How do biological characteristics of primary intracranial tumors affect their clinical presentation in children and young adults?

Thomas P C Chu, PhD [1]

Anjali Shah, PhD [2]

David Walker, FRCPCH [3]

Michel P Coleman, FFPH [1]

[1] Cancer Survival Group, Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom.

[2] Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom.

[3] Children's Brain Tumour Research Centre, University of Nottingham, Nottingham, United Kingdom.

Correspondence: Thomas P C Chu, Cancer Survival Group, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom.

Email: thomas.chu@lshtm.ac.uk Tel: +44 20 7927 2551 Fax: +44 20 7436 4230

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Abstract

We demonstrated the pattern in presentation of primary intracranial tumors in a population-based cohort of patients aged 0–24 years identified from the National Cancer Registry for England, using linked medical records from primary care and hospitals. We used generalized additive models to estimate temporal changes in presentation rates. Borderline and malignant tumors presented at a similar rate in primary care (6.4 and 6.6 consultations per 100 patients each month) and in hospital (3.4 and 3.6). Benign tumors presented earlier but less frequently (rate = 4.4 and rate ratio = 0.75, 95% CI = 0.60–0.93 in primary care; rate = 2.6 and rate ratio = 0.83, 95% CI = 0.77–0.89 in hospital). Many tumors began presenting shortly before their diagnosis, but less aggressive tumors were likely to present earlier in primary care. Earlier detection of less aggressive tumors in primary care may reduce the risk of complications and morbidity among survivors.

Keywords

adolescents, brain tumor, children, epidemiology, infant, neuro-oncology, pediatric

1. Introduction

Primary intracranial tumors are not commonly seen by many clinicians (incidence rate = 34 per million children per year). However, they account for 25% of childhood cancers and are responsible for considerable morbidity and mortality.[1] Many brain tumors are not diagnosed early enough because of the variability of their presentation, which means children may only present with a few symptoms or signs from a very long list of possible clinical features. Many of these symptoms may be attributed to more common pediatric conditions, especially in the first few consultations, before the possibility of an intracranial tumor is considered.[2-5] We therefore have recommended persistence or recurrence of symptoms, instead of emergence of confirmatory features that may not be present until a tumor has reached an advanced state, as a more useful trigger for further investigations.[2, 6]

Delays in diagnosing an intracranial tumor result in patient distress and parental anxiety, and may lead to lengthy disputes with healthcare professionals. Parents' reactions to the eventual diagnosis are often very negative, especially when earlier opportunities exist for which a diagnosis could have been made.[7] Because of this, a delayed diagnosis could adversely affect trust and adaptation to subsequent treatment.

Studies on symptoms and signs of intracranial tumors were often limited to describing cases of a single morphological type, or examining a hospital-based cohort with little information from primary care.[8-14] We demonstrated variations in primary and secondary care presentation between different morphological types in a population-based cohort to identify opportunities for their earlier detection.

2. Methods

2.1. Patient cohort

Patients aged 0–24 years when diagnosed with a primary intracranial tumor between 1989 and 2006 in England were identified from the National Cancer Registry.[15] Intracranial tumors

are those that originated in the supratentorial compartment, midline, cerebellum, brainstem, ventricular system, meninges, cranial nerves or other intracranial locations as coded to the 9th or 10th revision of the International Classification of Diseases (ICD), and with a compatible morphology code from the diagnostic groups III, IX.b.2, IX.d.8 and X.a in the third edition of the International Classification of Childhood Cancer.[16-18]

Tumors in the central nervous system are classified by their histological degree of malignancy as one of WHO grade I to IV.[19, 20] This information is not routinely captured by the National Cancer Registry because the grade of a neoplasm outside the central nervous system represents its degree of differentiation, which is a different concept. Intracranial tumors are also classified as benign (the fifth digit of morphology code = /0), borderline (/1) or malignant (/3) by neuropathologists according to ICD for Oncology, promulgated by the World Health Organization and the International Agency for Research on Cancer.[21-23] For central nervous system tumors, behavior and WHO grade are closely related: benign and borderline tumors generally have a low grade (WHO I or II) and malignant ones a high grade (WHO III or IV). For example:

	Morphology	Grade	Behavior
Choroid plexus papilloma	9390/0	I	0 (benign)
Atypical choroid plexus papilloma	9390/1	II	1 (borderline)
Choroid plexus carcinoma	9390/3	III	3 (malignant)

This mapping is not exact and depends on cell type. Instead of using data from deriving WHO grade of an intracranial tumor, we analyzed data on tumor characteristics as recorded by neuropathologists.

We excluded registrations using the same criteria as for the production of National Statistics in England: records with invalid dates, unknown sex, unknown vital status, secondary or metastatic tumors, patients not resident in England and Wales or records that failed Office for National Statistics validity checks. [24] Synchronous (different tumors with identical

diagnosis date belonging to an individual) or multiple primary tumors (in the same location in an individual) were also excluded since those patients were likely to have a genetic syndrome (e.g. neurofibromatosis, tuberous sclerosis), and thus outside the scope of this study.

We obtained linked primary care records from Clinical Practice Research Datalink (CPRD, formerly General Practice Research Database) for patients diagnosed during 1989–2006, and linked records of in-patient stays in National Health Service hospitals in England from Hospital Episode Statistics (HES) for patients diagnosed during 1997–2006. The data in CPRD cover 5–10% of the UK population but are representative in age, sex and ethnicity (compared with UK Census 2011), and the diagnoses on cancer contained within have been validated internally and externally.[25, 26]

Linkage of hospital records to the National Cancer Registry was carried out by the Thames Cancer Registry and the Northern and Yorkshire Cancer Registry and Information Service, and linkage of primary care records was commissioned by CPRD.[27, 28]

2.2. Presentation rates

We analyzed each occurrence of presentation within the longitudinal history of healthcare use by calculating monthly presentation rates, from the total number of relevant primary care consultations and hospital admissions accrued among brain tumor patients divided by the total observation time for the cohort.

A presentation was assumed to be relevant when one of the presenting features in a CPRD consultation record or the main reason for admission in a HES episode record was from one of the eight symptom groups, categorized after a manual search of the full list of diagnostic codes: headache; other features of raised intracranial pressure (e.g. nausea, vomiting); convulsions; visual disturbances (e.g. features of cranial nerves II, III, IV or VI dysfunction); focal neurological deficits; growth or endocrine disorders; behavioral or cognitive problems; and general or non-specific symptoms (e.g. delayed milestone, irritability).

We also classified each hospital episode as ‘non-emergency’ or ‘emergency’ based on the method of admission. Episodes were classed as ‘emergency’ when a patient was admitted via the emergency department, directly by the general practitioner (directly or after consulting the duty hospital doctor), urgently from an outpatient clinic, or by urgent transfer from another hospital.

The total observation time for the cohort is the sum of each patient’s observation time. For calculating hospital presentation rates, the observation time began on the later of the date of birth or the start of HES data and ended with the earlier of the date of death or the end of HES data. For primary care presentation rates, observation time began on the date of registration with the primary care practice and ended with the earliest of the date of birth, transfer-out date (if a patient had switched to a practice outside CPRD coverage), or last collection date (when data were last submitted by the practice). Each person’s observation time was divided into monthly intervals before and after the date of diagnosis in the National Cancer Registry, which has an international standard definition.[29, 30]

We estimated presentation rates and their confidence intervals for 0–1, 1–3, 3–6, 6–12 and over 12 months from the definitive diagnosis of an intracranial tumor in generalized linear models, with the number of consultations or in-patient episodes as the response and the logarithm of the length of observation time as the offset. We also illustrated changes in presentation rate graphically (in supplementary materials) to overcome the problem of dividing continuous time into these artificial intervals. Data on healthcare use after diagnosis have been included to reduce statistical uncertainty associated with estimating rates of presentation around diagnosis, when those were clinically most important, by placing them at the center of the longitudinal data.

Because the monthly rates showed wide fluctuations, the underlying trend was delineated using generalized additive modelling with a locally weighted regression (LOESS) smoother.[31] LOESS is a computationally intensive procedure for smoothing serial observations by fitting

a low-degree polynomial in a contiguous subset of neighboring observations centered on the index presentation. Weights are assigned to each observation in the regression model such that their size are inversely related to the distance from the observation of interest – reflecting that more distant events carry less weight in influencing the index presentation. The predicted mean value of the index observation is estimated from this weighted regression modelling process, which is repeated for each observation until the predicted value of every observation has been estimated.[32-34]

Generalized additive modelling was carried out using functions in the 'gam' package and in the statistical language R.[35, 36] Computationally intensive calculations were carried out on the High Performance Computing cluster at the London School of Hygiene and Tropical Medicine.

3. Results

We identified 9,799 patients diagnosed with a primary intracranial tumor between 1989 and 2006 (including 5,061 patients diagnosed since 1997) from the National Cancer Registry, after excluding 279 patients with ineligible records. We obtained 3,787 linked CPRD records of 181 patients during 1989–2006 and 60,351 linked HES records of 3,959 patients diagnosed during 1997–2006. Patients with linked records had similar age and sex to those without any linked records. Patients with fast-growing tumors (e.g. embryonal tumor, glioma or choroid plexus tumor) or those sited close to strategic or key structures (e.g. brainstem, cerebellum and around the ventricles) were more likely to have a link record in HES than in CPRD, which was expected from our clinical experience. Further details of the cohorts and their linkage characteristics have been described elsewhere.[2]

3.1. Primary care consultations

The overall pre-diagnosis presentation rate for benign intracranial tumors was 25% lower than for malignant tumors (rate = 4.4 per 100 patients each month, rate ratio = 0.75, 95% CI

= 0.60–0.93), and the presentation rate for borderline tumors was similar to that for malignant tumors (rate = 6.4, rate ratio = 0.88, 95% CI = 0.76–1.01) (Table 1).

Much of the increase in the presentation frequency of malignant intracranial tumors occurred in the final six months before their eventual diagnosis (Table 2). The presentation rate of borderline tumors began to increase earlier at 6–12 months before diagnosis, and over 12 months before diagnosis in benign tumors. The peak presentation rate was reached within one month of diagnosis: 65.4 per 100 patients each month (95% CI = 40.1–106.8) in benign tumors, which was less than half the magnitude of the rate for borderline (177.6, 146.4–215.4) or malignant tumors (158.2, 134.8–185.7).

Many gliomas, embryonal tumors, choroid plexus tumors, pineal gland tumors and a substantial proportion of germ cell tumors (Figure 1 and Figure S3, S4, S6, S7 and S10 in supplementary material) are of malignant behavior, but they had a lower overall pre-diagnosis presentation rate than pilocytic astrocytomas (Figure 2), after adjusting for age and year of diagnosis (Table 1).

3.2. Hospital presentations

The overall pre-diagnosis presentation rate for borderline intracranial tumors was similar to malignant tumors (all admissions: rate ratio = 0.97, 95% CI = 0.92–1.03; for emergency admissions: rate ratio = 0.98, 95% CI = 0.91–1.06), and that for benign tumors was 17% lower than malignant tumors for all admissions (0.83, 0.77–0.89) and 42% lower for emergency admissions (0.58, 0.51–0.66) (Table 1).

The temporal pattern in the rate of hospital presentations for benign, borderline and malignant intracranial tumors was very similar up to 1–3 months before their diagnosis (Table 3). The presentation rate rose to peak levels in benign (rate = 104.3 per 100 patients each month, 95% CI = 96.3–113.0) and borderline tumors (142.7, 134.9–151.1) in the final month before diagnosis, but that in malignant tumors continued to rise to an average of over

one visit per patient each month (151.8, 95% CI = 148.4–155.4) at 1–3 months after diagnosis (Table 3).

Emergency hospital presentations increased with time but were uncommon up to one month before diagnosis (between 2.8 and 3.5 per 100 patients each month) (Table 4). A steep increase in the presentation frequency occurred in the final month before diagnosis, with the highest rate occurring in borderline (81.0 per 100 patients each month, 95% CI = 75.1–87.3) and malignant tumors (79.2, 75.9–82.8).

Many primary intracranial tumors started to present in hospital only in the last 1–2 months before their definitive diagnosis despite their morphological heterogeneity. For example, the hospital presentation rate of embryonal tumors (Figure 3) and of tumors in the sellar region (Figure 4) began to increase from the baseline at a similar time in the natural course of events before diagnosis. The difference between those two tumors of very different behavior was in the intensity of overall hospital service use and of emergency presentation in the month when they were eventually diagnosed. This presentation pattern was unlike the one seen in primary care, in which very few consultations came from patients with embryonal tumors until 1–2 months before diagnosis, whereas consultations began earlier and were more frequent from patients with tumors in the sellar region (pituitary tumors, craniopharyngiomas).

4. Discussion

The underlying pattern of presentation of intracranial tumors was remarkably similar despite differences in their cell type and malignant potential: the frequency of presentation increased steadily with time in the pre-diagnosis period and rose steeply in the final few months to a peak at around diagnosis, before falling sharply after diagnosis. Although our primary interest was in the presentation pattern before diagnosis, we have also included events after diagnosis to demonstrate (instead of assuming) the frequency of healthcare use peaked at the time of diagnosis. The main differences in presentation pattern between tumor types

were the point at which presentations began to rise rapidly from the background rate of healthcare use, indicating the earliest time at which brain tumors could be detected, and the intensity of consultations or admissions around diagnosis. Our findings support the hypothesis that presentation of symptoms attributable to an underlying intracranial tumor occurs with increasing intensity as the tumor grows and invades surrounding tissues, and that increase in the frequency of primary care or hospital visits may in itself be a more useful trigger for in-depth investigations than the presence of some specific features (such as focal neurological signs).[2, 37-39]

Patients had been presenting in primary care for some months before they began to present in hospitals, and this was recorded as an increase in presentation rate in secondary care that came after the increase in primary care. The steep increase in consultation rates in highly malignant tumors (embryonal tumors, gliomas and choroid plexus tumors) occurred closer to diagnosis than predominantly benign tumors (in the sellar region, meninges or nerve sheath) (Figure S3–S9 in supplementary material). This suggested opportunities exist in primary care for earlier diagnosis of benign or borderline brain tumors, ones that have the potential to cause significant morbidity and life-threatening complications if left undetected.

The increase in frequency of hospital presentations began at a similar time in the natural history of intracranial tumors regardless of their morphology. The peak presentation rate was higher for malignant tumors such as astrocytomas, embryonal tumors, choroid plexus tumors, germ cell tumors and pineal gland tumors than for benign tumors (Figure S1, S3, S5–S10 in supplementary material). This implied patients with malignant tumors were admitted to hospital more frequently, presumably due to the occurrence of complications (e.g. raised intracranial pressure, hydrocephalus or intracranial hemorrhage) in patients who were not diagnosed in primary care. This finding is consistent with previous observations that rapidly growing tumors generally have some of the shortest time to diagnosis.[2, 4, 10-12, 40-42]

4.1. Strengths and limitations

The linkage of primary and secondary care records to the National Cancer Registry has enabled investigation of the pattern of healthcare use in patients with a rare disease, which would have been logistically prohibitive if patients had to be recruited as a conventional cohort.[43-45] Although the proportion of patients with linked primary care records was small, our cohorts represented patients with demographics typically seen in primary care and with tumor characteristics consistent with our clinical experience because of the population coverage of CPRD.[25]

Earlier studies on diagnostic delays in children were often carried out using a hospital-based cohort in a specialist center and frequently limited to a specific tumor type.[4, 10, 11, 40] In this study, we examined every tumor morphology and behavior in two related population-based cohorts to highlight the similarities and differences in presentation pattern in both primary and secondary care. The pre-diagnosis period in which consultation frequency was above the background rate was much shorter in malignant brain tumors than in benign tumors, a phenomenon that was consistent with previous studies on highly aggressive tumors such as medulloblastomas.[10, 11, 40] Rather than directly estimating a symptom interval in each patient to estimate diagnostic delay for the entire population, we have chosen to estimate the pattern of healthcare service use in the population to quantify delay. Our approach avoids the inherent inaccuracy associated with measuring individual symptom interval,[46] which is commonly defined as the length of time between the date of diagnosis and “the first presentation” of a relevant set of symptoms.[47] Although an internationally recognized standard exists for the definition of date of diagnosis in cancer research,[29, 30] we are not aware of the a similar standard for defining “the first presentation”. The “first presentation” is often presumed to be the earliest consultation as recalled by patients or the earliest presentation deemed to be associated with an underlying tumor in a clinician’s opinion. This lack of a robust definition causes difficulty in ensuring reproducibility and comparability of results between studies and in examining trends in diagnostic delay. We have avoided this

problem by tracing each patient's contact with healthcare service throughout their entire history using the same symptom list and algorithm, and examining the resulting pattern in the study population.

For children with a suspected brain tumor in the UK, the pattern of referral for investigation from primary to secondary care is similar to that for adults. In other healthcare systems, such children are often first seen by primary pediatric physicians, who have direct access to comprehensive investigations, including neuroimaging, as well as rights to admit patients directly to secondary care. International differences in the pattern of referral for investigations could affect outcomes. International comparison of survival in patients with brain tumors of similar biological characteristics may provide useful insights into the relationship between different health systems and outcomes.

4.2. Conclusion and implications

Despite their histological heterogeneity, the presentation patterns of brain tumors in children and young adults are more similar than expected. Variations are associated with differences in their malignant potential and their presumed speed of growth. Benign brain tumors present earlier in primary care than malignant tumors, but the difference in time at which brain tumors become symptomatic is less pronounced in secondary care. Malignant tumors are much more likely to present as an emergency in secondary care than benign tumors. These observations mean fewer opportunities exist in primary care for an earlier diagnosis of highly malignant tumors until serious complications have developed.

Efforts to promote early diagnosis of brain tumors in children and young adults should therefore emphasize recognizing the increase in frequency of consultations in primary care, instead of focusing on the presence of specific symptoms or signs.[2] Many patients detected in primary care are likely to have a benign or borderline intracranial tumor, and long-term morbidity in this group could be reduced by minimizing the risk of irreversible neurological damage from insidious tumor growth or from prolonged raised intracranial pressure.

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Author contributions

TPCC searched the literature, designed the study, carried out data management and statistical analysis, interpreted the findings and drafted the manuscript. AS helped with literature search, study design and contributed to interpretation of findings. DW helped with literature search. MPC helped with literature search, secured data access, advised on study design, data analysis and interpretation of findings. All authors contributed to revision of the manuscript.

TPCC and MPC have full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of conflicting interest

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Ethical approval

This study was approved by the Research Ethics Committee at the London School of Hygiene and Tropical Medicine (reference 5566). Use of patient information was approved by the Patient Information Advisory Group (succeeded by the National Health Service Health Research Authority Confidentiality Advisory Group) under Section 60 of the Health and Social Care Act 2001 and Section 251 of the National Health Service Act 2006 in England and Wales (reference PIAG 1-05(c)/2007 and PIAG 3-06(f)/2008).

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Figures and Tables

Figure 1 Pattern of primary care presentations in children and young adults with an embryonal tumor before and after diagnosis (time = 0): England, 1989–2006.

Change in monthly presentation rates (gray dots) after LOESS smoothing (solid line).

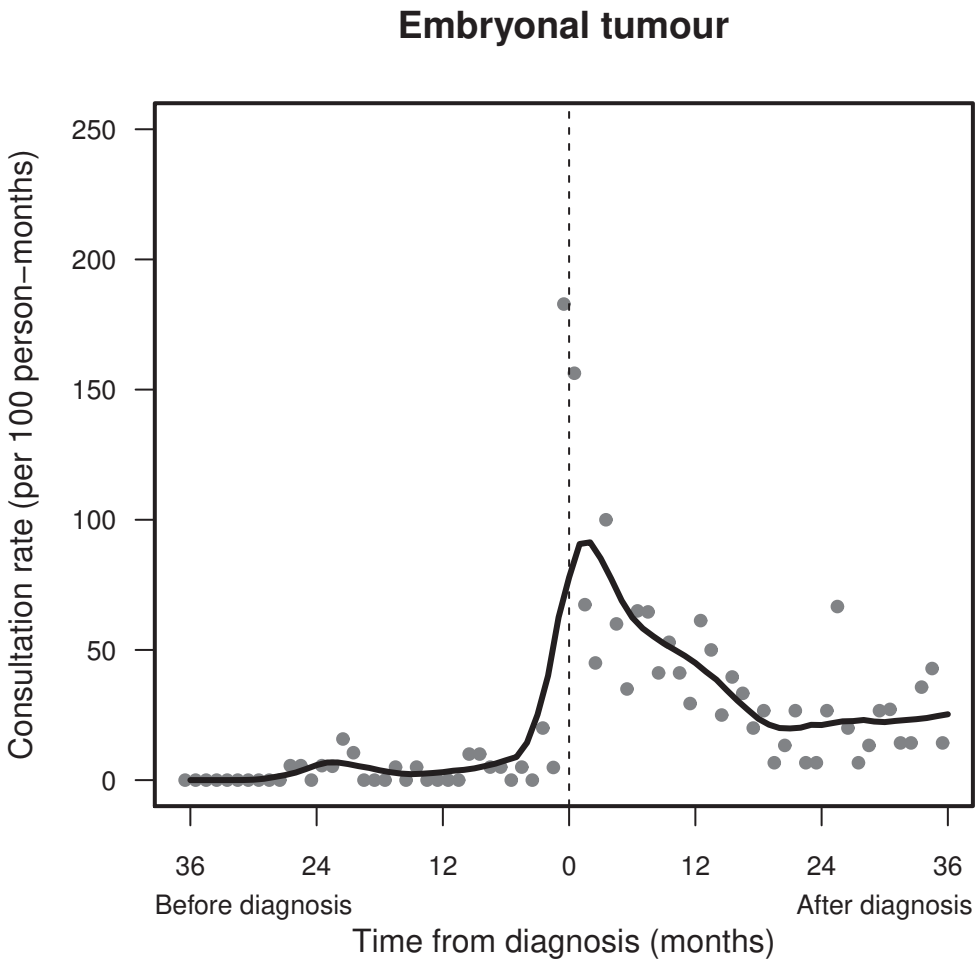
Embryonal tumour
Consultation rate (per 100 person−months)
250
200
150
100
50
0
36
24
12
0
12
24
36
Before diagnosis
After diagnosis
Time from diagnosis (months)

Figure 2 Pattern of primary care presentations in children and young adults with a pilocytic astrocytoma before and after diagnosis (time = 0): England, 1989–2006.

Change in monthly presentation rates (gray dots) after LOESS smoothing (solid line).

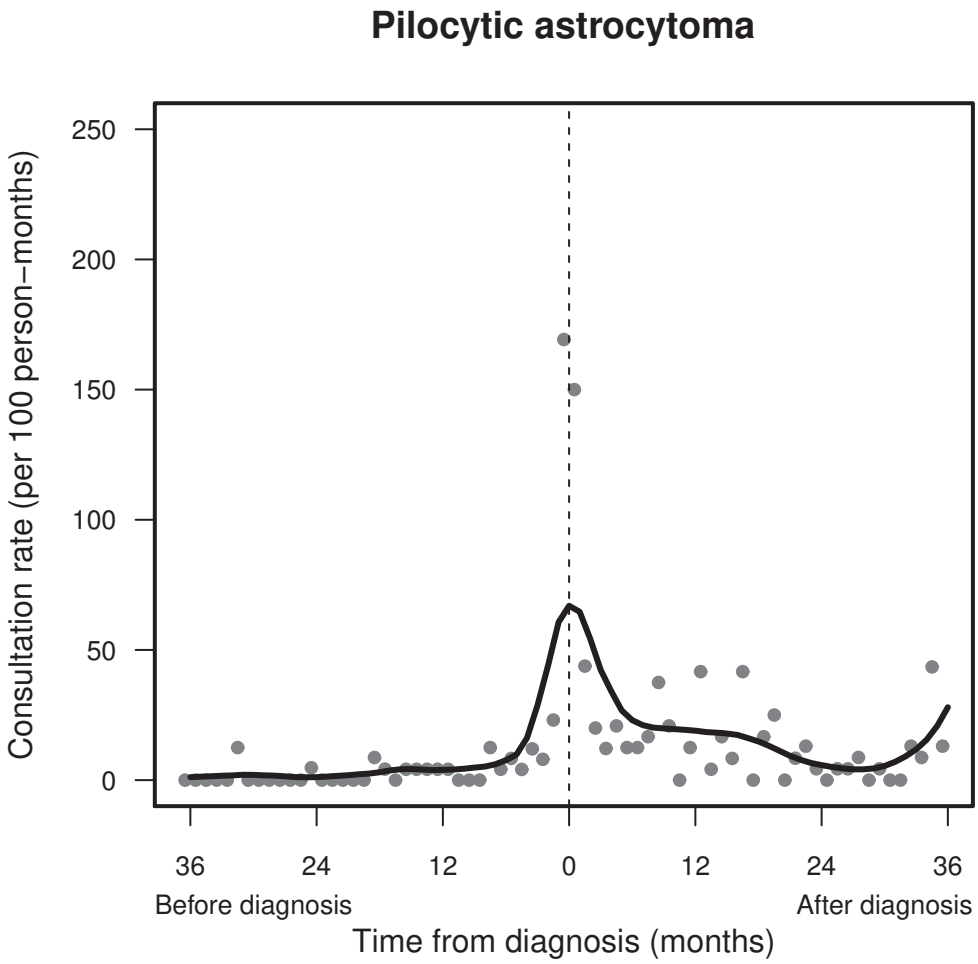
Pilocytic astrocytoma
Consultation rate (per 100 person−months)
250
200
150
100
50
0
36
24
12
0
12
24
36
Before diagnosis
After diagnosis
Time from diagnosis (months)

Figure 3 Pattern of hospital presentations in children and young adults with an embryonal tumor before and after diagnosis (time = 0): England, 1997–2006.

Change in monthly rates of all presentations (black dots) after LOESS smoothing (black line), and of emergency presentations (gray dots) after LOESS smoothing (gray line).

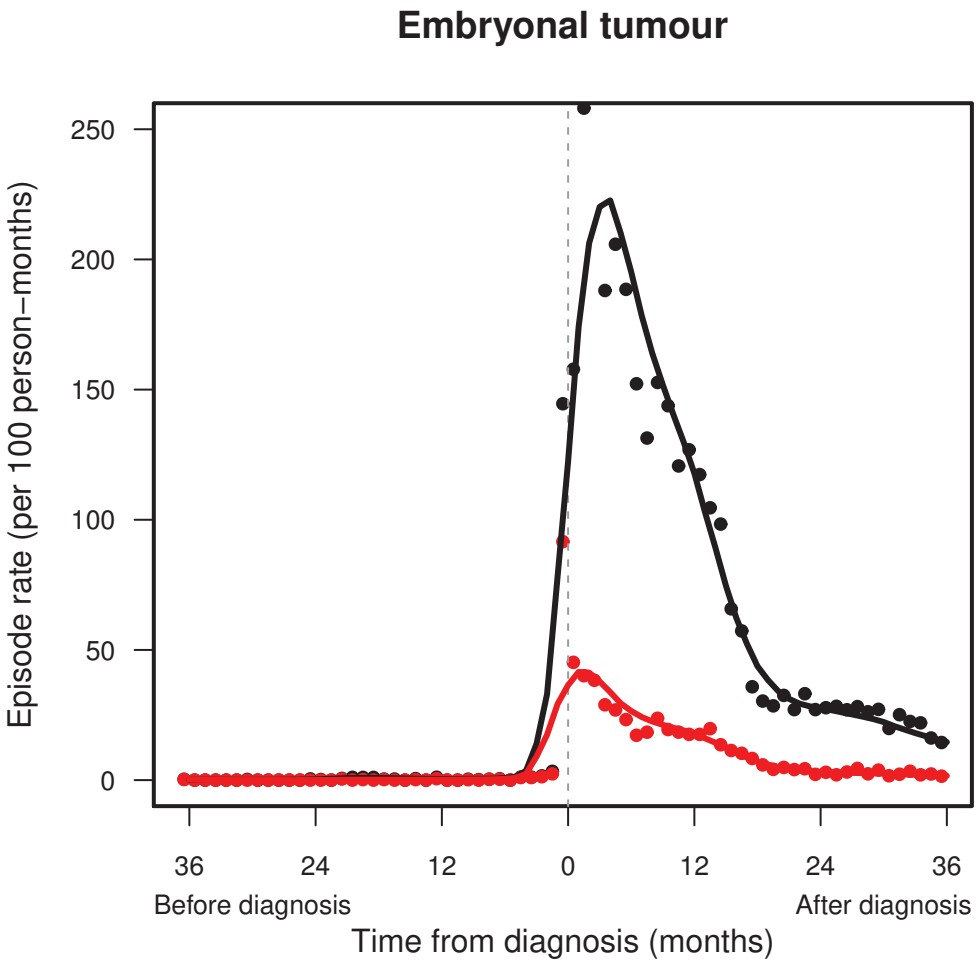
Embryonal tumour
Episode rate (per 100 person−months)
250
200
150
100
50
0
36
24
12
0
12
24
36
Before diagnosis
After diagnosis
Time from diagnosis (months)

Figure 4 Pattern of hospital presentations in children and young adults with a tumor in the sellar region before and after diagnosis (time = 0): England, 1997–2006.

Change in monthly rates of all presentations (black dots) after LOESS smoothing (black line), and of emergency presentations (gray dots) after LOESS smoothing (gray line).

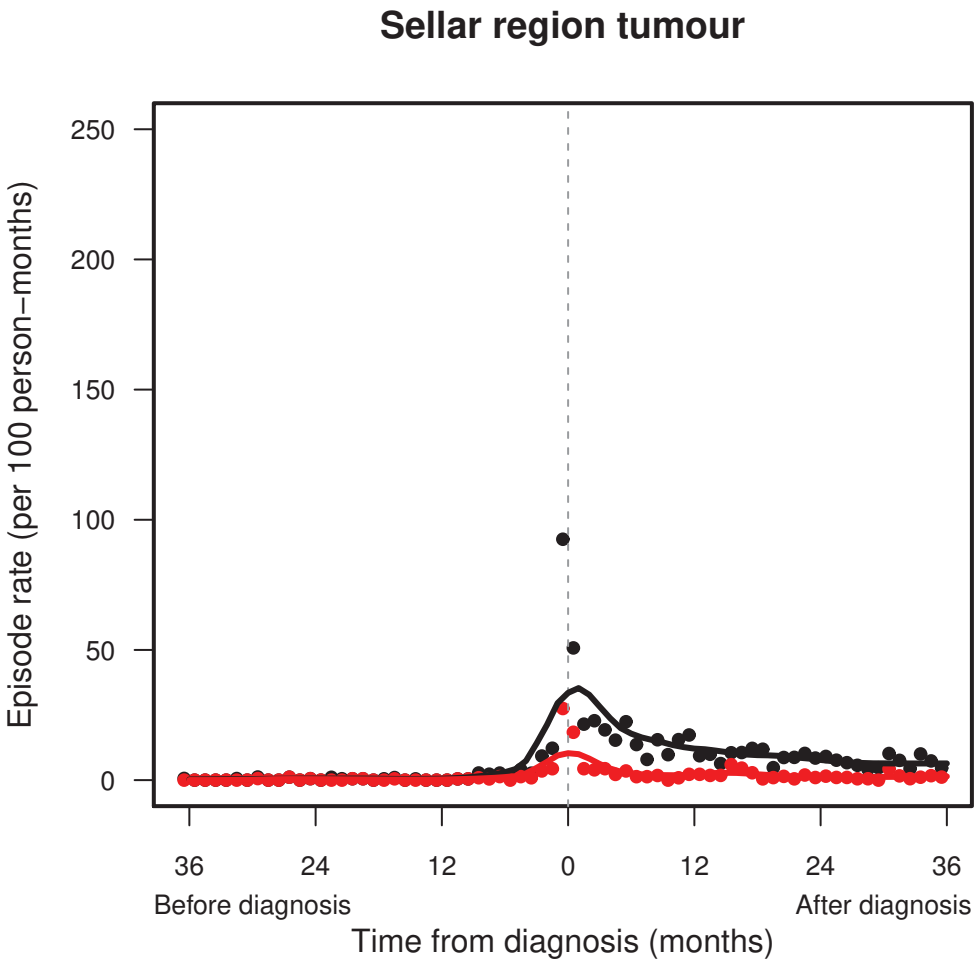
Sellar region tumour
Episode rate (per 100 person−months)
250
200
150
100
50
0
36
24
12
0
12
24
36
Before diagnosis
After diagnosis
Time from diagnosis (months)

Table 1: Presentation rate (per 100 person-months) before an intracranial tumour diagnosis from CPRD (1989–2006) and HES-linked registrations (1997–2006) in patients aged 0 to 24 years in England.

	Primary care presentations				Hospital presentations							
					All admissions				Emergency only			
	Count	Rate	Rate ratio*	95% CI	Count	Rate	Rate ratio*	95% CI	Count	Rate	Rate ratio*	95% CI
Tumour morphology												
Astrocytoma												
all other subtypes	260	8.3	1.00	reference	1,773	3.7	1.00	reference	869	1.8	1.00	reference
pilocytic	83	5.0	0.46	0.35 – 0.59	1,282	3.6	0.93	0.87 – 1.00	725	2.0	1.07	0.96 – 1.18
Embryonal tumour	79	4.2	0.41	0.32 – 0.53	1,004	3.5	0.85	0.78 – 0.92	629	2.2	1.07	0.96 – 1.19
Glioma	117	8.2	0.74	0.58 – 0.94	847	3.3	0.90	0.83 – 0.98	426	1.6	0.92	0.82 – 1.03
Sellar region tumour	80	4.6	0.50	0.38 – 0.66	326	2.4	0.74	0.66 – 0.84	106	0.8	0.50	0.41 – 0.61
Choroid plexus tumour	30	5.5	0.64	0.43 – 0.91	503	4.2	0.90	0.81 – 0.99	334	2.8	1.19	1.04 – 1.35
Germ cell tumour	32	3.8	0.45	0.31 – 0.65	264	2.9	0.89	0.78 – 1.02	143	1.6	1.00	0.83 – 1.19
Nerve sheath tumour	40	7.3	0.88	0.61 – 1.25	153	2.0	0.62	0.52 – 0.73	48	0.6	0.40	0.30 – 0.53
Meningioma	22	3.0	0.32	0.20 – 0.50	168	2.4	0.78	0.66 – 0.91	74	1.0	0.71	0.55 – 0.89
Pineal gland tumour	46	12.5	1.16	0.83 – 1.58	64	3.1	0.75	0.58 – 0.96	50	2.4	1.19	0.88 – 1.57
Haemangioma			no patient		22	2.1	0.70	0.45 – 1.04	13	1.3	0.85	0.47 – 1.41
Other specified tumour	77	8.0	0.85	0.64 – 1.12	169	3.0	0.90	0.76 – 1.05	67	1.2	0.73	0.56 – 0.92
Unspecified neoplasm	89	5.2	0.54	0.42 – 0.69	398	4.4	1.28	1.14 – 1.42	156	1.7	1.01	0.85 – 1.20
Tumour behaviour												
Malignant	532	6.6	1.00	reference	4,608	3.6	1.00	reference	2,498	1.9	1.00	reference
Benign	111	4.4	0.75	0.60 – 0.93	842	2.6	0.83	0.77 – 0.89	308	0.9	0.58	0.51 – 0.66
Borderline	312	6.4	0.88	0.76 – 1.01	1,523	3.4	0.97	0.92 – 1.03	834	1.9	0.98	0.91 – 1.06

* Estimated rate ratios were adjusted for age and year of diagnosis.

CPRD = Clinical Practice Research Datalink, HES = Hospital Episode Statistics.

Table 2: Primary care presentation rate (per 100 person-months) from CPRD-linked registrations in intracranial tumour patients aged 0 to 24 years, England, 1989–2006: by tumour behaviour and time from diagnosis.

Time from diagnosis (months)	Benign			Borderline			Malignant		
	Count	Rate	95% CI	Count	Rate	95% CI	Count	Rate	95% CI
Before diagnosis									
12+ months	46	2.0	1.5 – 2.7	125	2.9	2.4 – 3.5	246	3.5	3.1 – 4.0
6–12	17	13.8	8.6 – 22.3	25	7.7	5.2 – 11.4	40	7.4	5.5 – 10.1
3–6	11	17.5	9.7 – 31.5	29	17.6	12.2 – 25.3	35	12.7	9.1 – 17.7
1–3	15	32.3	19.5 – 53.6	31	27.3	19.2 – 38.8	45	24.4	18.2 – 32.6
0–1 month	16	65.4	40.1 – 106.8	103	177.6	146.4 – 215.4	150	158.2	134.8 – 185.7
After diagnosis									
0–1 month	12	46.2	26.2 – 81.3	80	140.4	112.7 – 174.7	116	123.4	102.9 – 148.0
1–3	18	34.6	21.8 – 54.9	41	36.6	26.9 – 49.7	100	57.4	47.2 – 69.8
3–6	14	18.3	10.8 – 30.9	45	27.4	20.5 – 36.7	137	55.3	46.8 – 65.4
6–12	12	8.3	4.7 – 14.6	66	20.8	16.3 – 26.4	171	37.2	32.0 – 43.2
12+ months	234	9.6	8.4 – 10.9	767	17.5	16.3 – 18.8	1,109	22.2	20.9 – 23.5

CPRD = Clinical Practice Research Datalink.

Table 3: Hospital presentation rate (per 100 person-months) from HES-linked registrations in intracranial tumour patients aged 0 to 24 years, England, 1997–2006: by tumour behaviour and time from diagnosis.

Time from diagnosis (months)	Benign			Borderline			Malignant		
	Count	Rate	95% CI	Count	Rate	95% CI	Count	Rate	95% CI
Before diagnosis									
12+ months	66	0.2	0.2 – 0.3	127	0.4	0.3 – 0.4	442	0.4	0.4 – 0.5
6–12	48	1.5	1.2 – 2.0	54	1.2	0.9 – 1.5	174	1.2	1.1 – 1.4
3–6	46	2.8	2.1 – 3.7	68	2.8	2.2 – 3.5	167	2.3	2.0 – 2.6
1–3	86	7.6	6.2 – 9.4	81	4.9	3.9 – 6.0	331	6.6	5.9 – 7.3
0–1 month	596	104.3	96.3 – 113.0	1,193	142.7	134.9 – 151.1	3,494	137.8	133.3 – 142.4
After diagnosis									
0–1 month	194	34.1	29.7 – 39.3	554	67.4	62.0 – 73.3	3,149	127.2	122.9 – 131.8
1–3	195	17.2	14.9 – 19.8	721	44.1	41.0 – 47.5	7,293	151.8	148.4 – 155.4
3–6	212	12.5	10.9 – 14.3	869	35.6	33.3 – 38.1	6,921	99.8	97.5 – 102.2
6–12	275	8.1	7.2 – 9.1	1,534	31.7	30.2 – 33.3	9,596	75.9	74.4 – 77.5
12+ months	1,163	3.9	3.7 – 4.1	4,808	10.7	10.4 – 11.0	15,887	18.4	18.1 – 18.6

HES = Hospital Episode Statistics.

Table 4: Emergency presentation rate (per 100 person-months) from HES-linked registrations in intracranial tumour patients aged 0 to 24 years, England, 1997–2006: by tumour behaviour and time from diagnosis.

Time from diagnosis (months)	Benign			Borderline			Malignant		
	Count	Rate	95% CI	Count	Rate	95% CI	Count	Rate	95% CI
Before diagnosis									
12+ months	29	0.1	0.1 – 0.1	48	0.1	0.1 – 0.2	147	0.1	0.1 – 0.2
6–12	26	0.8	0.6 – 1.2	28	0.6	0.4 – 0.9	71	0.5	0.4 – 0.6
3–6	21	1.3	0.8 – 2.0	35	1.4	1.0 – 2.0	95	1.3	1.1 – 1.6
1–3	39	3.5	2.5 – 4.7	46	2.8	2.1 – 3.7	175	3.5	3.0 – 4.0
0–1 month	193	33.8	29.3 – 38.9	677	81.0	75.1 – 87.3	2,010	79.2	75.9 – 82.8
After diagnosis									
0–1 month	70	12.3	9.7 – 15.6	216	26.3	23.0 – 30.0	781	31.6	29.4 – 33.9
1–3	51	4.5	3.4 – 5.9	158	9.7	8.3 – 11.3	1,135	23.6	22.3 – 25.0
3–6	45	2.6	2.0 – 3.5	154	6.3	5.4 – 7.4	1,161	16.7	15.8 – 17.7
6–12	52	1.5	1.2 – 2.0	254	5.3	4.6 – 5.9	1,553	12.3	11.7 – 12.9
12+ months	289	1.0	0.9 – 1.1	867	1.9	1.8 – 2.1	2,793	3.2	3.1 – 3.3

HES = Hospital Episode Statistics.

Supplementary material

- Figures represent temporal change in presentation rate in children and young adults (age at diagnosis = 0–24 years) with intracranial tumor before and after diagnosis (time = 0 at brain tumor diagnosis) in England.
- Left: primary care presentations (1989–2006)
    - grey dots: observed rates
    - black line: predicted rates after locally weighted regression (LOESS) smoothing
- Right: hospital presentations (1997–2006)
    - black dots: observed rates of all admissions
    - red dots: observed rates of emergency admissions only
    - black line: predicted rates of all admissions after LOESS smoothing
    - red line: predicted rates of emergency admissions after LOESS smoothing

Chu TPC, Shah A, Walker D, Coleman MP. How do biological characteristics of primary intracranial tumors affect their clinical presentation in children and young adults? PMID: 29724124

Figure S1

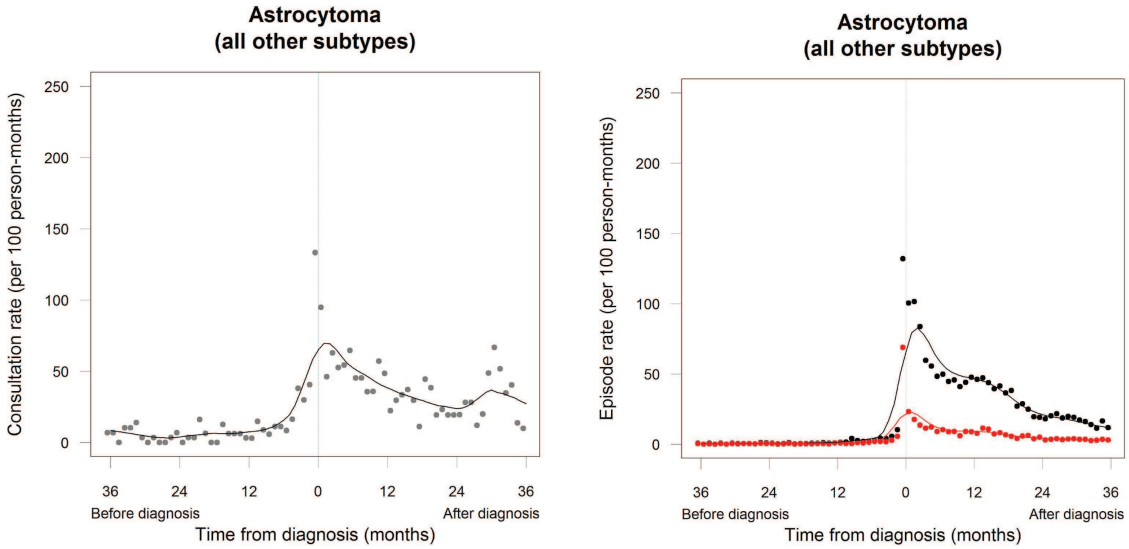

Figure S2

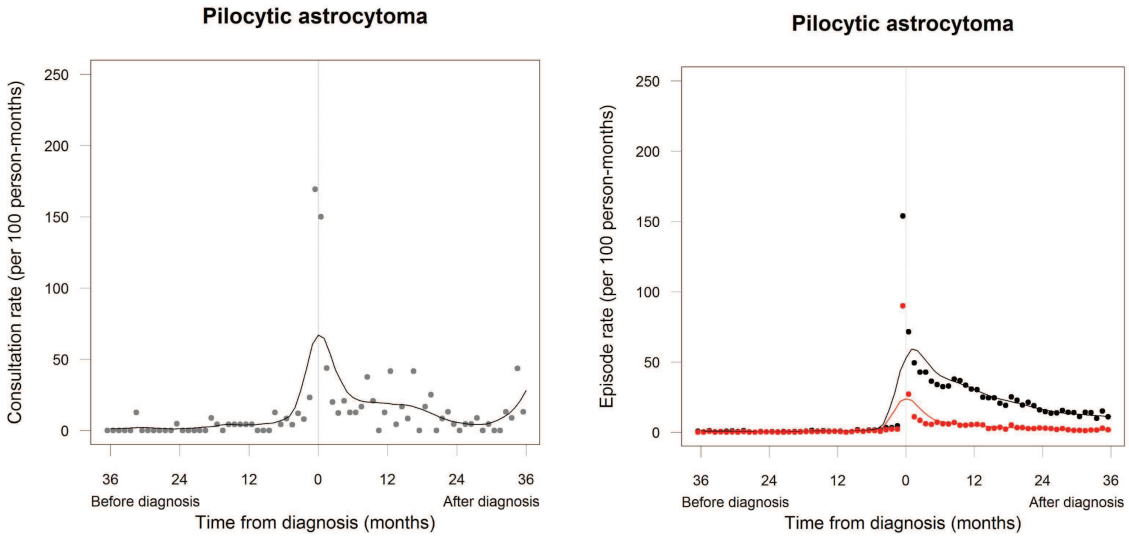

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Figure S3

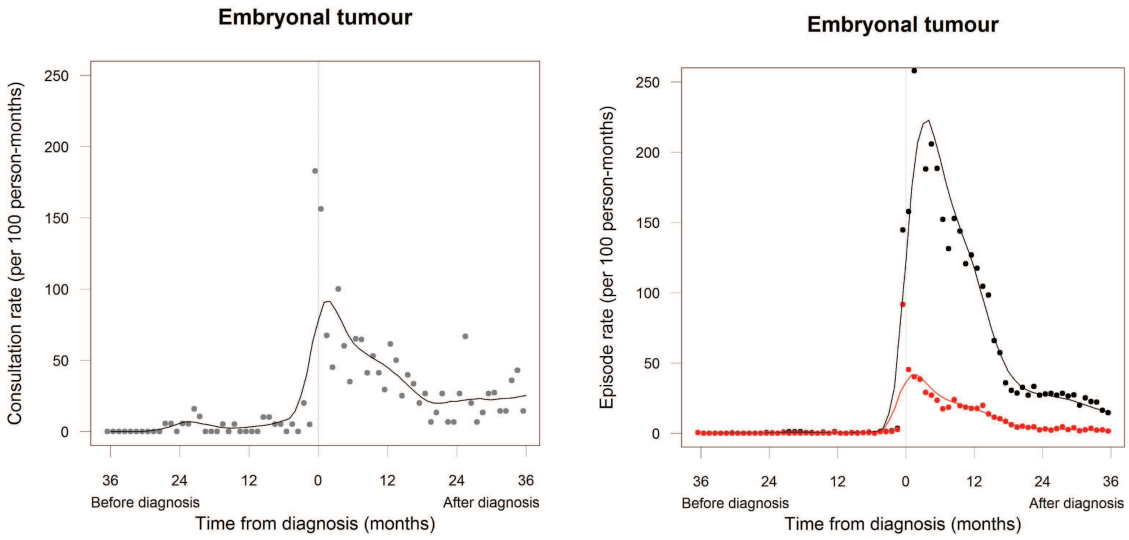

Figure S4

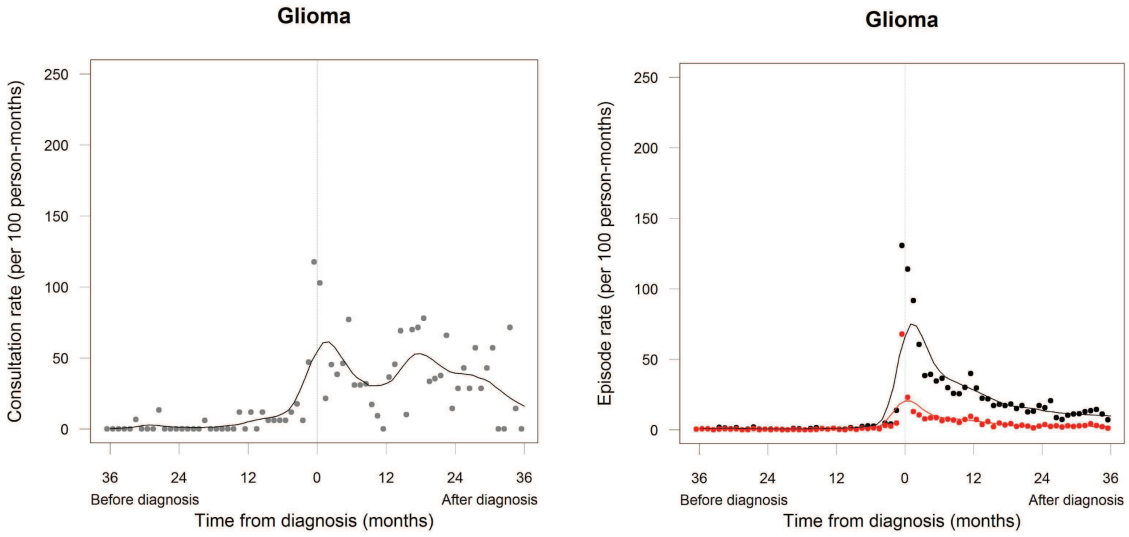

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Figure S5

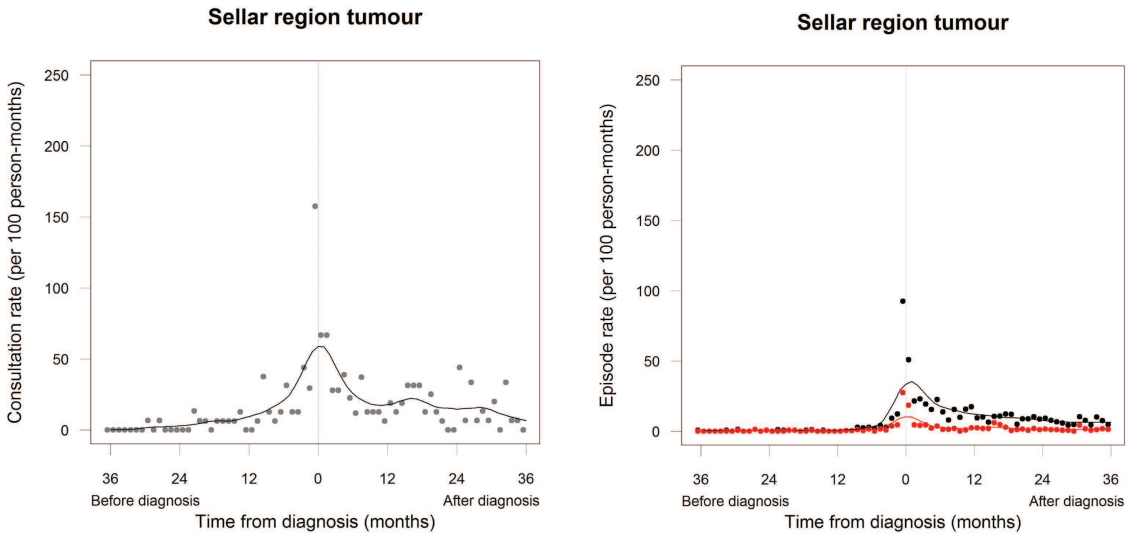

Figure S6

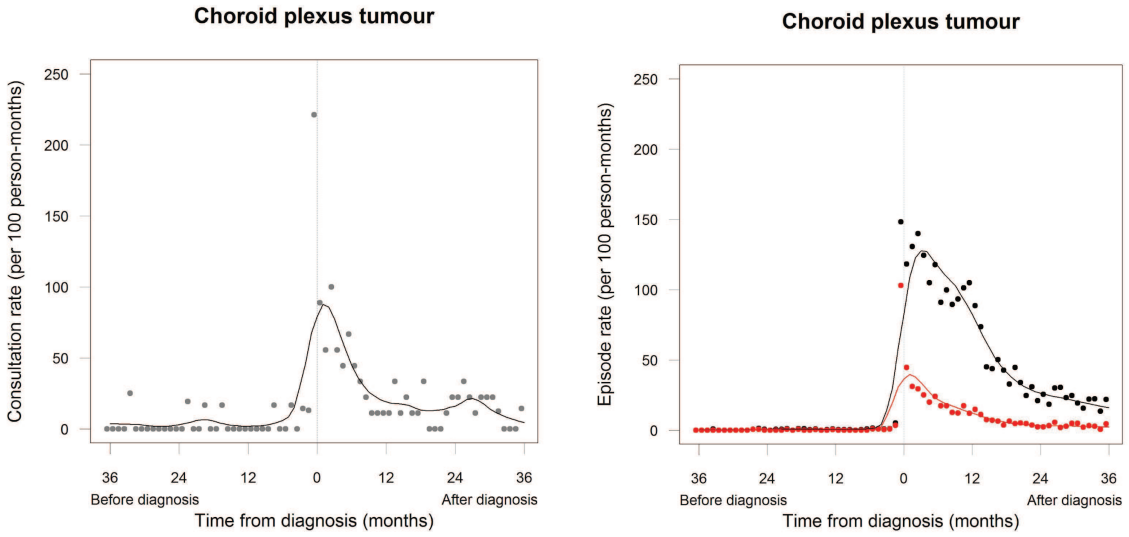

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Figure S7

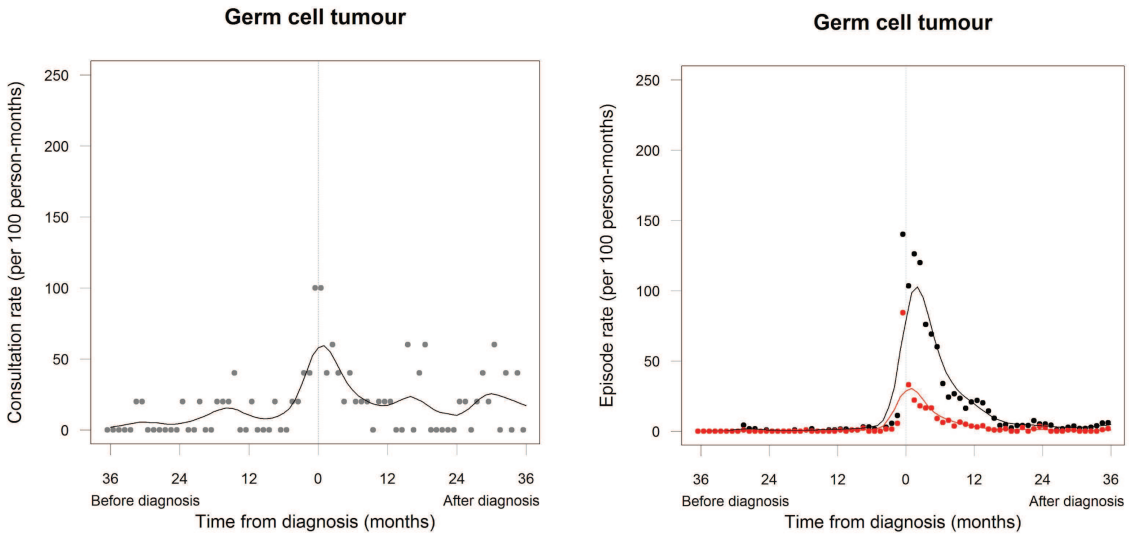

Figure S8

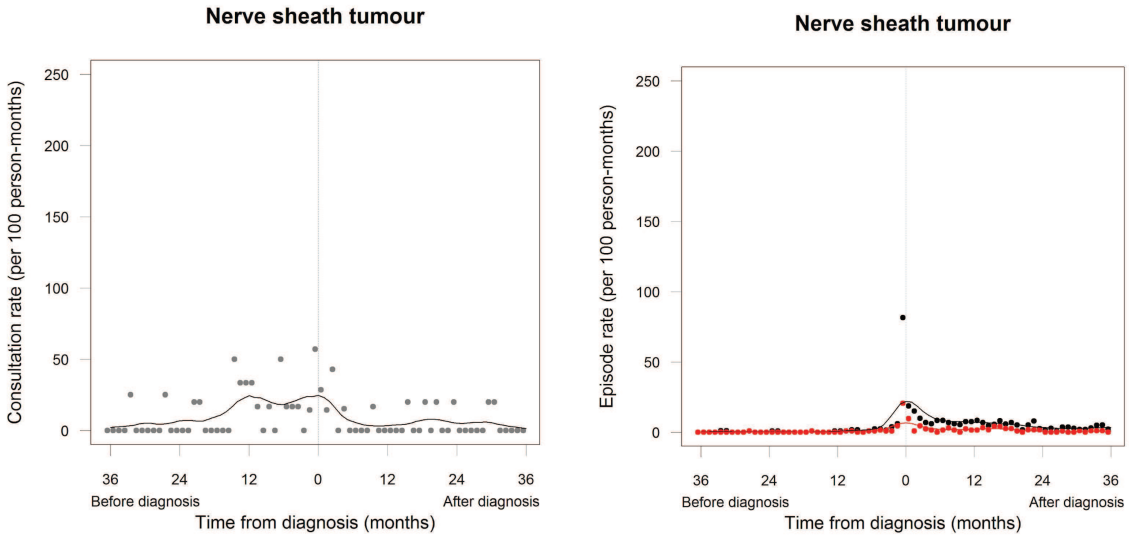

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Figure S9

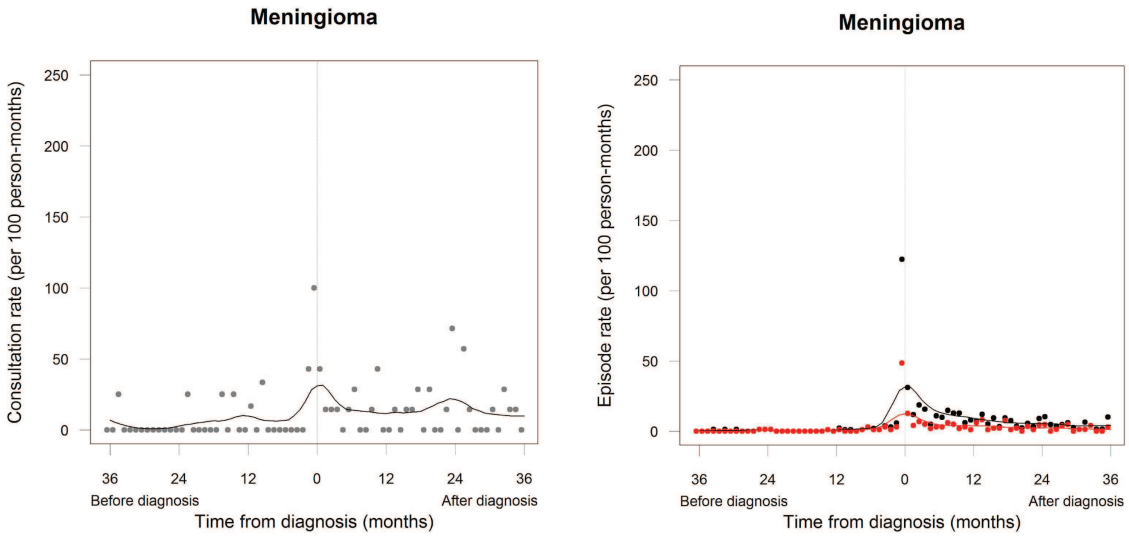

Figure S10

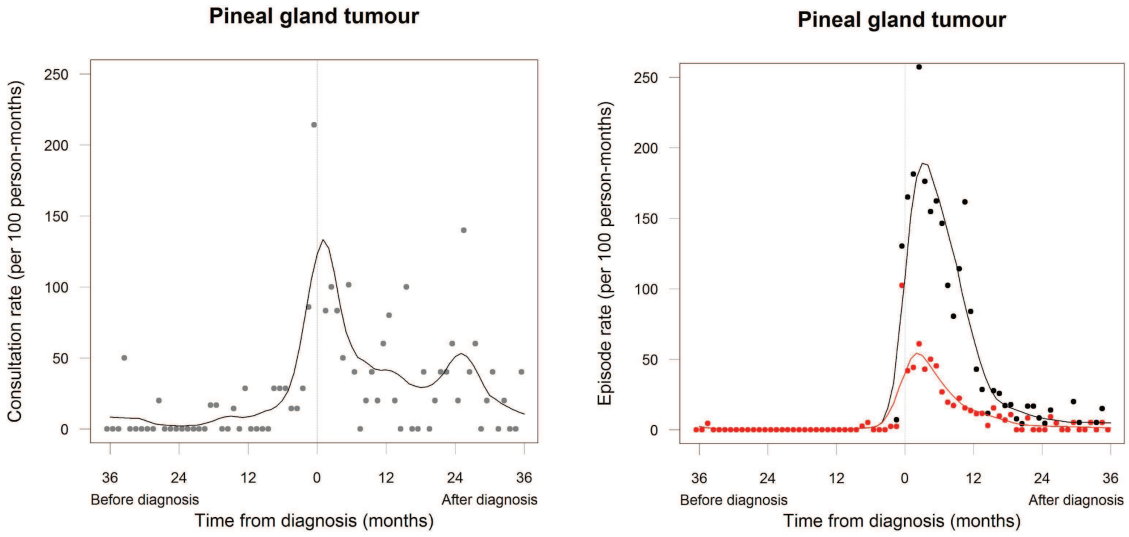

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Figure S11

No patient in primary care cohort.

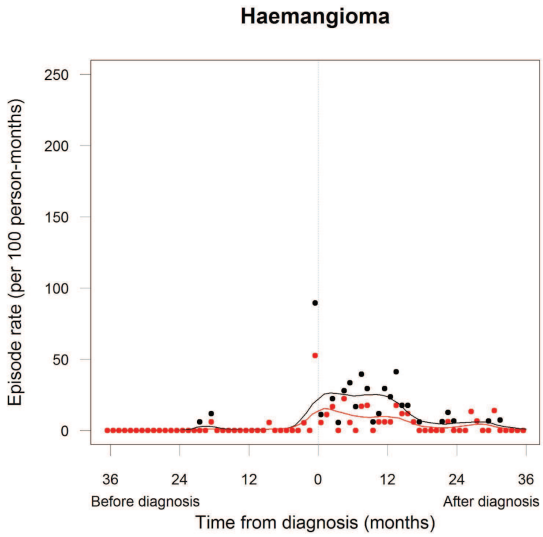
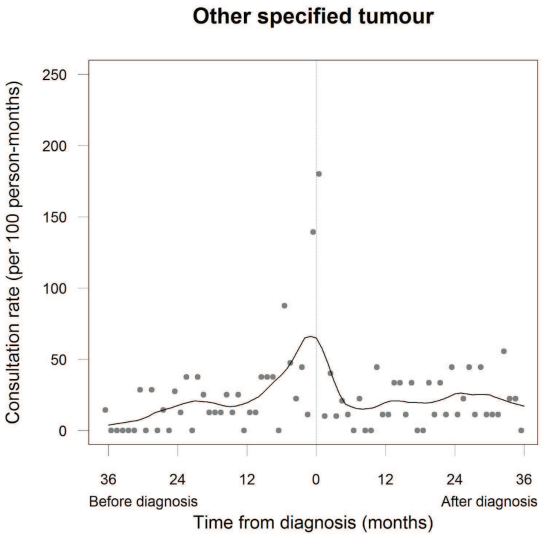


Figure S12



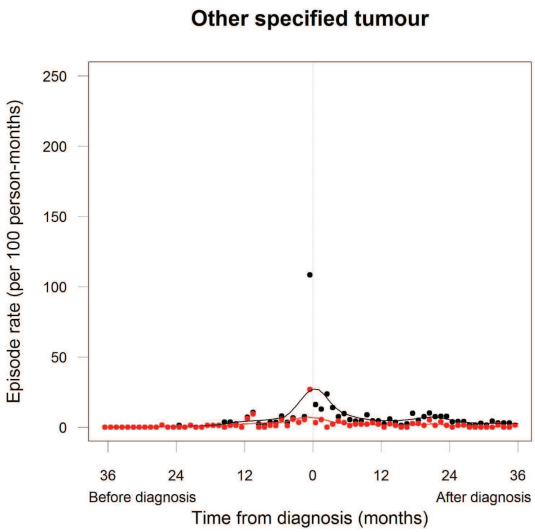


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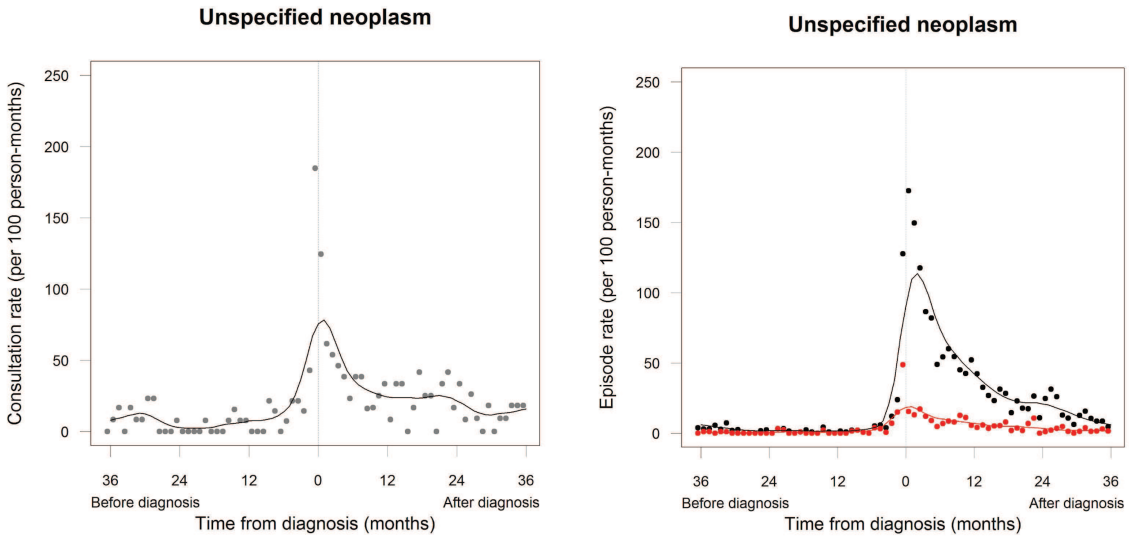
Figure S13



Chu TPC, Shah A, Walker D, Coleman MP. How do biological characteristics of primary intracranial tumors affect their clinical presentation in children and young adults? PMID: 29724124