Outcome in children with brain tumours diagnosed in the first year of life: long-term complications and quality of life

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Abstract

OBJECTIVE: To study the outcome in children with brain tumours diagnosed in the first year of life, we followed up 27 consecutive children who were diagnosed between 1980 and 2005 in a single institution. METHODS: Tumour control and neurological, endocrine and cognitive complications and their impact on behavioural and emotional adjustment and health-related quality of life (HRQoL) were comprehensively assessed in 11 survivors (mean follow-up time 12.3 years). RESULTS: Persistent neurological complications occurred in 9/11 patients, endocrine and growth complications in 4/11, and cognitive deficits leading to school problems/impaired choice of occupation in 8/10. Behavioural and psychological adjustment problems were reported by 4/6 patients and 7/10 parents. HRQoL as rated by patients and their parents was considerably lower than that of healthy controls. In comparison with healthy controls, social functioning was rated by the patients and the parents as the QoL dimension most affected. HRQoL was lowest for patients with high-grade tumour histology and more intense therapy. CONCLUSION: Long-term survivors of brain tumours diagnosed in the first year of life are not only at great risk of neurological and cognitive complications, but also of social isolation thereby substantially decreasing self-rated HRQoL.
Outcome of children with brain tumours diagnosed in the first year: long-term complications and quality of life

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ABSTRACT

Object: To study the outcome in children with brain tumours diagnosed in the first year of life, we followed up 27 consecutive children who were diagnosed between 1980 and 2005 in a single institution.

Methods: In 11 survivors (mean follow-up time 12.3 years), tumour control, neurological, endocrine, and cognitive complications, and their impact on behavioural and emotional adjustment and health-related quality of life (HRQoL) were comprehensively assessed.

Results: Persistent neurological complications occurred in 9/11 patients, endocrine and growth complications in 4/11, and cognitive deficits leading to school problems/impaired choice of occupation in 8/10. Behavioural and psychological adjustment problems were reported by 4/6 patients and 7/10 parents. HRQoL as rated by patients and their parents was considerably lower than that of healthy controls. In comparison with healthy controls, social functioning was rated by the patients and the parents as the QoL dimension most affected. HRQoL was lowest for patients with high-grade tumour histology and more intense therapy.

Conclusion: Long term survivors of brain tumours diagnosed in the first year of life are not only at great risk of neurological and cognitive complications, but also of social isolation thereby decreasing self-rated HRQoL substantially.
INTRODUCTION
Brain tumours in children under one year of age account for 3 to 11% of total childhood brain tumours.[1-4] The most common types are glioma, choroid plexus papilloma, ependymoma, primitive neuroectodermal tumour (PNET), atypical teratoid/rhabdoid tumour (AT/RT), and teratoma.[5-8] There are significant differences between brain tumours in infancy and those occurring at a later time-point: location is more often supratentorial, tumours are larger at presentation, biological behaviour tends to be more aggressive, and surgical resection is more difficult due to smaller anatomic structures and to more complicated anaesthesia, translating into higher surgical mortality.[3, 6, 9-14] Whereas treatment of histologically non-malignant tumours generally consists of surgical resection alone, malignant tumours are treated postoperatively with chemotherapy with or without delayed radiotherapy.

It has been shown that long term survival of infants with brain tumour is significantly worse than that of older children, the most important determinant of survival being histology and degree of resection.[3, 8, 15, 16] Not yet sufficiently documented in this specific group of patients are the late treatment complications and the impact that such late effects have on the social and psychological adjustment and the health-related quality of life (HRQoL) of survivors.

Interest in the measurement of HRQoL has expanded considerably over the past 10 years, with an increasing appreciation of the importance of the patient’s perspective.[17] According to the World Health Organization, HRQoL is to be regarded as a multi-dimensional concept that includes physical, social, cognitive, and emotional functioning.[18] The subjective perception and appraisal of functioning is as important as objective health, because individuals with the same objective health status may report very different quality of life.[19] For assessing HRQoL in paediatric populations, there is wide agreement that instruments should be multidimensional, sensitive to cognitive development, easy to complete, and encompass the broadest age range possible. Furthermore they should meet the psychometric requirements of sensitivity, reliability and validity.[20-23]

To study the outcome in children with brain tumours diagnosed in the first year of life, we followed up 27 consecutive patients, who were diagnosed between 1980 and 2005 in a single institution. In survivors, a comprehensive assessment of neurological and endocrine complications and their impact on behavioural and psychological adjustment and HRQoL was performed using qualitative and quantitative measures, i.e. conventional medical follow-up, semi-structured interview, and various questionnaires.
PATIENTS AND METHODS

Patients
Between January 1980 and December 2005, a total of 407 children (age 0.0 - 16 years) were diagnosed with a brain tumour at the University Children's Hospital of Zurich, Switzerland. Twenty-seven of those 407 were less than one year old at diagnosis (low-grade glioma, n=6; high-grade glioma, n=2; medulloblastoma, n=4; supratentorial PNET, n=2; choroid plexus papilloma, n=5; ependymoma, n=4; AT/RT, n=3; teratoma, n=1). All diagnoses except for one were confirmed by histological assessment of a tumour specimen obtained at surgery and in two cases at autopsy. One diagnosis (thalamic low-grade glioma) was made exclusively on clinical and radiological grounds. The mean age at diagnosis for these 27 patients was 0.4 years (range, 0.0 to 0.9 year). As of November 2006, 12 of them were alive and 1 patient (with low-grade glioma) was lost to follow-up. Of the 12 patients in continuous follow-up, 1 patient (with low-grade glioma) was excluded from the study because her parents declined to participate. Of the 11 study patients, 5 patients were female and 6 were male: their mean age at diagnosis was 0.4 years (range, 0.0 to 0.9 years) and their mean age at assessment was 12.7 years (range, 4.0 to 22.0 years). Tumour location was supratentorial in 10 patients and infratentorial in 1 patient. Histological diagnoses included choroid plexus papilloma in 4 patients, anaplastic ependymoma in 2 patients, low-grade glioma in 2 patients, and anaplastic astrocytoma, atypical supratentorial PNET, and teratoma in 1 patient each. Approval to perform the study and to link study data to clinical data was obtained from the Institutional Review Board.

Semi-structured interview
After obtaining informed consent, patients and parents were interviewed by one author (NUG). Interviews took place either during an outpatient visit or by telephone. The data gathered in the interviews were intended to give a descriptive picture of the participant’s past and present life situation. Therefore, the interview included questions about time of diagnosis and treatment, current medication, physical health, satisfaction with physical appearance, cognitive functioning, emotional functioning, school or job performance, interpersonal relationships including family and intimate relationships, social activities, personal interests and wishes about the future (Appendix). The questions were phrased in an easily comprehensible way and almost every question had a yes/no answer. Interviews were conducted with parents of all patients as well as with those 8 patients capable of answering the questions.

Munster Heidelberg Abilities Scale
To assess the ability to perform daily life activities, the German ‘Fertigkeitenskala Münster-Heidelberg’ Scale (FMH, Munster Heidelberg Abilities Scale) was used[24]. The FMH is a standardized tool for measuring motor and verbal functioning. A point score leads to an age-related centile ranking similar to typical centiles in paediatrics. Consisting of 56 items like ‘can walk without aids’ or ‘earns money’, the FMH items are self-report scales (yes or no) developed for children, adolescents, and adults with brain tumours. Dimensions covered include locomotion, eating/drinking, personal hygiene, general independence, understanding and writing/reading/calculating. In the present study
the FMH was used for all patients. The scores of the study patients were expressed as age-dependent centile values based on the published scores of 971 healthy controls.[24]

**Youth self report (YSR)**
To assess behavioural and emotional problems, a German version of the YSR derived from the Child Behaviour Checklist (CBCL) was used.[25, 26] It is a self-administered form designed for use with children and adolescents aged 11 to 18 years. The questionnaire consists of 120 items addressing a variety of behavioural and emotional symptoms. It yields scores for 8 narrow-band clinical sub-scales (withdrawal, somatic complaints, anxiety and depression, social problems, thought problems, attention problems, aggressive behaviour, and delinquent behaviour), 2 broadband scales (internalising and externalising behaviour problems), and an overall Total Behaviour Problems Score. Subjects rated the occurrence of each symptom within the past 6 months and selected their response from 0 (not true) to 2 (often or always true). The choice of cut-off points to denote clinically significant symptomatology in the various YSR scales is based on the recommendations of Achenbach.[27] Assuming that the YSR is also valid for young adults aged 18 - 22 years, the YSR was used in the present study for 6 patients between 11 and 22 years. One study patient in this age-range was not able to answer the questionnaire due to cognitive impairment; 4 patients were not assessed because their age was under 11 years. The scores of the study population were compared with norm scores provided from a sample of 1093 healthy Swiss children and adolescents.[26]

**Child Behaviour Check List (CBCL)**
To assess patients' behavioural and emotional problems from a parental point of view, a German version of the CBCL was used.[25 ,28] The CBCL is a parent-proxy report scale developed for children and adolescents aged 4 to 18. In order to compare parent reports with self-reports, the CBCL items correspond with the YSR items. Also, narrow and broadband scales are the same as in the YSR, as are the cut-off points. In the present study, the CBCL was used for the parents of 10 patients. One patient was excluded because of severe cognitive impairment. The scores of the study population were compared with norm scores provided from a community sample of 1093 Swiss children and adolescents.[29]

**Paediatric Quality of Life Inventory (PedsQL™)**
To measure HRQoL, a German version of the PedsQL was used.[17, 30] The PedsQL is a modular instrument for measuring HRQoL in children and adolescents aged 2 to 18 years (parent report), or 5 to 18 years (patient self-report). The 23-item PedsQL 4.0 Generic Core Scales are multidimensional self-report and parent proxy-report scales, which each encompass 8 items addressing physical health and 5 items addressing emotional functioning, social functioning, and school functioning. The scores of the study population were compared with the published scores of 401 healthy controls.[31] In the present study, 9 patients older than 5 years as well as the parents of all 11 patients completed the PedsQL 4.0 Generic Core Scales module. On a 5-point response scale subjects were asked how much each item had been a problem during the past month: 0 = never a problem, 1 = almost never a problem, 2 = sometimes a problem, 3 = often a problem, and 4 = (almost) always a problem. Through reverse scoring and linear
transformation of items (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) a scale was obtained in which higher scores indicate better HRQoL. Scale scores were computed as the sum of items divided by the number of items answered.

**Statistical analyses**
Patient-rated PedsQL scores were compared with the scores from healthy controls by one-sample t-tests. All other statistical analyses were performed by non-parametric tests due to the small sample size. Self- and parent-rated PedsQL scores were compared by Mann-Whitney U-tests. Spearman correlation coefficients were calculated to explore the relation between self-rated and parent-rated PedsQL scores and clinical factors. P values < 0.05 were considered as significant.

**RESULTS**

**Local tumour control and relapse-free interval**
The mean follow-up time of all 27 patients following diagnosis was 6.4 years (range 0.0 to 25.2 years). The 10-year overall survival was 48% and the 10-year progression-free survival was 37% as determined by the Kaplan-Meier method (Fig. 1).

For the 11 study patients, the mean follow-up time since diagnosis was 12.3 years (range, 3.3 to 21.8 years). Gross total tumour resection was achieved in 5 of 11 patients, and incomplete resection in 4 of 11 patients. One patient had tumour biopsy only and one patient had no tumour surgery. Postoperative chemotherapy was given to 5 patients; 3 of these patients received additional local conventionally fractionated radiotherapy (two patients, aged 3.1 and 3.4 years, each 54.8 Gy by external photon beam radiation; one patient, aged 1.8 years, with 60 Cobalt Grey Equivalent by three-dimensional conformal proton therapy). Tumour progression occurred in 2 patients (1 each with choroid plexus papilloma and anaplastic ependymoma). Both patients had gross total surgical removal of the recurrent tumour, 1 patient was given additionally postoperative radiotherapy (at the age of 3.4 years) (Table 1).

**Assessment of disabilities and their impact on HRQoL**
Together with the information obtained from the medical notes, the data gathered from the patients’ physicians, the patients’ parents as well as the patients themselves sought to give a description of the patients’ disabilities and their past and present life situation. Table 2 summarises this information.

**Neurological complications**
Nine (81%) of 11 patients had significant neurological complications that persisted during long-term follow-up. These complications included hemiparesis (n=5), strabismus (n=5), other visual impairment (n=4), ataxia (n=4), seizures (n=3), tetraparesis (n=1), facial nerve palsy (n=1), and hearing impairment (n=1).

**Endocrine/growth/physical functioning**
At the time of follow-up, 2 (18%) patients suffered from hypopituitarism, one of them (radiotherapy at age 3.4 years) receiving hormonal replacement therapy with corticosteroids, thyroid and sex hormones, the other patient (surgery near 3rd ventricle, no
radiotherapy) receiving therapy with thyroid hormone. Two (18%) patients had short stature (< 3rd percentile), 2 other patients (18%) were obese (body mass index > 97th percentile). Seven (64%) patients were affected by impairment of their physical fitness. Three (38%) of the 8 patients capable of being interviewed were dissatisfied with their physical appearance.

**School performance and occupation**

Seven of the study patients had difficulties in concentrating, 5 had significant language difficulties, and 4 had learning and memory difficulties. Significant school or occupational problems occurred in 8 of 10 patients of school or occupational age. Three patients attended a school for children with special needs, 3 were in a regular school, 2 of them needing remedial teaching, and 1 was still attending kindergarten, delaying school enrolment. Of the 3 patients of employable age, 2 were able to follow their preferred professional training. One patient (with 3rd ventricle choroid plexus papilloma) was doing perfectly well in professional training as a cook, without any kind of problems due to his former disease. Another patient (with temporal teratoma) was studying religious science at university (however, at a slower pace than usual due to significant problems concerning attention span and memory). The third patient (with frontal anaplastic astrocytoma) was so highly handicapped by being unable to communicate verbally as well as inability to move or do simple tasks by herself, that she could never receive any kind of education.

**Daily life activities**

Seven of the 11 study patients had FMH scores below the 25th centile, three of them below the 5th centile, indicating decreased age-appropriate ability to perform daily life activities. Low FMH centiles were associated with high-grade tumour histology, and treatment with radiotherapy (Table 1).

**Behavioural and emotional problems**

Based on the parent rated CBCL, 7 of 10 survivors had clinically significant behaviour problems, with 6/10 on the total, 5/10 on the internalising, and 1/10 on the externalising behaviour problems scale. On each of the parent-rated CBCL subscales, except thought problems and delinquent or aggressive behaviour problems, one to three patients had clinically significant scores. Two of six patients showed clinically significant elevated scores on the YSR total behaviour problems scale, 2/6 on the internalising behaviour problems scale, and 1/6 on the externalising behaviour problems scale. On the narrow band scales regarding social problems, the scores of 2/6 survivors were clinically significant. Two patients did not demonstrate clinical significance in any of the scales. In contrast to the self-rated YSR scales, the scores of the parent rated CBCL were more often significant (Figure 2).

**Health-related quality of life**

HRQoL was reported by 9/11 patients. One patient was below the validation age of 5 years and one patient was excluded because of her limited cognitive capacity to answer the PedsQL items. On average the patients rated their HRQoL lower in all domains than healthy controls (Fig. 3). The domains with the greatest discrepancies included social
functioning (patient mean: 60.0, control mean: 87.4; p = 0.02), psychosocial health (patient mean: 68.3, control mean: 82.3; p = 0.03), and school functioning (patient mean: 65.0, control mean: 78.6; p = 0.14). Emotional functioning was rated 75.0 vs. 80.9 (p = 0.12) and physical health 81.3 vs. 84.4 (p = 0.24). Notably, patients rated social functioning lower than school functioning. Physical health was the highest rated item. Total HRQoL as rated by the patients was lower than that of healthy controls (patient mean: 76.1, control mean: 83.0; p = 0.07). HRQoL was rated by parents of all 11 patients. The scores were equally rated lower in all domains compared to parents of healthy controls, with a higher discrepancy than that between patients and healthy controls themselves. Mean total HRQoL as rated by the parents of the nine patients described above was 56.5, compared to parental scores of healthy controls of 83.0 (p = 0.014). Again, the greatest discrepancies were seen in social functioning (patients’ parental mean: 55.0; healthy control’s parental mean: 91.56; p = 0.003). The scores were also lower for psychosocial health (55.0 vs. 86.6; p = 0.006), emotional functioning (55.0 vs. 82.6; p = 0.037), school functioning 75.0 vs. 85.5 (p = 0.054), and physical functioning (62.5 vs. 89.3; p = 0.065). Concordance between patient and parent ratings was variable, with lower parental ratings in all domains except for school functioning. HRQoL as rated by patients (p = 0.027) was lowest for patients with high-grade tumour histology and more intense therapy (Table 1). The parental rating of the patient less than 5 years of age rated HRQoL with a total score of 69.6, with lower scores than those of healthy subjects in all domains, especially in physical health. The parents of the patient unable to answer the questionnaire rated her total HRQoL as 44.6 (they made the comment that they were grateful she was alive in spite of all the difficulties).
DISCUSSION
With improved survival rates in paediatric brain tumours, awareness of significant
tumour- and/or therapy-related long-term complications, such as neurological, neuro-
psychological, endocrine and growth disturbances, has increased.[3, 6, 8, 13, 32-35] However, information about the impact of these complications on the social and
psychological adjustment and on the quality of life of the long-term survivors is scant,
and we are not aware of any studies which comprehensively evaluate these parameters in
long-term survivors of brain tumour diagnosed below the age of one year.

Nine of 11 patients showed persisting neurological complications. Endocrine dysfunction
due to hypopituitarism was found in 2/11, small stature in 2/11, and obesity in 2/11.
Seven of 11 patients had FMH scores below the 25th centile, indicating reduced age-
appropriate ability to perform daily life activities. The majority of patients had significant
impairments in at least one cognitive domain (attention deficits 7/11; language deficits
5/11; learning and memory deficits 4/11). These resulted in major school problems or
impaired choice of occupation in 8/10. Our results confirm previous findings. One study,
for instance, found significant neurological deficits in 8/13 patients diagnosed at less than
one year of age who survived more than 1 year after diagnosis, and only 2/7 children of
school age could attend a regular school without requiring remedial teaching.[8] Other
studies assessing children diagnosed during the first 1 to 3 years of life depending on the
series, consistently found significant neurological sequelae and neurocognitive deficits
also leading to major school problems in a majority of survivors.[3, 13, 36, 37]

However, school or occupational performance varied greatly in our series, ranging from a
perfectly healthy patient (3rd ventricle choroid plexus papilloma) successfully following
professional training as a cook to another patient (frontal anaplastic astrocytoma) unable
to communicate verbally or to show any other goal-directed activity.

Behavioural and emotional adjustment disturbances occurred in 4/6 patients according to
the self-rated YSR. Concordance between patient and parent ratings was variable, with
less favourable parent ratings in most domains. According to the parent rated CBCL, 6/10
patients showed clinically significant emotional and behavioural problems. Whereas
internalising problems (i.e. depression, anxiety, social withdrawal, and somatic
complaints) were frequent, externalising behavioural problems (i.e. hyperactivity,
impulsivity, defiance, and disruptive behaviour) were relatively rare. Our results are in
line with observations in older brain tumour patients, in whom clinically significant
emotional or adjustment problems were found in 17 to 67%.[18, 38-41]

Social functioning was rated by the patients and the parents as the HRQoL dimension
most affected. Seven of 11 patients had difficulties in making friends, and rejection by
peers was considered a problem in 4/10 patients. Besides social functioning, HRQoL was
rated lower by patients than by healthy controls in all other dimensions as well, i.e.
psychosocial health, school functioning, emotional functioning, and physical health. Most
other studies of HRQoL found similar results with consistently lower parental ratings
compared with patients’ self-reported scores. [40- 43] HRQoL in our study patients was
significantly lower in all self-reported as well as proxy-reported subscales (except for
self-reported physical health) than in long-term survivors of paediatric medulloblastoma diagnosed at older age.[41] Parental scores for physical health were comparable to those of long-term survivors of paediatric brain tumours diagnosed in older age groups, whereas proxy-reported psychosocial health scores were significantly lower in our study patients.[44] HRQoL in our study patients was comparable to that of long-term survivors of craniopharyngioma, who constitute a subgroup of paediatric brain tumour patients with an increased risk of low HRQoL.[40] Thus, our results confirm the finding of others that HRQoL including social functioning in long-term survivors of paediatric brain tumours is significantly reduced compared with that of healthy children, as well as the finding that HRQoL scores are generally lower when reported by proxies than by the patients themselves.[40, 41, 45] Even if comparisons between different studies must be interpreted cautiously in view of the small patient numbers in the diverse series, it appears that survivors of brain tumours diagnosed at less than one year of age are particularly prone to impairment of HRQoL.

In an effort to identify factors associated with unfavourable outcome, we compared FMH scores, self-rated HRQoL, and parent rated HRQoL with clinical factors (including gender, age at diagnosis, and therapy received). Poor functional outcome was associated with high-grade tumour histology, tumour progression, and the use of radiotherapy. HRQoL tended to be worse in patients with severe neurological, endocrine, and/or cognitive problems. However, no significant correlation between FMH scores and HRQoL was found, indicating differences in coping strategies.[46, 47]

Interestingly, the present series also contains survivors with fair to excellent functional, behavioural and HRQoL outcomes, who are able to attend a regular school or to undertake professional training in the profession of choice. Such good outcomes were associated with benign tumour histology and treatment by surgery alone. Thus, considering the enormous variation in outcome, to make a tentative prognosis on outcome for an infant with a newly diagnosed brain tumour, knowledge of tumour histology seems to be important. However, a precise prediction does not seem to be possible in all cases. This is illustrated by the pronounced differences in outcome between our patients with choroid plexus papilloma, ranging from absolute freedom from symptoms or impairments to low scores in physical functioning or in quality of life.

To our knowledge, this is the only study which comprehensively evaluates tumour control and functional, behavioural, and HRQoL outcomes in a population of patients with brain tumour under 1 year of age. However, we are aware of important limitations in this study: the sample size is small; tumour histology, tumour location, and treatment modality are highly heterogeneous; histological criteria have evolved over time; and formal neuropsychological testing has not been performed in all patients. Nevertheless, we believe that this study will help to acknowledge the manifold problems these survivors have to live with, being not only at great risk of neurological and cognitive impairment, but also of a reduced HRQoL due to psychological, emotional, and school problems, as well as social isolation. We further believe that besides progression-free and overall survival, oncologic treatment studies should address outcome measures such as physical, behavioural and emotional functioning as well as quality of life in a prospective
and longitudinal manner. The validated questionnaires used in our study exemplify a simple, but comprehensive, test battery that can be easily administered and may be completed in less than one hour. Over the years, as long-term survival is achievable in a rising number of children with brain tumour and as treatment options become more and more numerous, every effort should be made to identify the most promising treatment strategies not only in terms of disease-free survival but also regarding functional and psycho-social outcome. As treatment-related late effects may be especially devastating in patients treated at a young age, this is especially important in this subgroup of children. The first changes in this direction are already underway, such as delaying or even avoiding radiotherapy by administering prolonged and/or intensified chemotherapy, as well as by using conformal radiotherapy including proton therapy.[15, 34, 48-52] More refinement is still needed.
Appendix: Semi-structured interview questions

**Diagnosis**
How much do you know about your disease? Did or do you take a particular interest in it?
Is there anything concerning your disease which is difficult for you? If yes, what?
Is there anything concerning your disease which was difficult for you and which you now consider to be less difficult? Or vice versa?

**Present medication**
Do you take any medicine now? Which one? Are there medicines which you have taken in the past and which you don’t take any more?
Are you disturbed by having to take these medicines every day?
Do you have, or have you had, any side effects due to the therapy?

**Physical appearance**
Are you satisfied with your appearance? What disturbs you most about your appearance?
If you could, would you change anything about your appearance? If yes, what?

**General body fitness / Cognitive functions**
Do you feel your physical ability is affected by your illness? How much?
Do you take part in any sport? Which one? Is there any sport you like but which you can’t take part in?
Can you concentrate well at school, at work? Do you believe your ability to concentrate has been impaired by your illness? What about your speed in solving tasks or in understanding new things?
Do you often have gaps in your memory?

**Emotions**
What positive feelings do you have towards your illness? What negative feelings about your illness?
Are you afraid of getting ill again?

**School**
Which school do you or did you attend?
How do you get on at school? Do you have any difficulties? If so, are they due to your illness? Do you like going to school? If yes, why?
How often do you not attend school?
Do you feel comfortable in your class?
Did anything change in your relationship to your schoolmates after your illness? If yes, what?
Have people in your school/at work been informed about your illness? Did you tell them about it?

**Job**
Which job did you train for or would you like to train for? Is this the job of your dreams?
Have you started an apprenticeship? Did you finish it? If not, why?
Did or do you attend university?
What work do you do now? Are you happy with it? If not, why?
Did you have any other job before? Why did you change your job?

**Hobbies**
Do you have any hobbies? What are they?
Do you pursue your hobbies alone or with friends?
Are you a member of any club?
Do you play music?
Have you got a particularly strong interest in anything?
Do you have a pet?

**Social situation**
Do you live with your parents, with friends, or alone?
Do you live in a special home (hostel)?
How is your relationship with your parents/brothers and sisters? Do you often get angry with them? Would you prefer to live away from home?
Do you have a girl-/boy-friend, or have you ever had one?
If you have no relationship: do you miss it? Can you imagine your future without a partner?
Do you have a good boy-/girl-friend? Are you in touch with him/her? How often?
How do you relate to your teachers / schoolmates / colleagues?
How do you relate to the doctor treating you? Who is he/she? Does he/she support you? Does he/she give enough time to you? Does he/she explain to you, what he/she is going to do?
Are you independent in your daily life? Do you need help with particular things?
What is your source of income (wages/parents/state)? Do you receive a benefit? If yes, would you prefer any other source of income?

**Future**
How do you see your future?
What would you most like to happen?

**Additional comments**
REFERENCES

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### Table 1  Comparison of FMH scores and PedsQL scores with clinical factors

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>FMH (centile)</th>
<th>PedsQL (self-rated)</th>
<th>Gender</th>
<th>Age at diagnosis (years)</th>
<th>Tumour histology</th>
<th>Histological grade</th>
<th>Tumour location</th>
<th>Hydrocephaus</th>
<th>Tumour resection</th>
<th>Chemo-therapy</th>
<th>Radio-therapy</th>
<th>Tumour progression / relapse</th>
<th>Tumour reoperation</th>
<th>Follow-up since diagnosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1</td>
<td>NA</td>
<td>female</td>
<td>0.9</td>
<td>anaplastic astrocytoma</td>
<td>high</td>
<td>frontal</td>
<td>yes</td>
<td>incomplete</td>
<td>yes</td>
<td>54.8 Gy (local, parallel-opposed fields, photon beam, age 3.1 years)</td>
<td>no</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1-5</td>
<td>26.1</td>
<td>male</td>
<td>0.0</td>
<td>PNET, atypical</td>
<td>high</td>
<td>parietal</td>
<td>yes</td>
<td>total</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
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</tr>
<tr>
<td>3</td>
<td>1-5</td>
<td>80.4</td>
<td>female</td>
<td>0.2</td>
<td>choroid plexus papilloma</td>
<td>low</td>
<td>3rd ventricle</td>
<td>yes</td>
<td>incomplete</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>12.7</td>
</tr>
<tr>
<td>4</td>
<td>10-25</td>
<td>46.7</td>
<td>female</td>
<td>0.6</td>
<td>anaplastic ependymoma</td>
<td>high</td>
<td>4th ventricle</td>
<td>yes</td>
<td>total</td>
<td>yes</td>
<td>54.8 Gy (local, parallel-opposed fields, photon beam, age 3.4 years, after relapse)</td>
<td>yes</td>
<td>total 13.9</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10-25</td>
<td>57.6</td>
<td>female</td>
<td>0.4</td>
<td>low-grade glioma</td>
<td>low</td>
<td>thalamus</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>6.2</td>
</tr>
<tr>
<td>6</td>
<td>10-25</td>
<td>76.1</td>
<td>male</td>
<td>0.2</td>
<td>choroid plexus papilloma</td>
<td>low</td>
<td>3rd ventricle</td>
<td>yes</td>
<td>incomplete</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>total</td>
<td>12.1</td>
</tr>
<tr>
<td>7</td>
<td>10-25</td>
<td>87.0</td>
<td>male</td>
<td>0.6</td>
<td>fibrillary astrocytoma</td>
<td>low</td>
<td>thalamus</td>
<td>yes</td>
<td>biopsy</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>6.8</td>
</tr>
<tr>
<td>8</td>
<td>25-50</td>
<td>NA</td>
<td>male</td>
<td>0.7</td>
<td>anaplastic ependymoma</td>
<td>high</td>
<td>parietal</td>
<td>yes</td>
<td>incomplete</td>
<td>yes</td>
<td>60.0 CGE (local, 3D-conformal proton beam, age 1.6 years)</td>
<td>no</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>25-50</td>
<td>77.2</td>
<td>male</td>
<td>0.3</td>
<td>choroid plexus papilloma, atypical</td>
<td>low</td>
<td>lateral ventricle</td>
<td>no</td>
<td>total</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>13.1</td>
</tr>
<tr>
<td>10</td>
<td>50-75</td>
<td>54.4</td>
<td>female</td>
<td>0.1</td>
<td>teratoma</td>
<td>low</td>
<td>temporal</td>
<td>no</td>
<td>total</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>21.8</td>
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<tr>
<td>11</td>
<td>50-75</td>
<td>98.9</td>
<td>male</td>
<td>0.3</td>
<td>choroid plexus papilloma</td>
<td>low</td>
<td>3rd ventricle</td>
<td>yes</td>
<td>total</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>19.8</td>
</tr>
</tbody>
</table>

Patients are graded according to the FMH scores. FMH, Munster Heidelberg Abilities Scale. PedsQL, Paediatric Quality of Life Inventory. NA, not assessable. CGE, Cobalt Grey Equivalent.
Table 2 Disabilities of 11 long term infant brain tumour survivors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Affected patients (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological functioning</strong></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>5 / 11 (45%)</td>
</tr>
<tr>
<td>Strabismus</td>
<td>5 / 11 (45%)</td>
</tr>
<tr>
<td>Visual impairment (other than strabismus)*</td>
<td>4 / 10 (40%)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>4 / 11 (36%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 / 11 (27%)</td>
</tr>
<tr>
<td>Tetraparesis</td>
<td>1 / 11 (9%)</td>
</tr>
<tr>
<td>Facial nerve palsy</td>
<td>1 / 11 (9%)</td>
</tr>
<tr>
<td>Hearing impairment*</td>
<td>1 / 10 (10%)</td>
</tr>
<tr>
<td><strong>Endocrine functioning</strong></td>
<td></td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>2 / 11 (18%)</td>
</tr>
<tr>
<td><strong>Growth/physical functioning</strong></td>
<td></td>
</tr>
<tr>
<td>Height &lt; 3rd percentile</td>
<td>2 / 11 (18%)</td>
</tr>
<tr>
<td>Body Mass Index &gt; 97th percentile</td>
<td>2 / 11 (18%)</td>
</tr>
<tr>
<td>Dissatisfaction with physical appearance*</td>
<td>3 / 8 (38%)</td>
</tr>
<tr>
<td>Impaired fitness</td>
<td>7 / 11 (64%)</td>
</tr>
<tr>
<td><strong>Cognitive and school functioning</strong></td>
<td></td>
</tr>
<tr>
<td>Attention deficits</td>
<td>7 / 11 (64%)</td>
</tr>
<tr>
<td>Language deficits</td>
<td>5 / 11 (45%)</td>
</tr>
<tr>
<td>Learning and memory deficits</td>
<td>4 / 11 (36%)</td>
</tr>
<tr>
<td>Significant school problems/impaired choice of occupation</td>
<td>8 / 10 (80%)</td>
</tr>
<tr>
<td><strong>Social functioning</strong></td>
<td></td>
</tr>
<tr>
<td>Difficulties in making friends</td>
<td>7 / 11 (64%)</td>
</tr>
<tr>
<td>Rejection by peers</td>
<td>4 / 10 (40%)</td>
</tr>
</tbody>
</table>

*aClinical assessment not possible in one patient. bOnly patients capable of answering question by themselves.
FIGURE LEGENDS

**Fig. 1.** The Kaplan-Meier curves show the probability of progression-free survival (A) and overall survival (B) for 27 children with brain tumours diagnosed under 1 year of age.

**Fig. 2.** Behavioural and psychological adjustment problems as rated by the brain tumour patients (n=6; Youth Self Report) and their parents (n=6; Child Behaviour Checklist). The numbers of patients with clinically significant scores are shown. Parental scores of patients under 11 years of age are described in the text.

**Fig. 3.** Health-related quality of life (HRQoL) in survivors of brain tumours diagnosed under 1 year of age as rated by themselves (n = 9) and by their parents (n = 9) using the PedsQL 4.0 Generic Core. Compared with healthy controls, brain tumour survivors rated their HRQoL lower in social functioning (p = 0.02), psychosocial health (p = 0.03), emotional functioning (p = 0.12), school functioning (p = 0.14), and physical health (p = 0.24). Total HRQoL scores were lower in patients than in healthy controls (p = 0.07). Compared with parents of healthy controls, parental ratings of the patients’ HRQoL were significantly lower, with the most significant differences in social functioning (p = 0.003) and psychosocial health (p = 0.006). The difference in total HRQoL scores was highly significant as well (p = 0.014). Compared with patient ratings, parental ratings were lower in all dimensions except for school functioning. Horizontal lines are median values; solid box shows 25th to 75th centiles; whisker bars represent lowest and highest values. Parental total scores were 69.6 for one patient under 5 years of age, and 44.6 for one patient not capable of answering the questionnaire due to intellectual impairment.
What is already known on this topic
It has been shown that long term survival of infants with brain tumour is significantly worse than that of older children, the most important determinant of survival being histology and degree of resection.

What this study adds
This study documents the late treatment complications and the impact that such late effects have on the social and psychological adjustment and the health-related quality of life (HRQoL) of survivors of brain tumours diagnosed at age of less than one year.

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The authors declare no conflict of interest.
Fig. 1

A

B
Fig. 2

[Bar chart showing the number of patients with clinically significant scores across various behaviors.

- **Patients' rating (n=6)**
- **Parental rating (n=6)**

Behaviors include:
- Total Score
- Internalizing Behavior
- Externalizing Behavior
- Withdrawal
- Somatic Complaints
- Anxious/Depressed
- Social Problems
- Thought Problems
- Attention Problems
- Delinquent Behavior
- Aggressive Behavior]
Fig. 3

PedsQL 4.0 Generic Core Scales

- Controls (self-rating)
- Patients' rating (n=9)
- Parental rating (n=9)
- Controls (parental rating)