



# Natural history and management of incidentally discovered brain lesions suspect for neoplasm in the pediatric population

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Period: P7-P8

## Abstract

**Background** With the increasing use of neuroimaging, there has been seen an enhancement in the amount of incidentally discovered brain lesions in children, leading to a growing treatment dilemma for clinicians as a standardized treatment for these lesions is lacking.

**Objective** The aim of the study was to contribute to the improvement of knowledge on the management and natural history of incidentally discovered brain lesions in the pediatric population.

**Methods** A retrospective analysis of all patients with incidentally discovered brain lesions suspect for a neoplasm discussed in the Princess Maxima Center for Pediatric Oncology since 2018 was done.

**Results** We identified 77 patients of whom 50 patients were included as having a lesion suspect for a neoplasm. The average age at diagnosis was 9.9 years. In 43 patients (86.0%) clinical and radiological follow-up was the initial treatment. The average follow-up time was 35.9 months with a range of 1 to 134 months. In 17 patients radiographic changes were seen and for 6 patients the treatment modality was changed. One patient died and turned out having a high-grade lesion. Hemispheric tumors were associated with an increased risk of treatment change.

**Conclusions** For most incidentally discovered brain tumors follow-up is sufficient. We would recommend a clinical and radiological imaging schedule with scans at 3 and 6 months and annually after the detection of the lesion until ten years after diagnosis. More research needs to be done on prognostic factors for tumor progression and treatment change requirement.

Brain tumors are the second most common pediatric malignancy.<sup>1</sup> Also, approximately thirty percent of the pediatric deaths are caused by malignant brain tumors. This number is three times as high as the deaths caused by leukemia.<sup>2</sup> With the widespread utilization of neuroimaging for various indications and the improved resolution of neuroimaging, there has been reported an increase in the incidentally detected brain tumors in children.<sup>1</sup> The vast majority of these incidentalomas in the pediatric population are low-grade neoplasms or suspect for low-grade neoplasms (especially low grade gliomas (LGG)). Roth et al. showed that from all 27 patients who underwent surgery, 24 patients had low grade gliomas.<sup>2</sup> A lot of research on incidentalomas has been conducted in the adult population. Malignant transformation of LGG has been described to occur in up to half of the cases in adults. However, childhood LGG differ from adult LGG on both the molecular and histological levels. Also, they grow relatively slowly, rarely undergo malignant transformation, and may even undergo spontaneous regression. Based on different studies, it seems that incidentally discovered brain tumors in the pediatric

population remain stable in 69.2–100% of cases and therefore do not require intervention.<sup>3</sup> Additionally, pediatric LGG have a chance of less than 10% to undergo malignant transformation. However, the consequences of missing a high grade lesion can be disastrous.<sup>1</sup>

These incidentally discovered brain lesions present a challenge to clinicians as there is an absence of standardized management guidelines and because of a limited understanding about the natural history of these lesions.<sup>4</sup> Different treatment approaches can be followed, varying from repetitive imaging and clinical follow-up to biopsy or tumor resection or a combination of these options.<sup>5</sup> Unless the low chance of malignant transformation, some authors recommend early surgical intervention in order to improve survival, remove lesions before they become unresectable and to reduce the anxiety and uncertainty of the patient and his/her parents. Arguments against early surgical treatment might be that it is overtreatment for low grade lesions and surgery always brings about its risks. Radiological follow-up might be a more

suitable treatment modality for suspected low grade tumors. However, radiological follow-up delays the definitive diagnosis and there is always a risk of tumor progression or transformation.<sup>4</sup> Besides this treatment dilemma for clinicians, incidentalomas can cause serious anxiety and emotional burden for the patients and their parents when confronted with the different treatment options.<sup>1</sup>

In order to improve and extend the knowledge on the natural history and management of incidentalomas in children, we provide our longitudinal experience with incidentally discovered brain tumors in the pediatric population, the behavior of incidentalomas and predictive and prognostic risk factors contributing to medical decision making.

## Methods

This is a retrospective study in which patients with a brain lesion suspected to be a neoplasm that have been discussed in the Princess Maxima Center for Pediatric Oncology since its opening in 2018 were analyzed. All patients known at the neuro-oncology department were reviewed and children that were diagnosed with an incidentally found brain lesion suspect for a neoplasm under the age of 18 were included. Whether a lesion was suspected to be a neoplasm was determined based on the information from imaging reports. Imaging reports were provided by neuroradiologists working in the Princess Maxima Center for Pediatric Oncology.

Children with tumor predisposition syndromes, like neurofibromatosis type 1 and 2, tuberous sclerosis or Li-Fraumeni Syndrome were excluded. Also children with symptoms related to the brain lesion at the moment of diagnosis, children with missing data about the follow-up and children in whom the brain lesion turns out to be no tumor were excluded. For an overview of the inclusion- and exclusion criteria see table 1. This study was approved by the Biobank and Data Access Committee of the Princess

Maxima Center for Pediatric Oncology in Utrecht.

From the included patients data on age at diagnosis, gender, indication for initial imaging, imaging findings and changes in these findings during follow-up were recorded. Also, the initial treatment modality and changes in management, the follow-up regimen when a wait and scan regimen was chosen for, the indication for surgical procedure when surgery was done, the pathological diagnosis when material was obtained by surgery or biopsy were collected from the electronic patient records. The following dates were collected: date of diagnosis, the start of the treatment, date of the last treatment (if the treatment had been ended), date of change in radiological features, date of the last follow up, date of surgery and date of death.

<b>Inclusion criteria</b>	Patients under the age of 18
	Patients with an incidentally found brain lesion. <i>Incidentally found lesions are lesions that have been discovered on brain imaging performed during evaluation of unrelated complaints.</i>
	Patients with a lesion suspect for a neoplasm. <i>Lesions suspect for a neoplasm have one or more of the following radiological characteristics on MRI: mass effect, diffusion restriction, contrast enhancement and no/limited amount of perifocal edema.</i>
<b>Exclusion criteria</b>	Patients with a tumor predisposition syndrome
	Patients with related symptoms at the moment of diagnosis
	Patients from whom no information about follow-up was available

Table 1: Inclusion and exclusion criteria

## Statistical analysis

Descriptive statistics were used to summarize continuous variables as mean and/or median, and categorical variables were summarized using percentages. A Kaplan-Meier analysis was performed to determine if and when there was decided to change the treatment modality from a patient from a wait and scan regimen to another treatment modality. The estimates of associations are reported in terms of odds ratio (OR) and their respective 95% confidence intervals (CIs). The categorical outcomes were analyzed using Fisher's exact tests. All analyses were carried out in IBM SPSS Statistics 27.

## Results

From all 1259 patients that have been discussed in the Princess Maxima Center for Pediatric Oncology since its opening, 77 patients with incidental brain lesions were identified. From these patients, 27 patients were excluded because the lesion was suspected of being a benign lesion. The remaining 50 patients were included and had a brain lesion suspect for a neoplasm or a brain lesion from which the origin was unsure but could be a neoplasm (see figure 1).

The mean age at diagnosis was 9.9 years (median, 11.0; range 0.0-18.0 years). From table 2 can be seen that 22 patients were females (44.0%) and 28 patients were males (56.0%). The median age for male patients was higher than for female patients. Also, table 2 shows the indications for initial imaging. The most frequent indications for

initial imaging were trauma- and seizure workup. Also, 8 patients (16.0%) had 'other unrelated complaints' as indication for the diagnosis scan. These complaints for example included screening for Wilson's disease, screening because of familial occurrence of aneurysms, screening for a lung disease and urinary incontinence.

### MRI findings at diagnosis

The locations of all incidentalomas are shown in table 2. 27 patients (54.0%) had an incidentaloma located in the supratentorial area. In the supratentorial area incidentalomas were most frequently located in one of the hemispheres. 20 patients (40.0%) had infratentorial lesions from which most lesions were located in the cerebellum (12 patients, 60.0%). 49 patients (98.0%) were presented at first detection with one focal brain lesion, whereas only one patient had

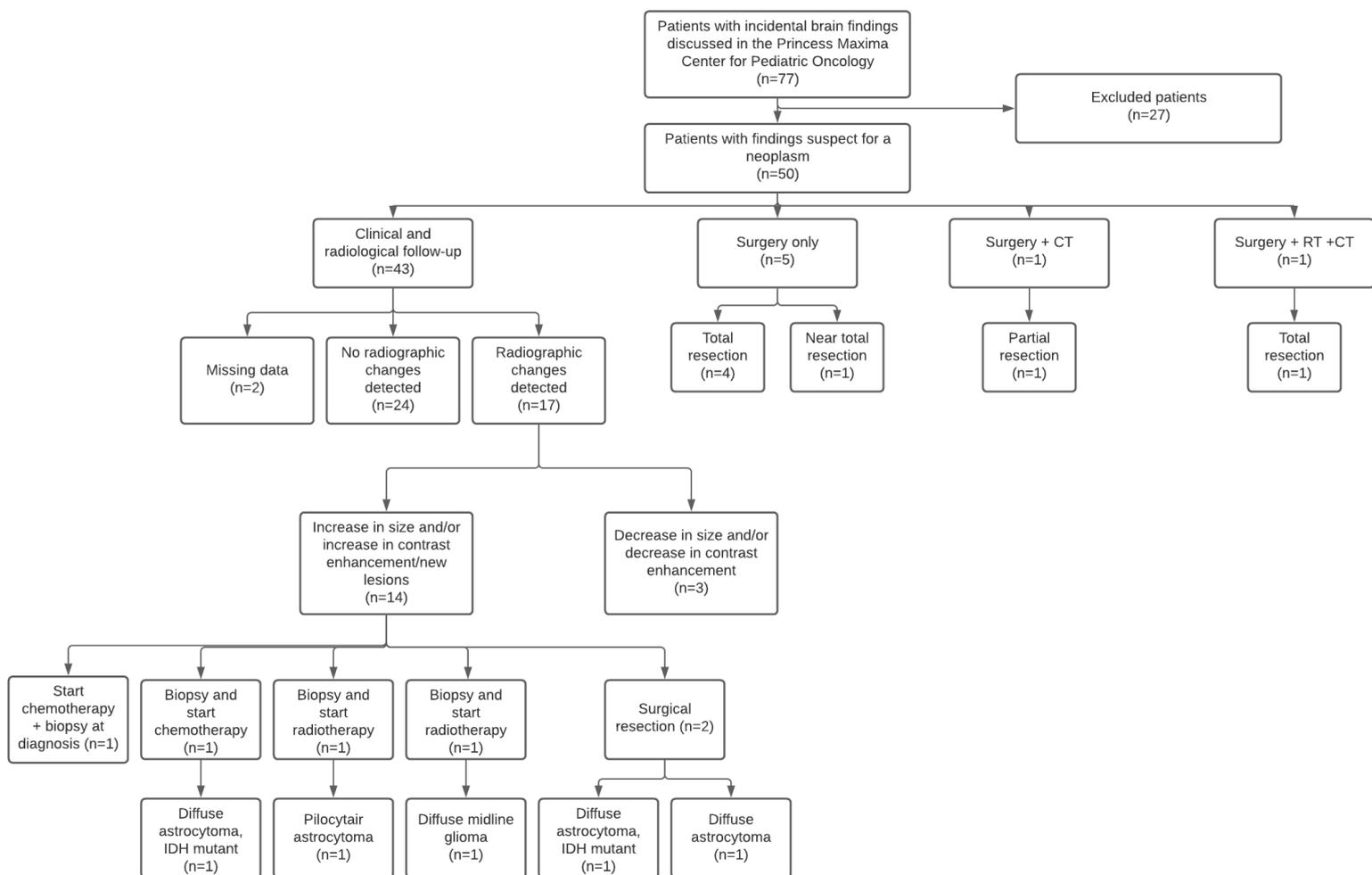


Figure 1: A flowchart showing study population, management plans and changes in radiographic features and management plans

	<b>N=50</b>	<b>Female (n=22)</b>	<b>Male (n=28)</b>
<b>Median age at diagnosis (IQR) - years</b>	11.0 (0.0-18.0)	9.5 (0.0-17.0)	11.5 (1.0-18.0)
<b>Indication for imaging - no. (%)</b>			
Headache workup	6 (12.0)	4 (18.2)	2 (7.1)
Trauma workup	8 (16.0)	6 (27.3)	2 (7.1)
Seizure workup	8 (16.0)	2 (9.1)	6 (21.4)
Developmental delay	3 (6.0)	2 (9.1)	1 (3.6)
Head/neck/spine complaints	2 (4.0)	2 (9.1)	0 (0.0)
Endocrinopathy workup	3 (6.0)	0 (0.0)	3 (10.7)
Consciousness problems	1 (2.0)	1 (4.5)	0 (0.0)
Research	3 (6.0)	1 (4.5)	2 (7.1)
Macrocephaly workup	1 (2.0)	1 (4.5)	0 (0.0)
Ear, nose, throat problems	4 (8.0)	0 (0.0)	4 (14.3)
Eye problems	3 (6.0)	0 (0.0)	3 (10.7)
Other unrelated complaints	8 (16.0)	3 (13.6)	5 (17.9)
<b>Location - no. (%)</b>			
Hemisphere	12 (24.0)	7 (31.8)	5 (17.9)
Chiasma/n.opticus	3 (6.0)	1 (4.5)	2 (7.1)
Ventricles	5 (10.0)	4 (18.2)	1 (3.6)
Corpus callosum	1 (2.0)	0 (0.0)	1 (3.6)
Cerebellum	12 (24.0)	5 (22.7)	7 (25.0)
Midline (thalamus, brainstem)	14 (28.0)	3 (13.6)	11 (39.3)
Extra-axial	1 (2.0)	0 (0.0)	1 (3.6)
Spinal cord	2 (4.0)	2 (9.1)	0 (0.0)

Table 2: Baseline table showing the median age at diagnosis, the indications for initial imaging and locations of the brain lesions

multiple lesions, namely three lesions. 39 patients (78.0%) had solid lesions, 3 patients (6.0%) had cystic lesions and 8 patients (16.0%) had lesions with both cystic and solid aspects. The mean maximum geometric diameter of the lesions at first detection was 28.8 mm (median, 15.5; range, 5.0-320 mm).

From 10 patients information on the size of the lesion was missing. From all patients, 27 patients (54.0%) had lesions with one of the following characteristics on the diagnosing scan: contrast enhancement, perilesional edema, mass effect or diffusion restriction. Table 3 shows the division over the different characteristics. It is visible that contrast enhancement is the most common characteristic.

	<b>N=50</b>
<b>MRI findings - no. (%)</b>	
Contrast enhancement	18 (36.0)
0-25% of lesion is enhanced	9 (18.0)
25-100% of lesion is enhanced	9 (18.0)
Perifocal edema	4 (8.0)
Mass effect	13 (26.0)
Diffusion restriction	4 (8.0)

Table 3: MRI findings on the diagnosis scan

### Clinical and radiological follow-up

Figure 1 shows that in 43 patients (86.0%) was chosen for clinical and radiological follow-up as initial treatment modality. In total 211 scans were made during follow-up. The mean amount of scans per patient was 5 scans (median 4, range 1-14 scans). The mean length of follow-up was 35.9 months (median, 33.0 months; range, 1.0-134.0 months).

In 17 patients (39.5%) radiographic changes were seen during follow-up, which mostly were increase in size and/or increase in contrast enhancement and/or development of new lesions. The mean time without radiological changes (time between diagnosis date and date of radiological changes) is 25.7 months (median, 21.0; range, 1.0-82.0 months). From these 17 patients, 8 patients experienced a progression of the lesion. Progression was defined as an increase in size of the lesion from 25% or more or the development of new lesions. In 5 of these patients with a progression of the lesion, a change in treatment modality from clinical and radiological follow-up to surgery, radiotherapy or chemotherapy or a combination of these was chosen for. The

mean progression free survival is 26.8 months (median, 17.5; range, 3.0-82.0 months). The patient from whom the lesion showed progression after 82 months is the only patient who died during the study. This patient (see patient 1 in table 4), for whom clinical and radiological follow-up was the chosen initial treatment modality, died 16 months after progression and 97 months after diagnosis of the incidentally discovered brain tumor.

Metastasis were seen in 4 patients (8.0%). For two of these patients the management plan was changed from follow-up to biopsy endoscopic third ventriculostomy or biopsy and radiotherapy (see table 4). For the other two patients, the initial management was surgery already.

Figure 2 shows a Kaplan Meijer curve which visualizes the course of the follow up for all patients. It shows that the 7 patients that underwent surgery at diagnosis were lost to follow-up immediately. It is visible that in total in 6 patients the treatment modality was changed from follow-up to another type of treatment for any reason. The changes in treatment modality were seen 6, 15, 24, 49, 61 and 91 months after diagnosis. Table 4 shows which alternative management plan was chosen for and which histopathological results were found. Also, a lot of cases were lost to follow-up as no more scans were available as they were done in a different hospital, the follow-up had been ended as the

Patient	Location tumor	MRI enhancement*	Perifocal edema*	Mass effect*	Diffusion restriction*	Progression	Metastasis	New treatment	Diagnosis pathology
Patient 1	Midline	yes	no	yes	no	yes	yes	Biopsy + RT	Diffuse midline glioma
Patient 2	Hemispherical	no	no	no	no	yes	no	Total resection	Diffuse astrocytoma
Patient 3	Hemispherical	no	no	no	yes	yes	no	Biopsy + CT	Diffuse astrocytoma
Patient 4	Hemispherical	no	no	yes	no	yes	no	Total resection	Diffuus astrocytoom IDH-mutant
Patient 5	Hemispherical	no	no	no	no	no	no	CT (+biopsy at diagnosis)	Pilocytair astrocytoma
Patient 6	Midline	no	no	no	no	yes	yes	Biopsy + ETV	Pilocytair astrocytoma

Table 4: Characteristics of patients for whom the treatment modality was changed  
 Abbreviations: CT, chemotherapy; RT, radiotherapy; ETV, endoscopic third ventriculostomy  
 \*radiological characteristics of the diagnosis scan

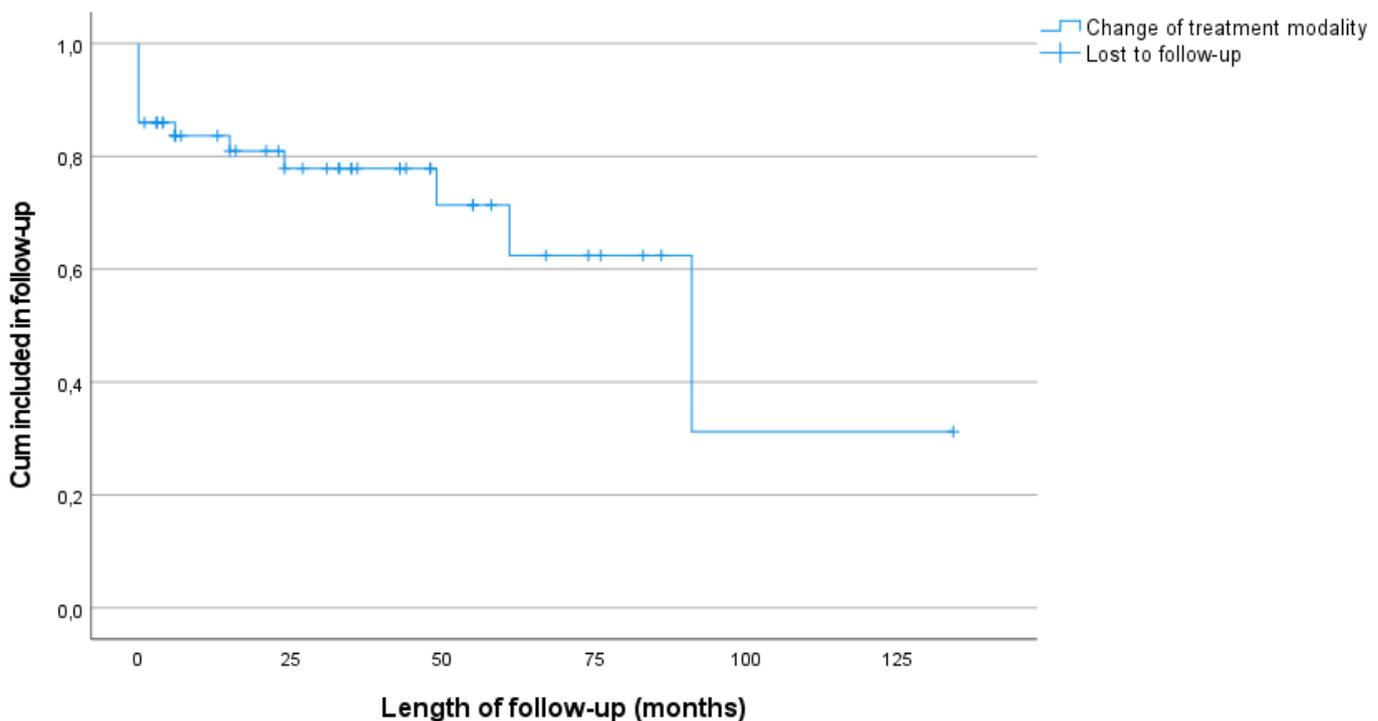


Figure 2: Kaplan Meijer analysis showing the course of the follow-up from the included patients, the cases that were lost to follow-up and the cases in which the treatment was changed

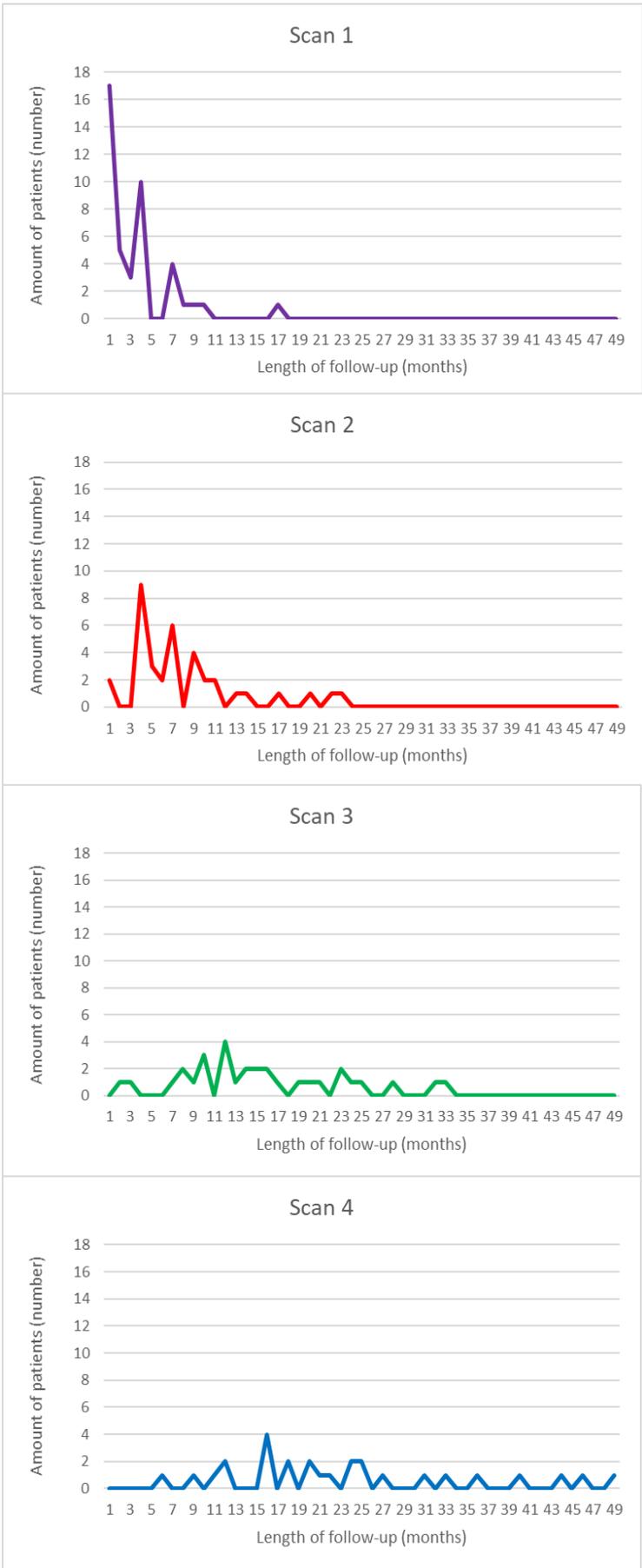


Figure 3: Division over follow-up time when scans 1-4 were done

lesion had been stable for a long time or as the lesion had just been detected. Figure 3 shows the division over time of scan one until four. It shows that most first follow-up scans were done within a month after diagnosis. The second scans were mostly done between 3 and 7 months after diagnosis. For scans three and four there is a greater spread in when scans were done over time. During the period of follow-up 3 patients (7.0%) developed symptoms due to progression of the brain lesion. One patient developed back pain. Two patients developed neurological and visual symptoms, which resulted for both in a change in treatment modality namely a biopsy in both cases, an endoscopic third ventriculostomy for one patient and radiotherapy for the other patient (see table 4).

### Surgery and histopathology

In total in 15 patients a type of surgery was performed ranging from a biopsy to a total resection of the lesion. In 7 patients (14.0%) surgery was the designated form of initial therapy (see figure 2) because of the recommendation of the provider and in one case because of a combination between atypical histopathology obtained from a biopsy at the moment of diagnosis and provider's recommendation. From one patient who underwent a biopsy at diagnosis no useful material was obtained. For all other patients table 5 shows the histopathological

diagnoses. It is visible that in 3 cases a high-grade neoplasm was found. For two of these cases, surgery was the initial type of treatment. For one case, watchful waiting was chosen for and this patient was operated later when the lesion increased in size. From the patients that underwent surgery later the mean time between diagnosis and surgery is 40.0 months (median, 24.0; range, 8.0-92.0 months).

From all 50 patients, in 10 patients (20.0%) a genetic mutation was detected in the tumor. An overview of all found mutations is given in table 6. The BRAF K11549 fusion mutation is the most frequent mutation, all associated with a pilocytic astrocytoma.

### Management decisions

Table 7 shows the univariate analyses of the location, the MRI findings (presence of contrast enhancement, perilesional edema, mass effect or diffusion restriction on the diagnosis scan) and tumor consistency and their odds ratios including the 95% confidence interval and p-value. Patients with a brain lesion located in one of the hemispheres were more likely to undergo a change in treatment modality, which means there was a need for a confirmed pathological diagnosis (OR = 7.25; CI: 1.12-47.00; P 0.04). All other locations and variables, including the continuous variable of

		Surgery total (N=14)	Surgery direct (N=9)		Surgery later (N=5)	
Pathology - no. (%)			Surgery outcome		Surgery outcome	
WHO I	Paranglioma	1 (2.0)	1 (2.0)	Biopsy at diagnosis (n=1)	0 (0.0)	
	Pilocytic astrocytoma	6 (12.0)	5 (10.0)	Partial resection (n=1) Near total resection (n=1) Total resection (n=2) Biopsy at diagnosis (n=1)	1 (2.0)	Biopsy + ETV (n=1)
WHO II	Plexus papilloma	1 (2.0)	1 (2.0)	Total resection (n=1)	0 (0.0)	
	Diffuse astrocytoma	1 (2.0)	0 (0.0)		1 (2.0)	Total resection (n=1)
WHO IV	Diffuse astrocytoma, IDH mutant	2 (4.0)	0 (0.0)		2 (4.0)	Biopsy only (n=1) Total resection (n=1)
	Diffuse midline glioma	2 (4.0)	1 (2.0)	Total resection (n=1)	1 (2.0)	Biopsy only (n=1)
	Medulloblastoma	1 (2.0)	1 (2.0)	Total resection (n=1)	0 (0.0)	

ETV= endoscopic third ventriculostomy

Surgery direct= surgery as initial treatment modality/biopsy at diagnosis followed by clinical and radiological follow-up

Surgery later= surgery when treatment modality was changed from follow-up to surgery

Table 5: Surgery and histopathological diagnoses

<b>Mutation tumor related - no. (%)</b>	<b>N=50</b>	<b>Histopathological outcome</b>
BRAF KIAA1549 fusion	4 (8.0)	Pilocytic astrocytoma (n=4)
MYB/MYBL1	1 (2.0)	Diffuse astrocytoma (n=1)
TP53 + ATRX	1 (2.0)	Diffuse astrocytoma, IDH-mutant (n=1)
FDGRFB	1 (2.0)	No histopathological diagnosis
7q21.11 deletion	1 (2.0)	No histopathological diagnosis
H3K27M	1 (2.0)	Diffuse midline glioma (n=1)
<b>Mutation not tumor related - no. (%)</b>		<b>Clinical outcome</b>
PIK3CA	1 (2.0)	Hemimegalencephaly (n=1)
<b>No mutation detected - no. (%)</b>	40 (80.0)	

Table 6: Detected mutations and associated histopathological outcome

Location	Radiological increase in size					Change in treatment modality				
	No (N=29)	Yes (N=14)	OR	CI	P value	No (N=37)	Yes (N=6)	OR	CI	P value
Cerebellum (n=9)	8 (27.6)	1 (7.1)	0.20	(0.02-1.81)	0.23	9 (24.3)	0 (0.0)			
Midline (n=13)	8 (27.6)	5 (35.7)	1.46	(0.37-5.70)	0.73	11 (29.7)	2 (33.3)	1.19	(0.19-7.43)	1.00
Hemispherical (n=12)	7 (24.1)	5 (35.7)	1.75	(0.44-6.98)	0.48	8 (21.6)	4 (66.7)	7.25	(1.12-47.00)	0.04
Infratentorial, other (n=1)	1 (3.5)	0 (0.0)				1 (2.7)	0 (0.0)			
Supratentorial, other (n=5)	3 (10.3)	2 (14.3)	1.44	(0.21-9.81)	1.00	5 (13.5)	0 (0.0)			
Spinal (n=2)	1 (3.5)	1 (7.1)	2.15	(0.13-37.19)	1.00	2 (5.4)	0 (0.0)			
Extra-dural (n=1)	1 (3.5)	0 (0.0)				1 (2.7)	0 (0.0)			
MRI findings	OR					CI				
Contrast enhancement (n=12)	7 (24.1)	5 (35.7)	1.75	(0.44-6.98)	0.48	11 (29.7)	1 (16.7)	0.47	(0.05-4.53)	0.66
Perilesional edema (n=2)	1 (3.4)	1 (7.1)	2.15	(0.13-37.19)	1.00	2 (5.4)	0 (0.0)			
Mass effect (n=10)	7 (24.1)	3 (21.4)	0.86	(0.19-3.97)	1.00	8 (21.6)	2 (33.3)	1.81	(0.28-11.80)	0.61
Diffusion restriction (n=2)	1 (3.4)	1 (7.1)	2.15	(0.13-37.19)	1.00	1 (2.7)	1 (16.7)	7.20	(0.39-134.22)	0.26
Tumor consistency	OR					CI				
Cystic (n=2)	2 (6.9)	0 (0.0)				2 (5.4)	0 (0.0)			
Solid (n=37)	25 (86.2)	12 (85.7)	0.96	(0.15-5.99)	1.00	32 (86.5)	5 (83.3)	0.78	(0.08-8.15)	1.00
Combination (n=4)	2 (6.9)	2 (14.3)	2.25	(0.28-17.91)	0.59	3 (8.1)	1 (16.7)	2.27	(0.20-26.27)	0.47
Tumor size (n=35)	22 (51.2)	13 (30.2)	1.00	(0.960-1.04)		30 (69.8)	5 (11.6)	1.025	(0.981-1.070)	

Table 7: Univariate analyses of radiological increase in size and change in treatment modality of patients with follow-up as initial treatment modality

P-value was calculated using Fisher's exact test

Abbreviations: OR, odds ratio; CI, confidence interval

lesion size, were not associated with increased odds of radiological increase or a change in treatment modality.

## Discussion

With the expanded use and the augmented quality of neuroimaging, the amount of incidental brain lesions has increased over the last decades.<sup>1</sup> This causes a treatment dilemma for clinicians as most incidentally discovered brain lesions suspect for a neoplasm are LGG for which clinical and radiological follow-up should be sufficient, but high-grade neoplasms should not be

missed.<sup>2</sup> However, a clear treatment protocol for which lesions can be managed by follow-up and which lesions should be surgically treated is lacking.<sup>4</sup> Therefore, this retrospective study was done in order to improve the knowledge on the natural history of incidentally discovered brain tumors and contribute to medical decision making concerning these lesions.

The median age at diagnosis of the included patients was 11.0 years. This is comparable to similar studies in which the median age varies between 7.5 years and 12 years. The average

time of follow-up was 35.9 months with a median of 33.0 months, which is also comparable to other studies<sup>1-2,4,6-9</sup> In 86.0% of the patients (43 patients) there was chosen for clinical and radiological follow-up as initial treatment modality. In most other studies, this percentage was lower as more children had surgery at diagnosis. For example, Wright et al. describes that only in 50.9% of the children was chosen for clinical and radiological follow-up, for Roth et al. this was 46.8% and for Kozyrev et al. 61.4%. In these studies the main reason for surgery is clinician's preference which indicates that clinicians in other countries might be educated differently and therefore make other decisions at the start of the treatment.<sup>1-2,9</sup>

In 17 patients (39.5% of the patients with follow-up as starting treatment modality) radiographic changes were seen during follow-up from which 14 patients (32.6%) showed an increase in size. These numbers differ greatly between different studies ranging from Ali et al. who describes progression of the lesion in only 8.3% of the patients to Bredlau et al. who reports that 38.4% of the patients in which follow-up was chosen for showed progression of the lesion.<sup>7,8</sup> It is interestingly to note that also the actions taken caused by the radiological changes differ between different studies. From the 14 patients with an increase of the lesion, in 6 patients the treatment modality was changed. This shows that changing the treatment modality is dependent on multiple factors, e.g. parental's preference.<sup>4</sup> This is in contrast with Kozyrev et al., Ali et al., Perret et al. and Roth et al. for which all patients with radiological changes an adjustment in treatment modality was decided for.<sup>2,6-7,9</sup> Also it depends on the definition of increase in size or progression. In this study, increase in size and progression are two different variables where increase in size is any increase of the lesion and progression was defined as increase in size of at least 25%.

In this study, one death has been reported. Contradictory, in other studies no patients died.<sup>1-2,4,6-9</sup> The patient died 97 months after diagnosis. The histopathological diagnosis of

the lesion was a diffuse midline glioma. At the diagnosis scan the lesion showed contrast enhancement, in which only a maximum of 25% of the lesion enhanced, and mass effect. A biopsy was done at diagnosis but no useful material was obtained. The first radiological changes were noticed 82 months (6.8 years) after diagnosis. Zaazoue et al. proposes a follow-up regimen with MRI and clinical examination for 5 years after detection of the lesion.<sup>4</sup> In the described case, progression would have been missed using this regimen. Therefore we propose clinical and radiological follow-up for at least 10 years. This has been supported before by Wright et al., describing a mean time of malignant transformation of 5.1 years.<sup>1</sup> Additionally, figure 2 shows that the management plan from another patient was changed after 61 months of follow-up which is approximately 5 years. This was because of the development of visual and neurological symptoms. This case therefore also supports the proposal of follow-up for at least 10 years.

Ali et al. recommends an imaging schedule consisting of scans at 3 months, 6 months, and then annually after the detection of the lesion.<sup>7</sup> This is nearly in line with figure 3 in which most first scans were done between 0 and 3 months, second scans between 3 and 6 months and third scans were done mostly between 8 and 16 months after diagnosis. Therefore we would also recommend this regimen. The patient that died did undergo an MRI annually until death. It is questionable whether more frequent radiological follow-up scans would have saved the patient as progression might have been detected in an earlier stage.

In this study, for 14 patients a histopathological diagnosis was available. From these 14 patients, 3 patients had a high-grade lesion. Two of these were diffuse midline gliomas and the other one turned out to be a medulloblastoma. One of the diffuse midline gliomas was resected at diagnosis, just like the medulloblastoma, and the other one was diagnosed by biopsy as the lesion showed radiological increase in size (see table 5). This means that 66.7% of the

pathologically confirmed high grade lesions were resected at diagnosis and therefore had characteristics that made clinicians feel uncomfortable with the decision for a wait-and-see policy. All other lesions were low-grade tumors. This is in agreement with other studies, in which either no or a few high-grade tumors have been reported.<sup>1-2,4,6-9</sup>

3 of the 43 patients with follow-up as initial management became symptomatic related to the tumor during follow-up. For two of these patients, the treatment modality was changed and one of these patients turned out to have a high-grade neoplasm (diffuse midline glioma). The development of symptoms during follow-up might be a sign of malignant transformation and a considered reason for a change in treatment modality.

No other studies found any patient or tumor dependent variables associated with increased odds of radiological progression, except for Zaazoue et al. reporting male gender with increased odds of radiological progression.<sup>4</sup> Zaazoue et al. did report increased odds of undergoing surgery for the following variables: tumor size, contrast enhancement and perilesional edema.<sup>4</sup> In this study we found that tumors located in one of the hemispheres was associated with the need for a confirmed pathological diagnosis. Theoretically, this would mean that hemispheric lesions should be observed more intensely. However, first more research should be done. Also, the added value of magnetic resonance spectroscopy (MRS) on top of normal MRI scans might be researched as it might give more information on the origin of a lesion and might therefore predict the lesions natural history.

### Limitations

The current study has several limitations. The first limitation is that the decision whether a lesion was suspect for a tumor was only based on radiological characteristics. This is a demanding job as many other benign pathologies have the same radiological characteristics as neoplasms. As this is the usual way of management of incidentally

discovered lesions, there is little to do about this. Additionally, this decision was made by different neuroradiologists and therefore interpersonal differences might have occurred. Another limitation is the retrospective character of the study. This may have contributed to selection bias and user bias. Nonetheless, all patients were discussed on the Tumor Board for Neuro-oncology so the decision whether a patient should undergo surgery directly at diagnosis or whether a patient can be followed-up with clinical and radiological follow-up was made by a diverse group of professionals who all have their own knowledge on a specific part of the treatment. The last limitation is that the overall follow-up time was relatively short. Additionally, some patients even had a shorter follow-up time as scans were done in another hospital and were therefore not available. Due to this, information might be lacking. Despite these limitations, compared to other similar studies, this study offers a relatively large study population of patients with incidentally found brain lesions resembling neoplasms.

### Conclusion

In conclusion, this study gives an overview of the natural history and management of incidentally discovered brain lesions in children. We saw that for most lesions watchful waiting as treatment modality was sufficient. Based on our findings, we would recommend an imaging schedule consisting of scans at 3 months, 6 months and then annually after the detection of the lesion until ten years after diagnosis. When a patient develops symptoms or the lesion shows radiological increase in size, a change in treatment modality should be considered. Hemispheric tumors tend to require a change in treatment modality more frequently. However, additional research should be done on patient and tumor dependent risk factors for tumor progression and the requirement of a change in treatment.

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