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Improving aspects of palliative care for children

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Chapter 2

The timing, duration, and management of symptoms of children with an incurable brain tumor: a retrospective study of the palliative phase

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Chapter 2

**Abstract**

**Background**
A brain tumor is diagnosed in 25% of pediatric oncology patients and carries a 30% mortality rate. To increase proactive support of children with a progressive brain tumor, we obtained information on timing, duration, and management of symptoms in the palliative trajectory.

**Methods**
A retrospective review of medical charts of patients treated at a children’s university hospital, who were dying from a brain tumor between May 2007 and September 2012.

**Results**
Thirty-four children were included. After 0–2480 days (median, 168 days) from initial diagnosis, incurable disease was evident, with death occurring after 1–603 days (median, 80 days). Palliative cancer-directed therapy was given to 23 (68%) patients. Early presenting symptoms were altered mobility, speech disorders, and loss of sight or hearing. The symptoms with the shortest duration were somnolence, dysphagia, and dyspnea. The most frequent symptoms were pain (91%), poor mobility (74%), and somnolence (71%). Pain necessitated a short period of intravenous treatment with morphine in 38% of patients, for a median 4 days, and sedation in 15%, for a median 2.5 days. Do-not-resuscitate agreements were discussed with all parents at 0–576 days before death (median, 50 days) and were agreed upon by 33 (97%) parents. Twenty-seven (79%) patients died at home, and one died in a hospice. Six (18%) patients were admitted for intravenous anticonvulsants, pain medication, and sedation until death.

**Conclusions**
This study reports specific information on the timing of occurrence and duration of symptoms. This information will provide support for pediatric oncologists in preparing parents and primary health care professionals and anticipating symptom management and timely end-of-life decision-making in the palliative care phase for children with a brain tumor.
Introduction

Each year approximately 120 children are diagnosed with a brain tumor in the Netherlands, and 30% of these children will die due to their disease. These patients need appropriate pediatric palliative care.

Pediatric palliative care is increasingly recognized as an important topic worldwide, and in 2014 the World Health Organization (WHO) released a new definition specific for pediatric palliative care, stressing the importance of anticipated care planning. To offer patients anticipated palliative care in line with this WHO definition, pediatric oncologists as well as primary health care professionals need specific knowledge on the trajectory of a disease. Although earlier studies have summarized the occurrence of symptoms in the palliative trajectory of a child with brain cancer, little is known about the timing and the duration of the occurrence of these symptoms. Information about the timing and the duration can contribute to anticipating palliative care by improving symptom management by means of preset medication steps and pro-active supportive care. Furthermore, this information can also be used to establish an individually anticipated care plan (IACP), in which the expected symptoms, their onset and a symptom management plan will be described. An individual anticipated plan adds considerable value in preparing the parents on the expected trajectory of the disease of their child; it can be used to optimize medical care in the home situation, obtain a maximal level of comfort for their child and can assist the parents while making end-of-life decisions. It can contribute to fulfillment of the wishes of parents and child, and to decisions about spending time at home and participation in social life including school. The plan might even enable the patient to stay at home until death.

The aim of this retrospective study is to describe the specific trajectory of an incurable brain tumor in children and focus on timing of occurrence and duration of symptoms. The secondary aim is to describe the timing and completeness of do-not-resuscitate (DNR) agreements by parent and child, and parent-child decisions on location of death.

Patients and methods

Patients

All patients below 18 years of age at initial diagnosis, who were treated at the department of pediatric oncology of our tertiary children’s university hospital, and died from a brain tumor between May 2007 and May 2012, were included.

The switch to palliative care was set on the date that the treating oncologist discussed with the parents that cure was considered impossible and cancer-directed therapy would no longer be given with curative intent.
### Table 1. Symptoms during palliative phase in children with a brain tumor, presented in literature

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Brain Tumor (n)</td>
<td>7</td>
<td>157</td>
<td>59</td>
<td>18</td>
<td>54</td>
</tr>
<tr>
<td>Presence of symptoms defined:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor appetite</td>
<td>100%</td>
<td>53%</td>
<td>58%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>57%</td>
<td>29%</td>
<td>39%</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>Pain</td>
<td>71%</td>
<td>64%</td>
<td>81%</td>
<td>56%</td>
<td>91%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>43%</td>
<td>83%</td>
<td>58%</td>
<td>11%</td>
<td>44%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>57%</td>
<td>62%/52%</td>
<td>63%/64%</td>
<td>6%</td>
<td>53%</td>
</tr>
<tr>
<td>Constipation</td>
<td>71%</td>
<td>45%</td>
<td>58%</td>
<td></td>
<td>35%</td>
</tr>
<tr>
<td>Disturbed consciousness</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td>71%</td>
</tr>
<tr>
<td>Reduced mobility/paralysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74%</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>56%</td>
</tr>
</tbody>
</table>

### Methods

Patients were selected from the database of our oncology department of children deceased between 2007 and 2012. Medical charts from patients were reviewed retrospectively by one author (CJ) on preset characteristics including demography, the type, staging and treatment of the brain tumor. Information about the palliative phase included duration and timing of all documented symptoms, administered pain medication, hospital visits and admissions, and date and place of death.

Potential conflicting information was discussed with a second author (ASM), and if data was still unclear, it was checked with the patient’s oncologist. Further data was collected from the updates of the IACP, as filled in by a structured format (containing information on the previous course of disease; potential type of symptoms and how to anticipate and respond to them; and preferences of parents including preferred location of death and DNR agreement), as well as from the notes from the weekly oncology meetings about each individual patient. The medical ethical board considered the
The palliative phase of children with a brain tumor

retrospective chart approach of our study to be within the regulations of the Dutch Medical Research Involving Human Subjects Act, with no requirement to retrieve informed consent from parents.

**Statistical analysis**
We used SPSS software 20.0 for statistical analysis. Binary outcomes were analyzed by Fischer’s exact test and in case of wide ranges in continuous outcomes, the Kruskal Wallis test was applied. P-values of and below 0.05 were considered significant.

**Results**

**Patients and treatment**
Thirty-four children were included (18 male, 16 female, age five months till 17.2 years at initial diagnosis, median 6.56). Eight patients had a medulloblastoma, seven patients a glioblastoma, five patients an atypical teratoid rhabdoid tumor, five patients a diffuse intrinsic pontine glioma, four patients an anaplastic ependymoma and five patients another specified tumor (two patients with choroid plexus carcinoma, one patient with malignant peripheral nerve sheath tumor, one patient with pilocytic astrocytoma, one patient with a germ cell tumor). Demographic characteristics as well as the tumor characteristics and treatment are presented in table 2.

Chemotherapy with curative intent was given to 26 (76%) of the patients with a median duration of 126 days (range 3-440 days). Seventeen (50%) patients received radiotherapy in curative setting. Eight patients (five with diffuse intrinsic pontine glioma (DIPG) and three with incompletely resected glioblastoma multiforme (GBM)) were considered incurable from diagnosis onwards.

After a median of 168 days from initial diagnosis (range 0-2480) care with curable intent, switched to palliative care. During the palliative phase, 23 (68%) patients received cancer-directed therapy. Reasons to stop palliative cancer-directed therapy were documented in 17 of these 21 patients and were toxicity in one patient, progression during therapy in 12 patients, and death in four. During the palliative trajectory, the median number of clinical hospital admission days was five (range 0-31) and median number of daycare admissions was zero (range 0-37). The percentage of admission days and visits as part of the palliative phase was 3% (range 0-100%) and 0% (range 0-13%) respectively.
Table 2. Patient characteristics and symptoms categorized per tumor type.

<table>
<thead>
<tr>
<th>Characteristics at initial diagnosis</th>
<th>Medulloblastoma</th>
<th>Anaplastic ependymoma</th>
<th>ATRT</th>
<th>DIPG</th>
<th>GBM</th>
<th>Other*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>7.2</td>
<td>6.6</td>
<td>5.5</td>
<td>6.9</td>
<td>9.0</td>
<td>6.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Range (range)</td>
<td>2.2 – 17.1</td>
<td>1.9 – 15.9</td>
<td>0.5 – 15.9</td>
<td>4.7 – 11.4</td>
<td>4.8 – 17.2</td>
<td>3.5 – 15.8</td>
<td>0.4 – 17.2</td>
</tr>
<tr>
<td>Metastases at initial diagnosis (%)</td>
<td>2 (25%)</td>
<td>2 (50%)</td>
<td>0 (40%)</td>
<td>0</td>
<td>0</td>
<td>3 (30%)</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Initial resection n(%)</td>
<td>6 (100%)</td>
<td>4 (100%)</td>
<td>4 (80%)</td>
<td>0</td>
<td>5 (80%)</td>
<td>3 (60%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Complete resection n(%)</td>
<td>6 (75%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td><strong>Days from initial diagnosis to incurable disease</strong></td>
<td>695 5</td>
<td>401 1.5</td>
<td>246</td>
<td>0</td>
<td>93</td>
<td>272</td>
<td>168</td>
</tr>
<tr>
<td>Median</td>
<td>156–1008</td>
<td>85-2480</td>
<td>109-469</td>
<td>0-0</td>
<td>0-231</td>
<td>71-617</td>
<td>0-2480</td>
</tr>
<tr>
<td><strong>Reason for start palliative phase n(%)</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (100%)</td>
<td>3 (43%)</td>
<td>0</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Incurable from diagnosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (100%)</td>
<td>3 (43%)</td>
<td>0</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Progression during treatment</td>
<td>1 (12.5%)</td>
<td>2 (50%)</td>
<td>4 (80%)</td>
<td>0</td>
<td>4 (57%)</td>
<td>4 (80%)</td>
<td>15 (44%)</td>
</tr>
<tr>
<td>Recurrence after CR</td>
<td>7 (87.5%)</td>
<td>2 (50%)</td>
<td>1 (20%)</td>
<td>0</td>
<td>0</td>
<td>1 (20%)</td>
<td>11 (33%)</td>
</tr>
<tr>
<td><strong>Anti-cancer therapy in palliative phase</strong></td>
<td>6</td>
<td>1 (25%)</td>
<td>0</td>
<td>2 (40%)</td>
<td>4 (57%)</td>
<td>5 (100%)</td>
<td>18 (53%)</td>
</tr>
<tr>
<td>Chemotherapy, n(%)</td>
<td>305 (3-350)</td>
<td>50 (range)</td>
<td>17 (3-350)</td>
<td>15 (3-350)</td>
<td>54 (3-150)</td>
<td>54 (3-350)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of palliative phase in days</strong></td>
<td>261</td>
<td>52</td>
<td>50</td>
<td>116</td>
<td>82</td>
<td>56</td>
<td>80</td>
</tr>
<tr>
<td>Median</td>
<td>19-603</td>
<td>1-243</td>
<td>5-92</td>
<td>68-576</td>
<td>7-227</td>
<td>47-326</td>
<td>1-603</td>
</tr>
<tr>
<td>Range</td>
<td>7-356</td>
<td>0-653</td>
<td>6-122</td>
<td>0-89</td>
<td>1-134</td>
<td>7-26</td>
<td>0-653</td>
</tr>
</tbody>
</table>

Abbreviations: ATRT atypical teratoid rhabdoid tumor, DIPG diffuse intrinsic pontine glioma, spNET supratentorial primitive neuro-ectodermal tumor, GBM glioblastoma multiforme

This table presents patient characteristics as well as documented symptoms categorized per tumor type.

1 2 patients with choroid plexus carcinoma, 1 patient with malignant peripheral nerve sheath tumor, 1 patient with pilocytic astrocytoma, 1 patient with a germ cell tumor, significant later start of palliative phase in children with medulloblastoma and anaplastic ependymoma, p 0,001, significantly more children with incurable disease at diagnosis in group DIPG and GBM, and more children with recurrence after complete remission in medulloblastoma group, p 0.001. 13 (62%) patients received chemotherapy only with a median duration of 50 (range 5-350) days. Three (14%) received radiotherapy only with a median duration of 17 days (range 16-18 days). Five (24%) received a combination of chemotherapy, median duration 85 (range 74-350) days, and radiotherapy, median duration 28 (range 6-39) days, no significant correlation between tumor type and duration of palliative phase.

Timing of occurrence of symptoms, duration of symptoms and treatment

In order to be able to compare the occurrence of symptoms with data from literature, we categorized the symptoms into 16 groups (table 3). The timing of symptoms was reported from the first moment the presence of a symptom was documented in the medical chart. To illustrate the timing and duration of symptoms, the start of each symptom for each patient individually is presented in weeks before death in figure 1.
Symptoms that present early during the palliative phase and with thus longest duration until death were altered mobility, speech disorders and loss of sight or hearing. Symptoms that occur much later during the palliative phase and are considered to last for a short period are somnolence, with a median start of four days before death (1-52), and dysphagia that started a median of 8 days before death (0-148). Also, dyspnea and incontinence occurred late and lasted only a short period, median respectively 12 (0-51) and 15 (5-51) days.

Thirty-one patients had pain, which started a median of 32 days (0-408) after switch to palliative care and lasted a median of 43 (2-225) days until death. Twenty two patients had headaches, six patients had pain in the back, neck and legs, one patient had facial pain and one patient had stomach pain. In one patient the location of pain was unspecified. Figure 2 presents the timeframes of subsequently introduced pain medication after switch to palliative care as applied for each individual patient. Dexamethasone was added to treat pain in 13 patients after a median of 32 days. Parenteral (subcutaneous or intravenous) morphine was started in 15 patients after a median of 76 days from the switch to palliative care and administered for 1-44 days (median 4) and sedation with midazolam after a median of 61 days in eight patients for 0-6 days (median 2,5) (five additional to morphine, in three patients as single regimen). After the patients died, all parents were invited for a personal evaluation interview with their oncologist. In 97% of the cases it was noted that parents experienced the treatment of pain as satisfactory.

The table provides information on the number and percentage of patients with each symptom.  
1 including imbalance, ataxia, muscle weakness, paralysis, broad walking pattern and tremors, 2 including bradyphrenia, agitation, confusion and amnesia, 3 including disturbed eye movements and an asymmetric face.
Figure 1. Timing of symptoms

Fig. 1. The lines provide the timing of occurrence and the duration of symptoms. The horizontal axis gives the number of weeks before death of all patients. The gray area describes how many patients are in the palliative phase in each week. Each separate line depicts how many patients are registered to have this symptom in each week. In the legend the symptoms are ranked from highest occurrence to lowest, and for each symptom the number of patients with the symptom is given as well as the median number of days before death the symptom occurred.

Fifteen patients had an increased intracranial pressure which started a median of 19 (0-292) days after switch to palliative care and lasted a median of 20(1-191) days until death. Five patients were treated with central nervous fluid tapping to reduce pressure via an Ommaya reservoir, lumbar taps or an extra-ventricular drain. Thirty of 34 patients received dexamethasone at some point in the palliative phase, 15 specifically for increased intracranial pressure. Epilepsy occurred in 19 patients, a median of 18 (0-294) days after switch to palliative care and 14 (1-323) days before death. Three patients were already treated with anti-epileptic medication since initial diagnosis. Three presented with seizures as a sign of tumor progression, which contributed to the decision to switch to palliative care. The other 13 patients developed seizures during the palliative phase, seven with durable response to anti-epileptic treatment. In six patients a refractory convulsive state initiated the terminal phase in which anti-convulsive medication was given to provide comfort until death for a median of three (2-4) days.
Figure 2. Pain medication during the palliative phase.

Fig. 2. This figure presents a timeline, in days, for each patient. The length of each timeline indicates the duration of the palliative period for the specific patient, presented in days. The colors indicate the duration that pain medication was used. Each medication was added to previous medications.

Agreements on DNR and/or to refrain from intensive-care unit admission were discussed for all 34 patients at a median of two (range 0-532) days after the switch to palliative care and at a median of 50 days (range 0-576) before death. By Dutch law patients over 12 years of age should be partner in this decision making process as well. This was performed in four out of eight patients older than 12, while in the other four patients the oncologist together with parents explicitly decided to avoid this issue due to extreme fear of dying during sleep in one patient, one for cultural reasons due to Islamic background, one patient was in a coma and one patient was physically incapable to join this discussion. Parents of one patient did not agree to any treatment restriction.

Patients death occurred at a median of 80 days after the switch to palliative care, (range 1-603), with no significant difference between tumor groups. Parents of a 17 year old boy with severe attention deficit disorder chose upfront to stay in a hospice until death. Death at home was feasible in 27 (79%) patients, while 6 (18%) died in the hospital: five (15%) at the pediatric oncology department and one at the pediatric intensive care unit. Twenty-five (74%) patients died during sleep or in a state of somnolence.
Chapter 2

Discussion

This report brings specific insight in the timing of occurrence and duration of symptoms of solely children with an incurable brain tumor. Recent descriptive studies documented the occurrence of symptoms at any time point during the final stage of an incurable brain tumor, reporting pain (56-81%), fatigue (11-83%), disturbed mobility 55-90% and dyspnea (22-57%) (Table 1).  

None of these publications provide specifics on the timing, duration nor treatment of the symptoms.

The frequencies reported seem to be broadly consistent with the frequencies observed in this study. The only clear discrepancy with former studies is the occurrence of fatigue; where other studies reported occurrence of fatigue in up to 90% of the cases, appearance of fatigue was only documented in 30% of the cases in this study. This discrepancy could be ascribed to little attention for the symptom by the health-care professional or lacking reports in the medical file.

In contrast to the other studies, this study additionally provided specifics on the timing, duration and the treatment of the symptoms. Figure 1 presents an overview of the trajectory of the symptoms in time of occurrence and duration in relation to the start of the palliative phase, and in relation to the time until death. This information on time-to-occurrence in relation to the start of the palliative phase has several practical applications; it provides new insight for health-care professionals and enables them to guide parents with more information on when to expect certain complaints and how to anticipate on them. For the health-care professional, information on early occurrence of altered mobility, speech disorders and loss of sight or hearing might contribute in providing adequate anticipated care with early access to the required medical aids. For the parents it might be comforting to know that the most burdening symptoms, such as somnolence, dysphagia and dyspnea, in general occur late in the trajectory of the disease and have a limited duration. Furthermore, insight in which symptoms have limited duration and therefore can be interpreted as an initiation of the terminal phase, enables anticipating end-of-life care and can be used in discussions preparing for end-of-life.

Anticipating symptom management based on information on timing and duration of the symptoms can be used in decisions about pain treatment. Adequate treatment of pain is highly important in pediatric palliative care, since unrelieved pain is not only a stressor for the child but also for its parents, and it can affect them heavily in their grief during the years after their child died. Still, pain is often documented to be treated insufficiently. Wolfe et al. and Heath et al. interviewed the parents of children who died of childhood cancer, about treatment of pain and other symptoms. They documented that the parents of respectively 44 out of 66 and 45 out of 76 children declared that there was insufficient pain management during treatment of their child.

In our cohort, care, including pain management, was evaluated with the parents of the deceased child by the treating oncologist. In contrast with former studies, it was noted
that in 97% of the cases the parents were satisfied with the way pain was treated. Although this high satisfaction of parents might be enhanced by recall bias, the difference in successful pain management between our cohort and earlier studies might also be attributed to the anticipating approach of our tertiary hospital and use of the IACP to provide specific care for the individual child. The IACP describes which medication should be administered to optimally treat the patients’ pain. It also describes the appropriate age-and patient specific method for evaluation of pain. By offering an anticipated treatment plan, we ensure that parents are sufficiently informed, and that pain medication is available in the home situation, so that pain medication can be added and/or intensified in case of worsening of the pain.

For all patients in our cohort, DNR agreements were made at a median of 50 days (range 0-576) before death. Bradshaw et al. report DNR discussions in 48% of their mostly pediatric cohort at a median of 11 days before death (range 0-409) and Gofton et al. in 70% of their adult cohort with a median of 39 days before death (range 1-198). This implies that in comparison with these other reports, discussion about DNR agreement was done more often and in an earlier stage of the disease of the child in our cohort. This policy of early DNR discussion is an important step in anticipating care in the palliative phase and enables children to stay at home in the final days of life.

The majority of our patients (82%) died at home during sleep or in a somnolent state. The percentage of patients who died at home is larger compared to studies from the US (44-57 %), Canada (35%) or Germany (40%). while the UK documented a similar percentage of 77%. This could be related to the anticipating palliative care, early DNR discussion, cultural differences and also the wide-range of primary care facilities available in UK and the Netherlands, including specialized child home care, to realize palliative and terminal care at home.

Despite these facilitating factors, 18% of the patients of our cohort died at the hospital. Of these patients, five were referred to the hospital with unexpected symptoms (reduced consciousness and convulsion) for diagnostic imaging, revealing progressive disease in all cases. Hospital admission could possibly have been prevented with improved anticipating education on the trajectory of disease to primary health care givers as well as to the parents. However, the diagnostic imaging showing progressive disease might have contributed to the parental acceptance of the terminal phase. Vickers et al., concludes that ensuring that everything possible has been done might be the only way for some parents to be able to cope with their child’s death.

**Strengths and limitations**

This is the first study reporting the specific trajectory of pediatric brain tumors and the time of occurrence and duration of symptom during this trajectory. By documenting all symptoms from the charts, instead of scoring preset symptom-checklists, this study gives a complete trajectory of the disease.
Selection bias was prevented by including all patients with an incurable brain tumor of the pediatric oncology ward of a large tertiary children’s hospital over a five year period. Still, a number of limitations to this study need to be acknowledged. First, the period described as palliative phase in different studies is limited in comparability due to a grey area in transition from curative to palliative phase. In our study, switch to palliative care was defined by discussion of the treating oncologist with parents that cure of the child was impossible and cancer-directed therapy would no longer be given with curative intent. However, a more gradually integrative transition can be seen in clinical practice.\textsuperscript{26,27}

Second, the retrospective chart-study design could result in some underestimation of symptoms. Symptoms that due to the retrospective design seem specifically reported less in comparison to earlier publications are fatigue and loss of appetite.

Third, the degree of burden as experienced by the patient from pain or any other symptom could only be distracted from the notes of professionals. In our department parents learn to evaluate pain treatment by using numeric scores, so we may assume that parents continue evaluating pain treatment during the palliative phase of their child likewise. However exact information was missing about the assessment method and who assessed pain during the palliative phase. Notes whether the consultation was performed telephonically or face to face were often missing.

Last, despite the detailed symptom information from the files there was no information available on quality of life of the child or to what extend the child was able to participate in normal life, for instance via Lansky score.\textsuperscript{28} Future prospective study designs on the trajectory of progressive and incurable cancer should take account of these limitations and gather this information more specifically.

**Conclusion**

This research extends our knowledge of timing of occurrence of symptoms in relation to the start of the palliative trajectory of a pediatric brain tumor, and how long these symptoms will exist before death occurs. This new knowledge will support pediatric oncologists to prepare parents and primary healthcare professionals and enables anticipating palliative care with upfront symptom management, and early end-of-life decision making in the palliative phase of children with a brain tumor.
Reference list


The palliative phase of children with a brain tumor

