A Case of Primary CNS Embryonal Rhabdomyosarcoma with *PAX3-NCOA2* Fusion and Systematic Meta-Review

Ryuma Tanaka (✉ rtanaka@mcw.edu)

Medical College of Wisconsin Department of Pediatrics <https://orcid.org/0000-0002-0132-052X>

Kyohei Inoue

Keio Gijuku Daigaku

Yuji Yamada

Keio University: Keio Gijuku Daigaku

Masanori Yoshida

National Center for Child Health and Development Research Center: Kokuritsu Kenkyu Kaihatsu Hojin
Kokuritsu Seikyo Iryo Kenkyu Center Kenkyujo

Haruko Shima

Keio University: Keio Gijuku Daigaku

Jumpei Ito

Keio University: Keio Gijuku Daigaku

Hajime Okita

Keio University: Keio Gijuku Daigaku

Tomoru Miwa

Keio University: Keio Gijuku Daigaku

Motohiro Kato

University of Tokyo: Tokyo Daigaku

Hiroyuki Shimada

Keio University: Keio Gijuku Daigaku

Research Article

Keywords: Primary CNS rhabdomyosarcoma, PAX3-NCOA2

Posted Date: July 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-693262/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Journal of Neuro-Oncology on August 16th, 2021. See the published version at <https://doi.org/10.1007/s11060-021-03823-6>.

Abstract

Purpose: Primary central nervous system (CNS) rhabdomyosarcoma is a rare mesenchymal tumor predominantly seen in children and associated with a poor outcome. We report a case of primary CNS rhabdomyosarcoma with *PAX3-NCOA2* fusion and present a systematic meta-review of primary CNS rhabdomyosarcoma to characterize this rare tumor.

Methods: We present the case of a 6-year-old boy with primary CNS rhabdomyosarcoma in the posterior fossa. In a systematic meta-review, we compare the demographic data of primary CNS rhabdomyosarcoma with data of rhabdomyosarcoma at all sites from the SEER database and analyze clinical factors associated with survival outcome.

Results: Our patient underwent gross total resection and received vincristine, actinomycin-D, cyclophosphamide with early introduction of concurrent focal radiation and remained alive with no evidence of disease for 2 years after the end of therapy. Histopathological review revealed embryonal-type rhabdomyosarcoma, and whole-transcriptome analysis revealed *PAX3 (EX6)-NCOA2 (EX12)* fusion. In all, 77 cases of primary CNS rhabdomyosarcoma were identified through the meta-review. The demographic data of primary CNS rhabdomyosarcoma were similar to data of rhabdomyosarcoma at all sites. Overall and event-free survival outcomes were available for 64 and 56 patients, respectively, with a 3-year OS of 29.5% and a 3-year EFS of 26.2%. The group that received trimodal treatment exhibited better survival outcomes, with a 3-year OS of 57.4% and a 3-year EFS of 46.3%.

Conclusions: Primary CNS rhabdomyosarcoma shares common histological, molecular, and demographic features with non-CNS rhabdomyosarcoma. A trimodal treatment approach with early introduction of radiation therapy may result in favorable survival outcomes.

Introduction

The first cases of primary central nervous system (CNS) rhabdomyosarcoma were described in the 1950s [1, 2]. The biology is not well understood, and whether this tumor is a rare variation of other CNS tumors or the CNS is a rare location of rhabdomyosarcoma has been debated [3, 4]. In the WHO 2016 classification of CNS tumors, primary CNS rhabdomyosarcoma is characterized by histological features of undifferentiated small cells and positive immunostaining for desmin and myogenin [5]. Generally, the prognosis of primary CNS rhabdomyosarcoma is poor, although successfully treated cases have been reported [6, 7].

Recently, molecular characterization of this rare tumor has revealed several features shared with non-CNS rhabdomyosarcoma. Multiple groups have reported cases of primary CNS rhabdomyosarcoma that harbor a *DICER1* mutation, which is commonly seen in embryonal rhabdomyosarcoma at genitourinary sites [8–11]. *PAX3-NCOA2* fusion in non-CNS rhabdomyosarcoma was also reported in a case of alveolar rhabdomyosarcoma of the pineal gland [12].

Here, we report the case of a 6-year-old boy with histologically defined embryonal rhabdomyosarcoma in the posterior fossa that was positive for *PAX3-NCOA2* fusion and negative for *DICER1* mutations. We also conducted a systematic meta-review of primary CNS rhabdomyosarcoma to better characterize the clinical features and treatment approach of this tumor.

Materials And Methods

DNA extraction, Sanger sequencing, and whole-exome sequencing

The genomic study was approved by the institutional review board, and parental consent was obtained prior to the study. Using a QIAamp DNA Mini Kit (QIAGEN), germline DNA and tumor genomic DNA were extracted from peripheral blood during remission and fresh-frozen tumor samples at diagnosis, respectively. Sanger sequencing of *DICER1* was performed and the sequence from exon 2 to exon 27 was compared with a known wild-type sequence, as described in a previous report [13]. For whole-exome sequencing, library construction was performed with a SureSelect Human All Exon Kit v6 (Agilent Technology). Enriched fragment libraries were then sequenced in a HiSeqX system (Illumina). Sequence alignment and detection of gene mutations and structural variations were performed using Genomon v.2.6.3 (<https://github.com/Genomon-Project/>).

Rna Extraction And Whole-transcriptome Sequencing

Total RNA was extracted from tumor cells at diagnosis using an RNeasy Mini Kit (QIAGEN). For paired-end whole-transcriptome sequencing, we used a NEBNext rRNA Depletion Kit (Human/Mouse/Rat) with RNA Sample Purification Beads and the NEBNext Ultra II Directional RNA Library Prep with Sample Purification Beads (NEW ENGLAND Biolabs) followed by paired-end cluster generation and sequencing using DNBSEQ-T7 (BGI). Sequence alignment and structural variation calling were performed using the Genomon pipeline.

Review Of Primary Cns Rhabdomyosarcoma In The Literature

We searched PubMed for articles published in English and without time restrictions. Key words were “central nervous system” or “cerebral” or “cerebellar” or “brain” or “spine”, and “rhabdomyosarcoma” and “primary”. Studies unrelated to CNS tumors and those that discussed CNS metastasis of rhabdomyosarcoma originating from other sites were excluded. Articles that discussed primary CNS rhabdomyosarcoma were reviewed in detail. Rhabdomyosarcoma arising from the meninges was excluded. Cases that were not found by the initial search and that were described in the reviewed articles were included if appropriate. In the survival analysis, only cases with descriptions of relevant information,

i.e., time from diagnosis to death, time from diagnosis to relapse, and treatment modalities at the first diagnosis, were analyzed.

Surveillance, Epidemiology, and End Results (SEER) Database

To compare data of primary CNS rhabdomyosarcoma cases in the literature to rhabdomyosarcoma data of a large cohort, we used the SEER database. The database information and software that were included in the analysis are described below. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, November 2018 Sub (1975–2017 varying) - Linked To County Attributes - Total U.S., 1969–2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.3.9.

Statistical Analysis

The log-rank test and Kaplan-Meier survival analysis were performed to identify prognostic and predictive factors of survival outcome. R package version 3.5.0. was used for the analysis.

Results

Our Case

A previously healthy 6-year-old boy presented with a one-month history of ataxia and gait disturbance. Physical examination revealed mild dysmetria of the left side. No abnormal pigmentation, axillary freckling, or bone lesions were noted. His family history was not significant for cancer or cancer predisposition. An MRI of the brain revealed a heterogeneously enhanced T1 hypointense, T2 isointense lesion measuring 53 mm in diameter at the left pontine-cerebellar angle and enlarged ventricles. MRI of the spine was negative for metastasis and disseminated disease. Selective catheter embolization of the left anterior inferior cerebellar artery (AICA) that was feeding the tumor was performed as previously described [14]. Then, the patient underwent gross total resection (GTR) of the tumor.

Histopathological review of the tumor revealed a mixture of small round cells and spindle cells. Immunostaining was positive for desmin, myogenin and MyoD, which is consistent with the diagnosis of embryonal-type rhabdomyosarcoma. Fluorescence in situ hybridization (FISH) and PCR for the *PAX3/7* genes were performed to detect fusions with *FOXO1*, which are characteristic of alveolar-type rhabdomyosarcoma, and the results were negative. To verify the primary tumor site, chest CT, abdominal MRI, and whole-body PET-CT were performed and revealed no evidence of tumors outside the CNS. Chest CT did not show pulmonary fibrosis, and the baseline thyroid hormone level was normal. Sanger sequencing of *DICER1* and whole-exome sequencing revealed no pathological mutations, whereas whole-transcriptome analysis showed the *PAX3-NCOA2* fusion at the 5' end of exon 6 of *PAX3* (NM_181461)

and the 3' end of exon 12 of *NCOA2* (NM_1321712). This fusion gene was verified by RT-PCR and Sanger sequencing (Fig. 1).

Four weeks after GTR, vincristine, actinomycin-D, cyclophosphamide (VAC) chemotherapy was initiated. Within two weeks from the start of chemotherapy, focal radiation consisting of a 45 Gy photon beam in 30 fractions delivered to the tumor bed was initiated; actinomycin-D was omitted during radiation therapy. VAC therapy was continued for 39 weeks, which is common in intermediate-risk non-CNS rhabdomyosarcoma. Total doses of 42 mg/m² vincristine, 0.54 mg/kg actinomycin-D, and 30.8 g/m² cyclophosphamide were administered without any grade III or IV nonhematological adverse events. Through the course of treatment, the patient's activity level was maintained, and he had a Lansky performance score of 90. MRI performed at 26 months from the end of therapy revealed no evidence of disease.

Clinical Features Of Primary Cns Rhabdomyosarcoma In The Literature

We identified 55 articles and 77 cases of primary CNS rhabdomyosarcoma, including our patient (Fig. 2, Supplementary Table 1). Diagnosis was predominantly in children, but cases in adults were also found. A similar pattern of age distribution was observed in the large cohort of 5013 cases of rhabdomyosarcoma at all sites from the SEER database, which included only eight CNS cases (Fig. 3A). The male to female ratio was 1.3 to 1 for both primary CNS rhabdomyosarcoma and rhabdomyosarcoma at all sites. The anatomical distribution of primary CNS rhabdomyosarcoma showed no predilection toward the supratentorial or posterior fossa (Fig. 3B). The histological subtype of primary CNS rhabdomyosarcoma was described in 27 cases, with 19 (70.4%) cases of embryonal, 6 (22.2%) cases of alveolar, and 2 (7.4%) cases of the pleomorphic type. In the SEER database cohort, histological descriptions were found in 3598 cases, with 1883 (52.3%) cases of embryonal, 1100 (30.6%) cases of alveolar, 490 (13.6%) cases of pleomorphic, and 125 (3.5%) cases of the spindle cell type. Molecular characterization of primary CNS rhabdomyosarcoma was described in seven cases, five (three embryonal, two unspecified histology) of which had *DICER1* mutations and two (one embryonal and one alveolar histology) of which had *PAX3-NCOA2* fusions.

To clarify prognostic and predictive factors of survival, we examined age, sex, disease dissemination at diagnosis, treatment, number of treatment modalities, extent of surgical resection, extent of radiation and chemotherapy regimens. The log-rank test revealed that disseminated disease was a poor prognostic factor and that non-GTR and fewer than three treatment modalities were poor predictive factors (Table 1). All 12 long-term survivors (> 24 months) who were treated with trimodal therapy received radiation prior to or concurrently with chemotherapy. The time from surgery to radiation was available in five cases and ranged from one to six weeks with a median of four weeks. Kaplan-Meier curves were generated based on available overall survival data of 64 patients and event-free survival data of 56 patients and showed a 3-

year OS of 29.5% and a 3-year EFS of 26.2% (Fig. 4.). The group that received trimodal treatment yielded better survival outcomes, with a 3-year OS of 57.4% and a 3-year EFS of 46.3%.

Table 1
Prognostic/Predictive Factors of Primary CNS Rhabdomyosarcoma

	OS		EFS	
	N = 64	P value	N = 56	P value
Age (years)		0.50		0.15
15 or younger	39 (60.9%)		35 (62.5%)	
16 or older	25 (39.1%)		21 (37.5%)	
Gender		0.58		0.10
Female	27 (42.2%)		24 (42.9%)	
Male	37 (57.8%)		32 (57.1%)	
Dissemination		0.006		0.01
Localized	56 (87.5%)		48 (85.7%)	
Disseminated	8 (12.5%)		8 (14.3%)	
Treatment		< .001		< .001
Surgery	18 (28.1%)		11(19.6%)	
RT	1 (1.6%)		1 (1.8%)	
Surgery + Chemo	1 (1.6%)		1 (1.8%)	
Surgery + RT	16 (25%)		16 (28.6%)	
Surgery + RT + Chemo	28 (43.8%)		27 (48.2%)	
# of treatment modalities		< .001		< .001
Two or fewer modalities	37 (57.8%)		30 (53.6%)	
Surgery + RT + Chemo	27 (42.2%)		26 (46.4%)	
Surgery		0.03		0.04
GTR	30 (46.9%)		27 (48.2%)	
Non-GTR	34 (53.1%)		29 (51.8%)	
Radiation	(N = 27)	0.85	(N = 27)	0.87
Focal	13 (48.1%)		13 (48.1%)	
Extended field	14 (51.9%)		14 (51.9%)	

OS: overall survival, EFS: event-free survival, RT: radiation therapy, Chemo: chemotherapy, GTR: gross total resection, VAC: vincristine + actinomycin D + cyclophosphamide, P values < 0.05 are in bold.

	OS		EFS	
Chemotherapy	(N = 28)	0.50	(N = 27)	0.24
VAC-based	13 (46.4%)		13 (48.1%)	
Others	15 (53.6%)		14 (51.9%)	
OS: overall survival, EFS: event-free survival, RT: radiation therapy, Chemo: chemotherapy, GTR: gross total resection, VAC: vincristine + actinomycin D + cyclophosphamide, P values < 0.05 are in bold.				

Discussion

Efforts to better understand primary CNS rhabdomyosarcoma have progressed, especially in the advancement of molecular studies. We discovered that our case harbors the *PAX3-NCOA2* fusion, which was also recently described by Jour et al. [12]. *PAX3-NCOA2* and *PAX3-NCOA1* were reported in both embryonal and alveolar rhabdomyosarcoma of non-CNS sites [15, 16]. Although our case harbors wild-type *DICER1*, which was confirmed by whole-exome and Sanger sequencing, *DICER1* mutations have been reported in both primary CNS and non-CNS rhabdomyosarcoma [8–11, 17]. A case of primary CNS rhabdomyosarcoma with NF1 was also reported, and an association between NF1 and non-CNS rhabdomyosarcoma is known [18–20]. We then further revealed the demographic similarities between CNS and non-CNS rhabdomyosarcoma. These findings collectively support the hypothesis that the CNS is a rare location for rhabdomyosarcoma and that this tumor type is not a variation of other CNS tumors. The reason that the commonly observed *PAX3/7-FOXO1* fusion genes have not been reported in CNS cases is still unknown. This might be related to the low incidence of alveolar type histology in reported primary CNS rhabdomyosarcoma cases. Molecular characterization of both CNS and non-CNS rhabdomyosarcoma requires further study [21].

Our meta-review confirmed that the survival outcome of primary CNS rhabdomyosarcoma is generally poor. As increasing evidence shows similarities with non-CNS rhabdomyosarcoma, it is reasonable to refer to existing data of non-CNS rhabdomyosarcoma when formulating treatment for primary CNS rhabdomyosarcoma. VAC chemotherapy or alternating VAC and vincristine plus irinotecan (VI) has been administered for intermediate-risk non-CNS rhabdomyosarcoma with a 4-year event-free survival of approximately 60% [22]. Our analysis did not demonstrate the superiority of VAC over other regimens. Concurrent focal radiation is commonly used for non-CNS rhabdomyosarcoma with some specific exceptions. Locoregional failure is the most common pattern of non-CNS rhabdomyosarcoma progression, and the optimization of the dose and timing of radiation is currently under investigation [23–26]. Based on the analysis of prognostic and predictive factors, a trimodal approach including maximum possible surgical resection, chemotherapy and radiation therapy is predicted to lead to relatively favorable outcomes. Although the data are limited, early introduction of radiation is applied primarily in long-term survivors. Early introduction of radiation therapy after surgery is a common practice in the treatment of CNS tumors and is also reasonable for primary CNS rhabdomyosarcoma.

Despite progress in understanding this rare tumor, some concerns remain and require further investigation. The age of the patient, location, and appearance of the primary CNS rhabdomyosarcoma on MRI can be misleading and clinicians may assume they are other CNS embryonal tumors. Accurate and timely diagnosis is critical in the formulation of a treatment plan, and a second opinion for the review of histopathology specimens in cases of uncertain diagnosis should be considered. Molecular studies have enabled clinicians to make this diagnosis and have decreased its turnaround time, which may aid in correcting the diagnosis. Penetration of the blood-brain barrier by chemotherapy drugs would be questioned if the same treatment as non-CNS rhabdomyosarcoma is applied to CNS tumors. The use of corticosteroids as antiemetics is a common practice in non-CNS sarcoma treatment and is discouraged for CNS tumors due to concerns about decreased drug penetration in the CNS. Given these concerns, it is essential that multidisciplinary specialists, including diagnostic radiologists, pathologists, molecular pathologists, oncologists specializing in sarcomas, and neuro-oncologists, work closely to manage patients with this rare tumor.

Conclusion

Primary CNS rhabdomyosarcoma shares common histological, molecular, and demographic features with non-CNS rhabdomyosarcoma. A trimodal treatment approach with early introduction of radiation therapy may result in favorable survival outcomes.

Declarations

Funding: This research was supported by AMED under Grant Number JP21cm0106509

Conflicts of interest/Competing interests:

The authors have no conflicts of interests to declare that are relevant to the contents of this article.

Availability of data and material:

The datasets generated during and/or analyzed during the current study are available in the Supplemental Table 1.

Code availability:

The software and codes used during the current study is available and shown in the method section.

Authors' contributions:

Conceptualization: Ryuma Tanaka, Kyohei Inoue; Methodology: Ryuma Tanaka, Kyohei Inoue, Yuji Yamada, Masanori Yoshida, Tomoru Miwa, Motohiro Kato; Formal analysis and investigation: Ryuma Tanaka, Yuji Yamada, Masanori Yoshida, Haruko Shima, Jumpei Ito, Hajime Okita; Writing original draft preparation: Ryuma Tanaka, Kyohei Inoue, Masanori Yoshida; Writing review and editing: Ryuma Tanaka,

Haruko Shima, Jumpei Ito, Hajime Okita, Tomoru Miwa, Motohiro Kato, Hiroyuki Shimada; Supervision: Tomoru Miwa, Motohiro Kato, Hiroyuki Shimada

Ethics approval:

The authors confirm that the current study was approved by the appropriate institutional review board and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate:

The authors confirm that patient's and/or parental/legal guardian's consent was obtained for the participation in the study.

Consent for publication

The authors confirm that patient's and/or parental/legal guardian's consent was obtained for publication.

References

1. Koide O (1957) [A case of primary rhabdomyosarcoma of the brain]. *Gan* 48: 645-647
2. Lopes De Faria J (1957) Rhabdomyosarcoma of cerebellum. *AMA archives of pathology* 63: 234-238
3. Bradford R, Crockard HA, Isaacson PG (1985) Primary rhabdomyosarcoma of the central nervous system: case report. *Neurosurgery* 17: 101-104
4. Al-Gahtany M, Shroff M, Bouffet E, Dirks P, Drake J, Humphreys R, Laperriere N, Hawkins C, Rutka J (2003) Primary central nervous system sarcomas in children: clinical, radiological, and pathological features. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery* 19: 808-817 doi:10.1007/s00381-003-0839-5
5. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta neuropathologica* 131: 803-820 doi:10.1007/s00401-016-1545-1
6. Namba K, Aschenbrener C, Nikpour M, VanGilder JC (1979) Primary rhabdomyosarcoma of the tentorium with peculiar angiographic findings. *Surgical neurology* 11: 39-43
7. Lafay-Cousin L, Lindzon G, Taylor MD, Hader W, Hawkins C, Nordal R, Laperriere N, Laughlin S, Bouffet E, Bartels U (2016) Successful treatment of primary intracranial sarcoma with the ICE chemotherapy regimen and focal radiation in children. *Journal of neurosurgery Pediatrics* 17: 298-302 doi:10.3171/2015.6.Peds14709
8. Koelsche C, Mynarek M, Schimpf D, Bertero L, Serrano J, Sahm F, Reuss DE, Hou Y, Baumhoer D, Vokuhl C, Flucke U, Petersen I, Bruck W, Rutkowski S, Zambrano SC, Garcia Leon JL, Diaz Coronado RY, Gessler M, Tirado OM, Mora J, Alonso J, Garcia Del Muro X, Esteller M, Sturm D, Ecker J, Milde T,

- Pfister SM, Korshunov A, Snuderl M, Mechttersheimer G, Schuller U, Jones DTW, von Deimling A (2018) Primary intracranial spindle cell sarcoma with rhabdomyosarcoma-like features share a highly distinct methylation profile and DICER1 mutations. *Acta neuropathologica* 136: 327-337 doi:10.1007/s00401-018-1871-6
9. Sakaguchi M, Nakano Y, Honda-Kitahara M, Kinoshita M, Tanaka S, Oishi M, Noguchi K, Fukuda M, Maeba H, Watanabe T, Hayashi Y, Ikeda H, Minato H, Ichimura K, Nojima T, Nakada M (2019) Two cases of primary supratentorial intracranial rhabdomyosarcoma with DICER1 mutation which may belong to a "spindle cell sarcoma with rhabdomyosarcoma-like feature, DICER1 mutant". *Brain Tumor Pathol* 36: 174-182 doi:10.1007/s10014-019-00352-z
10. de Kock L, Geoffrion D, Rivera B, Wagener R, Sabbaghian N, Bens S, Ellezam B, Bouron-Dal Soglio D, Ordóñez J, Sacharow S, Polo Nieto JF, Guillerman RP, Vujanic GM, Priest JR, Siebert R, Foulkes WD (2018) Multiple DICER1-related tumors in a child with a large interstitial 14q32 deletion. *Genes Chromosomes Cancer* 57: 223-230 doi:10.1002/gcc.22523
11. Das A, Roy P, Modi SK, Achari RB, Sen S, Singh A, Sukumaran R, Bhattacharyya A (2019) Germline DICER1-mutant intracranial sarcoma with dual chondroid and spindle cell morphology and pulmonary metastases treated with multimodal therapy. *Pediatric blood & cancer* 66: e27744 doi:10.1002/pbc.27744
12. Jour G, Serrano J, Koelsche C, Jones DTW, von Deimling A, Allen J, Snuderl M (2019) Primary CNS Alveolar Rhabdomyosarcoma: Importance of Epigenetic and Transcriptomic Assays for Accurate Diagnosis. *Journal of neuropathology and experimental neurology* 78: 1073-1075 doi:10.1093/jnen/nlz083
13. Seki M, Yoshida K, Shiraishi Y, Shimamura T, Sato Y, Nishimura R, Okuno Y, Chiba K, Tanaka H, Kato K, Kato M, Hanada R, Nomura Y, Park MJ, Ishida T, Oka A, Igarashi T, Miyano S, Hayashi Y, Ogawa S, Takita J (2014) Biallelic DICER1 mutations in sporadic pleuropulmonary blastoma. *Cancer Res* 74: 2742-2749 doi:10.1158/0008-5472.Can-13-2470
14. Yoshida K, Miwa T, Akiyama T, Nishimoto M, Kamamoto D, Yoshida K (2018) Primary Intracranial Rhabdomyosarcoma in the Cerebellopontine Angle Resected After Preoperative Embolization. *World neurosurgery* 116: 110-115 doi:10.1016/j.wneu.2018.05.054
15. Sumegi J, Streblow R, Frayer RW, Dal Cin P, Rosenberg A, Meloni-Ehrig A, Bridge JA (2010) Recurrent t(2;2) and t(2;8) translocations in rhabdomyosarcoma without the canonical PAX-FOXO1 fuse PAX3 to members of the nuclear receptor transcriptional coactivator family. *Genes Chromosomes Cancer* 49: 224-236 doi:10.1002/gcc.20731
16. Yoshida H, Miyachi M, Sakamoto K, Ouchi K, Yagyu S, Kikuchi K, Kuwahara Y, Tsuchiya K, Imamura T, Iehara T, Kakazu N, Hojo H, Hosoi H (2014) PAX3-NCOA2 fusion gene has a dual role in promoting the proliferation and inhibiting the myogenic differentiation of rhabdomyosarcoma cells. *Oncogene* 33: 5601-5608 doi:10.1038/onc.2013.491
17. de Kock L, Yoon JY, Apellaniz-Ruiz M, Pelletier D, McCluggage WG, Stewart CJR, Dickson BC, Rouzbahman M, Clarke BA, Foulkes WD (2020) Significantly greater prevalence of DICER1 alterations

- in uterine embryonal rhabdomyosarcoma compared to adenosarcoma. *Mod Pathol* 33: 1207-1219 doi:10.1038/s41379-019-0436-0
18. de Leeuw CN, Prayson RA (2019) Primary intracranial rhabdomyosarcoma in an NF1 patient. *Clinical neuropathology* 38: 84-86 doi:10.5414/np301133
 19. Li H, Sisoudiya SD, Martin-Giacalone BA, Khayat MM, Dugan-Perez S, Marquez-Do DA, Scheurer ME, Muzny D, Boerwinkle E, Gibbs RA, Chi YY, Barkauskas DA, Lo T, Hall D, Stewart DR, Schiffman JD, Skapek SX, Hawkins DS, Plon SE, Sabo A, Lupo PJ (2020) Germline Cancer-Predisposition Variants in Pediatric Rhabdomyosarcoma: A Report from the Children's Oncology Group. *J Natl Cancer Inst* doi:10.1093/jnci/djaa204
 20. Sung L, Anderson JR, Arndt C, Raney RB, Meyer WH, Pappo AS (2004) Neurofibromatosis in children with Rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma study IV. *J Pediatr* 144: 666-668 doi:10.1016/j.jpeds.2004.02.026
 21. Leiner J, Le Loarer F (2020) The current landscape of rhabdomyosarcomas: an update. *Virchows Arch* 476: 97-108 doi:10.1007/s00428-019-02676-9
 22. Hawkins DS, Chi YY, Anderson JR, Tian J, Arndt CAS, Bomgaars L, Donaldson SS, Hayes-Jordan A, Mascarenhas L, McCarville MB, McCune JS, McCowage G, Million L, Morris CD, Parham DM, Rodeberg DA, Rudzinski ER, Shnorhavorian M, Spunt SL, Skapek SX, Teot LA, Wolden S, Yock TI, Meyer WH (2018) Addition of Vincristine and Irinotecan to Vincristine, Dactinomycin, and Cyclophosphamide Does Not Improve Outcome for Intermediate-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 36: 2770-2777 doi:10.1200/jco.2018.77.9694
 23. Spalding AC, Hawkins DS, Donaldson SS, Anderson JR, Lyden E, Laurie F, Wolden SL, Arndt CA, Michalski JM (2013) The effect of radiation timing on patients with high-risk features of parameningeal rhabdomyosarcoma: an analysis of IRS-IV and D9803. *Int J Radiat Oncol Biol Phys* 87: 512-516 doi:10.1016/j.ijrobp.2013.07.003
 24. Casey DL, Chi YY, Donaldson SS, Hawkins DS, Tian J, Arndt CA, Rodeberg DA, Routh JC, Lautz TB, Gupta AA, Yock TI, Wolden SL (2019) Increased local failure for patients with intermediate-risk rhabdomyosarcoma on ARST0531: A report from the Children's Oncology Group. *Cancer* 125: 3242-3248 doi:10.1002/cncr.32204
 25. Ludmir EB, Grosshans DR, McAleer MF, McGovern SL, Harrison DJ, Okcu MF, Chintagumpala MM, Mahajan A, Paulino AC (2019) Patterns of failure following proton beam therapy for head and neck rhabdomyosarcoma. *Radiother Oncol* 134: 143-150 doi:10.1016/j.radonc.2019.02.002
 26. Bradley JA, Indelicato DJ, Uezono H, Morris CG, Sandler E, de Soto H, Mailhot Vega RB, Rotondo R (2020) Patterns of Failure in Parameningeal Alveolar Rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys* 107: 325-333 doi:10.1016/j.ijrobp.2020.01.035

Figures

Figure 1

Case of primary CNS Rhabdomyosarcoma with PAX3-NCOA2 fusion (A) MRI revealed a left cerebellopontine angle tumor with a low T1 signal and heterogeneous weak contrast enhancement. Histopathological review of the tumor revealed (B) Small round cell tumor (C) Spindle-shaped cells (D) Desmin(+), (E) MyoD1(+) (F) Ki-67 index of 70% and FKHR translocation-negative. (G) Sanger sequencing verified the presence of PAX3-NCOA2 fusion.

Figure 2

PRISMA flow chart PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of the primary CNS rhabdomyosarcoma meta-review.

Figure 3

Demographics of primary CNS rhabdomyosarcoma vs. all rhabdomyosarcoma (A) Age distribution of patients with primary CNS rhabdomyosarcoma showed similarities with age distribution of patients with rhabdomyosarcoma at all sites in a large cohort from the SEER database. (B) Sites of primary CNS rhabdomyosarcoma were distributed across the CNS without predilection for a specific location. The number of cases at each site are indicated in parentheses.

Figure 4

Kaplan-Meier Survival Prediction of Patients with Primary CNS Rhabdomyosarcoma (A) Kaplan-Meier curves for overall survival and event-free survival are plotted. (B) The overall survival curve was stratified by the surgery + radiation + chemotherapy group (red solid line) and the fewer than three modalities group (blue dashed line). (C) Event-free survival curves were stratified by the surgery + radiation + chemotherapy group (red solid line) and the fewer than three modalities group (blue dashed line).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [FinalCNSRhdbdomyosarcomaSupplementalTable.docx](#)