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Outcome after treatment of pediatric supratentorial ependymoma: long-term follow-up of a single consecutive institutional series of 26 patients

Trygve Lundar*, Bernt Johan Due-Tønnessen, Radek Fríč, Jarle Sundseth, Petter Brandal and Paulina Due-Tønnessen

Department of Neurosurgery, Oslo University Hospital, Oslo, Norway; Department of Oncology, Oslo University Hospital, Oslo, Norway; Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway

ABSTRACT

Background: Long-term outcome after surgical treatment of supratentorial ependymoma (STE) in children has not been extensively reported.

Findings: We identified 26 children who underwent primary tumor resection of STE between 1953 and 2011, with at least 8 years follow-up. Ten patients (38%) had anaplastic and 16 had low grade ependymoma. Four of 15 children (26%) treated in the years 1953–1976 survived more than 5 years, but the observed 10-year survival was only 7%. One patient lived for 37 years, and second surgery for a local recurrent lesion disclosed a glioblastoma, possibly secondary to radiotherapy. In contrast, the observed 5-year survival rate for 11 children treated in the years 1992–2011 was 8/11 (73%) and observed 10- and 25-year survival rates were 70% and 66%, respectively. Eight patients were alive and tumor-free with follow-up periods of 8–27 (median 18) years, all treated after 1992. Five of these long-term survivors were 23–39 years old with full-time (n = 3) or part-time (n = 2) work. The last three patients were still children (9–12 years old); one with good function and two with major neurological deficits. The majority of patients (n = 18) received adjuvant radiotherapy and eight children no adjuvant treatment. Repeated resections for residual or recurrent tumor were necessary in 11 patients (42%), mostly due to local disease with progressive clinical symptoms. Eight patients underwent only one repeat resection, whereas three patients had two or more repeat resections within 18 years after initial surgery. Four patients were tumor-free after repeated resections at the latest follow-up, 2–13 years after last surgery.

Conclusion: Pediatric STE has a marked risk for local recurrence even after gross total resection and postoperative radiotherapy, but survival has increased following the introduction of modern treatment in recent years. Repeated surgery is an important part of treatment and may lead to persistent tumor control.

Introduction

Ependymoma is the third most common intracranial tumor in children, and there is a paucity of large studies with more than 10 years of follow-up reporting observed long-term survival, recurrence patterns and quality-of-life following treatment for this disease [1]. Surgical resection, followed by radiotherapy has been standard treatment, while chemotherapy has only recently been advocated in very young patients to avoid harmful effects of radiation [2–9]. In contrast to other pediatric brain tumours, differentiation between high-grade (anaplastic) and low-grade tumors seems to be of limited prognostic value. In recent years, a number of molecular subgroups have been defined, and may lead to differentiation of treatment in the future.

As much as 90% of pediatric ependymopas are located intracranially, and about one third in the supratentorial compartment [3,10]. Survival rates for children treated for posterior fossa ependymoma (PFE) have been clearly inferior to those observed for medulloblastoma, particularly due to high local recurrence rates, even after postoperative radiotherapy given towards the surgical field [4,11,12]. Pediatric supratentorial ependymomas (STE) and PFE appear to be different entities, regarding age distribution as well as WHO grading.

We recently presented our long-term results for children treated for PFE and herein present long-term follow-up data from children treated for supratentorial intracranial ependymoma on our institution [13].

Methods

We retrospectively analyzed a non-selected, consecutive cohort consisting of children (aged 0–18 years at the time of first presentation) who underwent primary resection of STE at the Department of Neurosurgery, Oslo University Hospital (OUH), Oslo, Norway, between 1953 and 2011. OUH covers 55% of the Norwegian population, corresponding to a population of about 2.5 million of inhabitants (Southern & Eastern Norway). Patients were identified based on surgical protocols from the study period and data were analyzed data based on patient status at the end of...
2019. Case record data included sex, age at the time of primary tumour resection, treatment administered, recurrences including treatment of these and management of hydrocephalus. Resection grade was based on surgical notes in the pre-MRI era and on surgical notes as well as MRI findings in the MRI-era.

To assess the grade of dependence on assistance in daily living, the Barthel Index (BI) score was used [11]. This is a well established and validated scale using ten variables to measure performance in basic activities of daily living (ADL), primarily related to personal care and mobility. Scores range from 0 to 100: a higher score denotes greater independence. Educational outcome was simplified and categorized into normal versus special schooling, and employment attendance into open, sheltered or no work.

**Results**

**Clinical results**

We identified 26 patients, 10 boys and 16 girls (ratio 0.63), with median age of 7 years (range 0–18 years). The histological examination as conducted by an experienced neuropathologist was ependymoma WHO grade II in 16 cases and grade III in 10 cases. Fifteen (58%) children were in the first decade of life (Table 1). The 26 STE patients represented 26% of all pediatric ependymoma cases treated in our institution during the study period. Fifteen patients were treated in the early period (1953–1976), whereas eleven patients were treated in the years 1992–2011. There was a marked difference in observed 5-year survival between these eras; it increased from 26% to 73%. The observed 10- and 30-year-survival rates for the pre-MRI-subgroup were all 7% (Table 2). Due to the shorter follow-up of patients treated in the MRI-era, 10 and 20 years observed survival is still incomplete and at the moment 70% (n = 10) and 66% (n = 6), respectively (Table 3). Signs and symptoms of increased intracranial pressure and epileptic seizures were the leading clinical presentation.

**Primary surgery**

The aim of surgery was gross total resection (GTR) whenever feasible and this was achieved in 15 patients (58%), whereas subtotal resection (STR) was the result in 11 cases (42%). In the last period (1992–2010) GTR was achieved in 9 out of 11 patients (81%).

**Repeated resections**

Eleven patients (42%) underwent a second tumor resection (Table 1); three of these patients also had a third resection.
within the first three years after initial surgery. Two of these had five and six resections. In total, 19 repeated resections were performed in these 11 patients; the latest 36 years after the initial resection (Table 1). Seventeen repeated resections were due to local recurrences, whereas two patients had second resections in a different location: one patient in the posterior fossa 6 months after initial surgery for STE, and one patient a distant meningeal tumor (ependymoma) four years after initial surgery for STE. The latter patient, a now 23-year-old woman, was in full-time work as a district nurse and tumor-free according to MRI 16 years following the last tumor resection. Details of the 19 additional resections are given in Table 4.

Adjuvant therapy

Postoperative radiotherapy, most often 54 Gy, was administered towards the primary tumor location in 18 patients (69%, Table 1). Seven children did not receive any adjuvant treatment whatsoever, whereas two small children received chemotherapy – one as sole adjuvant treatment (Table 1). Patient number 26 underwent an additional tumor resection 5 years following primary tumor resection, where histological examination revealed glioblastoma (GBM) components in addition to ependymoma (WHO grade 3–4). Local radiotherapy (54 Gy) was thereafter administered combined with Temodal. After additional 4 years of follow-up, this child is tumor-free according to MRI, but with hemiparesis and mostly only non-verbal communication.

Among the eight tumor-free long-term survivors (Table 1), there are three patients who have been treated with surgical resection alone.

### Observed survival rates

For the 15 children undergoing primary surgery in the early period (1953–1976), the observed 1-month, 1-year, 3-year and 5-year survival rates were 93, 73, 47 and 26%, respectively (Table 2). Only one patient was alive after 10 years. This patient maintained a good life with full-time work for 36 years, until he had repeat surgery for what turned out to be a GBM – possibly secondary to postoperative radiotherapy.

For the 11 patients treated in the MRI-era (after 1987), the observed 1-month, 1-year, 3-year, 5-year, 10-year, 15-year, 20-year and 25-year survival rates were 100%, 100%, 82%, 73%, 70%, 62%, 66% and 66%, respectively (Table 3).

### Activities of daily living

Six of the long-term survivors had a good gross motor function. Their activities of daily life function were good. Barthel index score was 100 in all these patients (Table 1). The two remaining long-term survivors, however, had a poorer functional status; patient number 25 and 26 had BI scores of 60 and 50, respectively (Table 1).

### School, education and work

Five of the eight long-term survivors were adults 23–39 years old. They were all in full-time (n = 3) or part-time work (n = 2) (Table 1). The last three were 9–12 years old, one of them following a regular school programme, whereas the last two had a specialized school programme.

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### Table 2. Observed overall survival rates from STE patient cohort with treated before the introduction of MRI.

<table>
<thead>
<tr>
<th>Survival</th>
<th>Surgery</th>
<th>1-month</th>
<th>1-year</th>
<th>3-year</th>
<th>5-year</th>
<th>10-year</th>
<th>20-year</th>
<th>30-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients at risk</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Number of patients alive</td>
<td>15</td>
<td>14</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Number of patients alive</td>
<td>100</td>
<td>93</td>
<td>73</td>
<td>47</td>
<td>26</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

STE: supratentorial ependymoma.

---

### Table 3. Observed overall survival rates from STE patient cohort with treated after the introduction of MRI.

<table>
<thead>
<tr>
<th>Survival</th>
<th>0</th>
<th>1-month</th>
<th>1-year</th>
<th>3-year</th>
<th>5-year</th>
<th>10-year</th>
<th>15-year</th>
<th>20-year</th>
<th>25-year</th>
<th>30-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients at risk</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Number of patients alive</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Number of patients alive</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>82</td>
<td>73</td>
<td>70</td>
<td>62</td>
<td>66</td>
<td>66</td>
<td>66</td>
</tr>
</tbody>
</table>

STE: supratentorial ependymoma.

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### Table 4. Details on repeated resections in 19 patients.

<table>
<thead>
<tr>
<th>Patient number (WHO grade)</th>
<th>Resection grade</th>
<th>Interval between resections</th>
<th>Local/distant</th>
<th>Secondary pathology</th>
<th>Total survival</th>
<th>Survival after last resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (III)</td>
<td>GTR (RT)</td>
<td>0,5 years</td>
<td>Local</td>
<td>GBM</td>
<td>7 months</td>
<td>1 month</td>
</tr>
<tr>
<td>6 (II)</td>
<td>STR (RT)</td>
<td>36 years</td>
<td>local</td>
<td>GBM</td>
<td>37 years</td>
<td>1 year</td>
</tr>
<tr>
<td>11 (II)</td>
<td>STR (RT)</td>
<td>0,5 years</td>
<td>Post fossa</td>
<td>GBM</td>
<td>2 years</td>
<td>1,5 years</td>
</tr>
<tr>
<td>12 (II)</td>
<td>GTR (RT)</td>
<td>1 year</td>
<td>local</td>
<td>GBM</td>
<td>2 years</td>
<td>1 year</td>
</tr>
<tr>
<td>14 (II)</td>
<td>STR (no)</td>
<td>3 years</td>
<td>local</td>
<td>GBM</td>
<td>3,5 years</td>
<td>0,5 years</td>
</tr>
<tr>
<td>17 (III)</td>
<td>GTR (RT)</td>
<td>1, 2, 3, 4 years</td>
<td>local</td>
<td>GBM</td>
<td>3,8 years</td>
<td>0,5 years</td>
</tr>
<tr>
<td>21 (III)</td>
<td>GTR (No/RT)</td>
<td>3, 5, 8, 18</td>
<td>local</td>
<td>GBM</td>
<td>20 years</td>
<td>2 years, Alive</td>
</tr>
<tr>
<td>22 (III)</td>
<td>GTR (RT)</td>
<td>1 year</td>
<td>local</td>
<td>GBM</td>
<td>1,2 years</td>
<td>0,2 years</td>
</tr>
<tr>
<td>23 (III)</td>
<td>GTR (RT)</td>
<td>3 years</td>
<td>Distant</td>
<td>GBM</td>
<td>16 years</td>
<td>13 years, Alive</td>
</tr>
<tr>
<td>25 (III)</td>
<td>STR (Cyt)</td>
<td>4 months, 1 year</td>
<td>local</td>
<td>GBM</td>
<td>10 years</td>
<td>9 years, Alive</td>
</tr>
<tr>
<td>26 (III)</td>
<td>STR (Cyt/R)</td>
<td>5 years</td>
<td>local</td>
<td>E-III + GBM</td>
<td>8 years</td>
<td>4 years, Alive</td>
</tr>
</tbody>
</table>

---

### Table 2. Observed overall survival rates from STE patient cohort with treated before the introduction of MRI.

### Table 3. Observed overall survival rates from STE patient cohort with treated after the introduction of MRI.

### Table 4. Details on repeated resections in 19 patients.
Discussion

This report presents follow-up data from all 26 children up to 18 years of age who underwent surgical treatment for STE at our institution during a period of almost 60 years. It can therefore be considered as a short historical review on this topic in our institution. The number of children treated for STE is less than half compared to children treated for PFE in the same period \( (n = 58) \) [13]. The limited number of patients confirms the rarity of this disease and the incidence is in accordance with larger series of pediatric intracranial ependymomas [4,10]. The median age of seven years at primary surgery in our STE cohort was more than twice the median age in our series of children treated for PFE [13].

MRI is considered to be of great importance for diagnosis, surgical planning and follow-up of brain tumor patients. The data presented herein corroborated the importance of MRI, as survival in the MRI-era was better than in the pre-MRI-era. The finding fits well with data showing improvement in 5-year survival in pediatric PFE patients in the MRI-era compared to the pre-MRI-era (26% vs. 54%) [13] (Table 5).

When further comparing our PFE and STE cohorts, however, there were clear differences in 1-month, 1-year, 3-year and 5-year-survival. The numbers were 74, 56, 38 and 26% for PFE patients in the pre-MRI, while for the 15 STE patients the corresponding figures were 93, 73, 47 and 26%, respectively. This may be explained by a considerable number of intraoperative and early postoperative deaths in the PFE cohort, and that 26% of these very young children with PFE actually died within one month after the posterior fossa tumor surgery in early years — before modern operative facilities and dedicated neuroanesthesia were established. It is therefore not surprising that surgery for the supratentorial tumors in this early period was associated with 1-month mortality of ‘only’ 7%. Another difference is that median age of children with STE was twice as high. On the other hand, the long-term survival for STE children treated in the pre-MRI era was rather depressing with only one single 10-year survivor (7%), in contrast to the corresponding observed 20-year survival of children with PFE children of 24% from this early period of treatment (Table 6) [13].

Gross total resection (GTR) is considered crucial for probability of long-term survival in pediatric ependymoma [14]. Complete removal may be particularly difficult in laterally extending PFE, as parts of the tumor may be adherent to cranial nerves and vascular structures. In supratentorial cases, GTR may be easier and safer to achieve, and the inferior results observed in STE compared to PFE in the early period of treatment may therefore seem unexpected and disappointing. However, since the age distribution among children with PFE and STE is different, these entities may actually represent different biological entities. Recent studies support this view by differentiating between molecular subgroups of ependymoma [15,16]. Unfortunately, we did not have such data for our patients from the present cohort.

Our series was small, but the results for patients treated during two decades (1992–2011) were nevertheless hopeful, and in accordance with the larger series of 73 children presented by Lillard [10]. Their series is much larger and with median follow-up of 8 years. Of our 11 patients, there were 8 long-term survivors with follow-up periods ranging from 8 to 27 years; these were all tumor-free, although 4 of them had experienced repeated resection. Eight of these 11 patients were treated for anaplastic tumors, of whom 5 were long-term survivors. Three patients were diagnosed in their first year of life. One of them had an easily resectable frontal tumor (GTR) (grade 2) and had 11 years uneventful follow-up without any adjuvant therapy (Figure 1). The other two, however, had grade 3 tumors and presented with a more challenging course of disease. Both received chemotherapy after STR and went through additional resections, one of them also received radiotherapy (Figures 2 and 3). After follow-up periods ranging from 8 to 11 years all these three patients were tumor-free, the last two unfortunately with major neurological deficits.

Reported follow-up data including survival rates beyond 15–20 years are still scarce. In the present series, results from the pre-MRI era were quite miserable and indicated that surgical resection followed by radiotherapy gave little hope for cure and long-term survival. These historical results, also comparable to those from the Danish study (1960–1984) [7] confirmed the statement from the paper of Mørk and Løken published in 1977 describing patients with STE as having no hope for survival [17]. On the other hand, the results from the period after introduction of MRI were in accordance with those published by Marinoff et al. [12] and McGuire et al. [18], as well as Lillard et al. [10].

<table>
<thead>
<tr>
<th>Table 5. Observed survival in PFE and STE patients from the treatment period after the introduction of MRI in 1987.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>PFE Number of patients alive</td>
</tr>
<tr>
<td>Number of patients at risk</td>
</tr>
<tr>
<td>% of patients alive</td>
</tr>
<tr>
<td>STE Number of patients alive</td>
</tr>
<tr>
<td>Number of patients at risk</td>
</tr>
<tr>
<td>% of patients alive</td>
</tr>
</tbody>
</table>

PFE: posterior fossa ependymoma; STE: supratentorial ependymoma.

<table>
<thead>
<tr>
<th>Table 6. Observed survival in PFE and STE patients from the treatment period before the introduction of MRI in 1987.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>PFE Number of patients at risk</td>
</tr>
<tr>
<td>Number of patients alive</td>
</tr>
<tr>
<td>STE Number of patients at risk</td>
</tr>
<tr>
<td>Number of patients alive</td>
</tr>
<tr>
<td>% of patients alive</td>
</tr>
</tbody>
</table>

PFE: posterior fossa ependymoma; STE: supratentorial ependymoma.
use of immediate postoperative MRI as well as in the follow-up improve the management of these patients. During the same period changes in surgical techniques and neuro-anesthesia as well as adjuvant therapy may also explain some of the described improvements.

The limitation of the present study is obviously the small number of patients as well as its retrospective nature. Survival rates from the last decades were more favourable and the working capacity for the group of patients who reached adult life was encouraging. The three infants with 8–11 years follow-up were all tumor-free, but a question remains about the durability of this result. Our results support that GTR may be of prognostic value, even in case of repeated resection [10,16].

Several authors including Frandsen et al. point to the lack of extensive follow-up reports in medulloblastoma and ependymoma cohorts, and that long-term survival appears to decline.
Figure 2. Six-month-old girl presenting with macrocephaly. MRI showed an enormous tumor involving most of the right cerebral hemisphere, and a limited resection demonstrated anaplastic ependymoma, WHO grade 3. There was no tumor reduction after 3 months of chemotherapy, and a major resection was therefore conducted. Several shunt procedures were also undertaken. After a minor repeated resection of residual tumor, chemotherapy was administered. Despite severe left hemiparesis and after orthopedic procedures, she can walk unassisted for about 50 meters. The Barthel index is 60, and she can talk and understands, but is in need of special schooling. She has minor epileptic seizures, well controlled with antiepileptic medication. After 10 years of follow-up, she is tumor-free according to MRI.
over time – not least in ependymoma patients [3, 13]. Frandsen and coworkers base their analysis on large SEER data sets. Survival for PFE seems better after GTR and radiotherapy compared to GTR alone, however, after 5-year follow-up the prognostic value of adding radiotherapy to GTR is no longer present. In STE, postoperative radiotherapy is widely used, but some authors have presented small series with good outcome even after GTR alone [19, 20]. In the present series there were three long-term survivors falling in this category. Why a minor proportion of our patients did not receive postoperative RT seems unclear, except for the very young patients, where avoidance of RT was pertinent. For the others we believe this was based on the opinion of the treatment team at the actual point of time. Recently Merchant et al. [21] has suggested to abolish RT after GTR for low-grade STE, but give adjuvant treatment for pediatric patients after non-GTR as well as all cases with anaplastic STE.

Adjuvant chemotherapy has generally not been considered effective in treatment of pediatric ependymoma, in contrast to medulloblastoma/PNET [22, 23]. However, in recent years high-dose chemotherapy protocols are in use for ependymoma for treatment of very young children, in order to avoid detrimental late effects of radiotherapy in this age group [25–27]. Our last two infant patients fitted into this concept.

Marinoff et al. [12] discuss the poor long-term prognosis for pediatric patients with ependymoma. In recent years, modern molecular diagnostics and more distinct classification scheme have been established, demonstrating different groups of
ependymomas with significantly different prognosis [16]. Unfortunately, we did not have such data from our patients as our series spans six decades of practice. Hopefully, increased insight into biology of these challenging tumors will lead to improved treatment strategies and better long-term results.

**Conclusion**

Pediatric STE occurs mostly in small children, and there is marked risk for local recurrence even after gross total resection and postoperative radiotherapy. Repeated surgery is an important part of treatment and may lead to persistent tumor control. MRI has been essential in ependymoma management since 1987 and has contributed to considerable improvement of 10- and 20-year observed survival rates.

**Ethical approval**

For this type of study, formal consent is not required.

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**Disclosure statement**

All authors certify that they have no conflict of interest.

**References**