Child's Nervous System
https://doi.org/10.1007/s00381-020-04658-8

REVIEW ARTICLE

Management of incidental brain tumors in children: a systematic review

Jehuda Soleman[1,2,3] · Danil A. Kozyrev[1] · Liat Ben-Sira[4] · Shlomi Constantini[1,5] · Jonathan Roth[1,5]

Received: 15 April 2020 / Accepted: 28 April 2020

Abstract

Background Due to technical advancements and availability of neuroimaging, detection of incidental pediatric brain tumors (IPBT) is growing rapidly. The management of these asymptomatic lesions remains unclear; radiological, pathological, and clinical risk factors for further growth and malignant transformation (MT) are not well defined.

Methods We systematically reviewed the literature on the dilemmas and management of IPBT suggestive of a low-grade brain tumor (LGBT). Keyword searches of the PubMed and Medline (NCBI) databases identified studies on IPBT describing the prevalence, neuroimaging, management, or risk of MT through July 2019. References of the identified articles were also reviewed.

Results A total of 2021 records were screened. Fifty-nine full-text articles were reviewed, and 34 published studies were included. IPBT are diagnosed in 0.2–5.7% of children undergoing brain imaging for various reasons. The accepted approach for management of lesions showing radiological characteristics suggestive of LGBT is radiological follow-up. The rate at which additional intervention is required during follow-up for these apparently low-grade lesions is 9.5%. Nevertheless, the dilemma of early surgical resection or biopsy vs. clinical and radiological follow-up of IPBT is still unresolved. The risk in these cases is missing a transformation to a higher grade tumor. However, MT of pediatric LGBT is very rare, occurring in less than 3% of the cases of proven low-grade gliomas in children. The risk of future MT in pediatric low-grade gliomas seems to be greater in the presence of specific molecular markers such as BRAF V-600E, CDKN2A, and H3F3A K27M.

Conclusions The natural history, management, and prognosis of IPBT remain ambiguous. It seems that lesions suggestive of LGBT can initially be followed, since many of these lesions remain stable over time and MT is rare. However, controversy among centers concerning the ideal approach still exists. Further observational and prospective cohort studies, focusing on potential clinical and radiological characteristics or risk factors suggestive of high-grade tumors, tumor progress, or MT of IPBT, are needed.

Keywords Pediatric · Glioma · Incidental brain lesions · Malignant transformation · Incidentalomas · Incidental brain tumors

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00381-020-04658-8) contains supplementary material, which is available to authorized users.

✉ Jehuda Soleman
jehuda.soleman@gmail.com

[1] Department of Pediatric Neurosurgery, Tel Aviv Medical Center & Dana Children's Hospital Tel Aviv, Weizman Street 12, Tel Aviv, Israel

[2] Departments of Neurosurgery and Pediatric Neurosurgery, University Hospital and Children's University Hospital of Basel, Basel, Switzerland

[3] Faculty of Medicine, University of Basel, Basel, Switzerland

[4] Department of Pediatric Neuroradiology, Tel Aviv Medical Center & Dana Children's Hospital Tel Aviv, Tel Aviv, Israel

[5] Tel-Aviv University, Tel Aviv, Israel

Introduction

The rate of incidentally detected brain tumors in children (incidentalomas) is growing in recent years, due to availability and wide spread use of neuroimaging for various indications [1]. Management of these lesions is controversial, presenting clinicians and families with practical decision dilemmas [2, 3]. Treatment options in children vary between conservative (image and clinical follow-up), biopsy, or tumor resection [4]. In adults, it seems that early resection of incidentalomas that are suspected to be low-grade brain tumors (LGBTs), whenever feasible, may lead to better survival, due to minimizing risks

Published online: 06 May 2020

of malignant transformation (MT) [5–7]. However in children, as opposed to adults, MT of low-grade tumors (excluding cancer predisposition syndromes) rarely occurs, although data on potential risk factors for MT, such as age, sex, tumor size or location, radiological factors, and molecular biology, are still sparse [8]. The purpose of this article is to systematically review the literature on the prevalence, dilemmas, and different management options of incidental pediatric brain tumors (IPBT).

Methods

Our primary search was conducted using the PubMed and Medline (NCBI) databases and the following keywords in titles or abstracts: "brain incidentaloma," "children brain incidentaloma," "pediatric brain incidentaloma," "incidental cerebral mass lesion," "pediatric cranial incidentaloma," "children cranial incidentalomas," "incidental findings neuroimaging," "incidental brain lesions," "incidental brain tumors," "incidental cerebral lesions," "malignant transformation brain tumor children," "malignant transformation brain lesions children," "malignant transformation in low grade glioma in children." Databases were searched throughout July 2019. The inclusion criteria were first applied to titles and abstracts and then to full-text articles to determine final inclusion status.

Inclusion criteria included the following:

(1) restrictions to English language
(2) inclusion of pediatric patients (under the age of 20 years) only
(3) focus on incidental tumorous findings

We included studies that used both randomized and non-randomized designs, while case reports, reviews, and systematic reviews were included as well. Abstracts were reviewed by the authors, who systematically excluded duplicates. The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Articles were described systematically; however, formal meta-analysis was not performed due to heterogeneity across studies and the sparse number of highly qualitative studies. In addition, methods of long-term screening, follow-up physical exams, and radiographic inclusion criteria were not available in the vast majority of the studies and therefore could not be accounted for.

Results

Our search resulted in 34 relevant articles that met our inclusion criteria (Fig. 1). Five of the articles deal with the prevalence of IPBT [1, 9–12]. One article deals with specific neuroradiological imaging techniques for further differentiation of IPBT [13]. Ten articles analyze or discuss the potential management of these lesions (observation vs. intervention) [2, 3, 12, 14–20]. One article dealt with both the prevalence and the potential management of IPBT [12]. MT of a suspected pediatric LGBT or low-grade spinal tumor is described in 14 articles [8, 21–33]. Molecular analysis of MT in pediatric brain tumors is discussed in 5 articles [34–38].

Prevalence of suspected incidental pediatric LGBT

The occurrence of the so-called brain incidentalomas in children undergoing brain imaging for various reasons is about 25% (including various intra- and extra-axial lesions). Suspected incidental brain tumors are diagnosed in 0.2–5.7% of the cases [1, 9–12]. Most studies analyzing the rate of IPBT do not focus specifically on incidental brain tumors, but rather describe the overall prevalence for incidentally detected brain pathologies (including arachnoid cysts, paranasal sinus fluid, cyst or mucocele, vascular lesions, cavum septum pellucidum, and Chiari malformation).

In a study by Jansen et al., of 3966 children undergoing an MRI, in 25.6%, an incidental pathological brain finding was detected, with suspected LGBT seen in 7 children (0.18%) [10]. Graf et al., in their analysis of 185 children undergoing MRI, found an incidental lesion in 21.5% of the children, with 1.6% showing parenchymal tissue abnormality. They do not further specify the term "parenchymal tissue abnormality" [1]. Perret et al. analyzed 335 children with a primary central nervous system (CNS) tumor and found that in 5.7% of the cases, the diagnosis was an incidental finding [12]. Kaiser et al. found that 1 out of 114 healthy children (0.88%) undergoing an MRI displayed a suspected incidental mass lesion within the fourth ventricle [11]. Finally, Gupta et al. describe an overall rate of 8% incidental findings on pediatric MRI, although no specific rates for suspected LGBT are described. [9]

Radiological diagnosis and criteria of suspected incidental pediatric LGBT

Occasionally, the differential diagnosis between an LGBT and a pathology that is congenital or acquired of non-neoplastic origin may become an issue. Based on our systematic literature search, reports analyzing or discussing typical radiological characteristics suggesting a lesion to be of low or high grade do not exist. Radiological diagnostic criteria of presumed LGBT are not well defined. Due to these heterogeneities, some authors advocate further diagnosis using other imaging modalities such as positron emission tomography (PET). Pirotte et al. analyzed 55 IPBT on MRI, who further underwent PET imaging of the brain. PET imaging had a high sensitivity and specificity to detect tumor as well as malignant

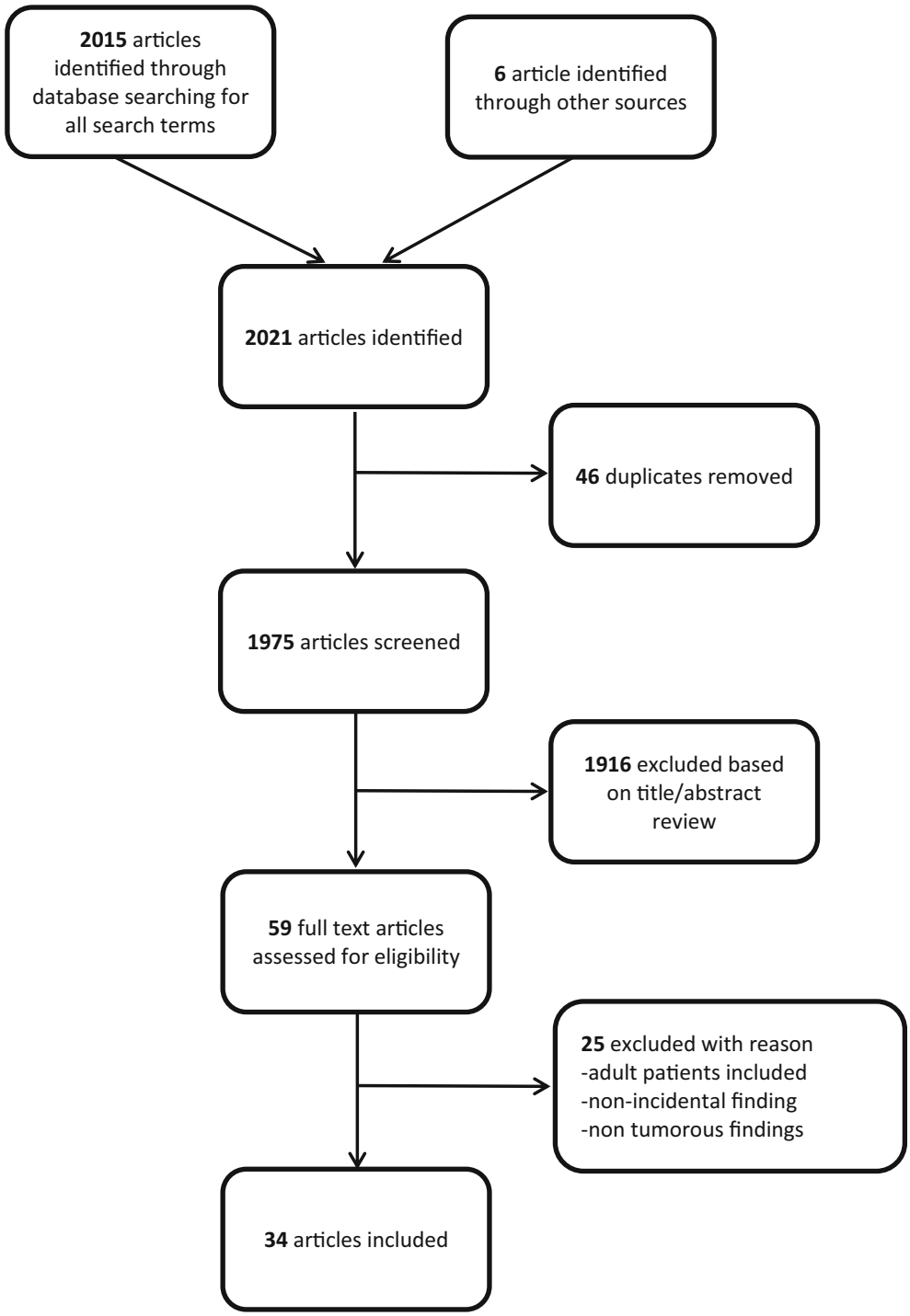

Fig. 1 Selection of articles included in this review

tissue, although the absence of PET tracer uptake does not definitively exclude tumor tissue [13].

Dilemmas concerning the management of suspected pediatric incidental LGBT

Once an incidental pediatric LGBT is suspected, many dilemmas and uncertainties arise for the child and parents, as well as for the caregivers. Due to the relatively low prevalence of these lesions, comparative data on the different treatment modalities (observation vs. intervention) are (and will probably stay) rather limited. To date, only 7 studies (plus 3 editorials) describe their experience in the management of IPBT (Table 1) [3, 12, 14, 15, 17, 19, 20]. Prospective studies comparing different treatment modalities, rate of MT, and time to intervention do not exist.

Table 1 Studies describing the experience in the management of incidental pediatric brain tumors

Author (year)	Study type	No. of patients with incidental brain tumors	Median age (range)	Location	Treatment	Follow-up (range)
Perret (2011)	Retrospective	19	5 y (1.0–14.9 y)	8 infratent 11 supratent	7 (36.8%) surgery at diagnosis, 12 (63.2%) follow-up, 2 (10.6%) delayed surgery (due to progression in size)	1.8 y (0.3–16.3 y)
Bredlau (2012)	Retrospective	21	12 y (1–18 y)	7 (33%) infratent 14 (67%) supratent	8 (38%) surgery at diagnosis, 13 (62%) follow-up°, 4 (19.2%) delayed surgery (due to progression in size)	32 m (1–104 m)
Roth (2012)	Retrospective	47	8.6 y (N/A)	26 (55.3%) infratent 20 (42.6%) supratent 1 (2.1%) multiple	25 (53.2%) surgery at diagnosis, 22 (46.8%) follow-up, 2 (4.2%) delayed surgery (due to progression in size)	6 y (5–70 m)
Ali (2014)	Retrospective	12	10 y (1–19 y)	8 (67%) infratent 4 (33%) supratent	12 (100%) follow-up 1 (8.3%) delayed surgery	16 m (2.7–59.5 m)
Zaazoue (2019)	Retrospective	144	12 y (1.5–17.3 y)	33 (23%) infratent 111 (77%) supratent	144 (100.0%) follow-up″, 12 (8.3%) delayed surgery$^{\alpha}$ (1 biopsy; due to progression in size), 1 (0.7%) LP showing meningoencephalitis treatment and continued follow-up	3.8 y (1–13.2 y)
Kozyrev (2019)	Retrospective	70*	8 y (1 m–20 y)	70 (100%) infratent	27 (38.6%) surgery at diagnosis, 43 (61.4%) follow-up, 12 (17.1%) delayed surgery	43.6 m (1–221 m)
Wright (2019)	Retrospective	55	8.8 y (0.5–18 y)	28 (50.9%) infratent 27 (49.1%) supratent	17 (30.9%) surgery at diagnosis (3 biopsy), 38 (69.1%) follow-up (10 showed progression in size, only 2 needed surgery), 2 (3.6%) delayed surgery	8.6 m (0.6–135.6 m)
Total	All retrospective	368	10 y (1 m–20 y)	180 (49%) infratent 187 (51%) supratent	84 (22.8%) surgery at diagnosis, 284 (77.2%) follow-up, 35 (9.5%) delayed surgery	32 m (06.–221 m)

No., number; *y*, years; *infratent*, infratentorial (including cerebellum and brainstem); *supratent*, supratentorial; *m*, months; *LP*, lumbar puncture

° 1 initially follow-up, then progression which stabilized, further follow-up

*Including only posterior fossa incidental brain tumors

″ Of these, 9 decreased in size over time, while 3 of these completely disappeared. One fluctuated in size over time

$^{\alpha}$ In 5 cases, surgery without radiological progression: 3 due to providers recommendation, 2 due to parental wish

Bredlau et al. published a series of 21 IPBT, diagnosed at a median age of 12 years, of which 13 (61.9%) were initially followed over a median period of 32 months (range 1–104 months). Of these 13, 5 (38.5%) children showed subsequent progression of their mass and 4 (30.8%) had surgery at the time of progression, while 1 lesion stabilized and was continuously followed. The remaining 8 patients showed stable disease and did not require intervention. Event-free survival in the 13 subjects monitored was 84% and 63%, at 12 and 24 months, respectively, with an overall survival (OS) of 100% [15]. Perret et al. included 19 children (median age of 7.6 years) with incidentalomas detected by MRI over a period of 15 years. Seven patients underwent immediate surgical resection, while the remaining 12 (63.2%) were followed with semi-annual clinical and radiological evaluations. Two patients (16.6%) underwent delayed surgery (one due to progression after 1.5 years and one at explicit request of the parents after 5 years of following), while the remaining 10 (83.4%) remained stable during the follow-up period [12]. Our group published a series of 47 children treated at 2 centers, with a median age of 8.6 years, presenting with IPBT. Of the 22 (46.8%) patients who were observed over a mean period of 25 months, only 2 (9%) were eventually operated (one due to development of symptoms after 1.5 years and one due to tumor progression after 2 years) [19]. In a published series of 12 children (median age of 10 years) with IPBT who were followed for a median time period of 16.7 months (range 2.7–59.5 months) one patient (8.3%) required surgery 9 months after initial diagnosis due to progression in size [14]. In a recently published series of 55 children with IPBT, 14 underwent surgical resection, 3 underwent biopsy, and 38 with benign imaging characteristics (defined as non-enhancing lesions, a size < 1.5–2 cm in diameter, and no surrounding edema or mass effect) at presentation were monitored. A malignant tumor was detected in 1 out of 17 patients who underwent surgery (resection or biopsy), while 10 out of 38 radiologically observed tumors showed growth in size during a median follow-up of 34.2 months. Out of these 10 patients, however, only in 2 patients did the tumor increase to a size requiring surgical resection [3]. Zaazoue et al. published a series of 144 pediatric incidental brain lesions indeterminate for neoplasm, with an average age at diagnosis of 11.2 years and an average follow-up of 3.8 years. In 21.5% ($n = 31$) progression was seen, with a mean time to progression of 32.3 months. A change in management was made in 9% of the patients ($n = 13$), including surgical resection in 11 patients, and biopsy or lumbar puncture in one patient each. Larger lesions and those with contrast enhancement or edema were significantly more likely to require surgery. They concluded that most incidental lesions indeterminate for tumor have an indolent and benign course, and should be followed radiologically. Finally, in a recently published series by our group analyzing 70 children from two centers with incidentally detected posterior fossa tumors, 27 underwent surgical resection, 31 were followed, while 12 underwent delayed surgery due to tumor size progression, changes in radiological characteristics, or parental decision [17]. Patients undergoing delayed surgery after a period of radiological and clinical follow-up showed in the vast majority (94.3%) LGBT or non-tumorous lesions after histopathological evaluation (Table 2).

Similar to the patterns seen in these 7 studies, incidentalomas in the general pediatric populations that have been followed seem to remain stable in 69.2–100% of the cases and do not require further intervention. Therefore, the authors of the aforementioned studies all concluded that clinical and radiological follow-up in IPBT has an important role.

The major drawback of all of these studies is their rather small cohort and the rather short follow-up time. The remaining 3 reports that we identified and included in this study on the management of suspected incidental pediatric LGBT are editorials and an international survey discussing the dilemmas and different treatment modalities in these patients [2, 16, 18].

Malignant transformation and molecular profiling of pediatric LGBT

MT of LGBT is a rather rare phenomenon in the pediatric population. Recent studies showed a low occurrence rate (2.9%) [34, 35, 38]. This stands in clear contrast to adult patients, where MT is estimated in up to 50% of the cases [32, 39, 40]. The rate of MT also seems to vary between different histological subtypes of pediatric LGBT. Even within one pathological entity, differences might exist based on the molecular profile of the specific lesion [23, 38].

MT of IPBT, suspected to be LGBT and treated by observation, is described only within the scope of case reports (Table 3) [8, 31]. Reports on confirmed LGBT showing MT after surgical removal exist too (Table 2) [21, 22, 24–27, 29, 30, 33]; however, in the majority of these cases, the patients received adjuvant chemo- or radiotherapy, which is known to be a risk factor for MT [28].

A study by Broniscer et al., including 11 children experiencing MT of an LGBT after a median time of 5.1 years, completed a molecular analysis of the resected tissue in all cases. In 9 cases, tissue diagnosis was available before and after MT [35]. TP53 overexpression and deletions of RB1 and/or CDKN2A were more common after MT. Note that eight of these patients underwent radio- and/or chemotherapy after resection of the LGBT, potentially contributing to the MT. A study by Castello et al. showed an association between hypermethylation of the UTSS region in the TERT promoter and MT of pediatric brain tumors [36]. Mistry et al. showed that BRAF V600E mutation and CDKN2A deletion are seen early in LGBTs that are at risk of MT into secondary high-grade brain tumors (HGBT) [38]. Finally, Frazao et al. suggest

that BRAF V600E mutation or CDKN2A/B MTAP co-deletions in pediatric gliomas may be used for stratifying patients for a stricter surveillance, since they occur more often in HGBT [37].

Discussion

Based on our systematic literature search, IPBT suspected to be LGBT occur in 0.2–5.7% of patients undergoing MRI. Differentiating by radiological criteria between low- and high-grade tumors is often challenging. Modalities such as PET or MR spectroscopy might help distinguish between the two. Within the seven available studies analyzing the management of suspected incidental pediatric LGBT, 368 children with a median age of 10 years were retrospectively analyzed. In 51% of the cases, the lesion was located supratentorial, and surgery at diagnosis was conducted in 22.8% of the patients. 77.2% of the children were managed conservatively through clinical and radiological follow-up and 68.8% did not need any further intervention after a median follow-up time of 32 months. Delayed surgical resection of the lesion after following the lesion for a certain period of time was indicated in 9.5% of the cases, due to radiological changes (e.g., new contrast enhancement) or progression in size of the lesion (Table 1).

Prevalence of suspected incidental pediatric brain tumors

Due to the growing availability of high-quality cranial imaging worldwide, as well as low threshold for imaging, the amount of incidentally detected lesions during the course of brain scanning is growing rapidly. The term "victims of modern imaging techniques (VOMIT)" describes the growing phenomenon of patients undergoing imaging for various reasons (e.g., trauma, unrelated symptoms, research) where an incidental asymptomatic lesion is detected, leading at times to a significant medical and psychological burden for the patient and family [41]. To date, the prevalence of incidental brain lesions in general, and of incidental suspected LGBT, remains unknown. In addition, the rate of incidentally detected brain lesions in general, and tumors specifically, is expected to rise, due to the increased use of brain imaging. Every incidentally detected brain tumor must provoke a multidisciplinary discussion of the suspected diagnosis, based on the radiological features and tumor location, and consequently trigger a case-by-case discussion on the options and the best management for each specific case.

Radiological diagnosis and criteria of suspected incidental pediatric brain tumors

LGBT generally are identified by the following imaging characteristics:

- Hypointense on T1-weighted MRI
- Hyperintense on T2-weighted and T2 fluid-attenuated inversion recovery (FLAIR) sequences
- Show a non-enhancing pattern
- No restriction on diffuse-weighted imaging (DWI)
- Smaller than 2 cm in diameter
- With no surrounding edema or mass effect [3, 14].

However, some consider asymptomatic tumors with a diameter larger than 2 cm, or with minimal mass effect or edema, still to be suspected incidental LGBT and not necessarily suspicious for malignancy [2, 15, 16]. It seems that incidental tumors showing restriction on DWI and/or contrast enhancement (but especially with the combination of both) have a higher probability of being high-grade and should prompt earlier treatment. In addition, radiological appearance is often misleading, showing an overlap between non-neoplastic lesions (e.g., hypothalamic hamartomas, inflammatory lesions) and LGBT, and even between HGBT and LGBT [19]. Another possible tool for obtaining additional information is MR spectroscopy. This modality may improve diagnostic accuracy and possibly help to differentiate between different tumor types. Single-voxel MR spectroscopy in particular has demonstrated an ability to determine brain tumor histology and grade in several multicenter studies [42, 43]. A combination of different types of MR spectroscopy (short and long TE) improves diagnostic accuracy for the three main pediatric brain tumors (medulloblastoma, pilocytic astrocytoma, and ependymoma), bringing it as high as 98% [44]. Another study showed the added value of combining MR spectroscopy (hydrogen 1) with conventional MR imaging, compared with MR imaging alone [45]. This was true for both high-grade and low-grade tumors, with promising results that might have an important role in evaluating pediatric incidentalomas. Multicontrast radiomics and artificial intelligence with deep learning may shed a light on both geometric characters and molecular biological traits of lesions, which may correlate with tumor grade and proliferation rate. Combining all-contrast radiomics models might precisely predict the biological behavior of the lesion, which may be attributed to presurgical personal diagnosis [46, 47].

MT markers in imaging

Currently, there are no specific radiological markers known to predict MT of LGBT. However, based on the published reports, it seems that if the observed tumor shows any changes,

Table 2 Histopathological diagnosis of suspected LGBT which were resected after initial observation

Author (year)	Delayed surgery (*n*, %)	Histology
Perret (2011)	2 (10.6)	Medulloblastoma Fibrillary astrocytoma
Bredlau (2012)	4 (19.2)	JPA (2×) Oligoastrocytoma (LG) Mature teratoma or dermoid cyst
Roth (2012)	2 (4.2)	CPP JPA
Ali (2014)	1 (8.3)	Astrocytoma grade II
Zaazoue (2019)	12 (8.3)	Oligodendroglioma (2×) Astrocytoma grade II (2×) JPA Neurocytoma Ependymoma Epidermoid cyst Craniopharyngioma Cavernous malformation Meningoencephalitis (biopsy) Non-diagnostic
Kozyrev (2019)	12 (17.1)	JPA (8×) Dermoid/epidermoid cyst (3×) Medulloblastoma
Wright (2019)	2 (3.6)	LGG (2×)
Total	35 (9.5) High grade: 2 (5.7) Low grade: 30 (85.7) Non-tumorous: 3 (8.6)	Low grade: JPA (13×) Dermoid/epidermoid cyst (5×) Astrocytoma grade II (3×) LGG (2×) Oligodendroglioma (2×) Oligoastrocytoma Ependymoma Neurocytoma Craniopharyngioma CPP High grade: Medulloblastoma (2×) Other/unknown: Meningoencephalitis Cavernous malformation Unknown

n, number of patients; *JPA*, juvenile pilocytic astrocytoma; *CPP*, choroid plexus papilloma; *LGG*, low-grade glioma

however subtle, on imaging, such as growth, new contrast enhancement, or restriction on DWI, the treatment course should be adjusted accordingly. Either the lesion is followed more closely with more frequent imaging, treated surgically without further delay, or treated by biopsy (if the lesion is deep or eloquent seated), followed by radiotherapy, chemotherapy, BRAF inhibitors, or close follow-up, depending on the histology and molecular profile of the lesion [8].

Observation vs. early intervention—an ongoing dilemma

The classic approach of treating suspected LGBT through observation has existed for over 30 years. Nevertheless, no clear consensus exists on whether we should observe or intervene surgically in incidental pediatric brain tumors. There is no clear evidence on which to base the decision of whether to follow or treat these lesions. It is therefore crucial to discuss these cases with an interdisciplinary panel and with the families, providing them with all of the treatment options. The burden of following these lesions over a long period of time might represent a significant psychological burden for the patient and/or the parents, in addition to various medicolegal aspects that arise when incidental brain tumors are diagnosed and followed. All these aspects must be considered and thoroughly discussed with the families, before reaching a decision concerning the management of these patients.

Time of intervention

A recently published survey (from our group) on the management of IPBT noted that recommendations regarding incidental lesions may be affected by time perspective, changing over time [2].

For example, in two presented cases, a significant percentage of the responders originally recommended follow-up; however, once the tumors showed progression in size, the recommendation changed and they were resected. Both tumors showed a pathology of malignant high-grade tumors (glioblastoma multiforme and medulloblastoma) [2].

On the other hand, we presented cases in which the primary recommendation by many colleagues was for resection; however, over time, and with proof of lesion stability, the recommendations shifted to a more conservative approach.

Of course, tumor behavior cannot be anticipated. Although rare, MT may occur. Therefore, some authors advocate a more aggressive treatment plan for pediatric incidentalomas that are even suspected to be LGBT [18]. Wisoff et al. demonstrated in their prospective natural history study that the single most significant factor influencing outcome in childhood LGBT is an extent of resection [48]. Therefore, according to their study, GTR of pediatric LGBTs should be the goal, if achievable with acceptable functional outcome. However, their series includes a heterogeneous cohort of children with LGBT, without distinguishing between incidental and non-incidental findings. Tumor location was also shown to have an impact on prognosis. Deep-seated lesions involving the brainstem, optic pathway, or basal ganglia have a worse prognosis than superficially seated cortical lesions, since a resection of these deep-seated tumors is not possible [18, 48]. Many studies analyzing adult LGBT argue that delayed operative management compromises the long-term outcome of these patients [49–55]. However, the risk of watchful waiting in adult LGBT is not comparable with childhood LGBT, since in childhood, they present as a different entity, differentiated on the molecular level, as well as histological level from adult LGBT. The childhood tumors typically grow relatively slowly, rarely undergo MT, and may even undergo spontaneous regression [18, 19, 32, 34, 38].

An additional drawback when managing incidental pediatric brain tumors through radiological observation is that no definitive pathological diagnosis can be made based solely on imaging. Incidentalomas encompass a variety of pathologies, varying in prognosis, and with histological results that might change the recommended course of management for these children. In addition, molecular diagnosis and targeted therapy options, based on genetic analysis of the tumor, may assist in prediction of the clinical course for individual cases and therefore influence the course of treatment, as suggested in a recent study by Mistry et al. [38]. Another theoretical consideration is that in some cases, early surgical resection might be advantageous, since potentially, the resection of smaller lesions would lessen off the operative morbidity, increase the ability to perform a GTR, and lower the risk of tumor growth and infiltration of adjacent vascular structures or eloquent brain regions. Finally, the psychological and social aspect of a child and a family burdened with the uncertainty of sequential imaging checks is an additional drawback of observation. In some cultural backgrounds, this may even come with stigma and marginalization, however real or perceived. Therefore, the "get it out and get it over with and get on with life" concept to provide certainty and closure for patients and their parents and thus get on with their lives is a very important aspect to consider when discussing the course of treatment.

Malignant transformation and molecular profiling of suspected LGBT

Molecular profiling of LGBTs might play a greater role than the histological grading when it comes to estimating the risk of MT [23, 34, 38]. Further, the molecular profile of an incidental pediatric brain tumor might have one of the larger impacts on the decision whether observation or intervention should be pursued [23, 38]. BRAF V600E mutation and CDKN2A deletion are seen early in LGBTs that are at greater risk of MT into secondary HGBT [37, 38]. Similarly, H3F3A K27M mutation in thalamic gliomas was described as a predictive risk factor for MT, although further, more robust evidence is needed to prove this statement [23]. Castelo-Branco et al. showed that in pediatric brain tumor upstream of the transcription start site (UTSS), hypermethylation is associated with tumor progression, malignancy, and poor prognosis. Whether this might represent an additional marker for MT must still be validated [36]. In LGBT with these molecular alterations, specific management modifications, including early surgical resection, more aggressive resection, and concomitant medical therapy (e.g., MEK inhibitors), might be indicated, due to the increased risk of MT.

Biopsy options

This raises the question of whether surgical needle biopsy is indicated even in incidental, small, non-enhancing suspected LGBT. For the adult population, it is suggested that surgical needle biopsy should be the standard practice, regardless of whether observation or intervention is pursued [56]. These suggestions, however, do not seem to apply for the pediatric population, since MT is rare, hardly justifying surgery for every child presenting with an incidental brain tumor. In addition, surgical needle biopsy presents significant limitations,

Table 3 Described cases of malignant transformation of diagnosed or suspected pediatric low-grade brain tumors

Author (year)	Age at diagnosis	Age at surgery	Adjuvant Rx or Cx	Localization	Initial diagnosis/suspected diagnosis	Diagnosis at transformation	Time to transformation	Molecular diagnosis
Incidentalomas managed by follow-up showing malignant transformation								
Unal (2008)	10 y	12 y	No	Parietal	LGG	GBM	2 y	N/A
Soleman (2017)	10 y	17 y	No	Fronto-basal	LGG	GBM	7 y	BRAF V-600E
Incidentalomas or symptomatic tumors initially surgically resected showing malignant transformation at recurrence								
Kleinman (1978)	5 y	5 y	Rx	Cerebellum	JPA	Malignant astrocytoma	48 y	N/A
Alpers (1982)	5 y	5 y	No	Occipital	JPA	Anaplastic astrocytoma	21 y	N/A
Schwartz (1990)	4 y	4 y	Rx	Cerebellum	JPA	GBM	28 y	N/A
Dirks (1994)[x]	5.3 y (mean)	Variable	Rx	5 OPG 1 thalamus	LGG	HGG	2–10 y	N/A
Jay (1994)	10 y	10 y[∞]	Rx	Temporal and brainstem	Ganglioglioma	Anaplastic ganglioglioma	3 y	N/A
Kim (2003)	4 y	4 y	No	Precentral	Ganglioglioma	GBM	4 y	p53 mutation and deletion
Zoeller (2010)	5 y	5 y	Cx	OPG	LGG	GBM	2 y	N/A
Mano[α] (2013)	10 m	4 y	Rx/Cx	Parietal	DNET	Anaplastic oligodendroglioma	4 y	Wild-type IDH1/2 no chromosomal copy changes of TP53, PTEN, EGFR, CDKN2A, ERBB2, and 1p/19q
Mano[α] (2013)	3 y	3 y	No	Frontal	DNET	Complex (aggressive) DNET	11 y	Wild-type IDH1/2 no chromosomal copy changes of TP53, PTEN, EGFR, CDKN2A, ERBB2, and 1p/19q
Ueda (2015)	8 y	23 y	No	Temporo-parieto-occipital	LGG/diffuse astrocytoma[∞]	HGG	15 y	N/A
Ishibashi (2016)	14 y	16 y	No	Thalamus	LGG	Anaplastic astrocytoma	2 y[μ]	H3F3A K27M mutation

y, years; *RX*, radiotherapy; *Cx*, chemotherapy; *OPG*, optic chiasmatic hypothalamic pathway glioma; *JPA*, juvenile pilocytic astrocytoma; *HGG*, high-grade glioma; *LGG*, low-grade glioma; *GBM*, glioblastoma

[x] Case series of 6 patients showing malignant transformation. All underwent radiotherapy before malignant transformation

[∞] The patient underwent 3 tumor resection surgeries, all showing histology of a ganglioglioma. Thereafter, they underwent radiotherapy

[α] 2 cases described

[∞] Biopsy was recommended at the time of diagnosis, however parents refused

[μ] Patient initially followed for thalamic tumor, after 2 years due to growth biopsy was undertaken showing a LGG. Two years later, further growth was seen and resection was done showing an anaplastic astrocytoma

such as sampling error, especially in small lesions, and the risk of morbidity [14]. It therefore seems that if tissue diagnosis is pursued, the decision between surgical needle biopsy and GTR should be based on the location of the tumor and potential surgically associated risks; for deep-seated lesions, a needle biopsy would be preferable, while a GTR would be recommended for superficial and/or accessible lesions GTR.

Shift of the pendulum towards a more aggressive approach in suspected pediatric incidental brain tumors?

Following our personal experience with a child who underwent MT following 6 years of observation for a stable lesion, our approach to incidental lesions suggestive of being LGBT has been modified over the years [8]. The pendulum of management decision has shifted slightly from a conservative approach of following these children radiologically, based on the belief that MT is almost non-existent in children, to a slightly more proactive approach, recommending biopsy once even a slight change is detected on follow-up imaging. This shift is influenced by the growing number of reports describing MT in pediatric LGBT [2, 8, 23, 30, 32, 33] on the one hand, as well as the recent studies analyzing molecular patterns which might suggest a risk for MT.

Note that in children suffering from a genetic syndrome, such as neurofibromatosis type 1 (NF1) or tuberous sclerosis complex (TSC), management of incidental brain tumors is often different. In these patients, suspected brain tumors are often followed radiologically, as long as the patient remains asymptomatic and the lesions are stable. If symptoms occur or tumor growth is seen, treatment decisions, including chemotherapy and targeted therapy with MEK inhibitors in NF1 or mTORi in TSC, can be made even without tissue sampling [57–59].

Future prospects

Apart from the question of whether to treat children with incidental suspected LGBTs conservatively or more aggressively, which is still a matter of great debate [2], many unanswered questions concerning the conservative treatment itself still remain. With which intervals should we follow these children, clinically and radiologically? Is there a difference in outcome of observed lesions between different age groups (e.g., infants vs. children vs. teenagers)? Should we treat teenagers like children (more conservatively), or rather like adults (early resection)? Are lesions located at specific locations within the brain more prone to be of malignant origin or are at a higher risk for MT? Studies analyzing specific locations, similar to our report on suspected incidental LGBT of the posterior fossa, are needed [17]. What radiological criteria would lead us to change the treatment course from observation to intervention? What is the role of other imaging modalities such as PET or spectroscopy? Often, children are diagnosed with incidental brain tumors as part of an endocrine evaluation of short stature, with the potential need for growth hormone substitution (GHS). The dilemma whether to treat these children with GHS is still ongoing [2]. While some studies show that GHS does not seem to influence recurrence, progression, or MT of cerebral tumors, some physicians are still reluctant to treat these patients with GHS [2, 60, 61]. All of these uncertainties should be the focus of future studies. Multicenter prospective studies on the true prevalence and incidence of IPBT are lacking. In addition, uniform and validated radiological criteria to detect lesions of low grade and low risk for MT should be an additional focus of future research. The management and natural history of observed tumors should be assessed based on large multicenter cohort studies.

Conclusion

IPBT are diagnosed in 0.2–5.7% of brain images, but represent a constantly growing entity. Identifying an incidental lesion suspected of being a tumor in a child poses a great burden for the patients, their families, and caregivers. Once an LGBT is suspected, radiological observation seems to be a valid management option, since in most cases, no further treatment is needed. Any change on imaging during follow-up should be taken seriously, and the management regimen should be adapted accordingly. Whether molecular biology of the tumor can predict MT, the risk of tumor progression, and/or overall survival, remains unknown.

Acknowledgments We would like to thank Mrs. Adina Sherer for the medical proof reading of this manuscript.

Compliance with ethical standards

Conflict of interest The authors have no potential conflicts of interest to disclose.

References

1. Graf WD, Kayyali HR, Abdelmoity AT, Womelduff GL, Williams AR, Morriss MC (2010) Incidental neuroimaging findings in nonacute headache. J Child Neurol 25:1182–1187. https://doi.org/10.1177/0883073809353149
2. Roth J, Soleman J, Paraskevopoulos D, Keating RF, Constantini S (2018) Incidental brain tumors in children: an international neurosurgical, oncological survey. Childs Nerv Syst 34:1325–1333. https://doi.org/10.1007/s00381-018-3836-4
3. Wright E, Amankwah EK, Winesett SP, Tuite GF, Jallo G, Carey C, Rodriguez LF, Stapleton S (2019) Incidentally found brain tumors in the pediatric population: a case series and proposed treatment algorithm. J Neuro-Oncol 141:355–361. https://doi.org/10.1007/s11060-018-03039-1

4. Gnekow AK, Kandels D, van Tilburg C et al (2019) SIOP-E-BTG and GPOH guidelines for diagnosis and treatment of children and adolescents with low grade glioma. Klin Padiatr 231:107–135. https://doi.org/10.1055/a-0889-8256
5. de Lima GLO, Duffau H (2015) Is there a risk of seizures in "preventive" awake surgery for incidental diffuse low-grade gliomas? J Neurosurg 122:1397–1405. https://doi.org/10.3171/2014.9.JNS141396
6. Opoku-Darko M, Lang ST, Artindale J, Cairncross JG, Sevick RJ, Kelly JJP (2018) Surgical management of incidentally discovered diffusely infiltrating low-grade glioma. J Neurosurg 129:19–26. https://doi.org/10.3171/2017.3.JNS17159
7. Potts MB, Smith JS, Molinaro AM, Berger MS (2012) Natural history and surgical management of incidentally discovered low-grade gliomas. J Neurosurg 116:365–372. https://doi.org/10.3171/2011.9.JNS111068
8. Soleman J, Roth J, Ram Z, Yalon M, Constantini S (2017) Malignant transformation of a conservatively managed incidental childhood cerebral mass lesion: controversy regarding management paradigm. Childs Nerv Syst 33:2169–2175. https://doi.org/10.1007/s00381-017-3566-z
9. Gupta SN, Gupta VS, White AC (2016) Spectrum of intracranial incidental findings on pediatric brain magnetic resonance imaging: what clinician should know? World J Clin Pediatr 5:262–272. https://doi.org/10.5409/wjcp.v5.i3.262
10. Jansen PR, Dremmen M, van den Berg A, Dekkers IA, Blanken LME, Muetzel RL, Bolhuis K, Mulder RM, Kocevska D, Jansen TA, de Wit MCY, Neuteboom RF, Polderman TJC, Posthuma D, Jaddoe VWV, Verhulst FC, Tiemeier H, van der Lugt A, White TJH (2017) Incidental findings on brain imaging in the general pediatric population. N Engl J Med 377:1593–1595. https://doi.org/10.1056/NEJMc1710724
11. Kaiser D, Leach J, Vannest J et al (2015) Unanticipated findings in pediatric neuroimaging research: prevalence of abnormalities and process for reporting and clinical follow-up. Brain Imaging Behav 9:32–42. https://doi.org/10.1007/s11682-014-9327-7
12. Perret C, Boltshauser E, Scheer I, Kellenberger CJ, Grotzer MA (2011) Incidental findings of mass lesions on neuroimages in children. Neurosurg Focus 31:E20. https://doi.org/10.3171/2011.9.FOCUS11121
13. Pirotte BJM, Lubansu A, Massager N, Wikler D, van Bogaert P, Levivier M, Brotchi J, Goldman S (2010) Clinical interest of integrating positron emission tomography imaging in the workup of 55 children with incidentally diagnosed brain lesions. J Neurosurg Pediatr 5:479–485. https://doi.org/10.3171/2010.1.PEDS08336
14. Ali ZS, Lang S-S, Sutton LN (2014) Conservative management of presumed low-grade gliomas in the asymptomatic pediatric population. World Neurosurg 81:368–373. https://doi.org/10.1016/j.wneu.2013.01.038
15. Bredlau A-L, Constine LS, Silberstein HJ, Milano MT, Korones DN (2012) Incidental brain lesions in children: to treat or not to treat? J Neuro-Oncol 106:589–594. https://doi.org/10.1007/s11060-011-0695-1
16. Di Rocco C, Frassanito P, Tamburrini G (2014) The never-ending struggle between the two souls of the neurosurgeon: to wait or to intervene. World Neurosurg 81:268–270. https://doi.org/10.1016/j.wneu.2013.02.073
17. Kozyrev DA, Constantini S, Tsering D, Keating R, Basal S, Roth J (2019) Pediatric posterior fossa incidentalomas. Childs Nerv Syst 36:601–609. https://doi.org/10.1007/s00381-019-04364-0
18. Pollack IF (2014) Management of low-grade gliomas in childhood. World Neurosurg 81:265–267. https://doi.org/10.1016/j.wneu.2013.01.104
19. Roth J, Keating RF, Myseros JS, Yaun AL, Magge SN, Constantini S (2012) Pediatric incidental brain tumors: a growing treatment dilemma. J Neurosurg Pediatr 10:168–174. https://doi.org/10.3171/2012.6.PEDS11451
20. Zaazoue MA, Manley PE, Kapur K, Ullrich NJ, Silvera VM, Goumnerova LC (2019) Natural history and management of incidentally discovered focal brain lesions indeterminate for tumor in children. Neurosurgery. https://doi.org/10.1093/neuros/nyz078
21. Alpers CE, Davis RL, Wilson CB (1982) Persistence and late malignant transformation of childhood cerebellar astrocytoma. Case report. J Neurosurg 57:548–551. https://doi.org/10.3171/jns.1982.57.4.0548
22. Dirks PB, Jay V, Becker LE, Drake JM, Humphreys RP, Hoffman HJ, Rutka JT (1994) Development of anaplastic changes in low-grade astrocytomas of childhood. Neurosurgery 34:68–78
23. Ishibashi K, Inoue T, Fukushima H, Watanabe Y, Iwai Y, Sakamoto H, Yamasaki K, Hara J, Shofuda T, Kanematsu D, Yoshioka E, Kanemura Y (2016) Pediatric thalamic glioma with H3F3A K27M mutation, which was detected before and after malignant transformation: a case report. Childs Nerv Syst 32:2433–2438. https://doi.org/10.1007/s00381-016-3161-8
24. Jay V, Squire J, Becker LE, Humphreys R (1994) Malignant transformation in a ganglioglioma with anaplastic neuronal and astrocytic components. Report of a case with flow cytometric and cytogenetic analysis. Cancer 73:2862–2868. https://doi.org/10.1002/1097-0142(19940601)73:11<2862::aid-cncr2820731133>3.0.co;2-5
25. Kim NR, Wang K-C, Bang J-S, Choe G, Park Y, Kim SK, Cho BK, Chi JG (2003) Glioblastomatous transformation of ganglioglioma: case report with reference to molecular genetic and flow cytometric analysis. Pathol Int 53:874–882
26. Kleinman GM, Schoene WC, Walshe TM, Richardson EP (1978) Malignant transformation in benign cerebellar astrocytoma: case report. J Neurosurg 49:111–118. https://doi.org/10.3171/jns.1978.49.1.0111
27. Mano Y, Kumabe T, Shibahara I, Saito R, Sonoda Y, Watanabe M, Tominaga T (2013) Dynamic changes in magnetic resonance imaging appearance of dysembryoplastic neuroepithelial tumor with or without malignant transformation. J Neurosurg Pediatr 11:518–525. https://doi.org/10.3171/2013.1.PEDS11449
28. Parsa CF, Givrad S (2008) Juvenile pilocytic astrocytomas do not undergo spontaneous malignant transformation: grounds for designation as hamartomas. Br J Ophthalmol 92:40–46. https://doi.org/10.1136/bjo.2007.125567
29. Schwartz AM, Ghatak NR (1990) Malignant transformation of benign cerebellar astrocytoma. Cancer 65:333–336. https://doi.org/10.1002/1097-0142(19900115)65:2<333::aid-cncr2820650225>3.0.co;2-3
30. Ueda F, Aburano H, Yoshie Y, Matsui O, Gabata T (2015) Malignant transformation of diffuse infiltrating glial neoplasm after prolonged stable period initially discovered with hypothalamic hamartoma. Neurol Neurochir Pol 49:441–445. https://doi.org/10.1016/j.pjnns.2015.08.003
31. Unal E, Koksal Y, Cimen O, Paksoy Y, Tavli L (2008) Malignant glioblastomatous transformation of a low-grade glioma in a child. Childs Nerv Syst 24:1385–1389. https://doi.org/10.1007/s00381-008-0716-3
32. Winograd E, Pencovich N, Yalon M, Soffer D, Beni-Adani L, Constantini S (2012) Malignant transformation in pediatric spinal intramedullary tumors: case-based update. Childs Nerv Syst 28:1679–1686. https://doi.org/10.1007/s00381-012-1851-4
33. Zoeller GK, Brathwaite CD, Sandberg DI (2010) Malignant transformation of an optic pathway glioma without prior radiation therapy. J Neurosurg Pediatr 5:507–510. https://doi.org/10.3171/2009.12.PEDS09173
34. Broniscer A (2015) Malignant transformation of low-grade gliomas in children: lessons learned from rare medical events. J Clin Oncol 33:978–979. https://doi.org/10.1200/JCO.2014.60.1823

35. Broniscer A, Baker SJ, West AN, Fraser MM, Proko E, Kocak M, Dalton J, Zambetti GP, Ellison DW, Kun LE, Gajjar A, Gilbertson RJ, Fuller CE (2007) Clinical and molecular characteristics of malignant transformation of low-grade glioma in children. J Clin Oncol 25:682–689. https://doi.org/10.1200/JCO.2006.06.8213
36. Castelo-Branco P, Choufani S, Mack S, Gallagher D, Zhang C, Lipman T, Zhukova N, Walker EJ, Martin D, Merino D, Wasserman JD, Elizabeth C, Alon N, Zhang L, Hovestadt V, Kool M, Jones DTW, Zadeh G, Croul S, Hawkins C, Hitzler J, Wang JCY, Baruchel S, Dirks PB, Malkin D, Pfister S, Taylor MD, Weksberg R, Tabori U (2013) Methylation of the TERT promoter and risk stratification of childhood brain tumours: an integrative genomic and molecular study. Lancet Oncol 14:534–542. https://doi.org/10.1016/S1470-2045(13)70110-4
37. Frazão L, do Carmo Martins M, Nunes VM, et al (2018) BRAF V600E mutation and 9p21: CDKN2A/B and MTAP co-deletions-markers in the clinical stratification of pediatric gliomas. BMC Cancer 18:1259. https://doi.org/10.1186/s12885-018-5120-0
38. Mistry M, Zhukova N, Merico D, Rakopoulos P, Krishnatry R, Shago M, Stavropoulos J, Alon N, Pole JD, Ray PN, Navickiene V, Mangerel J, Remke M, Buczkowicz P, Ramaswamy V, Guerreiro Stucklin A, Li M, Young EJ, Zhang C, Castelo-Branco P, Bakry D, Laughlin S, Shlien A, Chan J, Ligon KL, Rutka JT, Dirks PB, Taylor MD, Greenberg M, Malkin D, Huang A, Bouffet E, Hawkins CE, Tabori U (2015) BRAF mutation and CDKN2A deletion define a clinically distinct subgroup of childhood secondary high-grade glioma. J Clin Oncol 33:1015–1022. https://doi.org/10.1200/JCO.2014.58.3922
39. Ellis JA, Waziri A, Balmaceda C, Canoll P, Bruce JN, Sisti MB (2009) Rapid recurrence and malignant transformation of pilocytic astrocytoma in adult patients. J Neuro-Oncol 95:377–382. https://doi.org/10.1007/s11060-009-9935-z
40. Stüer C, Vilz B, Majores M, Becker A, Schramm J, Simon M (2007) Frequent recurrence and progression in pilocytic astrocytoma in adults. Cancer 110:2799–2808. https://doi.org/10.1002/cncr.23148
41. Hayward R (2003) VOMIT (victims of modern imaging technology)—an acronym for our times. BMJ. 326:1273. https://doi.org/10.1136/bmj.326.7401.1273
42. García-Gómez JM, Luts J, Julià-Sapé M, Krooshof P, Tortajada S, Robledo JV, Melssen W, Fuster-García E, Olier I, Postma G, Monleón D, Moreno-Torres À, Pujol J, Candiota AP, Martínez-Bisbal MC, Suykens J, Buydens L, Celda B, van Huffel S, Arús C, Robles M (2009) Multiproject-multicenter evaluation of automatic brain tumor classification by magnetic resonance spectroscopy. MAGMA 22:5–18. https://doi.org/10.1007/s10334-008-0146-y
43. Tate AR, Underwood J, Acosta DM, Julià-Sapé M, Majós C, Moreno-Torres À, Howe FA, van der Graaf M, Lefournier V, Murphy MM, Loosemore A, Ladroue C, Wesseling P, Luc Bosson J, Cabañas ME, Simonetti AW, Gajewicz W, Calvar J, Capdevila A, Wilkins PR, Bell BA, Rémy C, Heerschap A, Watson D, Griffiths JR, Arús C (2006) Development of a decision support system for diagnosis and grading of brain tumours using in vivo magnetic resonance single voxel spectra. NMR Biomed 19:411–434. https://doi.org/10.1002/nbm.1016
44. Vicente J, Fuster-Garcia E, Tortajada S, García-Gómez JM, Davies N, Natarajan K, Wilson M, Grundy RG, Wesseling P, Monleón D, Celda B, Robles M, Peet AC (2013) Accurate classification of childhood brain tumours by in vivo ^{1}H MRS-a multi-centre study. Eur J Cancer 49:658–667. https://doi.org/10.1016/j.ejca.2012.09.003
45. Julià-Sapé M, Coronel I, Majós C, Candiota AP, Serrallonga M, Cos M, Aguilera C, Acebes JJ, Griffiths JR, Arús C (2012) Prospective diagnostic performance evaluation of single-voxel 1H MRS for typing and grading of brain tumours. NMR Biomed 25:661–673. https://doi.org/10.1002/nbm.1782
46. Citak-Er F, Firat Z, Kovanlikaya I, Ture U, Ozturk-Isik E (2018) Machine-learning in grading of gliomas based on multi-parametric magnetic resonance imaging at 3T. Comput Biol Med 99:154–160. https://doi.org/10.1016/j.compbiomed.2018.06.009
47. Vamvakas A, Williams SC, Theodorou K, Kapsalaki E, Fountas K, Kappas C, Vassiou K, Tsougos I (2019) Imaging biomarker analysis of advanced multiparametric MRI for glioma grading. Phys Med 60:188–198. https://doi.org/10.1016/j.ejmp.2019.03.014
48. Wisoff JH, Sanford RA, Heier LA, Sposto R, Burger PC, Yates AJ, Holmes EJ, Kun LE (2011) Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group. Neurosurgery 68:1548–1554; discussion 1554-1555. https://doi.org/10.1227/NEU.0b013e318214a66e
49. Berger MS, Deliganis AV, Dobbins J, Keles GE (1994) The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. Cancer 74:1784–1791. https://doi.org/10.1002/1097-0142(19940915)74:6<1784::aid-cncr2820740622>3.0.co;2-d
50. Jakola AS, Myrmel KS, Kloster R, Torp SH, Lindal S, Unsgård G, Solheim O (2012) Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. JAMA 308:1881–1888. https://doi.org/10.1001/jama.2012.12807
51. Keles GE, Lamborn KR, Berger MS (2001) Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. J Neurosurg 95:735–745. https://doi.org/10.3171/jns.2001.95.5.0735
52. Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, Afra D, Cornu P, Bolla M, Vecht C, Karim AB, European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group, European Organization for Research and Treatment of Cancer Radiotherapy Cooperative Group (2002) Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 20:2076–2084. https://doi.org/10.1200/JCO.2002.08.121
53. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, Tihan T, VandenBerg S, McDermott MW, Berger MS (2008) Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 26:1338–1345. https://doi.org/10.1200/JCO.2007.13.9337
54. Pouratian N, Schiff D (2010) Management of low-grade glioma. Curr Neurol Neurosci Rep 10:224–231. https://doi.org/10.1007/s11910-010-0105-7
55. Morshed RA, Young JS, Hervey-Jumper SL, Berger MS (2019) The management of low-grade gliomas in adults. J Neurosurg Sci 63:450–457. https://doi.org/10.23736/S0390-5616.19.04701-5
56. Brown PD, Wald JT, McDermott MW et al (2003) Oncodiagnosis panel: 2002. Patient's symptoms not related to the lesion seen in the MR images. Radiographics 23:1591–1611
57. Fangusaro J, Onar-Thomas A, Young Poussaint T, Wu S, Ligon AH, Lindeman N, Banerjee A, Packer RJ, Kilburn LB, Goldman S, Pollack IF, Qaddoumi I, Jakacki RI, Fisher PG, Dhall G, Baxter P, Kreissman SG, Stewart CF, Jones DTW, Pfister SM, Vezina G, Stern JS, Panigrahy A, Patay Z, Tamrazi B, Jones JY, Haque SS, Enterline DS, Cha S, Fisher MJ, Doyle LA, Smith M, Dunkel IJ, Fouladi M (2019) Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. Lancet Oncol 20:1011–1022. https://doi.org/10.1016/S1470-2045(19)30277-3
58. Listernick R, Ferner RE, Liu GT, Gutmann DH (2007) Optic pathway gliomas in neurofibromatosis-1: controversies and

recommendations. Ann Neurol 61:189–198. https://doi.org/10.1002/ana.21107

59. Roth J, Roach ES, Bartels U, Jóźwiak S, Koenig MK, Weiner HL, Franz DN, Wang HZ (2013) Subependymal giant cell astrocytoma: diagnosis, screening, and treatment. Recommendations from the International Tuberous Sclerosis Complex Consensus Conference 2012. Pediatr Neurol 49:439–444. https://doi.org/10.1016/j.pediatrneurol.2013.08.017
60. Patterson BC, Chen Y, Sklar CA, Neglia J, Yasui Y, Mertens A, Armstrong GT, Meadows A, Stovall M, Robison LL, Meacham LR (2014) Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report from the childhood cancer survivor study. J Clin Endocrinol Metab 99:2030–2037. https://doi.org/10.1210/jc.2013-4159
61. Shen L, Sun CM, Li XT, Liu CJ, Zhou YX (2015) Growth hormone therapy and risk of recurrence/progression in intracranial tumors: a meta-analysis. Neurol Sci 36:1859–1867. https://doi.org/10.1007/s10072-015-2269-z