18 Management of Solid Tumor CNS Metastases in Children

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Introduction and Epidemiology

Essential differences between adult and pediatric solid tumors suggest that the two ought to, in many regards, be considered distinct pathological entities. This distinction is particularly profound in the case of central nervous system (CNS) metastases. While adult solid tumor brain metastases occur in approximately 20–40% of primary tumor cases, the frequency of solid tumor brain metastases reported in children is only 1–10%, or 6–13% reported at autopsy [1–14]. In adults, CNS metastases occur most frequently in cases of lung, breast, and gastrointestinal primary tumors and melanoma [1, 15]. In contrast, the most common solid primary tumor types to present with CNS metastases in the pediatric population are sarcomas (including soft tissue, Ewing, and osteosarcoma), melanomas (up to 18% prevalence), retinoblastomas, neuroblastomas, kidney tumors [including Wilms tumors and clear cell sarcomas of the kidney (CCSK), the latter of which have been found to have a 5–11% incidence of CNS metastases], and germ cell tumors (with a particularly high rate of CNS metastases in choriocarcinoma, up to 43%), reflecting an increased representation of undifferentiated tumor types [3, 16–18]. Additionally, rare lung tumors in children have been reported to have an increased incidence of CNS metastases, including pleuropulmonary blastoma (PPB), with up to 25% incidence, and alveolar soft part sarcoma, with 15–29% incidence [6, 19, 20].

Pediatric solid tumors can enter the CNS space via one of two mechanisms—direct extension, as with sinonasal tumors, or hematogenous metastatic spread which necessitates penetrating the blood-brain barrier (BBB). Treatments for CNS metastases tend to vary based upon primary tumor type, extent of intra- and extracranial disease, and goals of care. Decreased prevalence of CNS metastases in pediatric versus adult tumors suggests a difference in the BBB—the pediatric BBB may be less permeable to tumor cells or, more likely, have increased permeability to systemic therapies used to treat the primary tumor or extracranial metastatic spread. Additionally, since tumor-instigated myeloid precursor cells are believed to play a role in metastasis, the increased tendency of children to receive myeloablative therapy for high-risk primary tumors, particularly in the neuroblastoma population,

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may contribute to a reduction in CNS spread [21–23]. Similarly to adult cases, however, pediatric solid CNS metastases are generally associated with a very poor prognosis, with survival times of typically less than 1 year after diagnosis [17].

Tumor Characteristics and Pathophysiology

The majority of pediatric solid tumor brain metastases are solitary (approximately 60–90% of cases), in contrast to adult cases where multiple CNS metastases are common. Pediatric brain metastases are supratentorial in 85–100% of cases in recently published series, in contrast to primary pediatric brain tumors which present with an infratentorial predominance [3, 4, 6, 10]. Solid brain metastases tend to most commonly be located in the cerebral hemispheres (less frequently in the cerebellum and basal ganglia), presenting at the gray matter-white matter junction, as in adults, or in border zones between major cerebral vascular territories, suggesting an arterial delivery mechanism [17, 24]. Interestingly, in our surgical experience at Memorial Sloan Kettering Cancer Center (MSKCC), we have found numerous brain metastases at the pial interface, such as at the depth of a sulcus, suggesting a possible venous or cerebrospinal fluid (CSF) mechanism of tumor cell seeding (Fig. 18.1, unpublished observations).

Although the CNS is a common site of extramedullary spread in pediatric leukemia, it is rarely seeded by solid tumors in children [6, 25]. Because the occurrence of pediatric solid tumor CNS metastases is so infrequent, surveillance imaging in children diagnosed with a primary solid tumor is not routinely performed. Thus, most CNS metastases are diagnosed from imaging in the setting of presenting symptoms such as headache, nausea, vomiting, seizures, aphasia, visual field deficits, focal motor or sensory deficits, cranial neuropathies, ataxia, and altered mental status. These symptoms reflect the location and size of the tumor, extent of edema, presence of intratumoral hemorrhage, and occurrence of obstructive or communicating hydrocephalus [3–7, 9–11, 17]. Pediatric solid tumor CNS metastases are rarely the sole or initial metastases and, when they occur, are often a late disease finding.

Multiple retrospective studies have suggested that there may be a direct correlation between the occurrence of pulmonary metastases and brain metastases, across several different primary tumor types, with up to 70% of cases having a known pulmonary metastasis at the time of brain metastatic diagnosis [2–4, 6, 9, 13, 26]. Mechanistically, it is plausible that tumor cells shed into the pulmonary circulation from a lung metastasis have a direct route to the brain via the left atrium, with a subsequent direct arterial conduit to brain circulation; this is supported

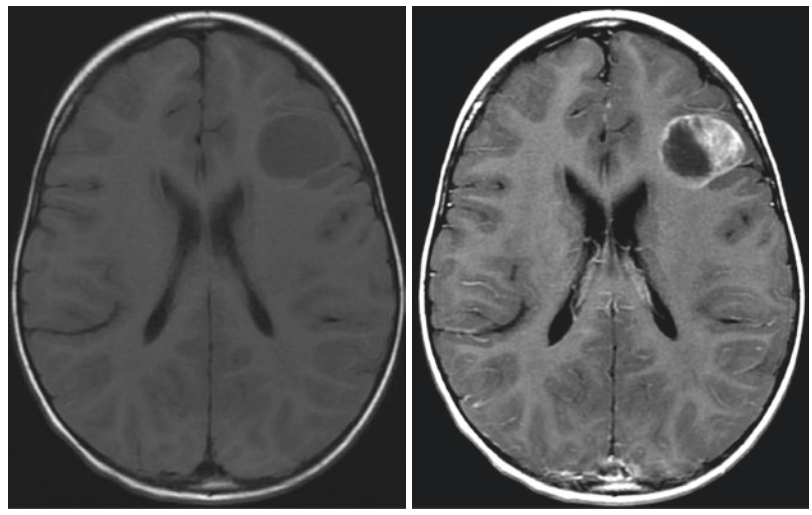

Fig. 18.1 T1-weighted MRI demonstrating a left frontal neuroblastoma metastasis at the pial interface. Pre- (left) and post-contrast (right) T1 MRI images of a neuroblastoma metastasis in a 7-year-old male patient illustrate the presence of tumor along the pial margin, a pattern commonly manifested in our cohort

by the presence of parenchymal metastases in major cerebral arterial border zones [2, 24]. Additionally, Kramer and colleagues at MSKCC found in their review of neuroblastoma cases with bone marrow involvement an association of lumbar punctures (LP) performed near the time of primary disease diagnosis with the development of CNS metastases, suggesting a possible direct hematogenous to CSF seeding mechanism [8].

Cumulatively across all histological subtypes, solid brain metastases in the pediatric population occur at a median age between 11 and 13 years and at a median interval of 8–16 months following the diagnosis of the primary tumor (Table 18.1) [2, 3, 6]. It has been suggested in multiple prior studies that the incidence of pediatric solid tumor CNS metastases is increasing [3, 6, 8]. However, the largest case series reported to date by Suki and colleagues from MD Anderson Cancer Center found that the proportion of patients with primary solid tumors developing CNS metastases remained relatively low at 1.4%, which was consistent with previously reported values from earlier studies [3]. Since pediatric CNS metastases are so rare and case studies have been limited to small cohorts, it has not yet been determined whether patients with this diagnosis have experienced an overall improvement in survival over time.

Treatment Options

Largely limited by small cohort sizes, evidence for the efficacy of different treatment regimens for pediatric solid tumor metastases remains sparse. Treatment options generally include surgical resection, radiation, chemotherapy, or primary tumor-specific immunotherapy. Brain edema can usually be managed with steroids during treatment.

Surgical Considerations

Surgical treatment depends upon multiple considerations, including tumor size, presence of hemorrhage, the type of primary tumor (specifically, whether it is radiosensitive or radioresistant), location, and neurologic symptoms. Surgical options for brain metastases can include resection, debulking (as with lesions extending into eloquent areas or deep brain structures), CSF diversion with shunting or endoscopic third ventriculostomy (ETV), or implantation of an intraventricular reservoir for therapeutic delivery. Long-term use of ventricular access reservoirs has been found to be safe—a recent study from our center reported a 4% rate of acute and relatively minor complications, including catheter migration and pericatheter cyst formation [28]. As some of these patients may develop hydrocephalus and require conversion of the intraventricular reservoir to a shunt, a programmable shunt can be implanted for both therapeutic CSF diversion and drug delivery (by increasing shunt resistance to the highest setting and thus effectively turning it "off" during the time of drug infusion).

Radiation

Radiation treatment may serve as a monotherapy or supplement surgical resection and/or systemic therapy; however, this is avoided if possible in children under 3 years of age, due to the likelihood of disruption of normal neurocognitive function during this critical period of brain development and the possibility of developing latent radiation-induced tumors such as meningiomas, gliomas, or sarcomas [29]. Whole brain radiation therapy (WBRT) remains the most common radiation treatment, delivered in fractionated doses, often totaling 10–50 Gy [2].

Stereotactic radiosurgery (SRS), however, is increasingly used and commonly preferred at our institution even for multiple metastases, offering the option of effective focal treatment while minimizing side effects, particularly in this vulnerable population. Recent studies have suggested that there is little to no survival benefit of WBRT over SRS, and in fact, that SRS alone may improve survival in select patient populations under 50 years of age and with less than four brain metastases [2, 30, 31]. This may be

Table 18.1 Case series of solid tumor CNS metastases in the pediatric population

Study reference	Institution	Primary cancer type	Years	Number of patients	Patient age at CNS diagnosis	Incidence of CNS metastases	Interval: primary diagnosis to CNS metastasis	Survival after primary diagnosis	Survival after CNS metastasis
Suki et al. [3]	MD Anderson	Mixed	1990–2012	54	11.37 years, median	1.4%	17 months, median	29 months, median	9 months, median
Wiens and Hattab [4]	Indiana University	Mixed, germ cell tumor predominance	1981–2011	26	10.6 years, median	2.2%, excluding germ cell primary tumors	18 months, median	34.8 months, median	12.5 months, median
Gobel et al. [32]	Ludwig Maximilians University (Munich, Germany)	Germ cell tumors	1982–2009	9	NR	1.1%	NR	NR	NR
Stefanowicz et al. [6]	Medical University of Gdansk (Poland)	Mixed	1992–2010	10	13.8 years, median	2%	8 months, median	NR	NR
Hauser et al. [7]	Semmelweis University (Budapest, Hungary)	Mixed	1989–2002	14	NR	3.4%	11.4 months, mean	21.9 months, mean	10.4 months, mean
Kebudi et al. [5]	Istanbul University (Turkey)	Mixed	1989–2002	16	10.5 years, median	1.45%	20 months, median	NR	2 months, median
Spunt et al. [11]	St. Jude	Germ cell tumors	1962–2002	16	NR	7.8%	NR	NR	NR
Paulino et al. [10]	University of Iowa	Sarcoma, neuroblastoma, Wilms tumor	1965–2000	30	14 years, median	4.9%	5 months, median	NR	4 months, median
Postovsky et al. [33]	Rambam Medical Center (Haifa, Israel)	Sarcoma	1990–2001	18	17.4 years, mean	4.3%	NR	NR	5.03 months, mean (death or last follow-up)

Kramer et al. [8]	MSKCC	Neuroblastoma	1980–1999	11	NR	6.3%, varying by study protocol	12.2 months, median	NR	6.7 months, median
Parasuraman et al. [34]	St. Jude	Ewing sarcoma (ES), rhabdomyosarcoma (RMS)	1962–1998	21	NR	ES: 3.3%, RMS: 2.4%	ES: 22 months, median; RMS: 12 months, median	NR	2.7 months, median
Lowis et al. [35]	UK Children's Cancer Study Group	Wilms tumor	1980–1995	7	NR	0.6%	19 months, median	NR	NR
Bouffet et al. [9]	Centre Leon Berard (Lyon, France)	Mixed	1987–1995	12	9 years, median	7.4%	15 months, median	NR	3 months, median
Rodriguez-Galindo et al. [16]	St. Jude	Melanoma	1962–1995	8	NR	18%	20 months, median	NR	5 months, median
Tasdemiroglu and Patchell [12]	University of Kentucky	Mixed	1982–1994	12	NR	7.8%, 4.5% parenchymal	327 days, mean	NR	5.2 months, mean
Weyl-Ben Arush et al. [36]	Rambam Medical Center (Haifa, Israel)	Mixed	1986–1990	6	NR	9.8%	13 months, median	NR	9.8 months, median
Marina et al. [27]	St. Jude	Osteosarcoma	1962–1989	13	NR	5.1%	3 months, median	NR	16 months, median
Baram et al. [37]	MD Anderson	Osteosarcoma	1980–1986	5	NR	5.7%	12 months, median	NR	NR
Graus et al. [13]	MSKCC	Mixed	1973–1982	31 (including postmortem diagnosis)	NR	22.3%, with 13% diagnosed at autopsy	Median ranges 8.5 months (rhabdomyosarcoma) to 22 months (osteosarcoma)	NR	NR
Vannucci and Baten [14]	MSKCC	Mixed	1951–1972	13 (including postmortem diagnosis)	NR	6%	23 months, median	NR	1 month (31.5 days), median

Characteristics of patients reported in case series of pediatric solid tumor metastases are summarized, including primary study center, dates, tumor subtype, number of patients included, average patient age, incidence of CNS metastasis, time interval between diagnosis of primary tumor and diagnosis of CNS metastasis, survival time after primary diagnosis, and survival time after CNS diagnosis. Averages are reported in each study, as either means or medians, as specified

due in part to the fact that SRS allows delivery of higher focal doses of radiation, rather than fractionated or hypofractionated doses, overcoming the radioresistance of certain primary cancer subtypes such as melanomas and sarcomas [2, 38, 39]. Importantly, SRS may be associated with fewer neurocognitive side effects than WBRT. In a Phase 3 randomized control trial comparing the outcomes of SRS alone to those of SRS plus WBRT, Chang and colleagues demonstrated decreased deficits in learning and memory in the group treated with SRS alone [40].

To date, the efficacy of SRS for metastases in the pediatric population has not been reported outside of case reports; however, this technique has been evaluated and found to be likely effective in cases of pediatric arteriovenous malformations (AVMs) and primary brain tumors, such as juvenile pilocytic astrocytomas (JPAs), recurrent ependymomas, and pineocytomas [2, 41–43]. The development of frameless, optically guided stereotactic systems has helped to overcome many of the difficulties of SRS in the pediatric population, such as intolerance of the headframe and the risk that movement could result in off-target effects, making this now a much more palatable treatment option [42].

Proton Therapy

Though not yet widely described for use in pediatric CNS metastases, proton therapy has been shown to be effective in both pediatric primary brain tumors (including astrocytic, embryonal, and ependymal tumors) and adult CNS metastases [44–46]. Characteristics of proton delivery optimize the risk-benefit profile, particularly for the pediatric population. Compared to photon therapy, protons can deposit more precisely at a desired depth in the oncologic target, reducing entry and exit doses and thus sparing surrounding normal tissues and enabling treatment of targets adjacent to critical structures [45]. Additionally, comparisons of proton therapy-treated primary pediatric CNS malignancies to historical photon beam-treated cohorts have shown non-inferiority or superiority in local control, progression-free survival, and overall survival while minimizing side effects, particularly in medulloblastoma patients receiving craniospinal irradiation (CSI) [46–50]. Given the reduction in the risk of neurocognitive deficits associated with proton therapy, it is a particularly appealing option in the susceptible pediatric population. With a favorable risk-benefit profile of proton versus photon beam therapy, proton therapy appears promising for the treatment of pediatric CNS metastases as well and will likely become more popular as a treatment option as specialized proton centers become more widespread.

Multimodal Treatment

Although pediatric solid tumor CNS metastases generally confer a grim prognosis, with survival in case studies described in months (Table 18.1), there are rare reports of long-term survivors, usually with patients who have received aggressive multimodal therapy incorporating surgical resection, radiation (often focal combined with craniospinal), chemotherapy, immunotherapy, and/or stem cell transplantation. Osawa and colleagues reported two cases of rhabdomyosarcoma achieving disease freedom at 8 and 10 months, respectively (whereas most rhabdomyosarcoma CNS cases succumb in under 1 year), through a combination of surgical resection, radiation to the tumor bed, ifosfamide/carboplatin/etoposide (ICE) chemotherapy, and additional CSI and allogenic stem cell transplantation in one of the patients [51]. Hauser and colleagues also reported a case of long-term survival of 44.8 months after CNS diagnosis in a patient undergoing surgery and receiving radiation, high-dose chemotherapy, and stem cell transplantation [7]. Notably, this was the patient in their reported cohort of 14 cases who received the most aggressive treatment regimen. Additionally, a few cases of long-term survivors with CNS osteosarcoma metastases treated with multimodal therapy have been reported to survive beyond 5 years (this disease is otherwise associated with a 6-month survival) [4, 27, 52]. Rare long-term survival with multimodal therapy has also been reported in

cases of CNS metastases from germ cell tumors, hepatoblastoma, melanoma, Wilms tumor, clear cell sarcoma of the kidney, and neuroblastoma [4, 11, 16, 53–56]. Croog and colleagues from our center demonstrated a survival advantage for CSI and intraventricular radio-immunotherapy in neuroblastoma patients with CNS relapse, postulating that neuroblastoma cells disseminate through CSF along the neuraxis, necessitating full craniospinal radiation [55]. Specifically, they advocate for simultaneous radiation of cranial and spinal fields to avoid potential reseeding and for treatment with either intrathecal or intraventricular delivery of therapeutics or systemic delivery of BBB-penetrating compounds such as irinotecan or temozolomide. With the advent of increasingly effective biological therapies for metastatic disease (such as the combination of nivolumab and ipilimumab checkpoint inhibitors), multimodal treatment options must always be considered [57].

Consideration of Prophylaxis

In contrast to the adult tumor and pediatric liquid tumor populations, pediatric solid tumors rarely develop CNS metastases, and thus, prophylaxis is generally not considered and is of unknown efficacy. Interestingly, in a comparison of Ewing sarcoma patients who received CNS prophylaxis (n = 92, WBRT and a single dose of intrathecal methotrexate) to those who did not (n = 62), Trigg and colleagues found no significant difference in the incidence of developing CNS metastases between the cohorts, suggesting prophylaxis may not be effective in preventing CNS spread, at least in this primary tumor type [58]. However, specific risk factors, such as a breach in the BBB, may render CNS prophylaxis warranted in certain cases. As mentioned, Kramer and colleagues found that prior LP in a neuroblastoma population was significantly associated with the development of CNS metastases; it may be beneficial to prophylactically treat such cases (undergoing LP for primary tumors known to have high risk of hematogenous spread and CNS seeding) with intrathecal chemotherapy [8].

Predicting the Occurrence of Pediatric CNS Metastases

While rare in incidence, pediatric solid tumor metastases tend to be associated more frequently with certain primary subtypes and metastatic disease characteristics. Certain rare primary tumors such as PPB, CCSK, and alveolar soft part sarcoma have been reported to have a higher incidence of CNS metastasis, approximately 25%, 5–11%, and 15–29%, respectively [18–20]. Additionally, although cases of choriocarcinoma comprised a small subset of their cohort, Suki and colleagues found that these were associated with a 43% incidence of brain metastases, suggesting that this germ cell subtype may have a particular predilection for the CNS [3]. Furthermore, as pulmonary metastases often predate or co-occur with CNS metastasis (as described previously), they appear to be a risk factor for CNS disease.

It remains to be determined whether there may be a role for CNS screening imaging in diagnosed pediatric solid tumor cases. This consideration remains controversial, as previous studies have found a high rate of false positives with computerized tomography (CT) imaging to survey for brain metastases in the melanoma population [59]. Risk factors such as primary tumor type (as those listed above are more neurotropic) and presence of pulmonary or other visceral metastases should be taken into account in determining whether CNS screening is warranted [16]. Although CNS metastasis has generally been considered a late-stage finding, continuing development of novel biological treatments, chemotherapies, and radiation regimens yields hope for combatting metastatic disease. With this, CNS screening should be performed for primary malignancy subtypes that have an effective systemic therapy, like melanoma [57].

Conclusions

CNS metastases in pediatric solid tumors remain a relatively rare and late-stage occurrence. This may reflect, in part, the early use of myeloablative therapy for pediatric primary

tumors, depleting the myeloid precursor pool, or an increased permeability of the pediatric BBB, thus facilitating delivery of systemic therapy into the brain. However, certain primary tumor subtypes, as well as the presence of pulmonary metastases, are associated with increased incidence of CNS pathology in the pediatric population. Previous studies have suggested that aggressive multimodal therapy may confer a survival advantage. Taken together, we propose that careful screening of select cases with risk factors for CNS metastasis, particularly in certain tumor subtypes and those with effective therapies available for metastatic disease, may enable better outcomes.

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