Atypical Teratoid Rhabdoid Tumours (ATRTs) – a 21-year institutional experience

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Abstract

Purpose: Atypical Teratoid/Rhabdoid Tumours (ATRTs) are malignant embryonal tumours of childhood that affect the central nervous system (CNS). We aim to determine which factors, including patient age, extent of resection (EOR), presence of distal metastasis and use of adjuvant therapies, affect overall survival in children with Atypical Teratoid/Rhabdoid Tumours (ATRTs) treated at this single centre.

Methods: Retrospective cohort review of patients with histological diagnosis of ATRT treated over 21-years (1999-2020) was conducted. Data on demographics, tumour location, presence of metastasis, use of adjuvant therapy, extent of resection (EOR), complications, neurological outcome post-surgery, and overall survival were collected. Kaplan-Meier survival analysis was performed.

Results: A total of 45 children (mean age 2 years) underwent 64 operations. 25 patients were <1-year of age. Gross-total resection (GTR) pre-adjuvant therapy was achieved in 15, near-total resection (NTR) in 15, subtotal resection STR) in 9, and biopsy in 6 children. Most children had good neurological outcomes post-operatively (28/45 with GOS 5). 14 patients survived longer than 4 years. Survival analysis showed a significant difference in median survival in favour of GTR and localised disease. There was no significant difference in median survival between patients <1-year vs >1-year of age (p=0.84).

Conclusion: We find that presence of metastasis was an important factor in poor survival of patients with ATRT. GTR, where possible, may confer significant survival benefit in ATRT. Children aged <1-year appear to have performed as well as those >1-year and therefore should be considered for radical surgery.

Introduction

Atypical Teratoid/Rhabdoid Tumours (ATRTs) are embryonal tumours of childhood that affect the central nervous system (CNS), and represent 1-2% of paediatric CNS tumours. They are highly malignant tumours most commonly affecting children between 1 and 2 years of age [1,2].

Rorke *et al.* defined ATRTs as a separate entity from primitive neuroectodermal tumor (PNET) tumours in 1996 [3]. Such tumours are predominately composed of rhabdoid cells; they are negative for germ-cell tumour markers and are distinguished from PNETs by characteristic abnormalities on chromosome 22q11. The diagnostic molecular marker for ATRT is bi-allelic germline deletion or inactivation of *SMARCB1* or *SMARCA4,* or negative immunohistochemistry staining of its gene products, including hSNF5 or INI1 [3,4].

Despite improved diagnosis, recognition and molecular identification of ATRT, outcomes in patients with this aggressive tumour remain poor. Currently reported survival rates are around less than 50% at 1 year after diagnosis [6,7].

There is evidence that older age, supratentorial location, no distal metastasis, a surgical gross total resection and adjuvant chemotherapy may all improve survival [8-11]. However, even with advancements in treatment modalities, there remains a paucity of evidence regarding the optimal management of these patients, likely owing to the rarity of the disease and interacting variables.

The aim of this study was to determine which factors, including patient age, extent of resection (EOR), presence of distal metastasis and use of adjuvant therapies, affect overall survival in children with ATRT at this single centre. We review our findings in the context of the current literature.

Materials and Methods

Study design

A retrospective cohort and survival analysis of children with a diagnosis of ATRT, treated over 21 years at Great Ormond Street Hospital for Children (GOSH), was conducted (1999-2020).

Inclusion criteria

All patients had a histological diagnosis of ATRT and were managed in consensus with the regional paediatric neuro-oncology multi-disciplinary group.

Clinical variables studied

Data on basic demographics (and molecular pathology) were collected. Main clinical variables studied included (1) age at diagnosis, (2) tumour location and extent of metastases, (3) extent of resection (EOR) and (4) use of adjuvant treatment.

Radiological evaluation

EOR was determined by paediatric neuroradiologists quantitatively using volumetric analysis of postsurgical magnetic resonance imaging (MRI) and defined as follows: (1) Gross Total Resection (GTR) – complete tumour resection with "a clean surgical field under the microscope at the end of the procedure and no evidence of residual disease on post-operative MRI" i.e. 100% resection, (2) Near Total Resection (NTR) – more than 90% resection, (3) Sub Total Resection (STR) – 10 to 90% tumour resection and (4) Biopsy – less than 10% tumour resection.

Outcomes

Outcomes studied included complications, neurological outcome post-surgery (Glasgow Outcome Score) and overall survival in months.

Statistical analysis

We compared the survival between the following variables (A) Age (<1 year vs. >1 year), (B) EOR (defined above as Biopsy, STR, NTR and GTR) and (C) Presence of metastases (M0 vs. M1-M4). If patients had more than one surgical procedure, maximal EOR was considered. Patients who underwent more than one operation were characterized and stratified by the maximal EOR achieved overall both before the initiation of adjuvant therapy ('maximal EOR pre-adjuvant therapy'; including patients that underwent early 2^{nd} look surgery before adjuvant therapy) and after initiation of adjuvant therapy ('maximal EOR achieved pre- or post-adjuvant therapy').

Kaplan-Meier survival curves were compared using the log-rank (Mantel Cox) test or Cox regression analysis and results were presented as median survival (months). Overall survival (OS) was defined from the date of tissue diagnosis to date of death.

Multivariate analysis was also performed. The association of EOR and presence of metastasis with survival time (in years) as the independent variable was assessed using a multiple linear regression model. The following 6 co-variates were included and tested: age (years), male gender, posterior fossa location of tumour epicentre, presence of metastasis (M1-M4), GTR and administration of radiotherapy. We also performed a correlation matrix analysis with Pearson r (or Spearman).

Hazard ratio's (Mantel-Haenszel, with confidence intervals) were calculated for the binary comparisons (age <1 vs. >1 year, GTR vs NTR and STR combined, and M0 vs M1-4). These are subsequently presented on a respective Forest plot, comparing this paper's Hazard Ratio's with the contemporary ATRT literature results.

A p value below 0.05 was considered statistically significant. Statistical analyses were computed using GraphPad Prism (Version 8.4.2).

Results

Demographics and age

A total of 45 children diagnosed with ATRTs underwent a total 64 operations. Mean age at diagnosis was 2-years (range: 2 days-14 years). Most children were <1-year of age (n=25) (Figure 1A). In total, 3/45 patients were lost to follow-up.

Tumour location

The majority of tumours were in the posterior fossa (30/45; 66.7%) followed by supratentorial (8/45; 17.8%) and pineal region (5/45; 11.1%). There was one isolated peri-orbital tumour and one tumour that was predominantly leptomeningeal in its location. The epicenters of the posterior fossa tumours were predominantly 4^{th} ventricular (19/30), 4^{th} ventricular with extension into the cerebello-pontine angle (CPA) (3/30) and primarily in the CPA (8/30) (Figure 1B). Most patients had localised disease (28/45; 62%).

Number of surgical resections

Most patients had one respective surgical procedure (30/45) with 11/45 having two operations and 4/45 having three. Of the patients that had more than one operation, 4 underwent their 2^{nd} operation prior to initiation of adjuvant therapy (i.e. early second look surgery 'pre-adjuvant therapy').

Adjuvant therapy and follow-up

Adjuvant therapy was initiated in 37/45 patients: chemotherapy alone in 23/45, chemotherapy combined with proton beam therapy (PBT) in 1/45, and chemotherapy combined with radiotherapy (DXT) in 13/45. A total of 7/45 patients received no adjuvant therapy owing to disease severity. No information was available in one patient.

Extent of surgical resection

Overall, pre-adjuvant therapy, GTR was achieved in 15/45, NTR in 15, STR in 9, and Biopsy alone (<10%) in 6 children. Table 1 summarises data for all patient group types, considering those who did not undergo adjuvant therapy (n=7) or were lost to follow-up (n=3): (1) all patients (maximal EOR achieved 'pre-adjuvant therapy'), (2) all patients (maximal EOR achieved), (3) Patients with adequate follow-up and treated with adjuvant therapy (maximal EOR achieved 'pre-adjuvant therapy') and (4) Patients with adequate follow-up and treated with adjuvant therapy (maximal EOR achieved).

Complications

A total of 15 complications occurred (33.3%), of which one (a post-operative haematoma) resulted in a return to theatre for a craniotomy, and one patient required a cysto-peritoneal shunt to treat a persistent posterior fossa pseudomeningocoele. The commonest complication was a change in neurology (cranial nerve palsy or limb weakness) post-operatively (n=6), followed by CSF leak (n=4) seizures (n=2).

Outcome

Most children had good neurological outcomes following surgery, with 28/45 having a Glasgow Outcome Score 5.

Survival analysis

A total of 35 patients underwent Kaplan-Meier survival analysis (the 7 patients with no adjuvant therapy and 3 lost to follow-up were excluded). Overall, 14 patients survived over 4 years and the overall median survival was 11 months.

There was no significant difference in median survival between patients <1-year vs patients >1 year of age (p=0.84) (Figure 2A).

Where EOR was evaluated, we report results for maximal EOR before adjuvant therapy (Table 2) and maximal EOR achieved overall (before or after adjuvant therapy, Table 3; Figure 2B). When all resections were considered (before or after adjuvant therapy), there was a significant difference in median survival

(years) in favour of EOR (Mantel-Cox Log-rank p=0.01): GTR undefined* with minimum median survival of 4.14 years (n=17; range 0.37-10.12), NTR 0.73 years (n=12; range 0.13-6.92), STR undefined* with minimum median survival of 4.59 years (n=3; range 0.13-7.1) and biopsy 0.7 years (n=3; range 0.55-1.02).

There was a significant difference in median survival (years) in favour of patients with localised disease (M0) compared to patients with metastasis (M1-4) (p=0.001) (Figure 2C).

Due the small numbers (n=3) in STR group (and wide range), an additional survival analysis comparing GTR (n=17) to NTR and STR combined (n=15) was performed. GTR has significantly greater survival compared to STR and NTR combined which was 0.76 (n=15, range 0.13-7.1) (p=0.03) (Figure 2D).

A GTR subgroup survival analysis of age <1-year (n=8) vs patients >1 year (n=9) of age showed no significant difference in the median survival (5.6 years, p=0.50).

Hazard Ratio's

Hazard ratio's for binary survival comparisons were: Age <1 year, 0.91 (0.37 – 2.28), GTR (vs. NTR and STR combined) 0.32 (0.12-0.87) and presence of Mets 8.01 (2.74-23.5) (Figure 3).

Multivariate analysis

A multiple linear regression model adjusted for 6 independent variables confirmed a statistically significant association between survival and radiotherapy (β = 2.42; 95% CI, 0.44 to 4.41; p=0.02) and survival and presence of metastasis (β = -2.05; 95% CI, -3.94 to -0.16; p=0.03) (Table 4). The correlation of the variables with one another is demonstrated in the multivariate correlation matrix (Figure 4).

Discussion

Key findings

ATRT is a highly malignant tumour with a poor prognosis, and lack of standardised treatment protocols means that elucidating treatments to improve outcome and survival can be challenging. In this study, we reviewed a single centre's surgical outcomes over a 21-year period, and report on the key factors affecting survival in a cohort of patients with histologically confirmed ATRT.

Of the 45 patients who underwent surgery for ATRT, 14 patients survived longer than 4 years. The overall median survival for all patients with ATRT undergoing surgical debulking or resection was 11 months.

To date, this is largest the single-centre series of ATRT cases (Table 5). The key finding of this study was that the presence of metastasis, including any degree of disease spread from the original site, had a significant effect on overall survival, in both univariate and multivariate analysis. Univariate analysis also demonstrated a significant difference in median survival (years) in favour of greater resection. Patients aged less than one year did not have worse survival compared to those greater than one year of age.

Genuine surgical complications (excluding medical complications and disease progression) were common (15 of 45 cases, 33.3%) with a temporary neurological deficit being the most common, followed by CSF leaks. Only two of 45 patients required a return to theatre for surgical complications (one haematoma, and one permanent need for CSF diversion). This information is important when it comes to counselling families about surgery and the natural history of the disease.

Review of literature

We reviewed the contemporary literature on outcomes in ATRT. Figure 3 summaries the studies that report a hazard ratio for the key variables studied in this series (age, metastasis, extent of resection, and adjuvant therapy), including our single centre series ratio's. Table 5 summarises survival data in recent reports on ATRT, with this paper's findings included.

Median survival: We reported an overall median survival of 11 months in patients with ATRT undergoing surgery. In our literature review the median survival was 11.05 months, concurring with our findings (Table 5). The highest survival reported was 77 months, and the lowest was 3.5 months (Table 5) [8,12]. The most common reported median survivals are between 9–17 months, consistent with our results [2,3,7,14-16].

Age: Age has frequently been reported as significant factor in survival of patients with ATRT. Fischer Valuck et al. reviewed outcomes of 361 patients registered with US National Cancer Database (NCD) between 2004-2012 [17]. They found that increasing age conferred less mortality (HR 0.5) (Figure 3) [17]. Similarly, Biswas et al report that patients younger than 5 years of age had an increased mortality (HR 3.2) (Figure 3) [18]. One explanation for this may be that older children (5 years or more) tolerate the side

effects of adjuvant treatments and can undergo radiotherapy. They may also suffer from fewer surgical complications.

In contrast, we found that age did not have a significant effect on survival (HR 0.91 for age <1 year). However, we compared those aged less than, or greater than 1 year and most studies use 2 years as a boundary for comparison (see Table 5), which may explain why our findings are different. Another explanation is that our centre undertakes early surgery (due to early diagnosis and referrals which are common at this specialized children's hospital) which may even result in improved survival, therefore mitigating the effect of age. Indeed, the subgroup analysis for GTR, comparing survival in those <1 year and >1 year also found no significant difference. We might conclude from this that even those <1 year should be considered for GTR.

In our patients posterior fossa epicentre was commoner in children over 1 year of age (Figure 4 correlation matrix). There is evidence that supratentorial disease is associated with better survival [8-11]. This also may explain why we found little difference between the two age groups (<1 and >1 years of age), as the benefit of older age (and receiving radiotherapy) was balanced by infants having a greater proportion supratentorial disease (known to have better survival).

Metastasis: In this study we found the presence of distant disease to be an especially important risk factor (HR 8.01). Fischer Valuck et al's large 361 patient review found that the presence of metastasis increases the risk of mortality (albeit to a lesser degree, HR 1.59) supporting our results [17]. In our series, 30 of 45 ATRT cases were centered on the posterior fossa, and 15 patients had metastatic disease. The presence of disease away from the initial epicentre is common, with multiple studies reporting distant disease (Table 5) [8,12, 17,18-27]. Therefore, identification of therapies that slow or halt metastatic spread in ATRT will undoubtedly improve survival. In our series children with metastatic disease were also less likely to receive radiotherapy (Figure 4). The poor survival in this group is likely a multifactorial outcome, resulting from the failure to achieve GTR (particularly if there is leptomeningeal involvement), and the consequence of craniospinal radiotherapy in children under three years old.

Extent of resection: In this study, univariate analysis found that the greater the resection, the better the survival, and overall HR for gross total resection was 0.32, therefore conferring a protective benefit to a degree. This is consistent with results by Biswas et al. and Rao et al. who found that less resection resulted in a higher risk of mortality (HR 7.06 and 1.36 respectively) (Figure 3). Richards et al also had similar findings. In their univariate analysis overall survival for patients with GTR was significantly higher

than for patients with STR or NTR (p 0.048) and in multivariate analysis EOR showed a trend towards significance [27]. Out of the GTR group 66.6% of patients were still alive, whilst this number was only 29% for NTR, 12.5% for STR and 33.3% for the biopsy group [27].

Our survival analysis comparing all four resection subgroups (GTR, STR, NTR and Biopsy), the STR group had a spuriously high median survival, likely owing to low number (n=3) and one patient of these three surviving for 7 years. For this reason, we performed an additional analysis combining STR with NTR and compare these two to GTR. The median survival for patients undergoing GTR (median of at least 4.1 years) was significantly better than those who underwent STR or NTR (median of 0.76 years), concurring with previous studies findings. However, this effect was lost after multivariate analysis, suggesting that GTR is needed in combination with other treatments, likely owing to the major effect of distant of metastasis.

Adjuvant therapy: Whilst the majority received a form of adjuvant therapy, only 13 had radiotherapy (in combination with chemotherapy) and one patient received proton beam therapy. This is likely owing to the large proportion of young children (under the age of 1 year old) in our report.

Studies have shown that withholding radiotherapy results in poorer survival [17,18]. Biswas et al report a hazard ratio of 9.3, underlining the importance of adjuvant therapy in ATRT [18]. Numerous other studies have reported a survival improvement with use of adjuvant radiotherapy [19, 24]. One study reported the use of stereotactic radiosurgery (SRS) as an adjuvant therapy, which was found to slightly improve survival, with a hazard ratio of 0.16 [20].

However, radiotherapy is rarely used in children under the age of 3 years, and alternative adjuvant treatment strategies are being tested. Trimodal therapy (surgery, chemotherapy and radiotherapy) has been shown to have improved survival rates, with one study reporting 5-year survival of almost 50% [17]. High-dose chemotherapy followed by autologous stem cell rescue (HD-SCR) is also being used more frequently. In Schrey et al's literature review including 332 patients, 28.6% had received this form of therapy. They showed improved survival after HD-SCR with a hazard ratio of 0.39 [19]. Nicolaides et al even suggested that for a subset of patients this form of treatment can be curative [28].

Strengths and Limitations

As all other studies that have been published in the field of ATRT surgery, this is a retrospective cohort, without a control group. However, our series is the largest from a single centre and the overall survival (11 months) is consistent with very large multi-centre analysis findings.

Conclusion

ATRT remains a highly challenging tumour to manage, despite advancements in diagnostic tests and treatment options. An aggressive surgical strategy, where possible, appears to confer significant survival benefit in ATRT. In this series children aged <1 year appear to have performed as well as those >1 year, including those who underwent GTR. We find that presence of metastasis was an important factor in poor survival of patients with ATRT. The main future research priorities should be aimed at determining what factors (environmental or genetic) are associated with better survival and outcome, with the aim to produce a consensus on optimal treatment protocols.

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Table Legends

Table 1. Extent of resection in our cohort of patients

Table 2. Median Survival including patients with maximal extent of resections pre-adjuvant therapy*

Table 3. Median Survival including patients including maximal extent of all resections (before or after adjuvant therapy) *

Table 4. Multivariate analysis of variable affecting ATRT survival

Table 5. Summary of studies reporting presence of age, metastasis, and survival

Figure Legends

Figure 1. Demographics A. Histogram of age B. Distribution of ATRT location in total cohort (n=45).

Figure 2. Kaplan-Meier survival curves comparing survival in patients with ATRT with maximal extent of resections (including before and after adjuvant therapy). (A) Age (<1 year vs. >1 year), (B) EOR (defined above as Biopsy, STR, NTR and GTR), (C) Presence of Mets (M0 vs. M1-M4) and (D) Additional analysis comparing GTR to NTR and STR combined.

Figure 3. Summary of studies reporting Hazard Ratio (HR) for variables of age, metastasis, extent of resection and adjuvant therapy. Size of diamond reflects the weight of the study.

Figure 4. Multivariate correlation matrix (r, Pearson correlation coefficient) illustrating the relationship of the variables on survival and one-another. Dark blue indicates strong positive correlation and dark red indicates strong negative correlation.