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A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: a population-based cohort study (CCLG CNS9702)

Tore Stokland, Jo-Fen Liu, James W. Ironside, David W. Ellison, Roger Taylor, Kathryn J. Robinson, Susan V. Picton, and David A. Walker

Children's Brain Tumour Research Centre, Division of Human Development, Queen's Medical Centre, University of Nottingham, Nottingham (T.S., J.-F.L., D.A.W.); Children's Cancer and Leukaemia Group, University of Leicester, Leicester (T.S., J.-F.L., K.J.R.); National CJD Surveillance Unit, University of Edinburgh, Western General Hospital, Edinburgh (J.W.I.); South West Wales Cancer Institute, Singleton Hospital, University of Swansea, Wales, Sketty Lane, Swansea (R.T.); Department of Paediatric Oncology, Children's Day Hospital, St James's Hospital, Beckett Street, Leeds (S.V.P.); Department of Pathology, St Jude Children's Research Hospital, Memphis, Tennessee (D.W.E.); Department of Paediatrics, University Hospital of North Norway, Tromso, Norway (T.S.)

The purpose of this study was to identify risk factors for the progression of low-grade glioma in children from a large population-based cohort. Patient and tumor details of a national cohort of children with low-grade glioma, recruited into an international multidisciplinary clinical strategy, were subjected to univariate and multivariate analyses of progression-free survival and overall survival. From the cohort of 798 patients, 639 patients were eligible, with a median age 6.71 years (0.26–16.75 years); 49% were males; 15.9% had neurofibromatosis type 1, 63.7% pilocytic astrocytoma, 5.9% fibrillary astrocytoma, 4.2% mixed neuronal-glial tumors, and 3.6% others; 21.1% were diagnosed clinically. Anatomically implicated were 31.6% cerebellum, 24.6% chiasma/hypothalamus, 16.0% cerebral hemispheres, 9.9% brain stem, 6.1% other supratentorial midline structures, 5.9% optic nerve only, 4.5% spinal cord, and 1.4% others. The 5-year overall survival and progression-free survival in the whole cohort were 94.6% and 69.4%, respectively. There was a significant association between age and site (*P* < .001) and extent of tumor resection and site (*P* < .001). Multivariate analysis identified young age, fibrillary astrocytoma, and extent of surgical resection as significant independent risk factors for progression. Hypothalamic/chiasmatic tumors demonstrated the most sustained tendency to progress. In conclusion, the influence of age and anatomical site upon the risk of tumor progression suggests that these factors strongly influence tumor behavior for the majority of pilocytic tumors. Age <1 year and 1–5 years, fibrillary histology, completeness of resection, and chiasmatic location are candidates for stratification in future studies.

Keywords: children, low-grade astrocytoma, low-grade glioma, multivariate, prognostic factors.

Low-grade gliomas (LGGs) constitute 40% of central nervous system (CNS) tumors in children.[1] They are heterogeneous both anatomically and clinically. Histologically, they are separated by World Health Organization (WHO) classification into grades I and II.[2] Pilocytic astrocytomas (PAs; WHO grade I) are most common in children, whereas diffuse fibrillary astrocytomas (FAs; WHO grade 2) are less common than in adults. LGGs are associated with neurofibromatosis type 1 (NF1)[3] and can arise throughout the brain and the spinal cord. Tumors may occasionally present with leptomeningeal metastases, whereas large and progressive tumors can threaten life, despite treatment. Surgical resection, where possible, is the

preferred treatment. However, certain anatomical sites are unsuitable for complete resection. Nonsurgical treatments with radiotherapy and, more recently, chemotherapy are in trial. Incompletely resected or unresected tumors may progress, remain stable, or even spontaneously involute.[4,5]

Focus on childhood benign astrocytomas is justified by the coincidence of the early age distribution and the brain's state of growth and development at the time of onset, determining the ages at which certain treatment options, particularly radiotherapy, can be considered. Despite the high frequency of LGG in children, no consensus exists for identifying children at a sustained risk for tumor progression. There have been no population-based cohort studies of prognostic factors published previously; those published are either retrospective, institution-based,[6–13] or multi-institutional clinical trials selecting patients for chemotherapy.[14–19] Most studies deal with optic pathway gliomas (OPGs)[6,9,11,12,18,19] or gliomas of other specific locations,[7,10] whereas studies of prognostic factors at all sites are fewer.[8,13–17] Most studies are small, with only 3 including more than 100 patients.[8,13,19] Children are reported to have a better prognosis than adults.[20–22] However, within childhood, studies on the prognostic value of age as a risk factor are inconclusive. This may be due to the variable selection of patients at different institutions, the small size of many studies, specific eligibility criteria related to inclusion in clinical trials, specific anatomical location(s) recruited for study, different age limits for risk evaluation, and variable endpoint: progression-free survival (PFS) or overall survival (OS).

Identification of prognostic factors in childhood LGG will be important for tailoring treatment in future clinical studies. To address this, this study was done on the LGG patient cohort of the Children's Cancer and Leukaemia Group's (CCLG, formerly UKCCSG) study CNS9702. This population-based cohort was used to test the following hypothesis: "The risk of tumor progression in LGG in children is determined by age, sex, NF1 status, anatomical site, histopathology and extent of tumor resection."

Patients and Methods

Patients

The CCLG (formerly UKCCSG) opened CNS9702 first as a pilot study and then formally in February 1997. The study was closed in April 2004. All patients less than 16 years of age with LGG (WHO grades I and II), including mixed neuronal-glial tumors, were eligible through the CCLG network of 22 treatment centers. This network registered 80%–86% of the UK cases of childhood LGG registered by the national childhood cancer registry during this time period. Patients with tumors at all anatomical sites were recruited until 2002, when cerebellar tumor registration was discontinued after an interim surgical review prior to this study's hypothesis development. Patients with MR findings and

clinical features typical of LGG, mostly NF1 patients with classical OPG, could be included in the study without biopsy. Clinical report forms were reviewed to confirm the dates of diagnosis/birth, gender, and NF status. Completed were the central reviews of histopathology, anatomical site, timing and extent of tumor resection, timing and choice of nonsurgical treatment, dates of tumor progression, death, and last follow-up.

Treatment strategy

CNS9702 was part of an LGG study by the International Consortium of Low-Grade Glioma (ICLGG) with an integrated multidisciplinary strategy for all patients (Fig. 1). Primary surgical resection or biopsy was recommended for all, except in patients with typical chiasmatic tumors and in NF1 patients, where a clinical diagnosis was acceptable. Subsequently, further observation or nonsurgical therapy was determined by imaging evidence of progression or by the presence of severe symptoms or threat to vision. Chemotherapy was recommended for patients aged <5 years with vincristine (1.5 mg/m² once a week for 10 weeks, thereafter every fourth week for 10 cycles) and carboplatin (550 mg/m² every third week for 4 cycles, thereafter every fourth week for 10 cycles). Radiotherapy was recommended for patients aged >5 years. Focal radiotherapy employed a margin of 1–2 cm around the gross tumor volume. The radiation dose was 54 Gy for children with intracranial tumors and aged >5 years and 50 Gy for spinal cord tumors and children aged <5 years with intracranial tumors. For patients who subsequently progressed on imaging or symptomatically, reconsideration of surgical resection and subsequent age-stratified, nonsurgical therapy was recommended. There was good compliance with age stratification for radiotherapy and chemotherapy (Fig. 1).

Methods

The central histopathology review blind to other clinical details was conducted by J.W.I. and D.W.E. The pathology review of sections from the registered cases included an assessment of tumor histopathology on hematoxylin and eosin–stained sections, with immunohistochemistry performed as required for diagnosis and subclassification. The WHO classification for grade I and II gliomas and mixed neuronal-glial tumors was used[2] (Table 1). Ependymomas were ineligible. The anatomical review of imaging reports (T.S. and D.A.W.) was performed blind to clinical details (Table 1). Isolated optic nerve tumors were classified separately from optic pathway tumors involving the chiasm. Tumors spanning multiple areas and metastatic tumors were allocated according to the predominant primary component of tumor.

Extent of surgical resection was based on the local reports. The definition followed the recommendation of the Brain Tumour Subcommittee of the Société Internationale d'Oncologie Pédiatrique[23] using both
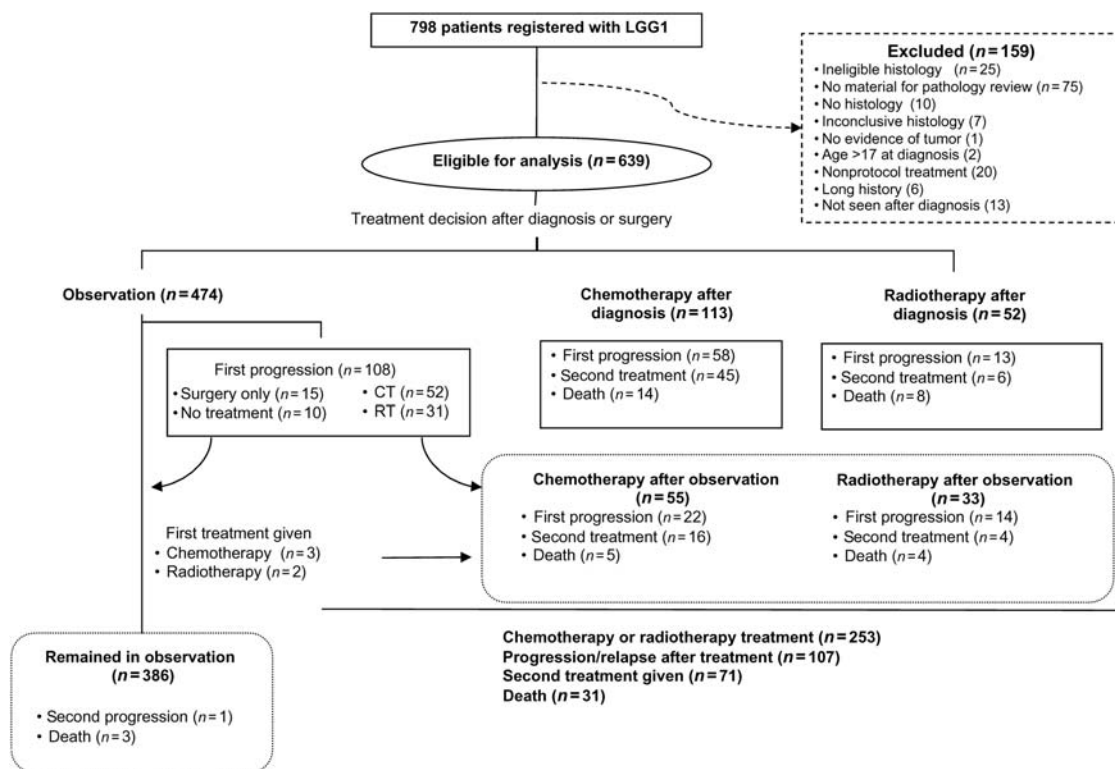
Fig. 1. Study population and treatment strategy.

surgical and radiological judgments: total resection= both neurosurgeon and neuroradiologist's judgments agree that there is no residue (S1, R1); near total resection=small residue that may be invading, with or without radiological enhancement (S2, R1−2); partial resection=measurable residual tumor of any size, and the surgical assessment may or may not agree (S1−3, R3); biopsy=both surgical and radiological findings agree that there has been no change postoperatively (S4, R4). Tumor progression was defined by the local reports of imaging and/or symptomatic progression. Institutions obtained approval as required by their local district research ethics committees. Informed consent was obtained from all patients and/or their legal guardian.

Statistical methods

Survival curves were calculated using the Kaplan–Meier method. Time-to-event endpoint was defined as death from all causes for OS or first progression for PFS. Deaths as a first event without evidence of glioma recurrence ($n = 4$) were censored in PFS analysis. The difference in survival distributions were tested by the log-rank test. For multivariate analysis, Cox's proportional hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Predictors included in the adjusted model were age at diagnosis (<1, 1–3, 3–5, 5–10, and >10 years), gender, NF1 status, pathology, anatomical site, treatment decision after diagnosis and surgery (observation,

chemotherapy, and radiotherapy), and the extent of tumor resection and metastasis within the CNS. All variables were fitted as dummies. The significance level for all analyses was set at 5%. Statistical analyses were performed with Statistical Package for Social Services, 14.0 (SPSS Inc., Chicago, IL) or STATA 9.0 (Stata Corp., College Station, TX).

Results

Recruitment and strategy

Of 798 registered patients, 159 were excluded, most due to missing material for the central pathology review or change in histological diagnosis, 20 patients being regraded as high-grade glioma, leaving 639 for analysis. Four hundred and seventy-four (74.2%) were initially observed (median age: 7.43 years; Fig. 1). One hundred and sixty-five (25.8%) started nonsurgical treatment (median age: 4.95 years), 113 had chemotherapy (median age: 3.65 years), and 52 had radiotherapy (median age: 9.36 years).

Clinicopathological characteristics

The median age of the whole cohort was 6.71 years (range: 0.26–16.75). The age distribution was bimodal with peaks at 4 and 13 years (Fig. 2A). Sex distribution was equal with 313 males (49.0%). NF1 was reported in 101 patients (15.9%), no patients with NF2 were recorded.

Table 1. Pathology, site, and metastasis

	Eligible for analysis (n = 639)	
	n	Percent[a]
Pathology		
Pilocytic astrocytoma	407	63.7
Pilomyxoid astrocytoma	9	1.4
Fibrillary astrocytoma[b]	38	5.9
Other astrocytomas[c]	23	3.6
Astrocytoma NOS[d]	11	1.7
Subependymal giant cell astrocytoma	6	0.9
Pleomorphic xanthoastrocytoma	3	0.5
Cerebral astrocytoma with extensive calcification[e]	3	0.5
Mixed neuronal-glial tumors	27	4.2
Ganglioglioma	14	2.2
Dysembryoplastic neuroepithelial tumor (DNET)	11	1.7
Desmoplastic infantile astrocytoma/ganglioglioma (DIA/DIG)	2	0.3
Clinical diagnosis (no biopsy performed)	135	21.1
Site		
Cerebral hemisphere	102	16.0
Frontal	18	2.8
Parietal	17	2.7
Temporal	38	5.9
Occipital	11	1.7
Ventricles lateral and third ventricle	18	2.8
Optic nerve only	38	5.9
Chiasma/hypothalamus	157	24.6
Other supratentorial midline	39	6.1
Thalamus	29	4.5
Basal ganglia	6	0.9
Pineal gland	4	0.6
Cerebellum[f]	202	31.6
Brain stem	63	9.9
Midbrain	16	2.5
Pons	19	3.0
Medulla oblongata	13	2.0
Cervicomedullary	6	0.9
Fourth ventricle	9	1.4
Spinal	29	4.5
Cervical	8	1.3
Thoracal	20	3.1
Conus	1	0.2
Others[g]	9	1.4
Metastasis within CNS		
No	583	96.4
Yes	22	3.6

Abbreviations: CNS, central nervous system; NOS, not otherwise specified.
[a]Of all biopsied tumors (*n* = 504): pilocytic astrocytoma 80.8%, pilomyxoid astrocytoma 1.8%, fibrillary astrocytoma 7.5%, other astrocytomas 4.5%, and mixed neuronal-glial tumors 5.4%.
[b]All diffuse grade II astrocytoma were fibrillary, no gemistocytic, or protoplasmic astrocytoma.
[c]There were no oligodendrogliomas diagnosed.
[d]Not possible to ascertain whether pilocytic or diffuse astrocytoma due to limited size of biopsy.
[e]Provisional classification of this entity pending further investigations.
[f]Cerebellum tumors not recruited in the last part of the study period (36.1% of all in the recruitment period).
[g]Multiple site (*n* = 5) and difficult to decide (*n* = 4).
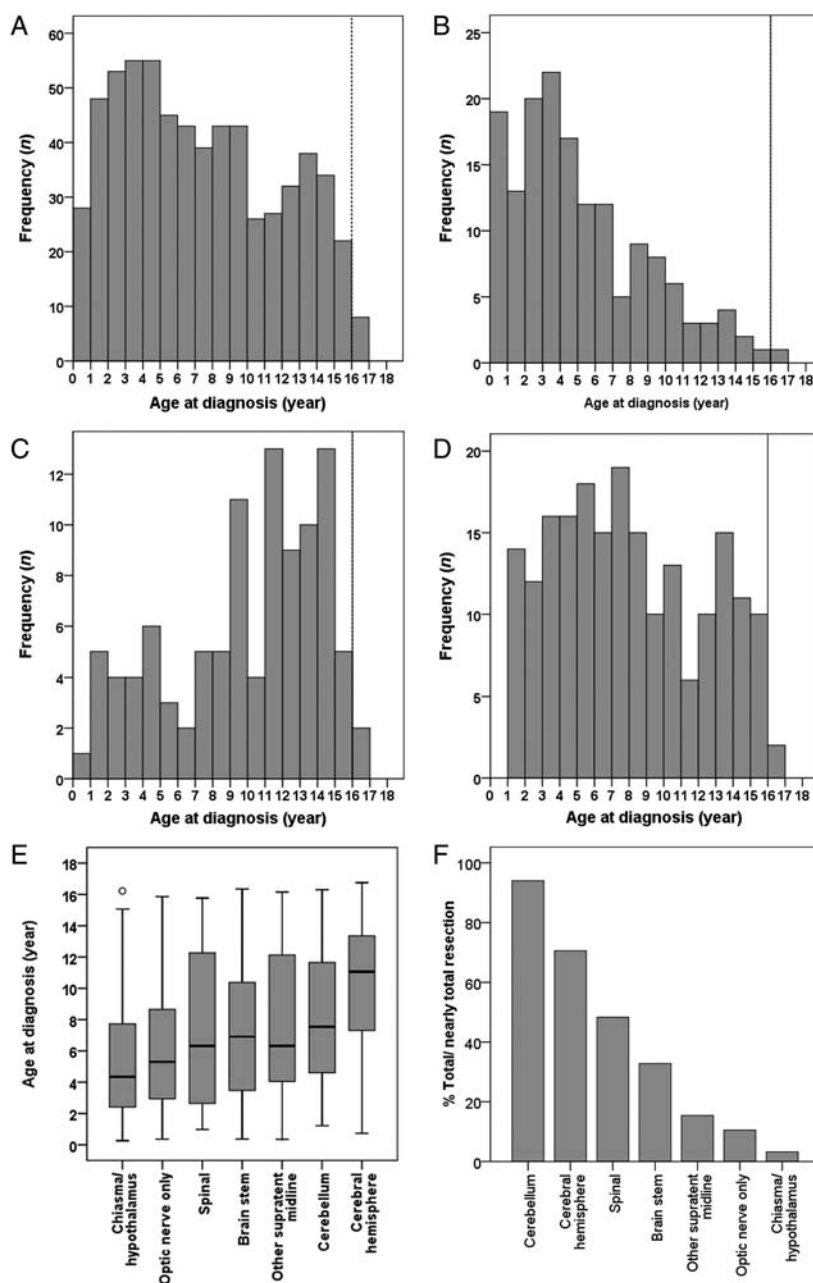
Fig. 2. Age and site distribution. (A) Age distribution, all; (B) age distribution, chiasma/hypothalamus; (C) age distribution, cerebral hemisphere; (D) age distribution, cerebellum; (E) median age by site; (F) extent of tumor resection by site.

The results of histopathology review are shown in Table 1. PA (63.7%) predominated, followed by diffuse FA (5.9%), mixed neuronal-glial tumors (4.2%), pilomyxoid astrocytoma (PMA; 1.4%). A group of miscellaneous entities included subependymal giant cell astrocytomas, which were all ventricular ($n = 6$), and pleomorphic xanthoastrocytomas ($n = 3$), unclassifiable astrocytomas ($n = 11$), and 3 unusual cerebral astrocytomas with extensive dystrophic calcification, which had neither typical diffuse nor pilocytic features. There were no oligodendrogliomas or gemistocytic or protoplasmic variants of diffuse astrocytoma. A clinical diagnosis was accepted in 135 (21.1%), including 8 patients who had noninformative

biopsy and 1 patient recruited based on typical imaging before surgery whose tumor material was not available for central review; 90 (87.4%) were associated with NF1.

The relative frequency of tumors at anatomical sites is shown (Table 1). Recruitment of cerebellar cases was discontinued in 2002; the proportion of cerebellar cases during the period 1994–2001 was 36.1% compared with an overall proportion of 31.6%. Brain stem tumors were heterogeneously distributed (e.g. tectum/midbrain vs pons), and spinal tumors were mostly thoracic. Metastatic spread at the time of diagnosis was recorded in 22 out of the 639 patients; 34 patients had missing data.

Total surgical resection was recorded in 205 patients (32.3%), near total resection in 105 (16.6%), partial resection in 87 (13.7%), biopsy only in 103 (16.2%), and no surgery in 134 (21.1%); 5 patients had no surgical resection data.

Correlation between variables

Age-incidence distributions differed significantly ($P <$ .001) among anatomical sites: chiasmatic/hypothalamic tumors had a skewed distribution toward younger age, hemispheric tumors had a skewed incidence toward the older age groups, cerebellar tumors had a bimodal age distribution with peaks at 7 and 13 years, none occurring below 1 year (Fig. 2B–F). Patients less than 1 year had predominantly supratentorial midline tumors, 19 of the 28 being at the chiasma/hypothalamus. There was no significant difference in age distribution between FA and PA (median 8.89 vs 7.35, $P =$ .705); median age of clinical diagnosis patients was younger, at 5.06 years. PA predominated at all sites, whereas FA was infrequent in the cerebellum and the optic pathway (1.5% and 0.4%), occurring at a frequency of 11%–17% at other sites ($P <$ .001). The association between NF1 and optic pathway tumors was more marked in isolated optic nerve (70%) than chiasmatic/hypothalamic (37.5%) tumors. Surgical resectability of tumors was dependent on the tumor site ($P <$ .001); cerebellar tumors were resected in 94.0% of patients, whereas in chiasmatic/hypothalamic tumors, only 3.2% were subtotally or completely resected (Fig. 2F).

Univariate analysis of survival

After a median follow-up (time to last follow-up or death) of 4.26 years (0.01–10.15), 3- and 5-year PFS for the whole cohort was 73.0% and 69.4% (Fig. 3A), respectively, and 3- and 5-year OS was 96.68% and 94.62% (Table 2, Fig. 4A). Histopathology predicted for PFS, with PA and FA having 5-year PFS of 71.5% and 42.6%, respectively ($P <$ .001; Fig. 3B). Clinically diagnosed cases had similar PFS to PA. Minor histopathological subgroups were too small to analyze, although only 5 of 9 PMAs were alive after a short observation time.

Age predicted for PFS, with <1, 1–3, 3–5, 5–10, and >10 years having 5-year PFS of 41%, 56%, 58%, 79%, and 77.2%, respectively ($P <$ .001; Fig. 3C). This pattern was most prominent in tumors of chiasma/hypothalamus but also at other sites (Fig. 3D). There was nearly identical PFS in the age groups 1–3 and 3–5 years, and likewise in 5–10 and >10 years. In contrast to PFS, OS did not differ between the 1–5- and >5-year age groups (Fig. 4B).

There was no difference in PFS for NF1 status for the whole cohort (Fig. 3E), although NF1+ patients with chiasmatic/hypothalamic tumors had significantly better PFS than those without NF1, with 5-year PFS 70.8% vs 46.7%, respectively ($P <$ .001; Fig. 3F). Tumor location was associated with different patterns in PFS, with isolated optic nerve tumors and cerebellar tumors having 5-year PFS of 85%–86% and a survival curve plateau; supratentorial midline sites had a survival plateau curve with 5-year PFS of 49%–50%, whereas chiasmatic/hypothalamic tumors had 5-year PFS of 50.2% with a survival curve with no plateau (Fig. 3G). Total resection predicted for 5-year PFS of 94% vs 48.6% for partial resection ($P <$ .001; Fig. 3H). There was no gender difference.

Multivariate analysis

Age, histology, and extent of resection were independent risk factors for progression. Younger age groups (<1, 1–3, and 3–5 years) in general showed poorer outcome, but only ages 3–5 years reached significance in the multivariate model (adjusted HR: 1.87, 95% CI: 1.14–3.09; Table 2). On the basis of the similar PFS pattern observed in younger age groups, we have also tried fitting age as 4 groups (<1, 1–5, 5–10, and >10 years) in the multivariate model. Age group 1–5 years showed a significant increased risk for progression (adjusted HR: 1.74, 95% CI: 1.11–2.73). FA was an independent predictor of progression (adjusted HR: 1.99, 95% CI: 1.11–3.58).

Compared with total resection, there was an increased risk for progression observed in near total resection (adjusted HR: 8.19, 95% CI: 3.97–16.91), partial resection (adjusted HR: 12.27, 95% CI: 5.58–26.99), biopsy (adjusted HR: 11.38, 95% CI: 4.99–25.97), and no surgery (adjusted HR: 19.79, 95% CI: 6.11–64.14) based on the entire population.

Tumors in cerebral hemisphere(s), chiasma/hypothalamus, other supratentorial midline, brain stem, and spinal all showed a greater risk for progression than tumors at the cerebellum in univariate analysis. However, apart from chiasma/hypothalamus, which showed a borderline significance (adjusted HR: 1.74, 95% CI: 0.92–3.31), none remained significant after adjusting for other variables.

Forward and backward stepwise regression was used to explore predictors for progression. Variables in the best fitted model are age, pathology, and tumor resection, and HRs were similar to those derived from full models (data not shown).

Discussion

This population-based cohort, recruited over a 7-year period with a median follow-up time of 4.7 years, has permitted multivariate modeling of patient, tumor, and treatment variables predictive of tumor progression in a large series of LGGs. Such an analysis in such a large population-based cohort has not been published previously. The study complies with validity criteria recommended for systematic reviews[24,25] used in the only published systematic review of prognostic factors of LGG in children, studying optic pathway tumors.[26] The current study is focused upon a well-defined population, representing 80%–86% of the UK registrations.

A

Time to progression (years)

No. at risk (events)
639 (129) 428 (41) 241 (8) 97 (1) 15 (0) 0

B

Clinical diagnosis
Pilocytic astrocytoma
Fibrillary astrocytoma

Log-rank test $P < 0.001$

Analysis time

No. at risk (events)										
Pilocytic astrocytoma	407	(84)	282	(21)	173	(5)	70	(1)	10	(0)	0
Fibrillary astrocytoma	38	(14)	20	(5)	7	(0)	1	(0)	0	(0)	0
Clinical diagnosis	135	(20)	100	(10)	50	(3)	22	(0)	4	(0)	0

C

>10
5–10
1–3
3–5
<1

Log-rank test $P < 0.001$

Analysis time

No. at risk (events)										
<1	28	(14)	10	(1)	8	(2)	4	(0)	1	(0)	0
1–3	101	(24)	68	(16)	37	(0)	19	(0)	2	(0)	0
3–5	110	(32)	67	(8)	39	(3)	16	(1)	1	(0)	0
5–10	213	(34)	151	(5)	92	(3)	37	(0)	6	(0)	0
>10	187	(25)	132	(11)	65	(0)	21	(0)	5	(0)	0

D

5–10
>10
1–3
3–5
< 1

Log-rank test $P = 0.011$

Analysis time

No. at risk (events)										
<1	8	(4)	3	(0)	3	(0)	2	(0)	0	(0)	0
1–3	59	(12)	41	(6)	24	(0)	13	(0)	2	(0)	0
3–5	64	(17)	41	(3)	27	(1)	12	(0)	1	(0)	0
5–10	150	(22)	108	(4)	67	(1)	25	(0)	3	(0)	0
>10	163	(23)	112	(9)	56	(0)	19	(0)	5	(0)	0

E

NF1 (+)
NF1 (−)

Log-rank test $P = 0.2$

Analysis time

No. at risk (events)										
NF1 (+)	101	(15)	76	(9)	34	(0)	15	(0)	2	(0)	0
NF1 (−)	534	(113)	350	(32)	206	(8)	81	(1)	12	(0)	0

F

NF1 (+)
NF1 (−)

Log-rank test $P = 0.003$

Analysis time

No. at risk (events)									
NF1 (+)	58	(11)	41	(7)	19	(0)	6	(0)	0
NF1 (−)	98	(36)	49	(11)	26	(6)	10	(1)	0

G

Optic nerve only
Cerebellum
Cerebral hemisphere
Spinal
Brain stem
Other supratentorial midline
Chiasma/ hypothalamus

Log-rank test $P < 0.001$

Analysis time

No. at risk (events)										
Cerebral hemisphere	102	(13)	61	(6)	25	(1)	7	(0)	3	(0)	0
Optic nerve only	38	(4)	32	(1)	18	(0)	9	(0)	3	(0)	0
Chiasma/hypothalamus	157	(47)	91	(18)	46	(6)	17	(1)	1	(0)	0
Other supratentorial midline	39	(16)	20	(3)	10	(0)	5	(0)	0	(0)	0
Cerebellum	202	(20)	165	(7)	106	(0)	44	(0)	6	(0)	0
Brain stem	63	(17)	38	(4)	23	(1)	10	(0)	2	(0)	0
Spinal	29	(8)	17	(2)	10	(0)	3	(0)	0	(0)	0

H

Total
No surgery
Nearly total
Partial
Biopsy

Log-rank test $P < 0.001$

Analysis time

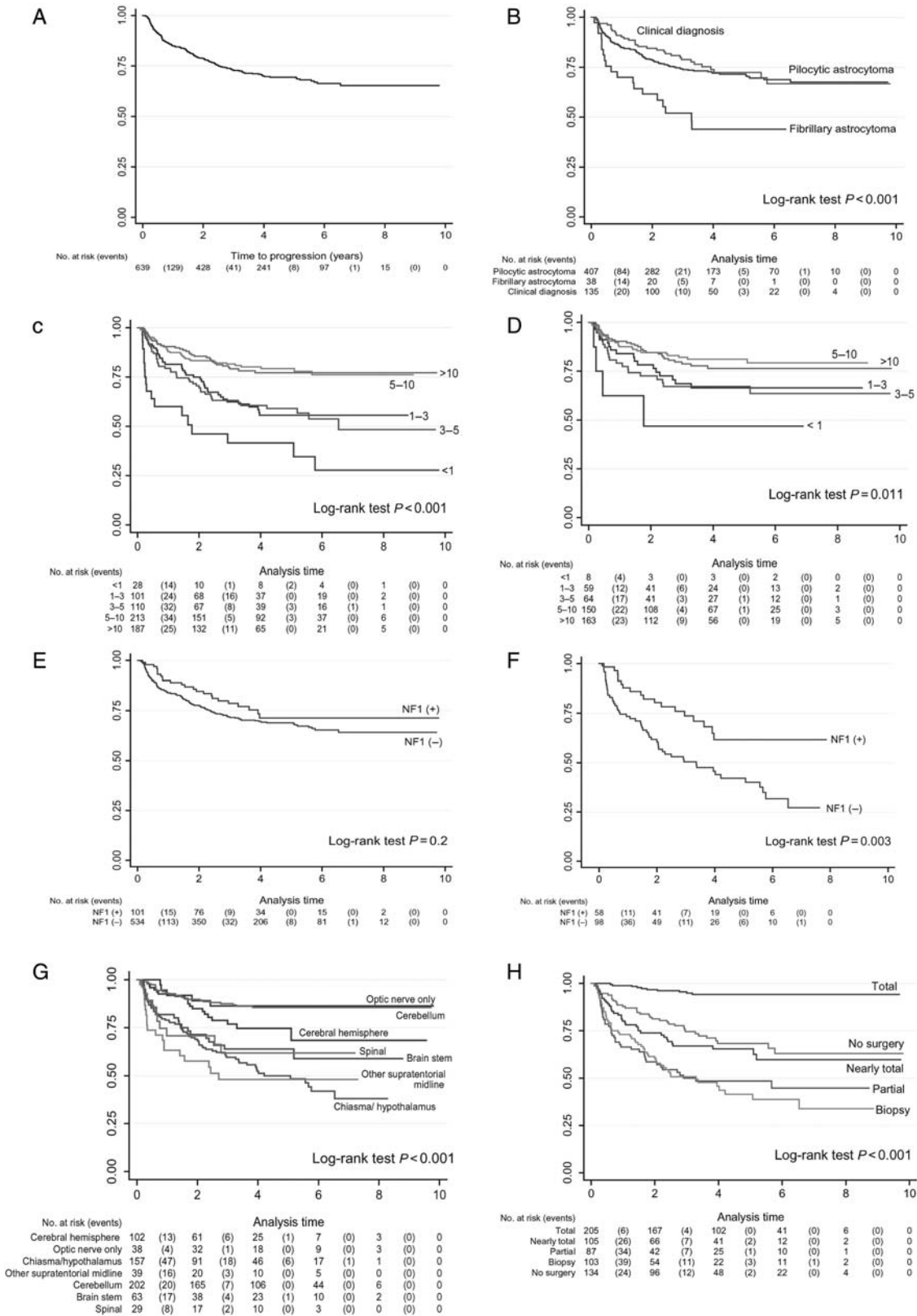| No. at risk (events)										
Total	205	(6)	167	(4)	102	(0)	41	(0)	6	(0)	0
Nearly total	105	(26)	66	(7)	41	(2)	12	(0)	2	(0)	0
Partial	87	(34)	42	(7)	25	(1)	10	(0)	1	(0)	0
Biopsy	103	(39)	54	(11)	22	(3)	11	(1)	2	(0)	0
No surgery	134	(24)	96	(12)	48	(2)	22	(0)	4	(0)	0

Fig. 3. The Kaplan–Meier curves of PFS. (A) PFS, all; (B) by pathology; (C) by age; (D) by age at nonoptic pathway glioma (non-OPG) sites; (E) by NF1 status; (F) by NF1 status at chiasma/hypothalamus; (G) by site; (H) by extent of tumor resection.

Table 2. Five-year overall survival, progression-free survival, and hazard ratios

	Total	Overall survival		Progression-free survival			
		Events	5-year OS (95% CI)	Events	5-year PFS (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Overall	639	34	94.6 (92.1–96.4)	179	69.4 (65.3–73.1)		
Sex			*P* = .734		*P* = .277	*P* = .277	*P* = .434
Female	326	19	94.0 (89.9–96.5)	98	67.6 (61.6–72.9)	1.00	1.00
Male	313	15	95.2 (91.6–97.3)	81	71.1 (65.3–76.2)	0.85 (0.63–1.14)	0.88 (0.63–1.22)
Age in 5 groups			*P* < .001		*P* < .001	*P* < .001	*P* = .015
>10	187	9	95.4 (90.5–97.8)	36	77.2 (69.6–83.1)	1.00	1.00
5–10	213	10	95.4 (90.8–97.8)	42	79.1 (72.4–84.3)	0.98 (0.63–1.53)	0.94 (0.59–1.49)
3–5	110	3	97.4 (89.5–99.4)	44	58.4 (47.7–67.7)	2.22 (1.43–3.45)	1.87 (1.14–3.09)
1–3	101	3	95.3 (86.1–98.5)	40	55.7 (44.6–65.4)	2.10 (1.34–3.30)	1.62 (0.97–2.70)
<1	28	9	75.6 (53.3–88.3)	17	40.9 (21.8–59.2)	4.69 (2.63–8.36)	1.82 (0.92–3.58)
NF1 status			*P* = .15		*P* = .20	*P* = .205	*P* = .192
NF1 (−)	534	32	94.1 (91.1–96.1)	154	68.8 (64.3–72.9)	1.00	1.00
NF1 (+)	101	2	97.6 (90.7–99.4)	24	72.2 (61.0–80.7)	0.76 (0.49–1.16)	0.65 (0.34–1.24)
Pathology review			*P* < .001		*P* < .001	*P* = .002	*P* = .008
Pilocytic astrocytoma	407	13	97.3 (94.6–98.7)	111	71.5 (66.5–75.9)	1.00	1.00
Fibrillary astrocytoma	38	9	76.5 (58.3–87.6)	19	42.6 (24.7–59.3)	2.37 (1.45–3.85)	1.99 (1.11–3.58)
Clinical diagnosis	135	4	97.4 (92.1–99.2)	33	72.3 (62.5–80.0)	0.88 (0.59–1.29)	0.28 (0.11–0.74)
Other eligible types[b]	32	6	69.1 (38.1–86.8)	10	55.6 (20.4–80.5)	1.94 (1.01–3.71)	1.22 (0.60–2.48)
Mixed neuronal-glial tumors	27	2	83.3 (40.7–96.4)	6	69.6 (43.4–85.4)	0.92 (0.40–2.09)	0.74 (0.31–1.78)
Site review			*P* < .001		*P* < .001	*P* < .001	*P* = .474
Cerebellum	202	2	98.4 (93.6–99.6)	27	85.4 (79.4–89.8)	1.00	1.00
Cerebral hemisphere	102	7	89.0 (73.4–95.7)	20	74.1 (61.6–83.1)	1.87 (1.05–3.34)	1.21 (0.63–2.34)
Optic nerve only	38	0	100.0	5	86.1 (69.7–94.0)	0.98 (0.38–2.54)	0.61 (0.16–2.28)
Chiasma/hypothalamus	157	12	94.4 (88.5–97.4)	72	50.2 (41.0–58.7)	4.43 (2.84–6.90)	1.74 (0.92–3.31)
Other supratentorial midline	39	3	91.7 (76.2–97.2)	19	48.9 (32.0–63.9)	5.32 (2.95–9.57)	1.64 (0.80–3.34)
Brain stem	63	8	84.8 (71.1–92.3)	22	63.7 (49.8–74.7)	3.22 (1.83–5.65)	1.23 (0.65–2.33)
Spinal	29	0	100.0	10	62.3 (41.1–77.8)	3.39 (1.64–7.00)	0.99 (0.45–2.16)
Extent of tumor resection			*P* < .001		*P* < .001	*P* < .001	*P* < .001
Total	205	1	98.9 (92.3–99.8)	38	94.0 (89.0–96.7)	1.00	1.00
Nearly total	105	1	98.9 (92.7–99.9)	54	65.6 (55.0–74.2)	8.23 (4.07–16.61)	8.19 (3.97–16.91)
Partial	87	10	90.0 (78.7–95.4)	42	48.6 (37.1–59.2)	14.11 (7.07–28.13)	12.27 (5.58–26.99)
Biopsy	103	17	83.3 (73.5–89.7)	35	41.4 (30.1–52.3)	14.96 (7.61–29.40)	11.38 (4.99–25.97)
No surgery	134	5	97.2 (91.4–99.1)	10	68.9 (59.2–76.7)	6.48 (3.23–13.01)	19.79 (6.11–64.14)
Metastasis within CNS			*P* = .003		*P* = .005	*P* = .006	*P* = .107
No	583	29	94.6 (91.9–96.5)	160	69.5 (33.0–74.8)	1.00	1.00
Yes	22	4	85.5 (61.4–95.1)	11	56.7 (65.1–73.4)	2.36 (1.28–4.35)	1.74 (0.89–3.41)

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; NF1, neurofibromatosis type 1; CNS, central nervous system.
[a]Adjusted for sex, age (in 5 groups), NF1 status, pathology (in 5 groups), site review (in 8 groups, results for 'others' [*n* = 9] not shown), extent of tumor resection, treatment decision after diagnosis (data not shown), and metastasis within CNS.
[b]Other eligible types: other astrocytoma (*n* = 23) and pilomyxoid astrocytoma (*n* = 9).

All patients eligible and entered into the study were followed up. In this study, referral bias cannot be entirely excluded. However, the proportion of UK childhood cancer registrations exceeds the 70% response rate normally taken as indicative of a representative sample. The sex and NF1 parameters of this cohort are comparable to other reports.[8,13]

The multidisciplinary strategy with predetermined clinical and imaging evidence of progression was used to justify clinical re-evaluation and the option for further therapy. The central anatomical and pathological reviews were performed blind to clinical details. The selection of PFS rather than OS as the primary endpoint provides more events for analysis and reduces the
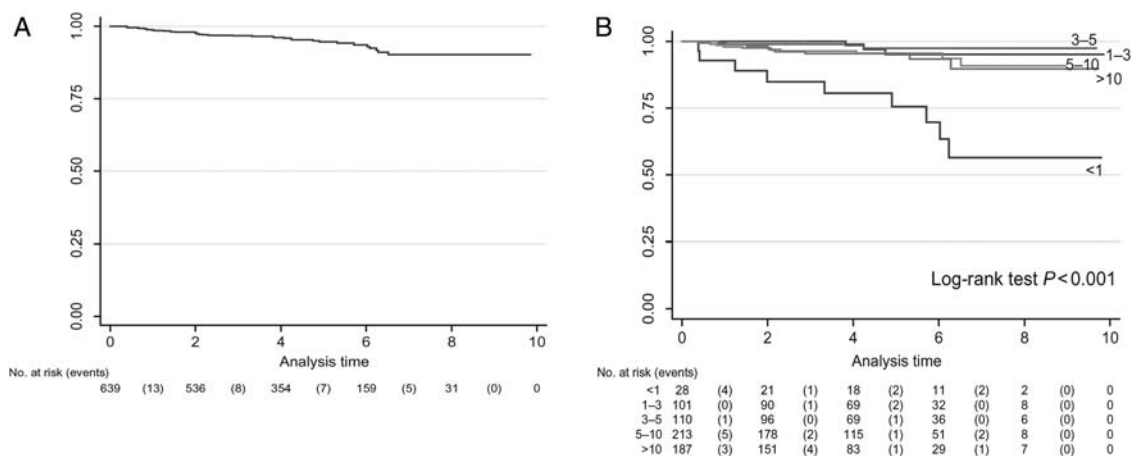
Fig. 4. The Kaplan–Meier curves of OS. (A) OS, all; (B) OS by age group.

confounding effects of multiple clinical interventions commonly used after tumor progression. The comparison of OS and PFS in selected categories permits proposals to be made for consideration in stratification in future trials. The prognostic analyses were based on HR within a multivariate analysis. The duration of follow-up was the only criterion not entirely met, the median follow-up time being 4.7 years against the recommendation of 5 years.

Expert central pathology review was the main method for exclusion of ineligible cases. The large number of patients and the small proportion of unclassifiable tumors make this cohort unique compared with others. Eighty percent of biopsied tumors were PA, which is a larger proportion than in other reports.[8,13,27–29] This difference may have been due to the enhanced use of the diagnosis "non-specific astrocytoma" in registry reports,[26] or referral bias within institutional reports. There were 39 (5.9%) cases of diffuse astrocytoma corresponding to the grade II LGG. At the time this histopathological classification was carried out, there were no known genetic abnormalities to assist with further biological subclassification. The subsequent identification of copy number gains at 7q34 in PAs and grade II LGG tumors,[30–34] tandem duplications involving *BRAF* fusion genes *KIAA1549-BRAF* and *SRGAP3-RAF1*,[31,32,34,35] and the latter fusion genes' capacity to give rise to anchorage-independent growth of NiH-3T3 cells[32,35] have highlighted a new method for exploring the biology of these tumors in addition to histopathological classification.

PMA is a relatively new histopathological entity that has been proposed as an independent adverse category for prognosis.[36] We applied strict criteria for the diagnosis of this entity, making the diagnosis only when there were no elements within the tumor that might suggest a diagnosis of PA with myxoid foci. PMA and PA are closely related. This LGG1 study has revealed a histopathological overlap, and there is now an established literature on the cases of PMA that have "recurred" as PAs.[37] In addition, it is clear that some PMAs have the characteristic BRAF/KIAA1549 fusion gene of PAs.[34] It is our view that the prevalence of PMA has previously been overestimated and that if it is to be a useful

diagnostic category, then histopathological evaluation has to be stringent. Our results are consistent with the poor prognosis of PMA found by others; however, this does not reach statistical significance in the multivariate analysis.

The clinical diagnosis of LGG without biopsy was accepted with typical imaging in cases predominantly associated with NF1, and by so doing, it is assumed that their biological characteristics are comparable to those seen in typical PAs. The survival curve pattern and PFS rates are comparable to those of biopsy-proven PAs, supporting the explanation and the adoption of these selection criteria for future trials. NF1 status has been reported as a favorable prognostic factor in OPG.[6,9,18] This study confirms this at the chiasma/hypothalamus location, although little difference could be shown at other sites.

The anatomical reclassification conducted in this study left very few cases unclassified. The childhood focus in patient recruitment means that the processes of brain growth and development are integral to the analysis. Age is proposed as a proxy for staging brain development, which from this analysis suggests an interaction between tumor behavior and different anatomical sites. There was a bimodal age distribution for the whole cohort. In the cerebellar group, none presented clinically under the age of 1 year. The chiasmatic/hypothalamic group shows an early peak (4 years of age) and a declining incidence in subsequent age groups, whereas the cerebral cortex tumors show a rising incidence with age. These different age-incidence patterns are intriguing, suggesting that they may be a product of time taken for tumors to reach a critical size for symptomatic presentation. Alternatively, that they could be an expression of the microenvironment at different sites and ages promoting differential rates of tumor development and growth.[38] This latter view, in our opinion, appears compatible with the very large, predominantly chiasmatic/hypothalamic tumors presenting under 1 year and the overall impact of early age (<5 years) on the risk for tumor progression in the univariate and multivariate analyses.

In this study, age <1 year was predictive of poorer OS, with 84.7% and 75.6% 3- and 5-year OS, respectively,

compared with 95.3%–100% 3-year OS and 95.3%–97.4% 5-year OS in the other age groups. This difference in OS between <1 year and other age groups in our study was statistically significant ($P < .001$). Many smaller studies on LGG in children have looked at age as a prognostic factor for OS, with inconsistent results. In the largest study, with 278 patients, there was no difference in OS between children <5 and >5 years.[13] The observation of a significant difference for children <1 year in this, the largest population-based study published to date, is in contrast to the previously published smaller and institution-based studies, the majority of which were restricted to OPG. The published meta-analysis of OPG concluded that age <1 year is an independent prognostic factor for survival at this site.[26]

PFS in this analysis showed a significant correlation with the age groups. Other published studies including LGG at all sites show young age (<2 or <5 years) being a negative prognostic factor for PFS,[8,17] whereas others could not verify this[13,15] or even found young age a positive prognostic factor for PFS.[14] Two studies that showed a significantly worse PFS in children <1 year compared with 1–5 and 5–10 years were stratified to recruit children for the trial of chemotherapy, in order to delay radiotherapy and its attendant neurotoxicity, in very young children.[18,19] This stratified design precludes full interpretation of the independent impact of age on outcome in these studies. The study by the Gesellschaft fur Paediatrische Onkologie und Haematologie (GPOH) identified age >10 years as a poor prognostic factor for PFS.[19] This is in contrast to our observation regarding the impact of age upon progression. One explanation may be that the GPOH study is also reporting a trial of chemotherapy, which may have selected older children with more resistant tumors requiring treatment at late stage. The same explanation may be applied to the study identifying age >5 years as a category with a worse PFS than <5 years.[14] Studies of OPG with other age cutoffs found young age either to be a negative factor[9,11,12] for PFS or to have no influence.[6]

We have observed a marked discrepancy between PFS and OS rates overall, and a particular discrepancy for the impact of different age categories upon these 2 outcome parameters. This discrepancy underlines the chronic nature of the clinical course for patients with these tumors, which threaten life infrequently, yet continue to be at a sustained risk for progression when unresectable. The discrepancy between age groups with respect to OS versus PFS would support the hypothesis we set out to test, that age is a factor determining the risk for tumor progression; this seems particularly applicable in hypothalamic/chiasmatic tumors in the <1- and 1–5-year age groups. Previously published studies reporting both endpoints showed similar impact of age (with cutoff at age 2, 3, or 5 years) for PFS and OS,[8,12,17] although this was not commented upon. In contrast, we consider this observation of the discrepant impact of age upon PFS and OS as important, justifying the proposal that age should be a major factor for stratification of future trials.

We note that the adjusted HRs remained significant or borderline significant in younger age groups, suggesting that the effect is probably independent of treatment groups. This is a challenging conclusion from this analysis. In this study, after registration and surgery, 474 (74.2%) patients were initially observed, of whom 108 (16.9%) subsequently progressed. One hundred and sixty-five patients (25.8%) received initial nonsurgical therapy at diagnosis: 113 (17.6%) received chemotherapy and 52 (8.1%) received radiotherapy; 58 (9.1%) and 12 (1.9%), respectively, progressed. The selection of these nonsurgical treatments was determined by age at diagnosis within the treatment strategy. The majority of first progressions (16.9%) occurred in patients after primary observation, compared with 11.1% after primary nonsurgical treatment and having done the analysis with and without treatment effects and presented the model with the inclusion of treatment decisions. We conclude that although there is an interaction between age and nonsurgical treatment, the greater proportion of progressions occurring after observation lends greater weight to age rather than treatment as a cause of progression, especially as treatment was given with the intention of delaying progression.

Optic pathway tumors constitute an important clinical group within LGGs, as their presentation is associated with a clinical concern about vision loss. Treatment is commonly initiated in order to "save vision." The anatomical classification conducted here permitted differentiation between isolated optic nerve and chiasmatic OPG. This anatomical separation was associated with marked differences in PFS at these sites within the optic tract (Fig. 3G), optic nerve tumors progressing very infrequently. A recent description of a more detailed anatomical and genetic classification of OPGs offers a new way to study the impact of therapy on the risk for vision loss and anatomical and genetic factors that may influence long-term visual outcomes.[39]

Most studies find PA a favorable prognostic factor,[7,10,13,17] but others not.[8,14] In this study, FA was an independent adverse risk factor for both PFS and OS, compared with PA. This effect was greater for OS than PFS, an observation not commented upon, yet recorded in previous studies.[7,17] This difference between OS and PFS rates emphasizes the sustained tendency of PA to progress compared with a more classical tumor paradigm for FA, where progression is more strongly linked to survival.

In conclusion, this is the largest population-based study of LGG in childhood published to date. It has identified significant interactions between age at presentation and anatomical site as well as anatomical site and resectability. It has identified age at diagnosis, histological grade, extent of surgical resection, and hypothalamic/chiasmatic location as significant predictors for tumor progression. It has emphasized the sustained risk for tumor progression in chiasmatic/hypothalamic tumors. Clinically, these factors underline the importance of surgical resection for control of tumor progression and will be used to stratify future clinical trials of new and hopefully more effective nonsurgical therapies. These observations support hypotheses being

tested in the current biological research in this field.[32,34,40,41] We propose the hypothesis that the risk for tumor progression at the hypothalamic/chiasmatic location diminishes with age and is a product of an interaction between tumor factors (genetic) and the ontogeny of factors determining characteristics of human brain growth and development within the hypothalamic/chiasmatic region.

Conflict of interest statement. None declared.

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Appendix

Authors' Contribution

T.S.: Anatomical review, clinical interpretation of analysis, drafted manuscript, international presentation of data; J.-F.L.: Statistical analysis, contributed to drafting of manuscript; J.W.I.: Central pathology review, manuscript review; D.W.E.: Central pathology review, manuscript review; R.T.: Contributed to ICLGG 1 study design, study conduct internationally and UK, radiotherapy data review, interpretation of analysis, drafting of manuscript; K.J.R.: Trial coordination, data management, preliminary analyses, manuscript review; S.V.P.: Contributed to manuscript review, UK Chief Investigator CCLG LGG 2003 (ICLGG2), Chair CCLG Astrocytoma Working Group; D.A.W.: Contributed to ICLGG 1 study design, international and UK study conduct, interpretation of international data set. CNS9702 UK Chief Investigator director of analysis, drafting of manuscript, senior and corresponding author.

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Childrens' Cancer and leukemia Group (CCLG) treatment centers

Royal Manchester Children's Hospital, Pendlebury, Manchester M27 4HA	Great Ormond Street Hospital, Great Ormond Street, London WC1N 3JH
Addenbrooke's NHS Trust, Hills Road, Cambridge CB2 2QQ	Royal Aberdeen Children's, Westburn Road, Aberdeen AB25 2ZG
Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol BS2 8BJ	Our Lady's Children's Hospital, Crumlin, Dublin 12, Ireland
St James's University Hospital, Leeds LS9 7TF	Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ
Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH	University College Hospital, NHS Foundation Trust, 250 Euston Road, London NW1 2PQ
Sheffield Children's Hospital, Western Bank, Sheffield S10 2TH	Royal Marsden NHS Trust, Downs Road, Sutton, Royal SM2 5PT
Institute of Child Health, Royal Victoria Infirmary, Newcastle Upon Tyne NE1 4LP	Children's Hospital for Wales, Heath Park, Cardiff CF14 4XW
University Hospital, Queens Medical Centre, Nottingham	Children's Hospital, Leicester Royal Infirmary, Leicester LE1 5WW
Southampton General Hospital, Tremona Road, Southampton SO16 6YD	Royal Hospital for Sick Children, Millerfield Place, Edinburgh EH9 1LF
Royal Belfast Hospital for Sick, 180 Falls Road, Belfast BT12 6BE	Children's Hospital, John Radcliffe Infirmary, Headington, Oxford OX3 9DU
RLC NHS Trust, Alder Hey, Eaton Road, Liverpool L12 2AP	

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