Article

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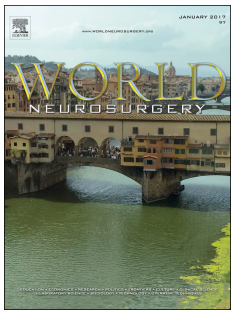

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The impact of surgical resection and adjuvant therapy on survival in paediatric patients with Atypical Teratoid Rhabdoid Tumour: Systematic review and pooled survival analysis

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Abstract

Background: Atypical teratoid/rhabdoid tumours (AT/RT) is a rare malignant neoplasm in the paediatric population. AT/RT is characterised by rhabdoid cells combined with the loss of either the INI1 or BRG1 protein from the tumour cells.

Objective: Our aim is to systematically review and analyse patient and tumour characteristics, prognosis, and impact of treatment on survival in paediatric patients with AT/RT confirmed by alterations in INI1 or BRG1. This systematic review is the first only to include paediatric cases of AT/RT confirmed with either INI1 or BRG1 alterations.

Methods: MEDLINE (Ovid) was searched using the terms "atypical teratoid/rhabdoid tumour" AND "paediatric/pediatric". Cases were included if confirmed by loss of INI1 or BRG1. The extracted dataset was analysed using descriptive statistics, log-rank test, and Kaplan-Meier survival analysis via SPSS.

Results: A total of 38 articles were included in this study. The average age at diagnosis was three years. The most common locations reported is the supratentorial region and cerebral hemispheres. Ninety-three patients were reported to show evidence of dissemination. The average overall survival was 29 months. A significant difference in survival was noted between the tumour location groups, particularly worst outcomes for patients with spinal AT/RT ($p = <0.001$), but not statistically significant differences in adjuvant therapy groups ($p = 0.581$) and the extent of surgical resection groups ($p = 0.262$).

Conclusion: Atypical teratoid rhabdoid tumour of the central nervous system in paediatric populations is a rare neoplasm associated with a poor prognosis in most patients.

Keywords: Atypical teratoid rhabdoid tumour, rhabdoid tumour, Paediatric, systematic review, CNS tumour, brain tumour

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Conclusion: AT/RT of the central nervous system in paediatric populations is a rare neoplasm associated with a poor prognosis in most patients. Future studies should be directed to find a standardised treatment protocol.

Keywords: Atypical Teratoid/Rhabdoid Tumour, Paediatric, Systematic review, Survival analysis

Introduction

Central Nervous System (CNS) Atypical Teratoid/Rhabdoid Tumour (AT/RT) is a rare and clinically aggressive tumour that most often affects children aged three years and younger but can occur in older children and adults.[1,2] CNS AT/RT is a histologically heterogeneous neoplasm characterised by scattered rhabdoid cells and large epithelioid cells accompanied by primitive neuroectodermal cells and mesenchymal and/or glial cells.[1] AT/RT is part of a more prominent family of rhabdoid tumours. In this review, the term AT/RT refers to CNS tumours only, and the term rhabdoid tumour reflects the possibility of both CNS and non-CNS tumours. Unless expressly noted in the text, this systematic exclusively refers to CNS AT/RT.

In paediatric patients, approximately one-half of AT/RTs arise in the Posterior Cranial Fossa (PCF).[3] AT/RT is associated with somatic and germline of SMARCB1 and SMARCA4, which are tumour suppressor genes that code for the proteins INI1 and BRG1, respectively.[4] Thus, the 2021 WHO classification of CNS tumours highlights that a neuropathological examination is not sufficient for diagnosis, and a genetic examination is mandatory for confirmation. There is no current standard treatment for paediatric AT/RT patients. Multimodality treatment consisting of surgery, chemotherapy, and radiation therapy is under evaluation by clinical trials. Recent data from AT/Rt registry suggests that up to 30% of patients present with disseminated disease.[5-7] Dissemination likely occurs through the leptomeningeal pathway, affecting various locations of the CNS and even extra-CNS organs. Therefore, it is not surprising that almost 35% are prone to synchronous and multifocal tumours.[8-11] The prognostic factors affecting the survival of patients with AT/RT remain unclear. Most published data on outcomes of patients with AT/RT are from small series and are retrospective. Initial retrospective studies reported an average survival from diagnosis of only about 12 months.[12-16] In a retrospective report, 2-year overall survival (OS) was better for patients who underwent a gross total resection (GTR) than those who had a subtotal resection (STR). However, in this study, the effect of radiation therapy on survival was less clear.[15] There are reports of long-term survivors.[17] Notably, improved survival has been reported for those who received intensive multimodality therapy.[6,10]

Given the limited number and dispersal of AT/RT cases in multiple case reports and case series, patient and tumour characteristics, overall prognosis, and impact of extent of resection and adjuvant therapy remain unclear. In addition, previously published systematic reviews and meta-analyses have included tumours without a genetic confirmation with INI1 or BRG1 alterations, resulting in an analysis of a heterogeneous population that may contain tumours that are not molecularly defined as AT/RT. This systematic review analysed patient and tumour characteristics, prognosis, and impact of treatment on prognosis in paediatric patients with AT/RT. The primary objective of this study was to pool-analysis all paediatric cases of AT/RT confirmed by alterations in INI1 or BRG1. This review is the first to only include paediatric cases of AT/RT confirmed with either INI1 or BRG1 alterations. The secondary objective of our study was to examine predictive factors for survival. Our primary hypothesis was that the extent of survival would be influenced by age, gender, the extent of surgical resection, adjuvant therapy, and tumour location.

Methods

This systematic review is reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our protocol was developed, registered, and published via the International prospective register of systematic reviews (PROSPERO) registration number: CRD42022300996.[18]

Research question

In patients with genetically confirmed AT/RT, what are the patient and tumour characteristics and how does age, gender, tumour location, the extent of resection, and adjuvant therapy impact survival outcomes?

Inclusion criteria

Articles that included paediatric AT/RT cases were included if the diagnosis was confirmed by alterations of either SMARCB1/SMARCA4 or INI1/BRG1. Studies published before the new update of the WHO 2021 Classification CNS tumours were included if they confirmed their diagnosis with the former-mentioned criteria.

Search strategy

We conducted a systematic review using MEDLINE (Ovid). We filtered results to studies published in English exclusively. We reviewed all articles published before December 2021. Search terms included "Atypical teratoid rhabdoid tumour" and "paediatric." Relevant articles' references were used to supplement the scope of our search. The supplementary material contains the adopted search strategy (Table A1).

Study selection

All the articles were exported into Rayyan, a professional research software widely used by collaborators for ease of study selection decisions.[19] Firstly, a minimum of two reviewers independently screened the titles and abstracts of the identified articles against the population, intervention, comparison, outcome, setting, and study design (PICOS) criteria defined in the protocol. Any disagreement between the reviewers' decisions prompted further discussion. If a disagreement persisted, a third reviewer resolved the conflict. The full texts of the remaining articles were also retrieved and screened independently by a minimum of two reviewers.

Data extraction

Data extraction was performed in two stages, a pilot stage, and a proper stage. The pilot stage consisted of having multiple authors, each going through the same ten selected articles to extract data. This strategy was adopted to ensure that all participant authors could extract data accurately to ensure homogeneity in the data reporting and ensure the data collection sheet captured all relevant and essential information from the included studies.

Studies that met our inclusion criteria were read in full-text, and the following data were extracted, summarised, and tabulated in an Excel proforma sheet: title, year of publication, name of the first author, study design, study location, population size, participants characteristics

(including sex, mean age, and age range), neuropathological diagnosis, intervention, and outcomes of care including follow-up durations, numbers of deaths reported and survival outcomes.

Data analysis

We collected patient demographics, tumour characteristics, survival, and treatment data. The data was analysed using SPSS v.26 (IBM, USA) for descriptive statistics and to deploy a log-rank test, assessing for differences in outcomes between GTR, STR, PR, and biopsy. Log-rank test was also used to assess for differences in outcomes between those that received radiotherapy (RT), chemotherapy, immunotherapy, RT and chemotherapy, chemotherapy and proton therapy, and chemotherapy and immunotherapy. Kaplan-Meier curves were used to estimate the survival function.

A multivariate linear regression was performed to assess and predict survival (months) from the explanatory variables: tumour location, dissemination, extent of resection, and adjuvant therapy.. Linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. independence of residuals was assessed by a Durbin-Watson statistic. Homoscedasticity was assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. Multicollinearity was assessed by tolerance values greater than 0.1. Studentized deleted residuals were assed for values greater than ±3 standard deviations, or leverage values greater than 0.2, and values for Cook's distance above 1. The assumption of normality was assessed by a Q-Q Plot. Regression coefficients and standard errors were tabulated. A p-value ≤ 0.05 was considered statistically significant. Patients with missing data for the variables were excluded from the analysis.

Results

A total of 237 results were found from the MEDLINE search (figure 1). Of the 237 results, 184 articles were deemed irrelevant to this study during the title/abstract screening stage. 38 articles were deemed eligible after matching our eligibility criteria. Articles were exuded during full-text screening for reasons including adult populations, wrong outcomes, or articles that included AT/RT cases with no confirmed diagnosis per the new WHO definition.

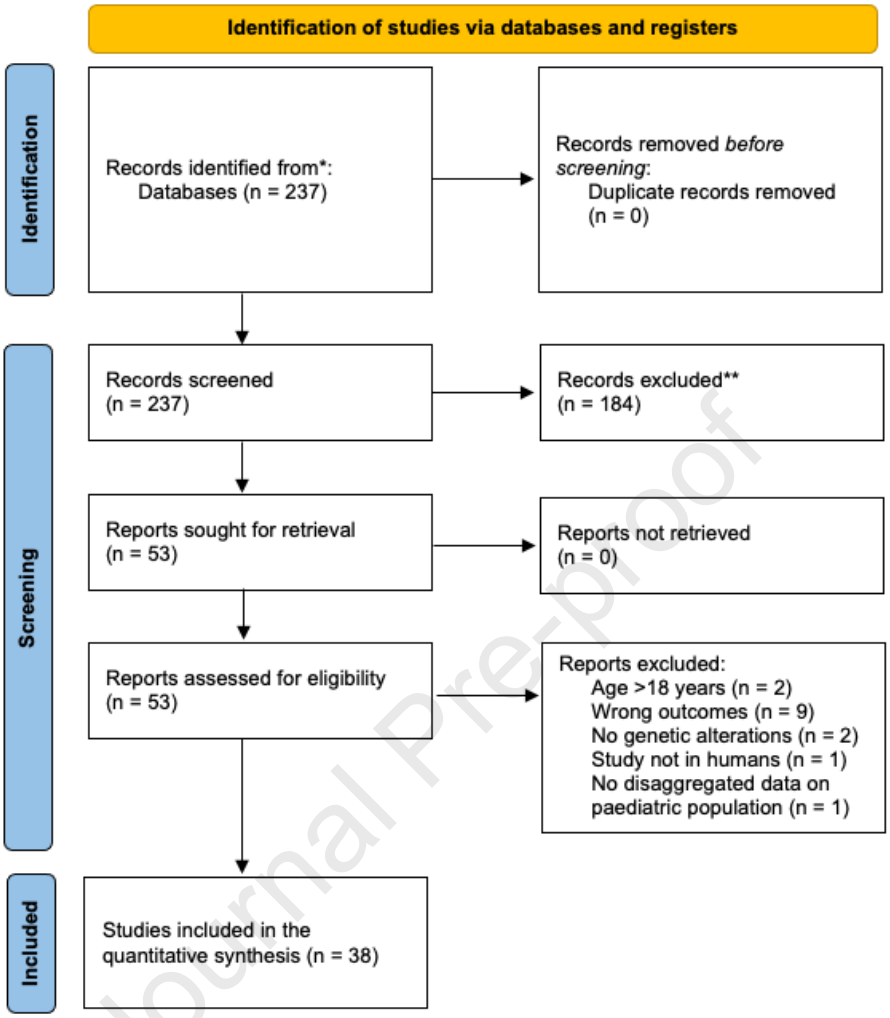

Figure 1. PRISMA diagram

Our systematic review found 165 paediatric patients diagnosed with AT/RT from the 39 articles included in this study (Table 1). Supplementary Table A2 includes all the patients included in the pooled analysis (1, 2, 4–9, 11–42). Of the 165 patients, the average age was 2.49 (± 2.94) years, ranging from 0.01 to 15.54 years. Of the 165 patients, 70 (40.7%) were females, 75 (43.6%) were males, and 27 (15.7%) were not identified.

Table 1

Patient and tumour characteristics from the included studies.

PATIENT	
Mean age at diagnosis – year (SD)	2.49 (2.94)
Female gender – no. (%)	70 (40.7%)
TUMOR	
Location – no. (%)	
Supratentorial	72 (41.9%)

Infratentorial	84 (48.8%)
Spine	9 (6%)
Unspecified	7 (4.1%)
Dissemination – no. (%)	16 (9.3%)
TREATMENT	
Surgery – no. (%)	
GTR	71 (24%)
STR	47 (42%)
PR	5 (2.9%)
Biopsy	8 (4.7%)
No surgical intervention	25 (14.5%)
Unspecified	16 (9.3%)
Adjuvant therapy – no. (%)	
Chemotherapy, PT	15 (8.7%)
Chemotherapy only	29 (16.9%)
Chemotherapy, RT	72 (41.9%)
Chemotherapy, Immunotherapy	3 (1.7%)
Immunotherapy only	3 (1.7)
RT, Immunotherapy	1 (0.6%)
RT	2 (1.2%)
No adjuvant therapy	40 (23.3%)
Unspecified	7 (4.1%)
PROGNOSIS	
Alive at follow-up – no. (%)	72 (41.9%)
Mean follow-up – years (SD, Range)	3.74 (3.5, 0.08–15.54)
Death – no. (%)	93 (54.1%)
Mean time-to-death – years (SD, Range)	0.85 (1.26, 0.01–8.84)
Unspecified – no. (%)	7 (4.1%)

GTR-gross-total resection; STR-subtotal resection; PR-partial resection; PT-proton therapy; RT-radiotherapy

Only 9 (6%) of the tumours were in the spinal cord, while the remaining 156 (94%) were split between supratentorial and infratentorial locations. The most common location was the infratentorial region (n = 84, 48.8%), followed by supratentorial region (n = 72, 41.9%). Only 7 patients did not have their tumour location reported (n = 7, 4.1%) (figure 2). Over the entire course of the disease, 16 (9.3%) patients were known to have experienced disseminated AT/RT.

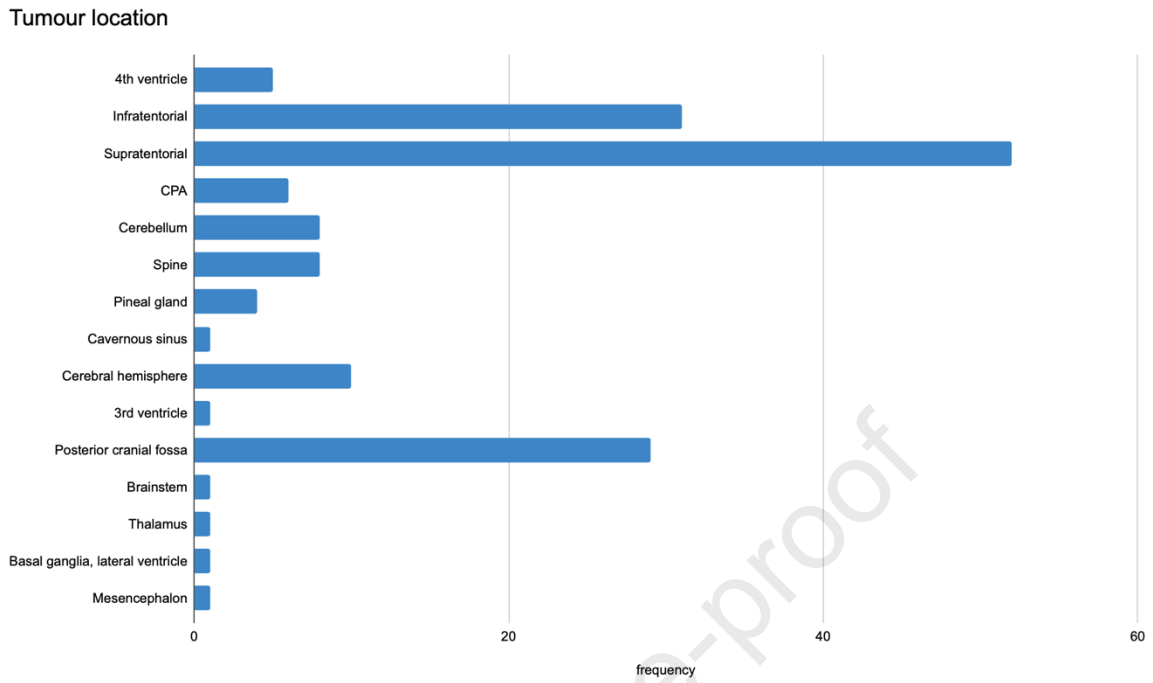

Figure 2. AT/RT tumour locations for the included cases.

Tumour location was a statistically significant factor on the log-rank test (Chi-square = 9.471, p = 0.009), demonstrating a significantly low survival rate for spinal tumours, compared to supratentorial and infratentorial tumours. The Kaplan-Meier curve is shown in figure 3.

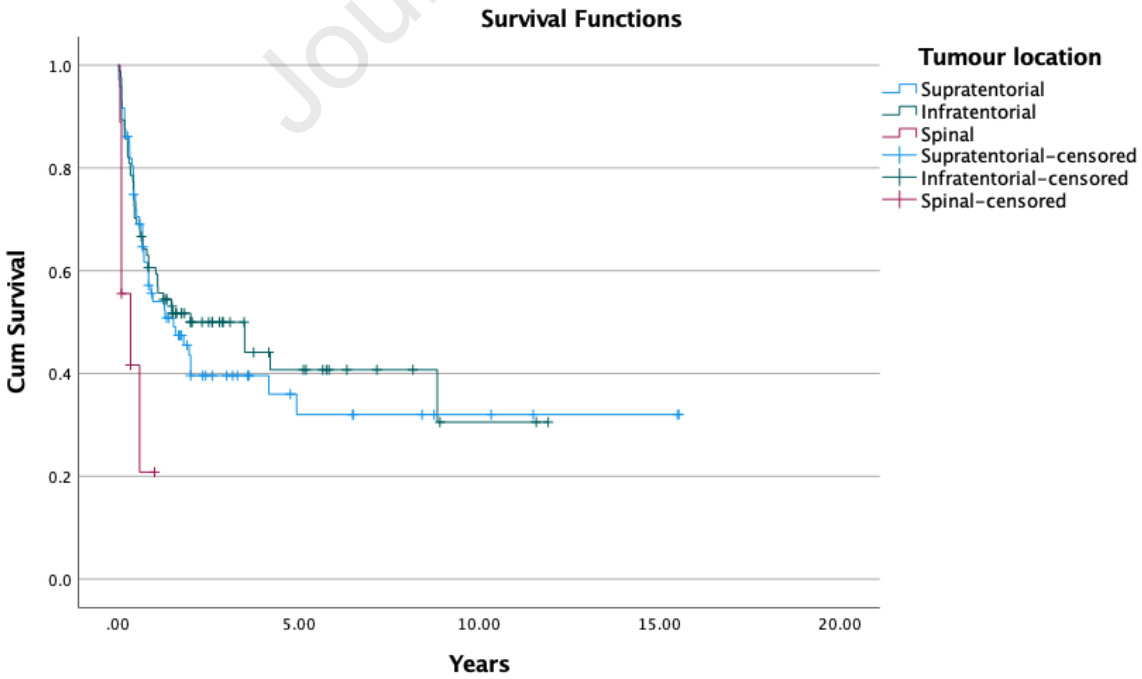

Figure 3. Kaplan-Meier curve for the tumour location.

Of the 165 cases, 71 (24%) had a GTR, 47 (42%) had STR, 5 (2.9%) had a PR, and 8 (4.7%) had a biopsy. The extent of resection was not reported in 16 cases, and 25 cases did not have any surgical interventions. This is a consequence of metastatic/disseminated disease where the intracranial/spinal tumours were inoperable. GTR was defined as 100% tumour resection with a concurrent absence of any visible residual tumour in the immediate postoperative MRI or CT scan. Most studies defined STR as >90% tumour resection. PR was defined as <50% tumour resection.

With regards to adjuvant therapy, 72 (41.9%) received combined radiotherapy and chemotherapy, 2 (1.2%) received radiotherapy only, 29 (16.9%) received chemotherapy only, 3 (1.7%) received immunotherapy only, 3 (1.7%) received combined chemotherapy and immunotherapy, and 1 (0.6%) received combined radio and immunotherapy. 40 (23%) cases did not receive adjuvant therapy, and 7 cases were unknown if any adjuvant therapy was administered.

Of the 165 patients, 93 (54.1%) had succumbed to their disease with an average time to death of 0.85 ± 1.26 years (range 0.01 – 8.84 years). 72 (41.9%) were alive at last follow-up with a mean follow-up of 3.74 ± 3.5 years (range 0.08 – 15.54 years). 2 patients experienced recurrent disease, after 1 month (n = 1) and 1 year (n = 1). 65 cases had no recurrence at follow-up, with follow-up ranging from 0.005 to 15.54 years.

Of the 71 that had a gross total resection, 35 (21.2%) had passed away an average time to death of 1.12 years after surgery. 47 (42%) patients had a subtotal resection, and 12 (57%) had passed away with time to death ranging from postoperative to 2.5 years after surgery. The 1 patient that had a biopsy died 2.1 years after diagnosis. When comparing those that received gross total resection, subtotal resection, Partial resection, biopsy, and no surgical intervention, there was a significant difference on the log-rank test (Chi-square = 10.107, p = 0.018), demonstrating a significant survival advantage with GTR compared to another extent of resections. The Kaplan-Meier curve is shown in Figure 4.

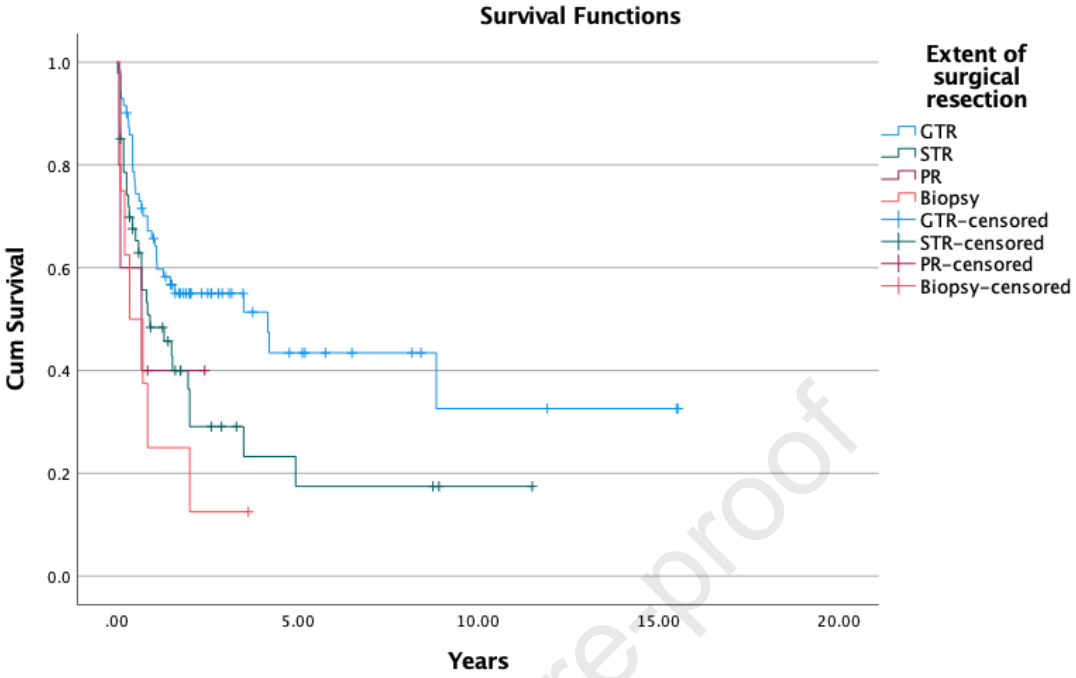

Figure 4. Kaplan-Meier curve for the extent of resection. GTR=gross-total resection, STR=subtotal resection, PR=partial resection.

Of the 28 patients that received combined radiotherapy and chemotherapy, 15 were alive at follow-up, ranging from 6 months to 17 years. Time to death for the remaining 13 of these 28 ranged from 3 months to 3 years after diagnosis. There were no patients alive at follow-up in the radiotherapy only, chemotherapy only, stereotactic radiosurgery only, and no adjuvant therapy groups. The 8 patients treated with radiotherapy died 2 weeks to 14 years after diagnosis. The 1 patient who received chemotherapy died 10 years after diagnosis. The two patients treated with stereotactic radiosurgery died 23 and 27 months after diagnosis. Of the 4 patients who did not receive adjuvant therapy, time to death ranged from the immediate postoperative period to 3 months after surgery. When comparing those that received radiotherapy and chemotherapy, radiotherapy only, and no adjuvant therapy, there was a significant difference in survival (Chi-square = 20.38, p = < 0.0001). Patients that received radiotherapy and chemotherapy had a significant increase in survival when compared with patients that received radiotherapy alone (Chi-square = 11.42, p = 0.0007) and patients that did not receive adjuvant therapy (Chi-square = 25.71, p = < 0.0001). There was no significant difference between The Kaplan-Meier curve, as shown in Figure 5. Gender was a statistically insignificant factor for survival (Chi-square = 2.378, p = 0.305). Table 2 collates the different chemotherapy and radiotherapy utilised in the eligible study.

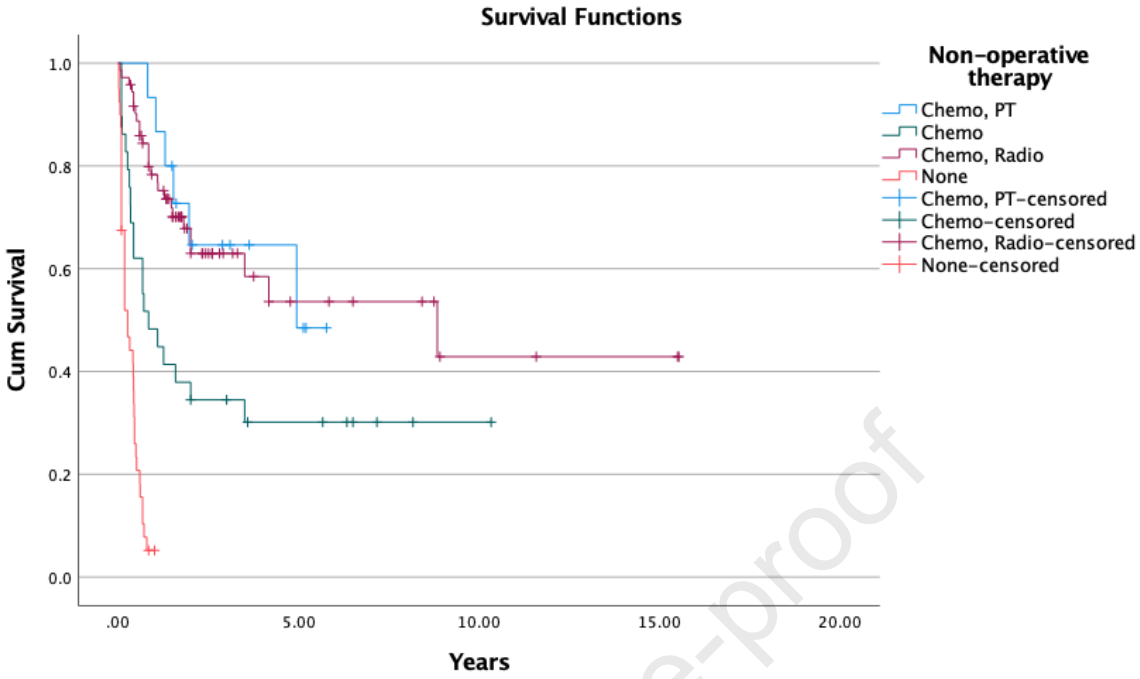

Figure 5. Kaplan-Meier curve for adjuvant therapy. Chemo, PT= chemotherapy and proton therapy; Chemo=chemotherapy; Chemo, Radio=chemotherapy and radiotherapy.

Predicting survival through multivariate regression analysis

A multiple regression was run to predict survival from tumour location, dissemination, extent of surgical resection and adjuvant therapy. The multiple regression model statistically significantly predicted survival (months), F(4, 29) = 3.539, p < 0.018, adj. R2 = 0.235. Dissemination and adjuvant therapy weighed the most statistical significance to the prediction, $p < 0.05$. Regression coefficients and standard errors can be found in Table 3.

Table 3.
Multiple regression analysis for survival

Survival	B	95% CI for B		SE B	ß	R^2	adj R^2
		LL	UL				
Model						0.328	0.235
Constant	65.526*	35.057	95.994	14.897			
Tumour location	-4.420	-19.083	10.242	7.169	-0.102		
Dissemination	-24.374**	-44.819	-3.929	9.996	-0.406**		
Resection	-5.512	-15.949	4.926	5.103	-0.172		
Adjuvant therapy	-4.424**	-8.747	-0.101	2.114	-0.359**		

Note: Model = "Enter" method in SPSS statistics; B = unstandardised regression coefficient; CI= confidence interval; LL = lower limit; UL; upper limit; SE B= standard error of the coefficient; ß = standardised coefficient; R^2 = coefficient of determination; adj R^2 = adjusted R^2
*$p < 0.01$. **$p < 0.05$

Table 2.
Chemotherapy and radiotherapy regimens, doses and respective survival outcomes as reported by the eligible studies.

Author year	Type of study	n	Median age (months)	Chemotherapy (route)	Radiotherapy	Survival outcomes
Weber 2016	Retrospective study	15	18.9	Pilot Protocol ATR EU-RHAB Protocol 2007 or 2010 (Intraventricular and intravenous) American DFC ATRT Protocol	Pencil beam scanning proton therapy	2-year overall- and progression-free survival was 64.6 and 66.0 %
DiPatri Jr 2015	Retrospective study	8	5.5	Modified Baby-POG: VCR, CDDP, cytoxan, and MTX. Modified IRS-III – VCR, dactinomycin, CTX, CDDP, doxorubicin, TMZ and MTX, cytarabine, and hydrocortisone. ACNS0333 regimen with VCR, MTX, VP, CTX, and CDDP. Intravenous (intrathecal – MTX only)	Focal radiation therapy (RT) using intensity-modulated delivery Dose: 5400 cGy fractions	Median OS 5 months (range 1 to 107 months)
Inoue 2014	Case report	1	18	IRS-III Protocol – Anthracycline-based chemotherapy (Intrathecal)	Cranial X-ray irradiation. 54 Gy in 1.8 Gy fractions using intensity-modified delivery	AWD at 29 months
Bush 2014	Case report	1	13	VCR, CTX, CDDP, VP, and high-dose MTX, followed by consolidation with high-dose CARBO/THIO and autologous stem cell rescue	At the completion of chemotherapy, the residual disease was not amenable to surgical resection and the child proceeded to cranial-spinal proton beam radiation.	DOD after 10 months
Han 2012	Case report	1	108	CDDP and CTX	Whole brain by Intensity-modulated radiation therapy, IMRT. Dose: 43Gy/24Fx+12.5Gy/5Fx. Spine by Intensity-modulated radiation therapy, IMRT. Dose: 18Gy/10Fx+18Gy/10Fx	DOD after 12 months
Park 2012	Clinical trial – Phase I/II	6	11.5	Pre-HDCT: Alternating CECV and CEIV x6 cycles HDCT: CARBO/THIO/VP then CTX/MELPH	Salvage after relapse/progression – radiotherapy. CSI/boost after HDCT	5 patients alive 16–70 months. 1 patient DOD 15 months
Bruggers 2012	Retrospective review	20	8.9	Induction A (n = 16) VCR/CDDP/CTX/VP. Induction B (n = 12) VCR/CDDP/IFOS/VP. Maintenance VCR/CDDP/CTX/VP. 6x maintenance chemotherapy CTX/ CDDP /VCR)	Radiation therapy doses and field designs varied among patients, depending on the age of the patient at the time of diagnosis, tumor site, specific study, and curative versus palliative intent.	Median survival 8 months
Heuer 2010	Case report	1	84	Boston AT/RT CNS clinical trial guidelines. intrathecal chemotherapy as well as systemic courses of VCR/doxorubicin and ultimately AD/CTX and additional courses of TMZ and AD. (Intrathecal and Intravenous)	Two months after surgery he received involved-field radiation over a 6-week period. 5400 Gy.	DOD after 42 months
Nicolaides 2010	Retrospective study	6	24	Pre-HDCT: MTX,CTX,VP,CDDP, VCR (HSII) HDCT: MTX,CTX,VP,CDDP, VCR (HSII), or T-IT, CDDP, VP, VCR, AD, IFOS, CTX, or MTX, CTX, VP, CDDP, VCR, IT-ARAC	Focal or none	PFS & OS 10 months (range 1–98 months)
Chi 2009	Clinical trial – Phase II	20	26	Modified IRS-III – Anthracycline-based induction chemotherapy regimen (Intraventricular)	54 Gy focal (n = 11) 36 Gy CSI + boost (n = 4) -	2-year PFS 53 ± 13% 2-year OS 70± 10%
Fidani 2009	Clinical trial	8	39	Pre-HDCT: ICE x2, CECAT x2 HDCT: VP/THIO/CTX	Received whole brain radiotherapy treatment 9-10 months after diagnosis	Median OS- 10
Gidwani 2008	Case report	1	4	Received five cycles of chemotherapy including CDDP, VCR, CTX, VP and high-dose MTX as per Headstart II protocol	initial dose of 45Gy with a boost to 55-60 Gy Not recived due to age tumor location and volume -	DFS 24 months

Janson 2006	Case series	2	20	4 pre-radiation cycles of VCR, dexrazoxane, doxorubicin, CTX, VP, and CDDP (intrathecal)	upfront 11 Gy Gamma Knife boost to a 2.6 cc residual radiographic mass in the right cerebellar peduncle 54 Gy/30 fractions/47 days posterior fossa radiotherapy	PFS
Abu Arja 2018	Case report	1	0.25	consisted of eight, 21-day cycles incorporating VCR, CDDP, doxorubicin, CTX, and triple intrathecal chemotherapy (MTX, hydrocortisone, and cytarabine). (Intraventricular and/or triple intrathecal)	Focal radiotherapy	PFS 17
Johann 2017	Observational study	10	20	CDDP, VP, CTX and VCR) followed by three cycles of high-dose chemotherapy: CARBO, THIO	54Gy	OS 53
Lee 2017	Observational study	9	32	High-dose chemotherapy	Radiotherapy	2-year OS: 62.2%. 2-year EFS: 46.7%
Byers 2017	Case report	1	12	Induction of 2 cycles: VCR, MTX, VP, CTX and CDDP.	adjunct proton beam radiation 45.92Gy/28 fractions/ 30 days	OS 18
Wang 2016	Observational study	22	24	VCR/Bevacizumab; TMZ; Ifosfamide/ Bevacizumab/ Docetaxel	Radiation therapy 30.6–39.6 Gy CSI/18–54 Gy focal or cranial	OS & EFS 17
Van Gool 2016	Clinical trial	7	31.5	Multi-drug chemotherapy, high-dose chemotherapy (Intrathecal)	Irradiation 60 Gy	OS 56.04
Tekautz et al. (2005)	Observational study		22 <3 years (12). 9 patients ≥3 years (3.9 years)	Multiple regimens	<3 years 2 local, 1 CSI + boost ≥3 years 7 patients CSI + boost	<3 years 2-year EFS 11 ± 6% 2-year OS 17 ± 8% . ≥3 years 2-year EFS 78 ± 14% 2-year OS 89 ± 11%
Lafay-Cousin et al. (2012)	Clinical trial – Phase II	50	16.7	MTX, CDDP, CPM, VCR, VP, (CB, THIO) x 3 CDDP, CPM, VCR, VP16, (CB, THIO) x 3 CDDP, CPM, VCR, VP, (CB, THIO) x 3 Systemic or triple intrathecal: aracytine, hydrocortisone, MTX	45 Gy cranial/780 focal, or 36 Gy CSI/18 Gy focal boost, or 36 Gy CSI/18 Gy focal boost	2-year OS 36.4 ± 7.7%

AD, actinomycin D; AWD, alive with disease; CARBO, carboplatin; CDDP, cisplatin; CECAT, cyclophosphamide, etoposide, carboplatin, thiotepa; CECV, cisplatin, etoposide, cyclophosphamide, vincristine; CEIV, carboplatin, etoposide, ifosfamide, vincristine; CR, complete response; CSI, craniospinal radiation; CTX, cyclophosphamide; DOD, died of disease; HDCT, high-dose chemotherapy; ICE, ifosfamide, carboplatin, etoposide; IFOS, ifosfamide; IT-ARAC, intrathecal cytosine arabinoside; MTX, methotrexate; THIO, thiotepa; T-IT, triple intrathecal chemotherapy; TVD, topotecan, vincristine, doxorubicin; VCR, vincristine; VP, etoposide; Temozolomide, TMZ.

Quality assessment: Risk of bias and critical appraisal

The studies included in this systematic review were case reports and case series. The risk of bias could not be assessed using the Cochrane Collaboration's tool for assessing the risk of bias. The JBI Critical Appraisal Checklist for Case Reports appraised the included case reports and case series. No concerns were noted over the quality of the included case reports and case series, though limitations to our conclusions are noted. On analysis, case reports and case series on paediatric AT/RT were prime examples of the importance of this type of study to derive hypothesis-generating research.

Discussion

Summary of the main findings

Following the 2021 WHO Classification of Tumours of the CNS, and with a particular focus on AT/RT, we included only cases with a confirmed neuropathological diagnosis with loss of function mutations of either INI1 or BRG1. Our systematic review has shown that the overall survival of paediatric AT/RT was 29 months. Additionally, factors such as supratentorial location, GTR, dissemination and chemo-radiotherapy are statistically significant to improve survival.

Tumour location and dissemination

A study conducted by Rao et al. found the most common location for the tumour in the infratentorial region (61.8%),[20] similar to our review, which found 48.8% of the reviewed cases in the infratentorial region. Paediatric AT/RTs have been found in males predominantly [20–22] in contrast to the prevalence of AT/RTs in adults that have reported higher rates in females.[23] While our study did find a slightly higher prevalence in males (43.6%) compared to females (40.7%), there was a significant number of patients (15.7%) that were unidentifiable. Recently gene-expression profiles and DNA methylation divided ATRT into three epigenetic subgroups (ATRT-MYC, ATRT-SHH, ATRT-TYR), each with distinct clinical features.[24] A study found that the subgroup ATRT-TYR were more common in the infratentorial region while ATRT-MYC mainly occurred in the supratentorial region, with ATRT-SHH occurring equally in both regions.[25] However, no study has been conducted on how the various subgroups affect the mortality rate in either adult or paediatric patients.

ATRT is known to spread through the subarachnoid space and can disseminate to various regions.[26] In our study, 16 patients were reported to show signs of dissemination; however, this number could be low as a variety of studies did not investigate dissemination. Dissemination seemed to occur in children 3 years or younger; 14 out of the 16 patients with dissemination were under the age of three; this is similar to a study conducted by Tekautz (2005).[27] While dissemination usually occurs in the CNS, a study in adult patients has found distant metastasis to the lungs.[28]

The impact of extent of surgical resection

Treatment options vary, with surgery being the primary treatment option. Surgery involves patients undergoing surgical resection of the primary lesion and can be classified into three groups based on the percentage of tumour removed; firstly, is gross resection tumour (GTR, no tumour), subtotal resection (STR, >90% of tumour removed) and finally partial resection (PR,

between <50% of tumour removed).[29] Our study found a considerable difference in the survival rate of patients depending on the extent of surgical resection, with patients that underwent GTR having a median survival of 4.167 years compared to only 0.9 years for STR and 0.639 years for PR, which align with the results from other studies that found a significant difference in survival between GTR and STR and the only slight difference between STR and PR.[30-32]

The impact of adjuvant therapy

There are a variety of adjuvant therapies given to treat ATRT. From our analysis, the combination of chemotherapy & radiotherapy is the most common (41.9%) being most common, followed by only chemotherapy (16.9%) and chemotherapy & proton therapy (8.7%). A combination of chemotherapy and radiotherapy seemed to have helped the patients the greatest, with a median survival of 8.842 years, followed by a combination of chemotherapy and proton therapy with a median survival of 4.942 years. Finally, patients that solely received chemotherapy had the lowest median survival of 0.833 years.

Given the rarity of ATRTs and the wide range of therapy regimens employed to date, no standard therapeutic strategy has been developed. Patients treated with multiple diverse chemotherapeutic protocols are frequently included in published case studies, making therapy standardisation challenging. Table 2 summarises the included studied and chemotherapeutic regimens. Intrathercal chemotherapy as an adjunct to systemic chemotherapy is gaining lots of traction as evident by our included studies. Athale et al. (2009) found that even without GTR, patients who received multiagent chemotherapy survived better, although this impact was especially noticeable in those < 3 years old who did not receive radiotherapy.[16] Without radiation, intrathecal chemotherapy improved overall survival (OS 10.5 months vs. 6.5 months, p = 0.011).[16] Modified IRS-III therapies include intrathecal chemotherapy as well as multiagent chemotherapy and focal radiation in patients who have non-metastatic disease. Although the numbers in all reports are modest, there appears to be better survival for patients treated with IRS-III-based de novo treatment and high-dose alkylating agent compared to other chemotherapeutic regimens.[16] However, it is difficult to pinpoint the impact of the IRS-III regimen alterations. As previously indicated, intrathecal ATRT treatment and directions chemotherapy have been linked to better survival in patients who did not undergo radiation.[16]

Delaying radiation in ATRT patients < 3 years old was associated with a significantly bad prognosis, and several clinical trials now use targeted radiation in far younger individuals than was previously believed appropriate.[27] Radiation has been linked to better survival in ATRT patients, particularly those who receive craniospinal radiation with a focused boost to the tumour bed. Tekautz et al. (2005) examined 31 ATRT patients treated from 1987 to 2007 to assess failure patterns and local control with radiation.[27] Patients' chemotherapy regimens and extent of resection varied, but all were treated with focused radiation alone or in combination with craniospinal irradiation (CSI). At a median follow-up of 48 months, the PFS was 32.2 10% and the OS was 53.5 10%. Using a Cox regression model, they discovered that patients with a GTR and stable illness before to RT were less likely to have an adverse event, but patients with delayed RT were more likely to have one. Delayed RT was defined as occurring 1 month after surgery. In their study, only disease progression prior to RT impacted overall survival. The presence of metastatic

disease at the time of presentation had no effect on PFS or OS. At 4 years, individuals with less than GTR had a local failure rate of 53.3 14 percent, while those with GTR had a local failure rate of 17.9 10 percent. Local failure occurred in 29 percent (2/7) of individuals who had immediate postoperative CSI vs 58 percent (7/12) of those who received delayed postoperative CSI. The six patients under the age of three who were alive at the time of the final follow-up before publishing all had focused RT.

Comparing paediatric and adult AT/RT

There are various clinical differences and similarities between adult and paediatric patients. As mentioned, most paediatric patients were males compared to a majority of female adult patients diagnosed with ATRT. From our analysis, the most common tumour location was in the infratentorial location compared to sellar and hemispheric in adults.[23] ATRT has a poor prognosis in both the paediatric and adult populations. Our study reported an average survival time of 10.2 months. These survival data are comparable to a reported median survival of 12–13.5 months in other studies,[33-34] similar to the reported median survival in adults of 11.1–14.3 months.[35-36]

Radiological findings of AT/RT

Radiological findings were also similar between adult and paediatric patients. A study conducted by Warmuth-Metz et al. on paediatric ATRT found 100% hyper-attenuation on CT scan, 44% were hypointense on T1 imaging, 73% were hypointense on T2 imaging, 63% had substantial enhancement, and 73% of patients showed possible necrotic areas or possible cysts [37]. These findings are similar to other studies conducted on children [38-39] and adult patients [40-43].

Our analysis shows that the extent of resection and the form of adjuvant therapy impacts survival. While our study did find that patients that received a combination of radiotherapy and chemotherapy or that received gross total resection did have increased survival. However, survival may be influenced by confound factors, and most patients analysed had surgery with a combination of adjuvant therapy, making it challenging to identify which form of treatment had the most significant impact on survival.

Limitations

Our conclusions are limited due to the small number of included cases. Although there may be many AT/RT cases in the literature, not all cases were confirmed neuropathologically. Thus, this new definition of the tumour may impede our survival analysis, although it may be a cornerstone to a new and accurate understanding of paediatric AT/RT. This phenomenon has also impeded our multi-regression analysis, where the differences in data completeness from one case to another prevented a more powered analysis. Another limitation was the heterogeneity of the chemotherapeutic, radiotherapeutic and other adjuvant therapy protocols utilised in each study. This heterogeneity is primarily due to the lack of a gold-standard protocol. This has prevented a more powered analysis to investigate the impact of each protocol on survival.

Conclusion

AT/RT is a rare malignant neoplasm of the CNS with a poor prognosis. The average survival is fewer than four years. Although the AT/RT occur most commonly in infratentorial or supratentorial regions, our systematic review demonstrates that AT/RT can also occur in the spine, significantly impacting survival, compared to intracranial AT/RT. From our systematic review, the extent of resection was a statistically significant factor in prognosis, but adjuvant therapy may also significantly impact prognosis. However, conclusions are difficult to be drawn due to the small number of paediatric cases in the literature. Future trials are being conducted on chemotherapeutic regimens to elucidate an effective protocol to improve survival. Case reports and systematic reviews of rare malignant neoplasms remain an important component of literature in neuro-oncology as it provides information that may reveal clinicopathological patterns and factors that impact prognosis as well as direct future studies.

Data availability statement

All datasets generated for this study are included in the manuscript and the supplementary files.

Authors' contribution

Abdullah Egiz: Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration. Siddarth Kannan: Data curation, Writing- Original draft preparation. Sarvin Farajzadeh Asl: Visualization, Formal analysis, Writing- Original draft preparation, Writing - Review & Editing.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tables
Table 1

Table 1
Patient and tumour characteristics from the included studies.

PATIENT	
Mean age at diagnosis – year (SD)	2.49 (2.94)
Female gender – no. (%)	70 (40.7%)
TUMOR	
Location – no. (%)	
Supratentorial	72 (41.9%)
Infratentorial	84 (48.8%)
Spine	9 (6%)
Unspecified	7 (4.1%)
Dissemination – no. (%)	16 (9.3%)
TREATMENT	
Surgery – no. (%)	
GTR	71 (24%)
STR	47 (42%)
PR	5 (2.9%)
Biopsy	8 (4.7%)
No surgical intervention	25 (14.5%)
Unspecified	16 (9.3%)
Adjuvant therapy – no. (%)	
Chemotherapy, PT	15 (8.7%)
Chemotherapy only	29 (16.9%)
Chemotherapy, RT	72 (41.9%)
Chemotherapy, Immunotherapy	3 (1.7%)
Immunotherapy only	3 (1.7)
Radiotherapy, Immunotherapy	1 (0.6%)
Radiotherapy only	2 (1.2%)
No adjuvant therapy	40 (23.3%)
Unspecified	7 (4.1%)
PROGNOSIS	
Alive at follow-up – no. (%)	72 (41.9%)
Mean follow-up – years (SD, Range)	3.74 (3.5, 0.08–15.54)
Death – no. (%)	93 (54.1%)
Mean time-to-death – years (SD, Range)	0.85 (1.26, 0.01–8.84)
Unspecified – no. (%)	7 (4.1%)

GTR-gross-total resection; STR-subtotal resection; PR-partial resection; PT-proton therapy; RT-radiotherapy

Table 1 legend: Patient and tumour characteristics from the included studies

Table 2.
Chemotherapy and radiotherapy regimens, doses and respective survival outcomes as reported by the eligible studies.

Author year	Type of study	n	Median age (months)	Chemotherapy (route)	Radiotherapy	Survival outcomes
Weber 2016	Retrospective study	15	18.9	Pilot Protocol ATR EU-RHAB Protocol 2007 or 2010 (Intraventricular and intravenous) American DFC ATRT Protocol	Pencil beam scanning proton therapy	2-year overall- and progression-free survival was 64.6 and 66.0 %
DiPatri Jr 2015	Retrospective study	8	5.5	Modified Baby-POG: VCR, CDDP, cytoxan, and MTX. Modified IRS-III – VCR, dactinomycin, CTX, CDDP, doxorubicin, TMZ and MTX, cytarabine, and hydrocortisone. ACNS0333 regimen with VCR, MTX, VP, CTX, and CDDP. Intravenous (intrathecal – MTX only)	Focal radiation therapy (RT) using intensity-modulated delivery Dose: 5400 cGy fractions	Median OS 5 months (range 1 to 107 months)
Inoue 2014	Case report	1	18	IRS-III Protocol – Anthracycline-based chemotherapy (Intrathecal)	Cranial X-ray irradiation. 54 Gy in 1.8 Gy fractions using intensity-modified delivery	AWD at 29 months
Bush 2014	Case report	1	13	VCR, CTX, CDDP, VP, and high-dose MTX, followed by consolidation with high-dose CARBO/THIO and autologous stem cell rescue	At the completion of chemotherapy, the residual disease was not amenable to surgical resection and the child proceeded to cranial-spinal proton beam radiation.	DOD after 10 months
Han 2012	Case report	1	108	CDDP and CTX	Whole brain by Intensity-modulated radiation therapy, IMRT. Dose: 43Gy/24Fx+12.5Gy/5Fx. Spine by Intensity-modulated radiation therapy, IMRT. Dose: 18Gy/10Fx+18Gy/10Fx	DOD after 12 months
Park 2012	Clinical trial – Phase I/II	6	11.5	Pre-HDCT: Alternating CECV and CEIV x6 cycles HDCT: CARBO/THIO/VP then CTX/MELPH	Salvage after relapse/progression – radiotherapy. CSI/boost after HDCT	5 patients alive 16–70 months. 1 patient DOD 15 months
Bruggers 2012	Retrospective review	20	8.9	Induction A (n = 16) VCR/CDDP/CTX/VP. Induction B (n = 12) VCR/CDDP/IFOS/VP. Maintenance VCR/CDDP/CTX/VP. 6x maintenance chemotherapy CTX/ CDDP /VCR)	Radiation therapy doses and field designs varied among patients, depending on the age of the patient at the time of diagnosis, tumor site, specific study, and curative versus palliative intent.	Median survival 8 months
Heuer 2010	Case report	1	84	Boston AT/RT CNS clinical trial guidelines. intrathecal chemotherapy as well as systemic courses of VCR/doxorubicin and ultimately AD/CTX and additional courses of TMZ and AD. (Intrathecal and Intravenous)	Two months after surgery he received involved-field radiation over a 6-week period. 5400 Gy.	DOD after 42 months
Nicolaides 2010	Retrospective study	6	24	Pre-HDCT: MTX,CTX,VP,CDDP, VCR (HSII) HDCT: MTX,CTX,VP,CDDP, VCR (HSII), or T-IT, CDDP, VP, VCR, AD, IFOS, CTX, or MTX, CTX, VP, CDDP, VCR, IT-ARAC	Focal or none	PFS & OS 10 months (range 1–98 months)
Chi 2009	Clinical trial – Phase II	20	26	Modified IRS-III – Anthracycline-based induction chemotherapy regimen (Intraventricular)	54 Gy focal (n = 11) 36 Gy CSI + boost (n = 4) -	2-year PFS 53 ± 13% 2-year OS 70± 10%
Fidani 2009	Clinical trial	8	39	Pre-HDCT: ICE x2, CECAT x2 HDCT: VP/THIO/CTX	Received whole brain radiotherapy treatment 9-10 months after diagnosis initial dose of 45Gy with a boost to 55-60 Gy	Median OS- 10

Gidwani 2008	Case report	1	4	Received five cycles of chemotherapy including CDDP, VCR, CTX, VP and high-dose MTX as per Headstart II protocol	Not recived due to age tumor location and volume	DFS 24 months
Janson 2006	Case series	2	20	4 pre-radiation cycles of VCR, dexrazoxane, doxorubicin, CTX, VP, and CDDP (intrathecal)	- upfront 11 Gy Gamma Knife boost to a 2.6 cc residual radiographic mass in the right cerebellar peduncle 54 Gy/30 fractions/47 days posterior fossa radiotherapy	PFS
Abu Arja 2018	Case report	1	0.25	consisted of eight, 21-day cycles incorporating VCR, CDDP, doxorubicin, CTX, and triple intrathecal chemotherapy (MTX, hydrocortisone, and cytarabine). (Intraventricular and/or triple intrathecal)	Focal radiotherapy	PFS 17
Johann 2017	Observational study	10	20	CDDP, VP, CTX and VCR) followed by three cycles of high-dose chemotherapy: CARBO, THIO	54Gy	OS 53
Lee 2017	Observational study	9	32	High-dose chemotherapy	Radiotherapy	2-year OS: 62.2%. 2-year EFS: 46.7%
Byers 2017	Case report	1	12	Induction of 2 cycles: VCR, MTX, VP, CTX and CDDP.	adjunct proton beam radiation 45.92Gy/28 fractions/ 30 days	OS 18
Wang 2016	Observational study	22	24	VCR/Bevacizumab; TMZ; Ifosfamide/ Bevacizumab/ Docetaxel	Radiation therapy 30.6–39.6 Gy CSI/18–54 Gy focal or cranial	OS & EFS 17
Van Gool 2016	Clinical trial	7	31.5	Multi-drug chemotherapy, high-dose chemotherapy (Intrathecal)	Irradiation 60 Gy	OS 56.04
Tekautz et al. (2005)	Observational study		22 <3 years (12). 9 patients ≥3 years (3.9 years)	Multiple regimens	<3 years 2 local, 1 CSI + boost ≥3 years 7 patients CSI + boost	<3 years 2-year EFS 11 ± 6% 2-year OS 17 ± 8% . ≥3 years 2-year EFS 78 ± 14% 2-year OS 89 ± 11%
Lafay-Cousin et al. (2012)	Clinical trial – Phase II	50	16.7	MTX, CDDP, CPM, VCR, VP, (CB, THIO) x 3 CDDP, CPM, VCR, VP16, (CB, THIO) x 3 CDDP, CPM, VCR, VP, (CB, THIO) x 3 Systemic or triple intrathecal: aracytine, hydrocortisone, MTX	45 Gy cranial/780 focal, or 36 Gy CSI/18 Gy focal boost, or 36 Gy CSI/18 Gy focal boost	2-year OS 36.4 ± 7.7%

AD, actinomycin D; AWD, alive with disease; CARBO, carboplatin; CDDP, cisplatin; CECAT, cyclophosphamide, etoposide, carboplatin, thiotepa; CECV, cisplatin, etoposide, cyclophosphamide, vincristine; CEIV, carboplatin, etoposide, ifosfamide, vincristine; CR, complete response; CSI, craniospinal radiation; CTX, cyclophosphamide; DOD, died of disease; HDCT, high-dose chemotherapy; ICE, ifosfamide, carboplatin, etoposide; IFOS, ifosfamide; IT-ARAC, intrathecal cytosine arabinoside; MTX, methotrexate; THIO, thiotepa; T-IT, triple intrathecal chemotherapy; TVD, topotecan, vincristine, doxorubicin; VCR, vincristine; VP, etoposide; Temozolomide, TMZ.

Table 3

Table 3.
Multiple regression analysis for survival

Survival	B	95% CI for B		SE B	*ß*	R^2	adj R^2
		LL	UL				
Model						0.328	0.235
Constant	65.526*	35.057	95.994	14.897			
Tumour location	-4.420	-19.083	10.242	7.169	-0.102		
Dissemination	-24.374**	-44.819	-3.929	9.996	-0.406**		
Resection	-5.512	-15.949	4.926	5.103	-0.172		
Adjuvant therapy	-4.424**	-8.747	-0.101	2.114	-0.359**		

Note: Model = "Enter" method in SPSS statistics; B = unstandardised regression coefficient; CI= confidence interval; LL = lower limit; UL; upper limit; SE B= standard error of the coefficient; *ß* = standardised coefficient; R^2 = coefficient of determination; adj R^2 = adjusted R^2
*$p < 0.01$. **$p < 0.05$

Table 3 legend: Multiple regression analysis for survival

Figures and table

Figure 1

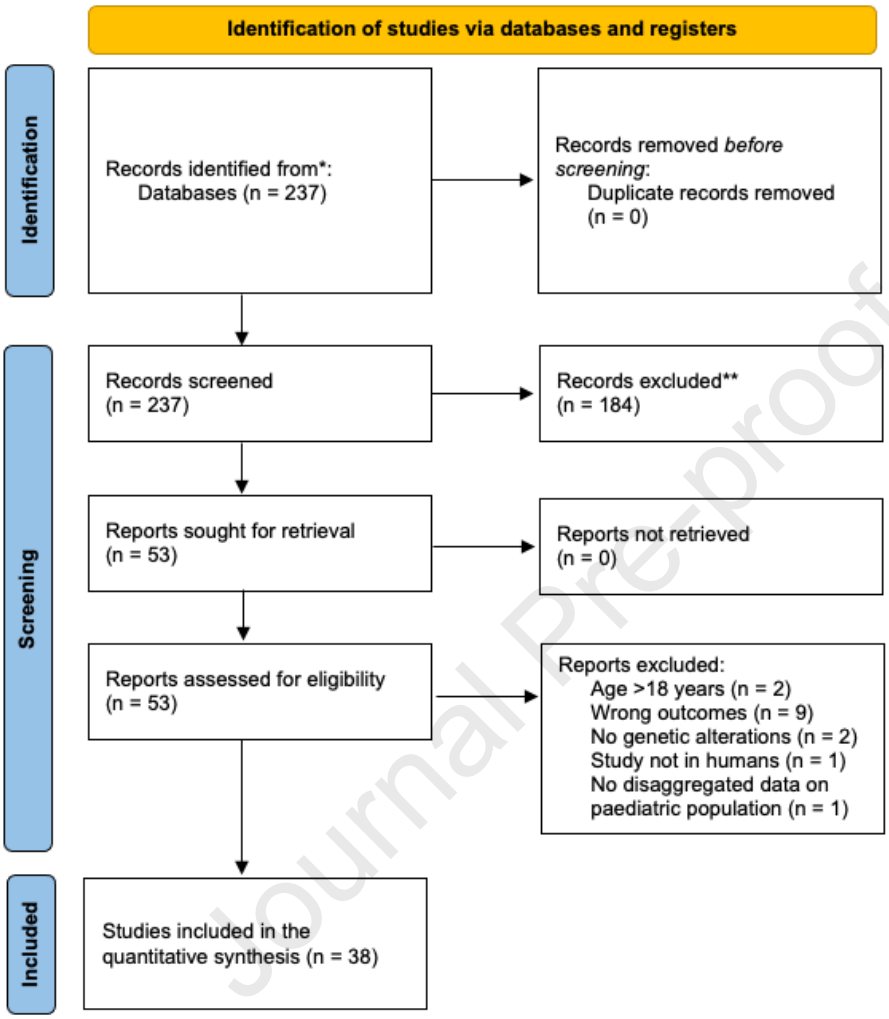

Figure 1 legend: PRISMA diagram

Figure 2

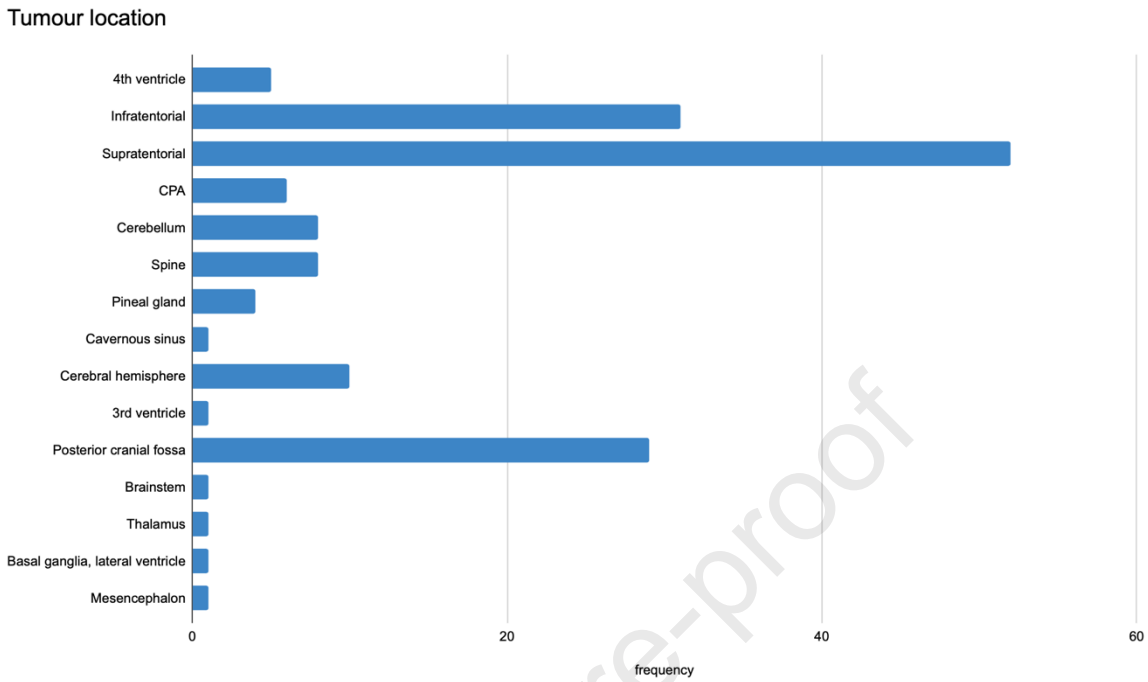

Figure 2 legend: AT/RT tumour locations for the included cases.

Figure 3

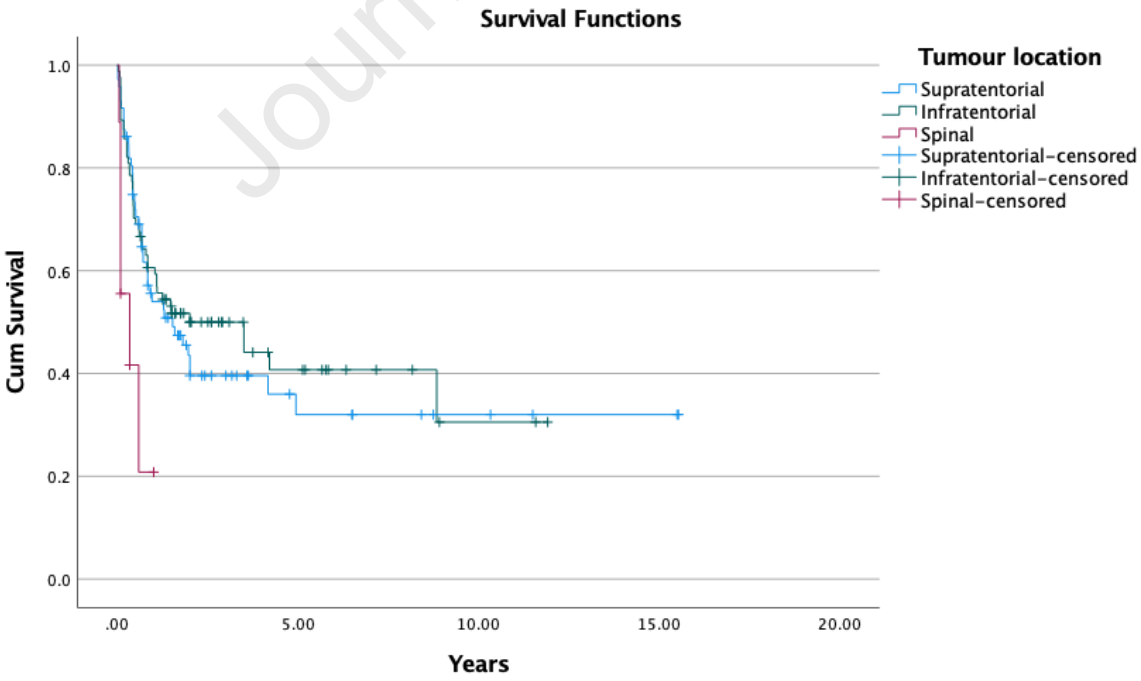

Figure 3. Kaplan-Meier curve for the tumour location.

Figure 4

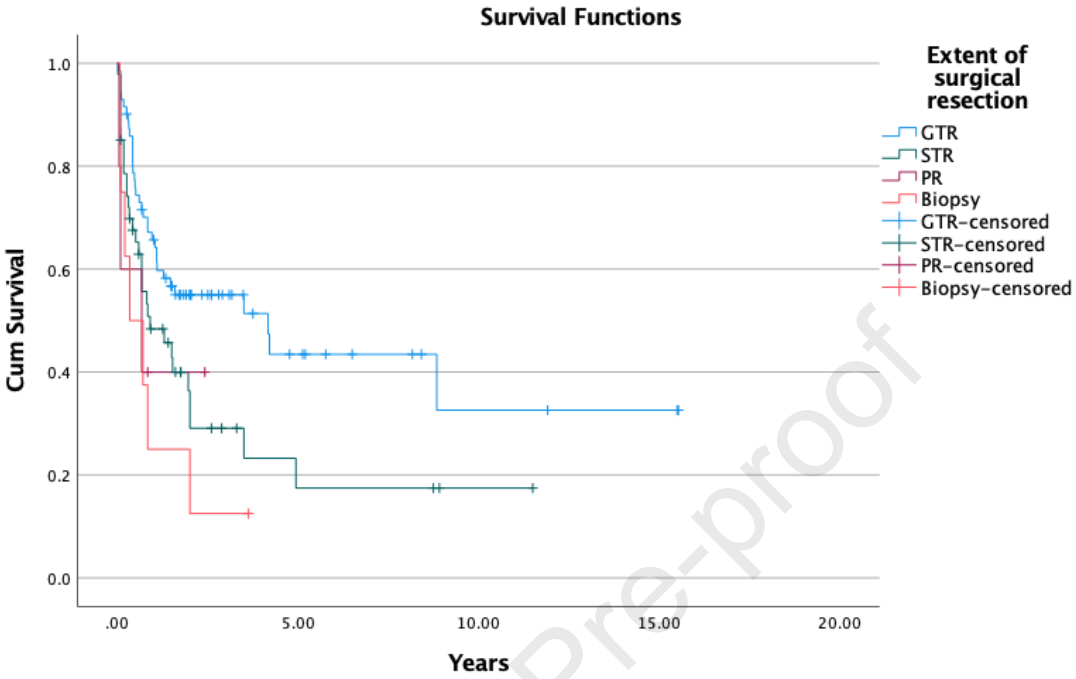

Figure 4 legend: Kaplan-Meier curve for the extent of resection. GTR=gross-total resection, STR=subtotal resection, PR=partial resection.

Figure 5

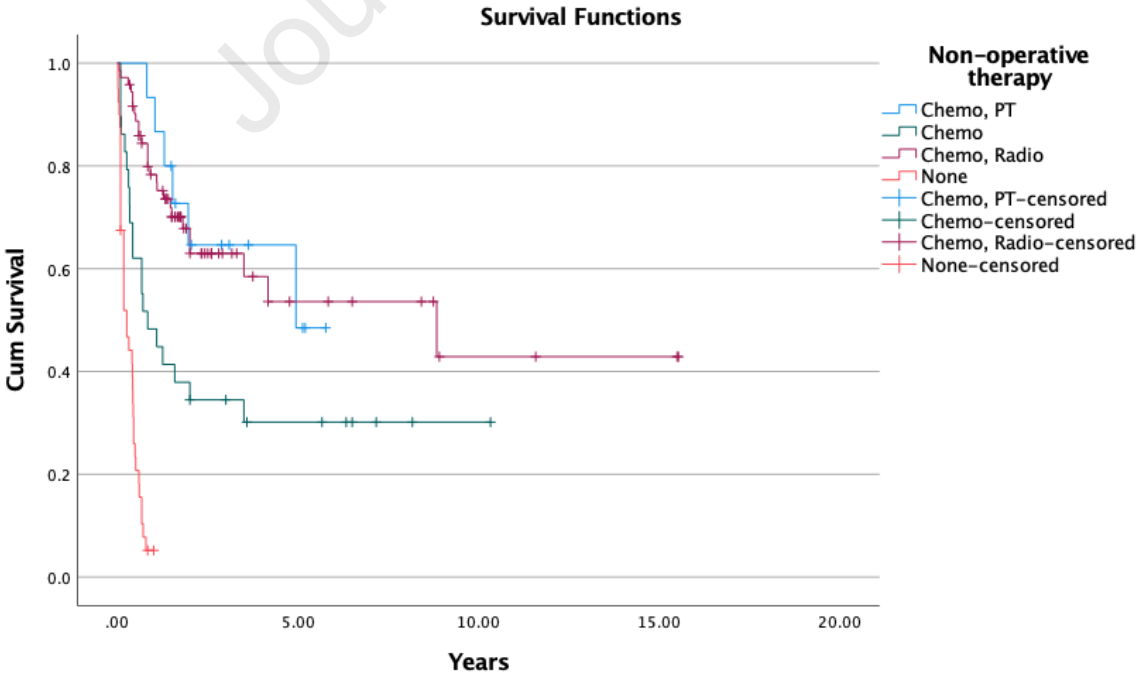

Figure 5 legend: Kaplan-Meier curve for adjuvant therapy. Chemo, PT= chemotherapy and proton therapy; Chemo=chemotherapy; Chemo, Radio=chemotherapy and radiotherapy

To:

Dr. Edward C. Benzel, MD

Editor-in-Chief,

World Neurosurgery,

27/03/2022

RE: Disclosure of interests

All authors declare no conflicting interests.

Sincerely,

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List of abbreviations (A–Z)

ATRT: Atypical Teratoid/Rhabdoid Tumour

BRG1: Brahma-related gene-1

GTR: Gross total resection

INI1: Integrase interactor 1

MRI: Magnetic Resonance Imaging

OS: Overall survival

PR: Partial resection

SMARCA4: SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily A, Member 4

SMARCB1: SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1

STR: Subtotal resection