lam et al. 2013; Sartip et al. 2013)	Dermatologic: Basal cell nevi/carcinoma, palmar/plantar pits Skeletal: Macrocephaly, frontoparietal bossing, bifid ribs, vertebral anomalies, odontogenic jaw cyst	Medulloblastoma
Familial colon cancer (Turcot)		
Mismatch repair gene-related (Barrow et al. 2009; Jasperson et al. 2010; Therkildsen et al. 2015)	Oncologic: Gastrointestinal, hepatobiliary, uterine, ovarian, ureteral cancers	Glioblastoma multiforme Other glioma
APC-associated (Attard et al. 2007; Jasperson et al. 2010)	Oncologic: Gastrointestinal and thyroid cancers, desmoid tumor, osteoma Other: Congenital hypertrophy of retinal pigment epithelium	Medulloblastoma
Exclusively cancer predisposing		
Li–Fraumeni Syndrome (Chompret et al. 2000; Gonzalez et al. 2009; Heymann et al. 2010; Hisada et al. 1998; Limacher et al. 2001; Olivier et al. 2003; Ruijs et al. 2010; Tabori et al. 2010)	Oncologic: Sarcoma, breast cancer, leukemia, lymphoma, adrenocortical carcinoma	High-grade glioma Choroid plexus carcinoma Medulloblastoma

(continued)

Table 1.3 (continued)

Syndrome	Select clinical features	Brain tumors
Rhabdoid Predisposition Syndrome (Bourdeaut et al. 2011; Eaton et al. 2011)	Oncologic: Renal and extrarenal rhabdoid tumors	Atypical Teratoid/ Rhabdoid Tumor (AT/ RT)
Multiple Endocrine Neoplasia Type 1 (Cuny et al. 2013; Stratakis et al. 2010)	Oncologic: Parathyroid tumor, well-differentiated endocrine tumors of the gastro-entero-pancreatic tract, carcinoid, adrenocortical tumor	Pituitary tumor (Most commonly prolactinoma)
DICER1 Syndrome (de Kock et al. 2014a, b; Schultz et al. 2014)	Oncologic: Pleuropulmonary blastoma, multinodular goiter, differentiated thyroid carcinoma, Seroli–Leydig cell tumor, cystic nephroma, cervical rhabdomyosarcoma	Pituitary blastoma Pinealoblastoma
Other conditions		
Rubinstein–Tabyi Syndrome (Bourdeaut et al. 2014; Milani et al. 2015)	Skeletal: Microcephaly, distinctive facies, broad/ angulated thumbs, and great toes Other: Congenital heart defect and intellectual disability	Medulloblastoma
Autosomal recessive		
Constitutional Mismatch Repair Deficiency Syndrome (Bakry et al. 2014)	Dermatologic: Café-au-lait macules Oncologic: Leukemia, lymphoma, gastrointestinal cancers	High-grade glioma
Fanconi Anemia (Dewire et al. 2009; Eiler et al. 2008; Pollard and Gatti 2009; Rizk et al. 2013)	Hematologic: Bone marrow failure Musculoskeletal: Microcephaly, thumb/radial abnormalities Oncologic: Leukemia, myelodysplastic syndrome, squamous cell carcinomas, and cervical cancer Other: Abnormal skin pigmentation and renal anomalies	Medulloblastoma

Nevoid Basal Cell Carcinoma (or Gorlin) Syndrome (PTCH1 and SUFU genes) is an uncommon condition affecting approximately 1 in 30,000 individuals (Evans et al. 2010). Characteristic clinical features typically emerge in adolescents or young adults including jaw keratocysts and basal cell carcinomas (Lam et al. 2013). The diagnosis may be suspected in childhood based on their distinctive cranial features including macrocephaly, frontoparietal bossing, and coarse facies and skin findings (e.g., multiple basal cell nevi and palmar/plantar pits). Approximately 5% of children develop medulloblastoma, generally of desmoplastic subtype, in the first few years of life (Amlashi et al. 2003; Cowan et al. 1997).

The utility of using radiotherapy in affected individuals should be carefully weighed against the high risk of shortly developing numerous basal cell carcinomas in the radiation field and the possibility of other secondary malignancies (e.g., meningiomas) (Sartip et al. 2013).

Turcot Syndrome

Turcot syndrome is characterized by the occurrence of brain tumors in the setting of a familial colon cancer syndrome. In these rare scenarios, pediatric brain tumors may be associated with germline mutations of the *APC* gene which cause Familial Adenomatous Polyposis (FAP) or mutations in the mismatch repair (MMR) genes (*MSH2, MLH1, MSH6, PMS2*) which cause Hereditary Nonpolyposis Colon Cancer (HNPCC, heterozygous MMR gene mutation) or Constitutional Mismatch Repair Deficiency Syndrome (CMMRD, biallelic MMR gene mutations, autosomal recessive) (Bakry et al. 2014; Hamilton et al. 1995). Constitutional *APC* mutations (FAP) confer a risk of medulloblastoma significantly higher than the general population, but still below 1% (Attard et al. 2007). Heterozygous MMR gene mutations (HNPCC) are associated with glioblastoma (GBM) with an estimated lifetime risk of about 1–3% (Barrow et al. 2009; Therkildsen et al. 2015). These GBMs typically occur in adults (peak around 40–50s); however, pediatric cases have been reported. In the absence of family history, these brain tumors may be the first indication of the underlying condition, with other features developing later. Patients with CMMRD, based on their café-au-lait macules, may initially be suspected to have NF1 (Bakry et al. 2014). They are at high risk of developing malignancies from early childhood: particularly leukemia, lymphoma, gastrointestinal cancers, and brain tumors. Brain tumors occur in about one-third to one-half of individuals and are predominantly high-grade gliomas. For all of the variations of Turcot Syndrome, there is a lack of information regarding radiation toxicities.

1.3.2.2 Conditions Exclusively Having Oncologic Features

Li–Fraumeni Syndrome (TP53 gene) is a rare condition associated with a high lifetime risk for developing a variety of different cancers. Approximately 73% of men and almost 100% of women with *TP53* mutations develop cancer (Chompret et al. 2000). This includes soft tissue sarcoma, osteosarcoma, brain tumors, premenopausal breast cancer, leukemia, and adrenocortical carcinoma which together comprise almost three-quarters of all LFS-associated malignancies (Gonzalez et al. 2009; Olivier et al. 2003; Ruijs et al. 2010). The median age of brain tumor diagnosis is 16 years of age. The primary brain tumor risks for children with LFS are high-grade glioma, choroid plexus carcinoma (CPC), and medulloblastoma (Olivier et al. 2003; Tabori et al. 2010). Due to the strong association that has been established between CPC and germline *TP53* mutations, a genetic evaluation should be considered in all of these patients (Tabori et al. 2010). At baseline, patients with LFS have a significant risk of multiple primary cancers. It is broadly accepted that radiation exposure raises this risk, although this has not been well quantified (Heymann et al. 2010; Hisada et al. 1998; Limacher et al. 2001). The standard practice is to treat with radiation when deemed necessary, with attempts to limit the field and/or dose, when possible.