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ORIGINAL PAPER

Does diagnostic delay result in decreased survival in paediatric brain tumours?

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Abstract To study the hypothesis that a delay in the diagnosis of paediatric brain tumours results in decreased survival outcome probability, we compared the prediagnostic period of 315 brain tumour patients (median age 6.7 years, range, 0 to 16 years) with progression-free and overall survival. The median prediagnostic symptomatic interval was 60 days (range, 0 to 3,480 days), with a median parental delay of 14 days (range, 0 to 1,835 days) and a median doctor's delay of 14 days (range, 0 to 3,480 days). The prediagnostic symptomatic interval correlated significantly with the patient age, tumour histology, tumour location and year of diagnosis, but not with gender. We then grouped the patients according to histology (low-grade glioma [*n*=77], medulloblastoma [*n*=57], high-grade glioma [*n*=40], craniopharyngioma [*n*=27], ependymoma [*n*=20] and germ cell tumours [*n*=18]). Contrary to common belief, long prediagnostic symptomatic interval or long doctor's delay did not result in decreased survival outcome probability in any of these groups. The effect of tumour biology on survival seems to be dominant and overwhelms any possible opposing effect on survival of a delay in diagnosis.

Keywords Brain tumour · Diagnosis · Survival outcome

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Introduction

As a group, brain tumours are the most common solid tumours in children [9]. They differ from primary central nervous system tumours occurring in adults not only in histology, localisation, management and prognosis, but also in clinical presentation [14]. At the onset of illness, the nature of neurological and systemic dysfunction is often non-specific and variable, and relates not only to the site of origin of the tumour, but also to the child's age and developmental level [20]. The diagnosis of brain tumours poses difficulties and this is sometimes reflected in long prediagnostic symptomatic intervals (PSI) [3, 4, 8, 13, 15, 16, 18, 22, 23]. The better availability of computed tomography (CT) and magnetic resonance imaging (MRI) since the 1990s has resulted in shorter doctor's delay [3]. However, the median PSI of a recently described cohort of 200 patients diagnosed between 1988 and 2001 was still 2.5 months (range, 1 day to 120 months) [23]. Understandably, parents frequently raise the question as to whether an earlier diagnosis could have been made and, if so, whether the "delay" adversely affects prognosis. Recent reports describe the symptomatology of paediatric brain tumour cohorts [3, 22, 23], but information on the potential influence of PSI and doctor's delay on prognosis is scant. The present study was undertaken to study the common belief that a delay in the diagnosis of paediatric brain tumours results in decreased survival outcome probability.

Patients and methods

A retrospective study was undertaken on children up to the age of 16 years with primary brain tumours, admitted consecutively to the University Children's Hospital of Zurich, Switzerland, from January 1980 to December 2004. The clinical signs and symptoms of part of this series (n=252) have been reported previously [3]. Medical case notes, referral letters, neurosurgical records, histopathology reports, follow-up and survival outcomes were reviewed by two independent investigators (K.K. and M. D.). The PSI was defined as the interval between the onset of signs/symptoms and the time of diagnosis by MRI, CT or other imaging techniques. The PSI was subdivided into an interval between symptom onset and the first medical consultation (parental delay), and an interval between the first medical consultation and diagnosis by CT, MRI or other imaging techniques (doctor's delay). Discrepancies in the PSI were noted for 32 patients. These cases were re-examined together with the last author, and a consensus was reached.

Statistical analyses

Since most data were non-normally distributed, medians and interquartile ranges (IQR) were calculated for descriptive statistics, and non-parametric exact methods were used in the analytical statistics. In order to assess potential associations between the patient characteristics and delays, the Wilcoxon-Mann-Whitney test was used for binary variables, the Kruskal-Wallis test for categorical variables and the Jonckheere-Terpstra test for continuously measured variables divided into ordered categories before analysis. Overall survival (OS) was defined as the probability of survival, with only death as the event; children who were alive were censored at their last follow-up. Progression-free survival (PFS) was defined as the probability of being alive and free of progression/relapse; death and progression/relapse were considered as events. For survival analysis, the Kaplan-Meier estimate and its 95% confidence intervals (95% CI) were calculated. Age at diagnosis, PSI and the doctor's delay were categorized into four groups, each according to their quartiles before analysis, since a linear association between these delay times and outcome could not been assumed. The log-rank test was used to detect

Table 1 Location and histology of the 315 brain tumours examined in this study

Location and tumour histology	Number of tumours	%
Infratentorial	136	43
Medulloblastoma	57	18
Low-grade cerebellar glioma	31	10
Brainstem glioma	19	6
Ependymoma	11	3
Other	12	4
Tumours of unknown histology	6	2
Supratentorial hemispheric	103	33
Low-grade glioma	29	9
High-grade glioma	18	6
Choroid plexus tumour	7	2
Ependymoma	8	3
Primitive neuroectodermal tumours	7	2
Oligodendroglioma	3	1
Other	27	9
Tumours of unknown histology	4	1
Supratentorial midline	76	24
Craniopharyngioma	27	9
Germ cell tumour	17	5
Low-grade glioma	14	4
Primitive neuroectodermal tumours	2	1
Other	11	3
Tumours of unknown histology	5	2

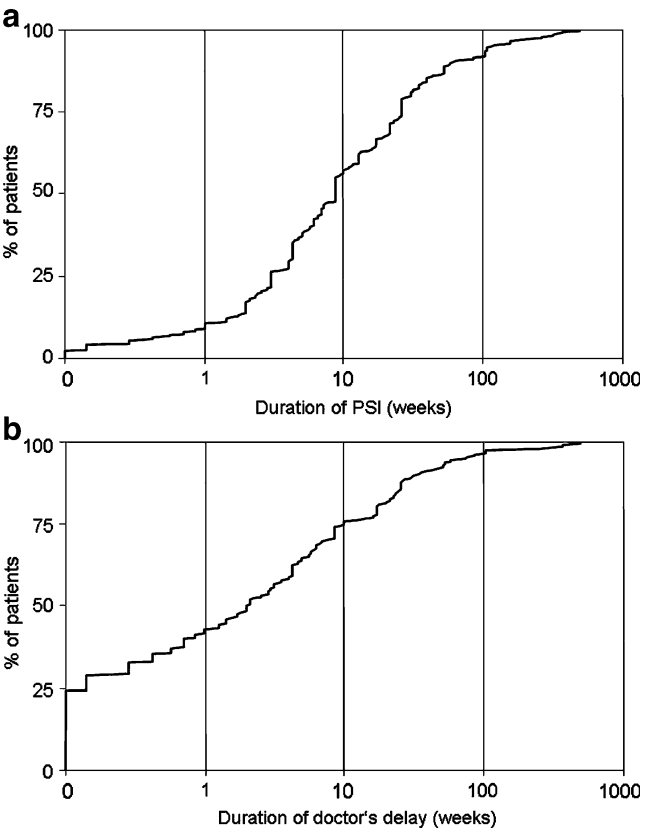

Fig. 1 **a** Cumulative distribution of the prediagnostic symptomatic interval (PSI) for 315 paediatric patients with brain tumours. **b** Cumulative distribution of the doctor's delay for 234 patients, where medical charts permitted subdividing the PSI into an interval between symptom onset and the first medical consultation (parental delay), and an interval between the first medical consultation and diagnosis by computed tomography (CT), magnetic resonance imaging (MRI) or other imaging techniques (doctor's delay)

differences in survival between different groups of patients. Two-sided tests were used throughout, and *P*-values below 0.05 were considered to be significant. StatXact 6 (Cytel Software Corp., Cambridge, MA, USA) was used for the exact non-parametric tests and S-PLUS 6.0 (Insightful Corp., Seattle, WA, USA) was used for the survival analyses and graphics.

Results

Patient and tumour characteristics

Three hundred and fifteen patients with a primary brain tumour were admitted to the University Children's Hospital of Zurich, Switzerland, between January 1980 and December 2004. The tumour characteristics of these patients are summarised in Table 1. They are comparable to those of larger series [14]. Therefore, the present cohort can be considered as adequately representative. The median age at diagnosis for all patients was 6.7 years (range, 0.0 to 16.0 years; IQR, 3.0 to 10.5 years). One hundred and eighty-five (59%) patients were male and 130 (41%) were female. Tumour location was infratentorial in 136 (43%) and supratentorial in 179 (57%) patients. Diagnoses were established by the histological assessment of a tumour specimen obtained at surgery in 274 (87%) patients and by typical imaging findings in 26 (8%) patients (e.g. diffuse intrinsic pontine glioma). In 15 (5%) patients with large tumours and poor general condition, no biopsy was undertaken and the histology remains unknown. The median follow-up time for all patients was 3.4 years (range, 0.0 to 25.3 years).

Prediagnostic symptomatic interval

The median PSI of all patients was 60 days (range, 0 to 3,480 days; IQR, 21 to 180 days), with a median parental delay of 14 days (range, 0 to 1,835 days; IQR, 0 to 46 days) and a median doctor's delay of 14 days (range, 0 to 3,480 days; IQR, 1 to 69 days) in the 234 (74%) patients where this distinction was possible. Figure 1a shows the overall cumulative distribution of PSI (*n*=315). Only 112 (36%) of the 315 brain tumours were diagnosed within 30 days from the onset of signs/symptoms. PSI was 31–60 days in 62 (20%) patients, 61–180 days in 75 (24%)

Table 2 Prediagnostic symptomatic interval (PSI), parental delay and doctor's delay (median and interquartile range [IQR]) in relation to age at diagnosis, gender, histology, tumour location and year of diagnosis

	PSI (days)	Parental delay (days)	Doctor's delay (days)
Age at diagnosis	JT=4.83, *P*<0.001	JT=2.23, *P*=0.025	JT=1.50, *P*=0.13
- Up to 4 years (*n*=100)	31 (14–62)	5 (0–27)	10 (1–49)
- 4 to 8 years (*n*=92)	63 (29–180)	21 (2–51)	14 (0–103)
- 8 to 12 years (*n*=62)	79 (33–270)	21 (0–48)	29 (6–66)
- ≥12 years (*n*=61)	106 (30–219)	11 (0–101)	20 (1–173)
Gender	WMW=1.44, *P*=0.15	WMW=0.55, *P*=0.58	WMW=1.57, *P*=0.12
- Female (*n*=130)	60 (21–180)	14 (0–49)	21 (2–120)
- Male (*n*=185)	53 (21–150)	14 (0–44)	13 (0–60)
Histology	KW=36.09, *P*<0.001	KW=15.1, *P*=0.017	KW=13.83, *P*=0.030
- Ependymoma (*n*=20)	30 (9–60)	5 (0–8)	5 (2–40)
- Medulloblastoma (*n*=57)	36 (21–60)	20 (3–40)	6 (0–30)
- Germ cell tumour (*n*=18)	39 (19–216)	14 (0–40)	14 (0–39)
- High-grade glioma (*n*=40)	49 (21–120)	10 (0–20)	13 (4–47)
- Low-grade glioma (*n*=77)	142 (42–195)	29 (3–86)	38 (2–148)
- Craniopharyngioma (*n*=27)	210 (81–445)	38 (4–135)	39 (7–338)
Location	KW=9.47, *P*=0.008	KW=6.57, *P*=0.039	KW=2.85, *P*=0.24
- Infratentorial (*n*=136)	45 (23–124)	17 (2–42)	10 (0–43)
- Supratentorial hemisphere (*n*=103)	60 (15–180)	7 (0–30)	13 (1–120)
- Supratentorial midline (*n*=76)	98 (30–360)	21 (0–75)	25 (1–180)
Year of diagnosis	JT=2.11, *P*=0.034	JT=0.57, *P*=0.57	JT=1.28, *P*=0.20
- 1980 to 1984 (*n*=66)	60 (30–210)	10 (0–30)	30 (4–165)
- 1985 to 1989 (*n*=51)	90 (30–202)	8 (0–56)	25 (0–96)
- 1990 to 1994 (*n*=61)	49 (21–175)	14 (0–46)	12 (0–60)
- 1995 to 1999 (*n*=59)	65 (28–180)	26 (0–90)	12 (0–70)
- 2000 to 2004 (*n*=78)	42 (17–118)	14 (1–37)	9 (2–49)

JT=Jonckheere-Terpstra statistic, exact *P*-value calculated; WMW=Wilcoxon-Mann-Whitney statistic, exact *P*-value calculated; KW=Kruskal-Wallis statistic, exact *P*-value calculated.

patients, 181–365 days in 31 (10%) patients and >365 days in 35 (11%) patients.

The cumulative distribution of the doctor's delay is shown in Fig. 1b. The doctor's delay was 0 days in 57 (24%) patients, 1–30 days in 81 (35%) patients, 31–60 days in 35 (15%) patients, 61–180 days in 33 (14%) patients, 181–365 days in 14 (6%) patients and >365 days in 14 (6%) patients. The doctor's delay, thus, exceeded 30 days in 96 (41%) of 234 patients. There was a non-significant trend that doctor's delays were longer compared with parental delays (Wilcoxon signed-rank statistic, 1.51, P=0.15).

The age at diagnosis was significantly associated with PSI, which was shorter in younger children (see Table 2). This was mainly due to a shorter parental delay in younger children, while doctor's delay was not significantly associated with age at diagnosis. There was no association, however, of gender with any of the three delay measures. Tumour histology was also found to correlate with PSI. Aggressive fast-growing tumours (e.g. medulloblastoma, germ cell tumours and high-grade gliomas) had a shorter PSI compared with slow-growing tumours (e.g. low-grade gliomas and craniopharyngiomas; Table 2). The tumour location was significantly associated with both PSI and parental delay, with supratentorial midline tumours having longer delays than supratentorial hemispheric (e.g. cases presenting monosymptomatically with focal seizures) and infratentorial tumours. During the study period of 25 years, there was a statistically significant decrease in the PSI. This was mainly due to a decrease in the doctor's delay, which might be explained by the improved availability of non-invasive imaging techniques. At the Children's Hospital of Zurich, CT was introduced in 1982 and MRI in 1986. The parental delays of the six most frequent brain tumours did not change significantly over time.

Survival probability

The progression-free and overall survival of the 315 patients are summarised in Fig. 2. The estimated 5-year and 10-year OS rates were 73% (95% CI, 68 to 79%) and 71% (66 to 77%), respectively. The estimated 5-year and 10-year PFS rates were 53% (95% CI, 47 to 59%) and 48% (42 to 55%), respectively.

Survival probability according to PSI

Progression-free and overall survival according to PSI are summarised in Fig. 3. In the group with the longest PSI (≥180 days, n=83), the survival probability was the highest (10-year OS 86% and PFS 61%), followed by the group with PSI <20 days (n=66; 10-year OS 71% and PFS 49%), the group with PSI 60–179 days (n=82; 10-year OS 66% and PFS 43%) and the group with PSI 20–59 days (n=84; 10-year OS 61% and PFS 39%). These differences were significant for both OS (P<0.001) and PFS (P=0.029).

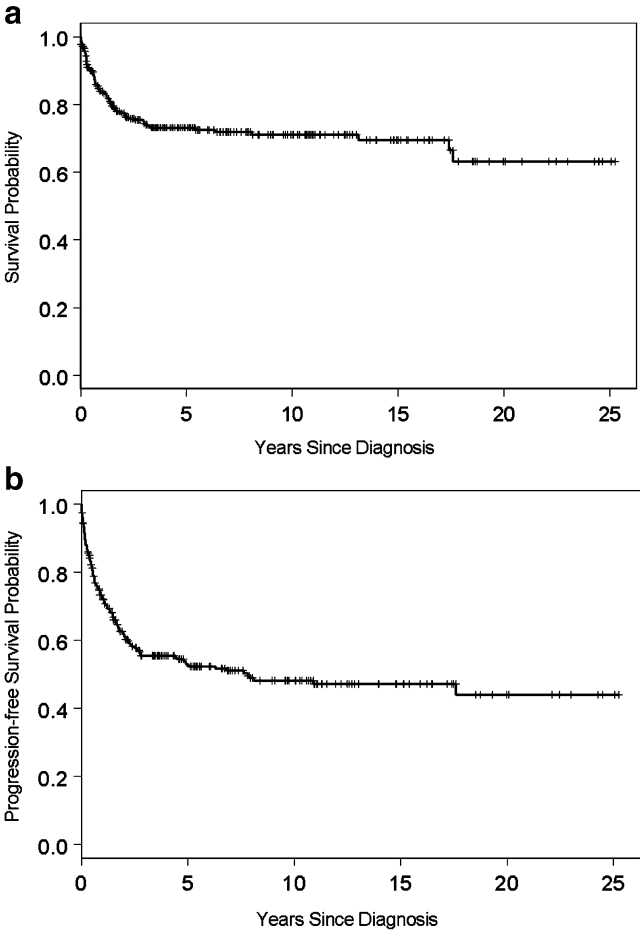

Fig. 2 a, b Estimated survival of 315 paediatric patients with brain tumours. Kaplan-Meier curves show the probability of overall survival (OS, **a**) and progression-free survival (PFS, **b**)

Survival probability according to doctor's delay

Progression-free and overall survival according to doctor's delay are summarised in Fig. 4. The survival probability was highest in the group with the longest doctor's delay (≥70 days, n=59, 10-year OS 78% and PFS 60%), followed by the group without any doctor's delay (<1 day, n=57; 10-year OS 67% and PFS 53%), the group with doctor's delay 14–70 days (n=62; 10-year OS 67% and PFS 40%) and the group with doctor's delay 1–14 days (n=56; 10-year OS 64% and PFS 49%). However, these differences were not statistically significant (P=0.24 for OS and P=0.64 for PFS).

Survival probability of histological subgroups according to PSI and doctor's delay

We then grouped the patients according to histology (low-grade glioma [n=77], medulloblastoma [n=57], high-grade

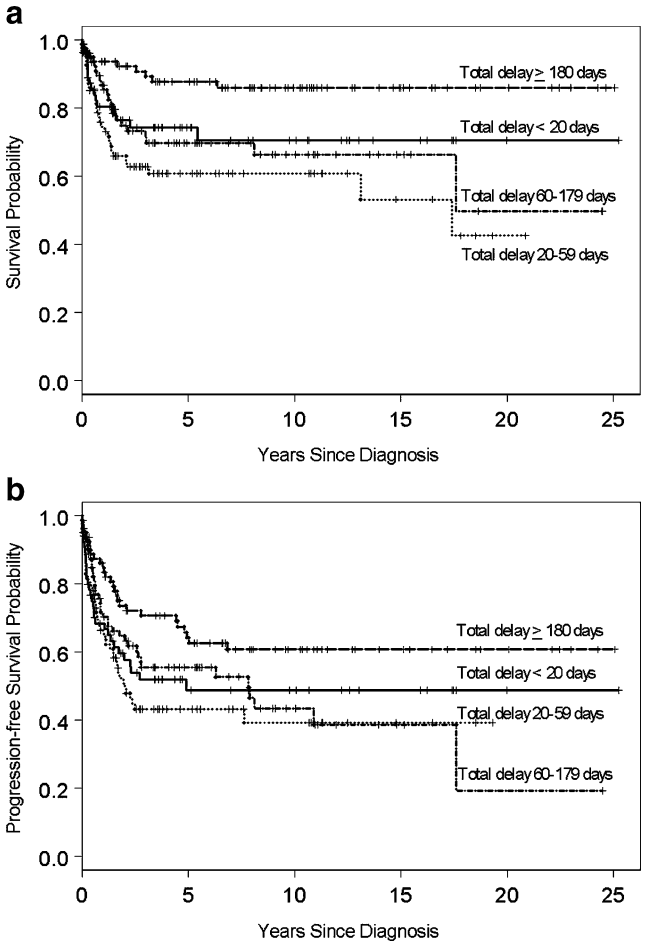

Fig. 3 a, b Estimated survival of 315 paediatric patients with brain tumours in relation to the duration of the PSI. Kaplan-Meier curves show the probability of OS (**a**) and PFS (**b**)

glioma [*n*=40], craniopharyngioma [*n*=27], ependymoma [*n*=20] and germ cell tumours [*n*=18]) and repeated the analyses. Despite the fact that both PSI and doctor's delay were significantly different between these subgroups (Table 2), shorter PSI or shorter doctor's delay did not result in better survival outcome probabilities in any of them (data are shown for the two largest groups, low-grade glioma and medulloblastoma; Table 3).

Discussion

Parents frequently tend to blame the primary care doctor for a "delay in the diagnosis" of a brain tumour and questions are raised as to whether an earlier diagnosis could have been made and, if so, whether the "delay" has adversely affected the prognosis. Therefore, in the current study, we tested the hypothesis that paediatric brain tumour patients with a shorter PSI have a better prognosis. Indeed, lay people may think that the child who is diagnosed with a brief history of symptoms/signs is more likely to have a smaller brain tumour that is easier to resect. The prognostic value of extensive tumour resection, which is controversial with regard to malignant brain tumours in adults, has been confirmed for a variety of childhood brain tumours, including medulloblastoma, supratentorial primitive neuroectodermal tumours, ependymoma and astrocytoma [2, 15, 17, 24, 25].

The PSI correlated significantly with the patient age, tumour histology, tumour location and year of diagnosis. This is in accordance with the literature [5, 16, 23]. Age differences in PSI may be attributed to age-related differences in the occurrence of tumour characteristics, such as brain tumour symptoms and tumour location relative to the tentorium, to differences in the tumour biology and to differences in medical care.

Contrary to common belief, the PSI correlated inversely with the progression-free and overall survival probability. Our findings are in accordance with the previously reported results of a smaller group of paediatric brain tumour patients (*n*=28; [19]) and the results of Halperin et al [11].

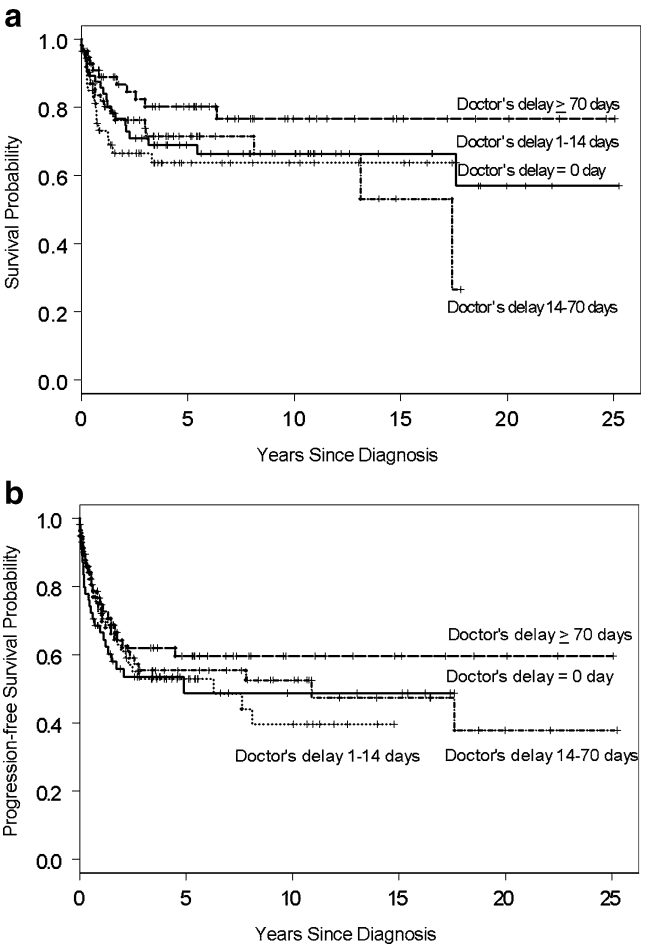

Fig. 4 a, b Estimated survival of 234 paediatric brain tumour patients, where medical charts permitted subdividing the PSI into a parental and a doctor's delay. Kaplan-Meier curves show the probability of OS (**a**) and PFS (**b**) in relation to the duration of the

Table 3 Survival probabilities (proportion in percentage and 95% confidence interval [CI]) according to PSI and doctor's delay

	10-year OS	10-year PFS
All tumours (*n*=315)	χ^2=16.4, *P*<0.001	χ^2=9.0, *P*=0.029
- PSI <20 days (*n*=66)	71 (59–85)	49 (37–64)
- PSI 20–59 days (*n*=84)	61 (50–73)	39 (28–54)
- PSI 60–179 days (*n*=82)	66 (55–80)	43 (32–60)
- PSI >180 days (*n*=83)	86 (78–95)	61 (50–74)
Tumours with known doctor's delay (*n*=234)	X^2=4.2, *P*=0.24	χ^2=1.7, *P*=0.64
- Doctor's delay <1 day (*n*=57)	67 (55–81)	53 (41–68)
- Doctor's delay 1–14 days (*n*=56)	64 (51–79)	49 (35–67)
- Doctor's delay 15–70 days (*n*=62)	67 (53–83)	40 (26–60)
- Doctor's delay >70 days (*n*=59)	77 (65–90)	60 (47–75)
Low-grade glioma (*n*=77)	X^2=2.5, *P*=0.48	χ^2=3.3, *P*=0.35
- PSI <20 days (*n*=10)	100	58 (31–100)
- PSI 20–59 days (*n*=13)	92 (79–100)	92 (79–100)
- PSI 60–179 days (*n*=26)	76 (52–100)	50 (27–92)
- PSI >180 days (*n*=28)	94 (83–100)	63 (45–88)
Low-grade glioma with known doctor's delay (*n*=58)	X^2=2.4, *P*=0.50	χ^2=0.6, *P*=0.90
- Doctor's delay <1 day (*n*=14)	100	76 (56–100)
- Doctor's delay 1–14 days (*n*=9)	100	83 (58–100)
- Doctor's delay 15–70 days (*n*=15)	74 (46–100)	53 (25–100)
- Doctor's delay >70 days (*n*=20)	82 (60–100)	70 (52–94)
Medulloblastoma (*n*=57)	X^2=1.1, *P*=0.77	χ^2=1.0, *P*=0.79
- PSI <20 days (*n*=12)	75 (54–100)	56 (34–94)
- PSI 20–59 days (*n*=27)	56 (40–80)	33 (19–59)
- PSI 60–179 days (*n*=14)	54 (33–90)	24 (5–100)
- PSI >180 days (*n*=4)	50 (19–100)	25 (5–100)
Medulloblastoma with known doctor's delay (*n*=49)	X^2=1.8, *P*=0.60	χ^2=1.3, *P*=0.72
- Doctor's delay <1 day (*n*=16)	60 (39–91)	38 (19–75)
- Doctor's delay 1–14 days (*n*=13)	39 (18–85)	23 (8–71)
- Doctor's delay 15–70 days (*n*=15)	57 (36–91)	31 (12–81)
- Doctor's delay >70 days (*n*=5)	50 (19–100)	25 (5–100)

χ^2 =log-rank statistic, 3 degrees of freedom

Analysing 122 medulloblastoma patients, they found that the PSI correlated inversely with metastatic stage at the time of presentation. Although not tested formally in their study, it can be assumed that patients with longer PSI had not only lower metastatic stages, but also had higher survival probability, because the metastatic stage is probably the most important clinical risk factor in medulloblastoma [1, 7, 12, 21, 25].

This suggests that, often, it is the biology of the disease that is the most important determinant for PSI and survival probability. Some rapidly growing aggressive brain tumours call attention to themselves more readily than slowly growing tumours. Perhaps the more slowly growing tumours allow the patient to adapt to the increase in intracranial pressure and impingement on normal tissue more readily than to a rapidly growing mass [6, 10, 11].

The doctor's delay did correlate with tumour histology, but not with the progression-free or overall survival probability. This is also in contrast to common belief and has potential legal implications. Alleged delay in diagnosis is a common plaintiff's assertion in cancer-related malpractice suits. It is a fact that the more aggressive tumours tend to be diagnosed after a shorter duration of symptoms than less malignant tumours: this makes it difficult to cite the long duration of symptoms, by itself, as a significant factor in support of the argument that, "if only the diagnosis had been made more quickly," then the patient would have had a better prognosis.

We believe that this study of a large series of children with brain tumours represents the first analysis of the relationships between PSI, doctor's delay and survival outcome probability. Clearly, this study has limitations. The numbers of patients in each histological category are small, the categories are not homogenous in terms of localisation and biology, and the treatment used over a relatively long period of time has not been uniform. As analysis relied on a retrospective review of medical records, it was not possible to assess the reliability with which the data regarding symptom onset and the division of symptoms into that occurring before and after medical advice was recorded. However, the results do indicate that the age at presentation and histology are determinants for PSI, and that a short PSI is not necessarily related with better survival outcome probability.

Instead of analysing the age at diagnosis, PSI and the doctor's delay by Spearman's correlation, we deliberately chose a method of analysis based on quartile grouping, since, primarily, it cannot be assumed that the association of delay with outcome is a linear one. As Figs. 2 (for PSI) and 4 (for doctor's delay) demonstrate for the whole set of patients, as does Table 3 for some important subgroups, this assumption would clearly have been wrong. Since there is no linear association between delay and outcome, we deliberately chose to perform log-rank tests of outcomes between subgroups of patients instead of performing Cox regression analysis.

Future studies are needed that prospectively analyse more homogeneous (histological and therapeutic) groups of brain tumour patients. It still remains to be tested whether long delays in diagnosis are associated with higher risks of perioperative morbidity and, therefore, reduced quality of life. Whilst a child might still survive with a brain tumour diagnosed over a prolonged symptom interval, there may be considerable impairment of cognitive function due to prolonged hydrocephalus or other tumour-related brain damage.

Independent of current and future study results, early diagnosis remains a high priority. Patients with biologically aggressive tumours are likely to profit from an early start of anti-neoplastic therapy, and patients with slow growing tumours might be salvaged from irreparable functional deficits. Furthermore, a prolonged diagnostic delay is associated with the high burden of uncertainty for the families involved.

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