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Primary intracranial soft tissue sarcomas in children, adolescents, and young adults: single institution experience and review of the literature

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Abstract

There is a paucity of literature reporting the outcome of intracranial sarcomas (IS) in children, adolescents, and young adults (CAYA). A multimodal therapeutic approach is commonly used, with no well-established treatment consensus. We conducted a retrospective review of CAYA with IS, treated at our institution, to determine their clinical findings, treatments, and outcomes. Immunohistochemistry (PDGFRA and EGFR) and DNA sequencing were performed on 5 tumor samples. A literature review of IS was also conducted. We reviewed 13 patients (median age, 7 years) with a primary diagnosis of IS between 1990 and 2015. Diagnoses included unclassified sarcoma (n = 9), chondrosarcoma (n = 2), and rhabdomyosarcoma (n = 2). Five patients underwent upfront gross total resection (GTR) of the tumor. The 5-drug regimen (vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide) was the most common treatment used. Nine patients died due to progression or recurrence (n = 8) or secondary malignancy (n = 1). The median follow-up period of the 4 surviving patients was 1.69 years (range 1.44–5.17 years). The 5-year progression-free survival and overall survival rates were 21 and 44 %, respectively. *BRAF*, *TP53*, *KRAS*, *KIT*, *ERBB2*, *MET*, *RET*, *ATM*, and *EGFR* mutations were detected in 4 of the 5

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Compliance with ethical standards

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tissue samples. All 5 samples were immunopositive for PDGFRA, and only 2 were positive for EGFR. IS remain a therapeutic challenge due to high progression and recurrence rates. Collaborative multi-institutional studies are warranted to delineate a treatment consensus and investigate tumor biology to improve the disease outcome.

Keywords

Sarcoma; Intracranial; Children; Young adults; Multimodality therapy

Introduction

Primary intracranial sarcomas (IS) are rare tumors that were first described by Bailey in 1929 [1]. Their reported incidence has varied in different studies, ranging from 0.1 to 4.3 % on the basis of a few case reports and retrospective case series [1–3]. The reason for this variation is the inconsistency in the definition of IS in multiple studies. Previous reports included entities such as giant cell sarcoma, reticulum cell sarcoma, circumscribed sarcoma of the cerebellum, and hemangiopericytoma, which contributed to the increase in the incidence rate of IS [4–8].

To date, no defined treatment strategies have been established for IS [9, 10]. Most reports show a multimodal approach, with surgery and adjuvant therapy. Radiation therapy is often used in the adjuvant setting for local disease control.

The biology of IS remains elusive, with a paucity of data regarding its tumorigenesis. Receptor tyrosine kinases (RTKs) and angiogenesis are survival pathways that are constitutively activated in many pediatric sarcomas [11–17]. Platelet-derived growth factor receptor (PDGFR), an RTK, has been found to be overexpressed in osteosarcoma, rhabdomyosarcoma, and Ewing sarcoma [18–22]. It plays a role in tumorigenesis and has both prognostic and therapeutic implications [11, 15, 17, 19, 23–28].

In this study, we report the clinical, molecular biology, and treatment characteristics and clinical outcomes of 13 children, adolescents, and young adults (CAYA) diagnosed with IS at our institution.

Patients and methods

The central nervous system (CNS) tumor database at The University of Texas MD Anderson Cancer Center (Houston, Texas) was searched to identify all CAYA patients (> 21 years old) with IS who had been diagnosed or treated from January 1990 to September 2015. Thirteen patients were identified. Their medical records were reviewed for clinical, radiological, surgical, and pathological data and details concerning treatment and outcome. Study approval was obtained from the MD Anderson institutional review board.

Primary IS was defined as sarcoma that originated in the brain from non-neuronal, non-glial, and non-reticular elements, with no previous evidence of systemic sarcoma and no sarcomatous transformation of a previously known benign tumor. Sarcomas that developed

following irradiation were included. On the basis of this definition, we excluded patients with entities such as primitive neuroectodermal tumor, gliosarcoma, reticulum cell sarcoma, Ewing sarcoma, hemangiopericytoma, and malignant meningioma.

Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were performed at diagnosis. Patients underwent CT of the chest, abdomen, and pelvis, as indicated by their clinical presentation. MRI of the spine was performed in 4 patients at diagnosis and 2 patients at recurrence; these 2 patients had clinical findings that were suggestive of neuroaxis and spine involvement. Bone scans (2 patients) and PET-CT (1 patient) were performed at diagnosis.

A pathological review and diagnoses were performed for all patients according to the current World Health Organization classifications of tumors of the CNS and tumors of the soft tissue and bone. Cytological analyses of the cerebrospinal fluid were performed in 5 patients.

Molecular testing and immunohistochemistry

DNA sequencing was performed in a Clinical Laboratory Improvement Amendments-certified laboratory. Due to limited tissue availability, only 5 samples were retrieved. DNA was extracted using the ARCTURUS PicoPure DNA extraction kit (ThermoFisher Scientific, Grand Island, NY, USA) and purified with Agencourt AMPure XP reagent (Beckman Coulter, Inc., Brea, CA, USA). Targeted sequencing for a panel (46 genes in the first sample and 50 in subsequent samples; Ion AmpliSeq Cancer Hotspot Panel v2, ThermoFisher Scientific) (Supplementary Table 1) was performed on an Ion Torrent platform in 4 of 5 samples [29]. A data analysis was performed using Torrent Suite (v.4.2.1, ThermoFisher Scientific) and in-house-developed software, OncoSeek. The sequences were aligned to HG19. Mutations were called at an allelic frequency of 10 % and confirmed with IGV (v.2.3.1, Broad Institute, Cambridge, MA, USA).

Five samples were retrieved and stained with EGFR and PDGFRA antibodies in a Clinical Laboratory Improvement Amendments-certified laboratory. Five micron-thick formalin-fixed, paraffin-embedded tissues were stained with EGFR (mouse monoclonal, clone 31G7, dilution 1:50; ThermoFisher Scientific) and PDGRA (C-20) (rabbit polyclonal, catalog #sc-338, dilution 1:50; Santa Cruz Biotechnology, Inc., Dallas, TX, USA) on a Leica Bond automatic immunostainer (Leica, Buffalo Grove, IL, USA).

Statistical methods

Data were summarized using standard descriptive statistics. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method, and group comparisons were performed using the log-rank test. OS was defined as the time from the date of initial pathological diagnosis or initial surgery to death from any cause or last visit. PFS was defined as the time from the date of diagnosis to the date of death, first progression, recurrence, occurrence of secondary malignancy, or last visit. A univariate Cox regression analysis was performed to assess the effect of variables of interest on OS and PFS. All analyses were carried out using SAS software version 9.3 (SAS Institute, Inc., Cary, NC, USA) and R 3.2.0.

Results

The clinical characteristics of the 13 study patients are summarized in Table 1. The median age at diagnosis was 7 years (range 1 week–20 years). Seven patients were male. Symptom duration was documented in 10 patients. The median duration was 2 months (range 1 week–1 year). Symptoms of increased intracranial pressure, in the form of headaches and vomiting, were present in 70 % of patients. Two patients presented with new-onset seizures as presenting symptoms, and 3 presented with motor weakness. Histopathological diagnoses included unclassified sarcoma (n = 9), rhabdomyosarcoma (n = 2), and chondrosarcoma (n = 2). A supratentorial tumor location was predominant in the majority of patients (n = 11). A cytological cerebrospinal fluid analysis was performed in 5 patients and was reported negative.

Pathology

The histological features of the different IS were similar to those of their extracranial counterparts. Tumors were composed of small round cells; large epithelioid cells with large nuclei and prominent nucleoli; or elongated, spindled cells arranged in interlacing fascicles (Fig. 1a). Mitotic activity and necrosis were noted in the majority of patients. Most unclassified sarcomas were vimentin immunoreactive (Fig. 1b, inset) and GFAP/S100 non-reactive, with peri-cellular reticulin deposition (Fig. 1b). A few tumors showed chondroblastic and rhabdomyoblastic differentiation and were classified as chondrosarcomas and rhabdomyosarcomas, respectively. As expected, rhabdomyosarcomas showed immunoexpression of the myogenic markers desmin, MyoD1, and myogenin.

Radiology

Brain CT, with and without contrast, was performed initially in all patients. MRI, with and without gadolinium contrast, was available for review in 7 patients. The largest diameter of the tumors on MRI ranged from 1.5 to 6.9 cm. All lesions demonstrated homogenous contrast enhancement. There was no leptomeningeal disease or spinal involvement on initial radiological examination. Involvement of the convexity dura or falx was present in all supratentorial lesions (Supplementary Fig. 1a, b). Calcification was observed on preoperative CT scan in 1 patient. Two supratentorial lesions were associated with hemorrhage at presentation (patients #11 and 12).

In the few available diffusion-weighted imaging studies, 1 patient with chondrosarcoma demonstrated restricted diffusion. Five lesions demonstrated parenchymal infiltration on MRI and involvement of more than 1 brain lobe or section. Two patients presented initially with a working diagnosis of a vascular malformation; a subsequent MRI revealed a contrast-enhancing mass that was suggestive of a neoplasm (Supplementary Fig. 1c, d).

Treatment

Treatment and related outcome data are summarized in Table 1. Five patients underwent gross total resection (GTR), 7 patients underwent subtotal resection, and 1 patient with a suprasellar lesion underwent a biopsy to confirm the diagnosis. Additional surgery was performed in 7 patients due to local recurrence (n = 5) and second-look surgery (n = 2) after

adjuvant chemotherapy. These 2 patients had initial near-GTR and underwent further surgery due to persistent contrast enhancement of the tumor bed on subsequent imaging during chemotherapy. GTR was achieved; both patients were found to have evidence of disease at the time of second surgery and remained free of disease after further therapy with focal radiation and chemotherapy. One patient underwent surgery as definitive treatment due to the low histological grade of the sarcoma.

Radiation therapy was given to 10 patients (focal radiation, $n = 9$): after the initial surgery in 3, after additional surgery in 4, and as delayed therapy (<3 years) in 2 after surgery and adjuvant chemotherapy. One patient with intracranial rhabdomyosarcoma received focal and cran-iospinal radiation at the discretion of the treating physician, with no evidence of tumor metastasis at diagnosis. All patients diagnosed after 2004 ($n = 5$) underwent proton beam radiation therapy. The radiation field, which included the surgical cavity plus an anatomically confined margin of 1 cm, was treated with a median dose of 60 Gy in 30 fractions. Two patients developed sarcoma at the radiation field after initially being diagnosed with pleomorphic xanthoastrocytoma and high-grade glioma 10 and 6 years later, respectively. Neither of the 2 patients with radiation-induced sarcoma had a cancer predisposition syndrome (e.g., neurofibromatosis or retinoblastoma). One patient underwent stereotactic radiosurgery (14 Gy) following subtotal resection of the tumor.

Ten patients underwent chemotherapy [after surgery ($n = 6$) or radiation therapy ($n = 4$)]. Chemotherapy was given as first-line treatment to 4 patients who were <3 years of age at the time of diagnosis. The 5-drug regimen (vincristine, doxorubicin, and cyclophosphamide, alternating with etoposide and ifosfamide) was given to 5 patients. The ICE chemotherapy regimen (ifosfamide, carboplatin, and etoposide) was administered in 3 patients. Temozolomide was given to 4 patients in conjunction with radiation therapy. One patient was treated with targeted therapy after a failure to respond to ICE chemotherapy. She underwent salvage chemotherapy with a backbone of temozolomide and irinotecan; dasatinib was added as a targeted agent. The patient remained in remission, with no disease recurrence, for 15 months. As part of the evaluation, she underwent genetic profiling; a *BRAF*^{V600E} mutation was revealed by DNA sequencing, and overexpression of PDGFRA was found by immunohistochemistry (IHC).

Molecular studies and IHC

Genetic profiling was performed in 4 of the 5 available tissue samples (inadequate DNA was available for 1 sample), and immunostaining for EGFR and PDGFRA was performed in all 5 samples. The following mutations were detected: *BRAF*, *TP53*, *KRAS*, *KIT*, *ERBB2*, *MET*, *RET*, *ATM*, and *EGFR*. *TP53* and *KIT* mutations were detected in 2 of the 4 samples. All 5 samples were positive for PDGFRA; only 2 were positive for EGFR (Fig. 1c, d). Table 2 summarizes the genetic testing and immunostaining results.

Outcome

The median follow-up period of the 4 surviving patients was 1.69 years (range 1.44–5.17 years). Two of the survivors underwent second-look surgery. Nine patients died due to local progression or recurrence ($n = 5$), distant metastasis ($n = 2$; lung and sacral spine), combined

local and distant metastasis (n = 1, spinal cord), or secondary malignancy (n = 1), with the earliest death at 18 days and the latest at 15.7 years. Eleven patients experienced recurrent or progressive disease, and 4 patients had no evidence of disease. One patient with rhabdomyosarcoma developed a second malignancy (glioblastoma multiforme) at the radiation field 10 years after the initial diagnosis. Long-term sequelae were present in the 4 survivors and included migraine headache (n = 1), mood swings (n = 1), mild unilateral hearing loss at the site of the initial tumor (n = 1), and learning disabilities (n = 2) at a median follow-up of 1.69 years.

The median OS and PFS durations were 1.88 and 1.03 years, respectively (95 % CI 1.03–15.72 and 0.44–3.17 years). The OS rates at 1, 2, and 5 years were 88, 44, and 44 %, and the PFS rates were 54, 31, and 21 % (Fig. 2a).

The results of the univariate analysis indicated that age at diagnosis, sex, and histology had no significant impact on the OS and PFS rates. Patients who had GTR had 1- and 5-year OS rates of 100 and 75 %, respectively, compared with patients who had <GTR (75 and 25 %; P value = 0.05) (Fig. 2b).

Discussion

This study is a report of patients with primary IS. To the best of our knowledge, it is the third largest study in the CAYA population that addresses clinical characteristics, treatment, and outcome and the first study to report on the molecular biology of such rare tumors.

The clinical presentation of IS does not differ from that of other intracranial space-occupying lesions. Similar to the findings of previous reports, IS was noted more commonly in the supratentorial region, with a predilection for the temporal and parietal lobes. Primary IS, unlike glial tumors, has metastatic risk outside the central nervous system. Metastatic disease has been reported in up to 40 % of patients and is associated with a poor prognosis [9, 10]. In addition to neuroaxis dissemination, the most frequent non-neural sites of metastasis are the bone and lungs, which necessitates neuroaxis, whole-body imaging (CT and PET scan), and lumbar CSF cytology at diagnosis and follow-up, as indicated.

The majority of the supratentorial lesions in our study showed dural or falx involvement. Intratumoral hemorrhage and increased vascularity have been described in previous cases of IS [9, 10, 30, 31].

In general, IS has a poor prognosis, although in a few instances, long-term survival has been documented [9, 10, 32, 33]. Most reports in the literature suggest that radical surgical resection is correlated with a better prognosis. Second-look surgery is recommended for residual or recurrent tumors, if feasible, as 2 of our 4 long-term survivors underwent second-look surgery. Focal radiotherapy is essential to achieving local tumor control. In the presence of metastatic disease, craniospinal irradiation appears to be an appropriate therapeutic option.

Although the role of chemotherapy is well defined in extracranial sarcoma, there is no consensus regarding its role or the optimal agents for the treatment of IS [9, 10]. The vast

majority of long-term survivors reported in the literature have undergone multimodal treatment, including chemotherapy, thus giving credence to the use of these agents [9, 10, 33]. The most commonly used agents in our study were ifosfamide, etoposide, carboplatin, vincristine, and cyclophosphamide (5 drugs), followed by ICE chemotherapy. Due to its well-established radiosensitizer effect, temozolomide was administered to 4 patients in conjunction with radiation [34]. Benesch et al. proposed the use of a “sandwich” regimen, in which chemotherapy is used before and after radiotherapy [10].

The 2 largest IS studies conducted in the past 2 decades were retrospective [9, 10]. In the El Ghatany study, the survival duration was shorter in patients with <GTR, metastatic disease, and age <1 year at diagnosis. Benesch et al. reported a trend toward a poorer outcome in patients with <GTR and sarcoma. The median time to progression was 6 months, and the median survival duration was 9.5 months [10]. In our series, patients who had GTR of the tumor had a trend towards superior survival. Table 3 summarizes the clinical characteristics and outcomes of these 3 series, including the current study.

There have been significant advances in our understanding of the genomic landscape of pediatric sarcoma [35]. The activation of several RTKs, including PDGFR, MET, KIT, and EGFR, are well known in pediatric sarcomas [11–17]. *KIT* and *MET* mutations were reported to play a role in tumorigenesis in osteosarcoma and rhabdomyosarcoma, with prognostic implications [16, 35]. *TP53* mutations are more common in osteosarcoma than in rhabdomyosarcoma and Ewing sarcoma. They induce tumorigenesis through the disruption of DNA repair and cell cycle regulation. Shukla et al. reported the presence of *BRAF* and *KRAS* mutations in Ewing sarcoma and rhabdomyosarcoma, indicating a role for RAS pathway activation in sarcoma tumorigenesis [13, 14]. PDGFR α and ERBB2 were found to be upregulated in rhabdomyosarcoma and synovial sarcoma and are known to confer therapeutic resistance [11, 15, 35].

Vascular endothelial growth factor receptor (VEGFR), PDGFR, EGFR, c-KIT, and HER2/ ErbB2/neu play significant roles in tumor angiogenesis [36, 37]. PDGF and its receptor are known to have a role in the pathogenesis, invasion, and distant metastasis of many sarcomas, including rhabdomyosarcoma, osteosarcoma, synovial sarcoma, chordoma, Ewing sarcoma, and chondrosarcoma and are correlated with poor prognosis and metastasis [15, 18–22, 24]. In addition, vascular pericytes, fibroblasts, and myofibroblasts express PDGFR and are involved in an autocrine or paracrine loop that causes tumor growth and progression in osteosarcoma and rhabdomyosarcoma [24, 38]. Using IHC, Kubo et al. demonstrated that the expression of PDGF-AA (80.4 %) and PDGFRA (79.6 %) was common and correlated with an inferior outcome in osteosarcoma (P <0.05) [19].

Furthermore, PDGFR expression and signaling were associated with poor prognosis in rhabdomyosarcoma and Ewing sarcoma, respectively [15, 23, 28]. PDGFRA and its downstream effectors, mitogen-activated protein kinase and Akt, were highly activated in both primary and meta-static tumors. Inhibition of PDGFRA had a dramatic effect on tumor cell growth, both in vitro and in vivo, and has proven beneficial in several types of sarcomas [11, 15, 17, 19, 24, 25, 27, 28].

The most common mutations in our cohort involved *KIT* and *TP53* (2 of the 4 samples); other mutations involved *BRAF*, *RET*, *KRAS*, *ATM*, *EGFR*, *ERBB2*, and *MET* (details in Table 2). Another interesting finding was that all 5 samples immunoexpressed PDGFRA but only 2 expressed EGFR by IHC. This novel finding of PDGFR expression may indicate that its role in tumorigenesis needs to be further evaluated in future trials.

Increasing knowledge of potential molecular targets along deregulated cellular pathways has helped to profile the development of novel therapies in sarcomas [23, 25, 28]. This small yet relevant study defines the importance of elucidating molecular biology in the armamentarium of IS diagnosis to enable us to add targeted therapy to the backbone of conventional treatment strategies.

The limitations of our study include its retrospective nature, small size, and the long time interval (2 decades), which reflects heterogeneous treatment approaches.

In conclusion, the prognosis of IS remains dismal, even with diverse therapeutic approaches. Upfront imaging for neuroaxis and extracranial spread are highly recommended. The 5-drug regimen and ICE chemotherapy are valid treatment approaches, in conjunction with surgery and radiation. Second-look surgery is encouraged, if feasible, for better local control. Collaborative multi-institutional studies are warranted to delineate the treatment strategy, understand the tumor biology, and identify prognostic factors to improve the outcome of IS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
The unclassified sarcoma in patient #8 was composed of interlacing fascicles of spindled cells (**a**, H&E, obj: 200X) and scattered mitoses (*yellow arrows*) (**A inset**, obj: 400X), with pericellular reticulin deposition (*black arrows*) (**b**, reticulin, obj: 200X), cytoplasmic vimentin immunoreactivity (**b inset**, vimentin, obj: 200X), and lack of immunoreactivity for glial markers (GFAP/ S100) (not shown). This tumor immunoreacted EGFR (**c**, EGFR, obj: 400X; the blood vessel at the top, indicated by the *yellow arrows*, served as an internal negative control) and PDGFRA (**d**, PDGFRA, obj: 400X)

Table 1

Patient characteristics, treatment modalities, and outcome

Patient	Age/sex	Diagnosis	Tumor location	Surgery	Radiation field/dose	Chemotherapy	Treatment sequence	Time to first progression (months)	Outcome (month)
1	13 years/F	Sarcoma, unclassified.	Parasagittal area	PR1, PR2	Focal 54 Gy	VadriaC/IE × (7)	S, S, RTH, CTX	5	DOD (15)
2	1 week/M	Sarcoma, unclassified	Thalamus and suprasellar	Biopsy	None	MTX and leucovorin, MOPP × (1)	S, CTX	-	DOD (1)
3	7 years/M	Rhabdomyosarcoma	Frontal lobe	PR	Focal 20 Gy + CSI 30 Gy	IE × (6) (first line), VCR, CPM × (6) (second line)	S, CTX, RTH, CTX	Not available	DOD (191)
4	2.7 years/M	Rhabdomyosarcoma	Parietal lobe	PR1, PR2, PR3	Focal 39.6 Gy	VAC × (9) (first line) IE × (4) (second line)	S, CTXS, RTH, CTX, S	7	DOD (16)
5	12.5 years/F	Sarcoma, unclassified	Tempo-parietal lobe	PR	Focal 59 Gy	VAC/IE × (6)	S, RTH, CHX	17	DOD (18)
6	20 years/F	Sarcoma, unclassified	Parieto-temporal lobe	GTR1, PR2, stereotactic biopsy, PR3	None	Alpha interferon × (1)/IFO × (5), VCR/Cis/MTX × (1) (first line), local BCNU (second line)	S, CTX, S, CTX, S	16	DOD (23)
7	18 years/F	Sarcoma, unclassified	Cerebellum and brain stem	PR1, SRS	Stereotactic 14 Gy	None	S, S, RTH	-	DOD (13)
8	3 years/M	Sarcoma, unclassified	Frontal lobe	PR1, GTR2	Focal - 60 Gy + Focal 54 Gy	TMZ*, Cis/VCR/DOX/IE (4) (first line), ICE × (6) (second line)	S, RTH, CTX, S, RTH, CTX	39	DOD (99)
9	20 years/M	Chondrosarcoma	Parietal lobe	GTR	None	None	S	-	NED (51)
10	2.6 years/M	Mesenchymal chondrosarcoma	Parieto-temporal lobe	GTR1, GTR2	Focal 60 Gy	VadriaC/IE × (14), VCR/IR/ TMZ × (2), TMZ*, weekly VCR × 6 weeks	S, CTX, S, RTH, CTX	11	NED (63)
11	16.9 years/M	Sarcoma, unclassified	Temporal lobe	PR1, GTR2	Focal 60 Gy	None	S, S, RTH	-	DOD (5)
12	5 years/F	Sarcoma, unclassified	Frontal lobe	GTR	Focal 60 Gy	TMZ*, ICE × (6)	S, RTH, CTX	-	NED (28)
13	2.9 years/F	Sarcoma, unclassified	Temporal lobe	GTR1, GTR2	Focal 60 Gy	ICE × (5), TMZ* followed by TMZ/IR/dasatinib × 1 year	S, CTX, S, RTH, CTX	5	NED (18)

Ffemale, Mmale, GTR gross total resection, PR partial resection, SRS stereotactic radiosurgery, CSI craniio-spinal irradiation, VadriaC vincristine, adriamycin, cyclophosphamide, IE ifosfamide-etoposide, MTX methotrexate, MOPP mechlorethamine, vincristine, procarbazine, prednisone, VCR vincristine, CPM cyclophosphamide, VAC vincristine, actinomycin D, cyclophosphamide, IFO ifosfamide, DOX doxorubicin, Cis cisplatin, BCNU carbustine, TMZ temozolomide, IR irinotecan. S surgery, CTX chemotherapy, RTH radiation therapy.

* radiosensitizer + different field, () number of chemotherapy cycles, DOD dead of disease, NED no evidence of disease

Table 2

Summary of detected mutations and immunohistochemistry results in 5 patients with intracranial sarcoma

Patient no.	Histology	NGS results			IHC results			
		Gene	HGVS	Location	Type	Protein change	Allelic frequency	PDGFRA EGFR
2	Sarcoma, unclassified	<i>MET</i>	NM_01127500.1(MET):c.1076G > A p.R359Q	Exon 2	SNV	Missense	42	Positive
4	Rhabdomyosarcoma	<i>TP53</i>	NM_000546.5(TP53):c.1040C > T p.A347 V	Exon 10	SNV	Missense	80	Positive
		<i>RET</i>	NM_020975.4(RET):c.2734C > T p.R912 W	Exon 16	SNV	Missense	14	Negative
		<i>EGFR</i>	NM_005228.3(EGFR):c.884G > A p.C295Y	Exon 7	SNV	Missense	10	
		<i>ATM</i>	NM_000051.3(ATM):c.3886C > T p.P1296S	Exon 26	SNV	Missense	10	
		<i>ERBB2</i>	NM_004448.2(ERBB2):c.2638G > A p.D880 N	Exon 21	SNV	Missense	10	
6		<i>KIT</i>	NM_000222.2(KIT):c.1684G > A p.E562 K	Exon 11	SNV	Missense	10	
	Sarcoma, unclassified	Not evaluable						Positive
8	Sarcoma, unclassified	<i>TP53</i>	NM_000546.5(TP53):c.743G > A p.R248Q	Exon 7	SNV	Missense	93	Negative
		<i>KRAS</i>	NM_004985.3(KRAS):c.35G > A p.G12D	Exon 2	SNV	Missense	91	Positive
13	Sarcoma, unclassified	<i>BRAF</i>	NM_004333.4(BRAF):c.1799T > A p.V600E	Exon 15	SNV	Missense	49	Positive
		<i>KIT</i>	NM_000222.2(KIT):c.1621A > C p.M541L	Exon 10	SNV	Missense	58	Negative

NGS new generation sequencing, IHC: immunohistochemistry, HGVS Human Genome Variation Society description of sequence variation in genomics, SNV single nucleotide variant

Table 3
Clinical characteristics, treatments, and outcomes of different studies of primary intracranial sarcomas

Study	Median age (years)	Patient number	Results	Surgery	Radiotherapy	Chemotherapy	Outcome
Al Ghatany et al. 2003	4.8	16	14 patients had IS and 2 had intraspinal tumors. Nine tumors had a supratentorial location. Six patients had CSF dissemination, and 1 had distant metastasis	15 (9 GTR, 6 PR)	11 (5 local 6 CSI, 1 WB)	Multiple regimens	9 alive; median survival 4.6 years, range 1 month–16 years
Benech et al. 2013	9.7	19	Diagnoses included sarcoma NOS (n = 8), embryonal RMS (n = 2), chondrosarcoma (n = 2), and malignant mesenchymal tumor (n = 2). Seventeen tumors had a supratentorial location. No CSF dissemination or metastasis was found at the time of diagnosis. One patient had multifocal bone metastasis at recurrence	16 (11 GTR, 5 PR, 1 biopsy)	11 (8 local, 3 CSI)	Multiple regimens	10 alive; median follow-up 5.8 years, 5-year OS and PFS 74 % and 47 %
Current Study	7	13	Diagnoses included SU (n = 9), RMS (n = 2), and chondrosarcoma (n = 2). A supratentorial location was present in 11 patients. No CSF dissemination or metastasis was found at diagnosis. Metastasis to lungs (n = 1), spine (n = 1), and CNS dissemination (n = 1) were found at recurrence	13 (5 GTR, 7 PR, 1 biopsy)	10 (9 local, 1 CSI)	Multiple regimens	4 alive; median follow-up 5.7 years, 5-year OS and PFS 44 and 21 %

IS intracranial sarcoma, *SU* sarcoma unclassified, *CSF* cerebrospinal dissemination, *NOS* not otherwise specified, *RMS* rhabdomyosarcoma, *GTR* gross total resection, *PR* partial resection, *CSI* craniotomical irradiation, *WB* whole brain, *OS* overall survival, *PFS* progression-free survival