ORIGINAL ARTICLE

Postoperative Surveillance Magnetic Resonance Imaging for Cerebellar Astrocytoma

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ABSTRACT: ***Introduction:*** Patients with low grade astrocytomas generally have good prognosis when total resection can be achieved, but surveillance neuroimaging is commonly performed to detect recurrence or progression. This study evaluated the utility and yield of such strategy for pilocytic and non-pilocytic cerebellar astrocytomas. ***Methods:*** A 20-year retrospective review was performed of patients undergoing resection of cerebellar astrocytoma at a single institution. A negative MRI string (NMS) ratio was computed as the fraction of total follow-up period over which surveillance neuroimaging was negative for recurrence or progression. Chi-squared analysis differentiated NMS ratio by resection extent and lesion histopathology. ***Results:*** Twenty-eight patients with pilocytic (n=15) and non-pilocytic (n=13) astrocytoma underwent 34 craniotomies, with total resection in 19 cases. Surveillance MRIs (n=167) among total resection patients were uniformly negative for recurrent disease at average seven years follow-up (NMS ratio = 1.0). The 43 surveillance MRIs among subtotal resection patients revealed disease progression in two patients within six months of operation (NMS ratio = 0.78, $p<0.05$). No differences in NMS ratio were observed between pilocytic and non-pilocytic astrocytoma subtypes. ***Discussion:*** This study illustrates pediatric patients with low-grade cerebellar astrocytomas undergoing total resection may not benefit from routine surveillance neuroimaging, primarily because of low recurrence likelihood. Patients with subtotal resection may benefit from surveillance of residual disease, with further work aimed at exploring the schedule of such follow-up.

RÉSUMÉ: Surveillance postopératoire par imagerie par résonance magnétique dans l'astrocytome cérébelleux. ***Contexte :*** Les patients porteurs d'un astrocytome de bas grade ont généralement un bon pronostic quand la résection totale est possible. Cependant, une surveillance en neuroimagerie est souvent effectuée afin de détecter une récidive ou une progression. Cette étude a évalué l'utilité et le rendement d'une telle stratégie quand il s'agit d'astrocytomes pilocytiques et non pilocytiques. ***Méthodes :*** Nous avons effectué une revue rétrospective, dans une seule institution, des dossiers de patients qui avaient subi une résection d'un astrocytome cérébelleux au cours d'une période de 20 ans. Nous avons calculé un indice de suivi IRM négatif, soit la fraction du temps total de suivi pendant laquelle la surveillance en neuroimagerie était négative, c'est à dire sans récidive ou progression. Le test du X2 a permis de différencier l'indice selon l'étendue de la résection et la lésion anatomopathologique. ***Résultats :*** Vingt-huit patients atteints d'astrocytomes pilocytiques (n = 15) et non pilocytiques (n = 13) ont subi au total 34 craniotomies et la résection a été complète chez 19 patients. La surveillance IRM (n = 167) chez tous les patients qui avaient subi une résection totale était négative quant à une récidive de la maladie après un suivi moyen de 7 ans (indice = 1,0). Les 43 IRM de surveillance chez les patients qui avaient subi une résection subtotale ont montré une progression de la maladie chez 2 patients dans les 6 mois qui ont suivi l'opération (indice = 0,78; $p < 0,05$). Aucune différence dans les indices n'a été observée entre les sous-types d'astrocytomes pilocytiques et non pilocytiques. ***Discussion :*** Cette étude démontre que les patients d'âge pédiatrique porteurs d'astrocytomes cérébelleux de bas grade qui subissent une résection totale, ne bénéficient probablement pas d'une surveillance de routine en neuroimagerie, principalement parce qu'ils sont à faible risque de récidive. Les patients chez qui la résection est subtotale peuvent bénéficier d'une surveillance de la maladie résiduelle. Cependant, le calendrier du suivi devra faire l'objet d'études ultérieures.

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The role of surgery for pediatric brain tumors is defined by tumor location, suspected histology, and patient clinical status. These tumors are frequently located in the posterior fossa and common histopathologies include medulloblastoma and astrocytoma.[1] Astrocytomas are derived from neoplastic astrocytes and can be grossly divided into those that are narrowly-infiltrative with defined operative margin such as pilocytic astrocytoma, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma, and those that are diffusely-infiltrative with ill-defined operative margin such as low-grade astrocytoma, anaplastic astrocytoma, and glioblastoma. Patients generally present with symptoms and signs of raised intracranial pressure, seizure, or focal neurological deficit, occasionally

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having either environmental risk factors (therapeutic and prophylactic irradiation, nitroso compounds) or genetic risk factors (Turcot syndrome, neurofibromatosis Type I, and p53 germ line mutations).

Surgery for astrocytoma is indicated to debulk neoplastic tissue and to obtain pathological diagnosis for adjuvant therapy. The greatest predictor of astrocytoma disease progression after surgery is the extent of resection. Among patients with subtotal resection, larger residual tumor volumes is reported to negatively correlate with outcome;[2] and further, the risk of disease progression is cited at six times greater following subtotal compared with total resection.[3] Nevertheless, such lesions can recur even after total resection, with Boch and coworkers[4] reporting a case of 54-year-old male presenting with histologically-proven recurrent disease 45 years after the initial complete resection. Further, Krieger and coworkers[5] report that 11% of their patients with pilocytic astrocytoma experienced recurrent disease with further anaplastic changes including perivascular cellularity.

Surveillance neuroimaging is performed to earlier identify recurrent or progressive disease, though the evidence supporting such resource utilization and the imaging schedule remains controversial. Tumor histology impacts the likelihood of recurrent disease, and Korones and coworkers[6] found an overall surveillance MRI detection frequency of 4.2% among 112 children treated for brain tumors. They report that patients with lower-grade disease were more likely to be asymptomatic at recurrence (10 of 13) compared with higher-grade disease (17 of 33), though that study was underpowered to detect differences in overall survival between groups. Steinbok and coworkers[7] further delineate how both tumor type and location impacts on the value of postoperative surveillance imaging among children. Asymptomatic recurrence occurred in 11.1% of scans after hypothalamic astrocytoma resection, whereas cerebellar astrocytoma, cerebral astrocytoma, and thalamic astrocytoma were between 0 and 2%. Further, fourth ventricular ependymoma recurrences were diagnosed at an image rate of 8.6%. This detection may translate into survival benefit for medulloblastoma and malignant glioma,[8-10] but such findings have not been described for low-grade astrocytic tumors.

The timing of surveillance neuroimaging is controversial, with the most consistent suggestion that those patients receiving subtotal resection require more frequent studies.[3,5,11] Beyond that, the time interval between such evaluations is highly variable, with purported benefits less frequent studies including more cost-effective resource utilization, more limited exposure to general anesthetic for younger patients, and less burdensome follow-up by care-givers.

The objective of this work was to review the surveillance neuroimaging experience at the Children's Hospital of Eastern Ontario, and hence to define the utility in applying such strategy in the routine care of brain tumor patients. This is of particular importance when the value of such radiographic evaluation is unknown for astrocytic tumors[6,11] and when clinical evaluation may alone have high negative predictive value against recurrent disease.[12] These findings contribute to a growing literature surrounding the appropriate frequency of neuroimaging for patients with low-grade astrocytomas who have undergone complete tumor resection.

Methods

A retrospective review was performed of the medical records of all patients undergoing surgical treatment for posterior fossa brain tumors at the Children's Hospital of Eastern Ontario between 1987 and 2007. Research ethics board approval was obtained, with patient consent not required for this retrospective study with de-identified subjects. Each case was examined by one of three available neuropathologists. Patients were included based on the final histopathological diagnosis of pilocytic astrocytoma or non-pilocytic astrocytoma (diffuse, fibrillary, unspecified low-grade) as the groups were not always distinguishable based on preoperative imaging alone. Cerebellar pilocytic astrocytomas commonly appear as well-demarcated cystic lesions on MRI with a hypo-intense to iso-intense contrast-enhancing mural nodule on T1-weighted imaging. Non-pilocytic astrocytomas are typically non-enhancing lesions, commonly not well-demarcated, and hyperintense on T2-weighted imaging. The presence of any positive histopathological features of pilocytic astrocytoma formed the basis of this classification, and included biphasic appearance of alternating dense and loose microcystic components, piloid appearance of the cytoplasmic processes, and the presence of brightly eosinophilic Rosenthal fibers. Those cases in which no positive features of pilocytic astrocytoma were observed were delineated as non-pilocytic. Only patients for whom incomplete chart information precluded collection of any follow-up information were excluded. Demographic variables recorded included sex, age at surgery, extent of surgery, and need and timing for of reoperation for disease recurrence or progression. Extent of surgical resection was judged as "total" or "subtotal" based on contrast-enhanced neuroimaging studies the day following operation. All postoperative MRI studies were evaluated for the presence of recurrent disease or residual disease progression, with surveillance protocols including T1, T1 with gadolinium contrast, T2, and FLAIR imaging sequences. Disease progression was defined as residual lesion enlargement in all three dimensions compared to the previous study. The timing of these surveillance studies was left to the discretion of the attending neurosurgeon.

Results of each MRI were delineated as positive or negative, defined as the absence or presence of recurrent disease for patients who underwent total resection and defined as the stability or progression of residual disease for patients who underwent subtotal resection. Those patients whose initial surgery involved total resection were followed for outcomes of disease recurrence and need for second operation. From the former, a parameter of negative MRI string (NMS) ratio is computed to reflect the total number of years with negative MRIs for disease recurrence as a fraction of the total follow-up period over which surveillance neuroimaging was performed. Those patients whose initial surgery involved subtotal resection were followed for outcome of disease stability and need for second operation. From the former, the NMS ratio is computed to reflect the total number of years with negative MRIs for disease progression as a fraction of the total follow-up period over which surveillance neuroimaging was performed.

All statistical analyses were performed at the $\alpha = 0.05$ level of significance. Student's t-test and chi-squared analyses were used to evaluate the demographic differences between patients

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Table 1: Demographic and follow-up information for the study patients

Patient	Age (years)	Gender	Diagnosis	Resection	Surveillance^ (# MRIs)	Follow-up (yrs)	Outcome*
1	4	F	Pilocytic	Total	4 (3)	5.5	No recur
2	10.5	M	Pilocytic	Total	7 (0)	3.25	No recur
3	10.25	M	Pilocytic	Total	6 (0)	2.25	No recur
4	8.33	M	Pilocytic	Total	6 (0)	7.00	No recur
5	6.13	M	Pilocytic	Total	6 (4)	4.83	No recur
6	8.73	F	Pilocytic	Total	7 (3)	5.25	No recur
7	5.3	M	Pilocytic	Total	8 (3)	8.42	No recur
8	1.9	F	Pilocytic	Total	8 (5)	10.50	No recur
9	5.7	M	Pilocytic	Total	9 (6)	9.67	No recur
10	12.1	F	Pilocytic	Total	11 (1)	5.75	No recur
11	3.4	F	Pilocytic	Total	10 (10)	10.16	No recur
12	8.37	F	Pilocytic	Sub-total	7 (1)	6.50	Stable
13	13.22	F	Pilocytic	Sub-total	6 (1)	2.16	Stable
14	4.90	M	Pilocytic	Sub-total	4 (4)	1.00	Stable
				Total	5 (4)	4.42	No recur
15	1.83	F	Pilocytic	Sub-total	3 (3)	0.25	Progress 3 months
				Sub-total	2 (2)	0.50	Stable
16	13.8	F	Non-pilocytic	Total	2 (0)	0.17	No recur
17	10.8	M	Non-pilocytic	Total	3 (0)	5.58	No recur
18	15.4	F	Non-pilocytic	Total	3 (0)	2.00	No recur
19	2.4	F	Non-pilocytic	Total	9 (9)	4.67	No recur
20	2.5	M	Non-pilocytic	Total	11 (7)	11.25	No recur
21	1.2	M	Non-pilocytic	Total	10 (10)	14.33	No recur
22	3.2	M	Non-pilocytic	Total	10 (7)	9.92	No recur
23	4.65	M	Non-pilocytic	Total	16 (7)	13.25	No recur
24	8.38	M	Non-pilocytic	Sub-total	4 (1)	1.58	Regress 18 months
25	2.00	F	Non-pilocytic	Sub-total	4 (4)	1.50	Stable
				Total	3 (3)	1.08	No recur
26	10.1	F	Non-pilocytic	Sub-total	4 (0)	1.50	Stable
				Total	9 (0)	6.75	No recur
27	7.23	F	Non-pilocytic	Sub-total	1 (0)	2.00	Stable
				Total	10 (0)	7.83	No recur
28	12.60	F	Non-pilocytic	Sub-total	2 (1)	0.50	Progress 5 months
				Total	6 (1)	1.83	No recur

^ Surveillance MRIs are delineated as total number of MRIs performed, followed by number of MRIs performed under general anesthetic. * Outcome reflects radiological disease status following each surgical intervention.

presenting with pilocytic astrocytomas and other low-grade astrocytomas, as well as differences between groups by extent of resection. The use of parametric tests was justified by testing the data fit to the normal distribution using the Shapiro Wilk W test. Descriptive statistics were used to evaluate the NMS ratio among patients receiving total resection for each of the two histopathologies.

Results

Patient Population

Among 339 patients undergoing surgery for brain tumors at the Children's Hospital of Eastern Ontario between 1987 and 2007, 225 were identified to have been studied by at least one MRI with an average of nearly nine studies per patient (range 0 - 33 per patient). General anesthetic was required in 45% of these cases (range 0 - 28 per patient), and average follow-up of these patients was 5.4 years.

Patients were further specified by tumor location and histology with 15 and 13 patients undergoing surgery for cerebellar pilocytic astrocytoma and non-pilocytic low-grade astrocytoma respectively. Patients with pilocytic astrocytoma were more frequently female (53%), with an average age of 7 ± 4 years (range 2 – 13 years) at surgery and an average follow-up of 6.4 years. Patients with non-pilocytic low-grade astrocytoma were more frequently female (54%), with an average age of 7 ± 5 years (range 1 – 15 years) at surgery, and an average follow-up of 7.0 years. These 28 patients underwent a total of 34 craniotomies and 216 surveillance MRI studies, and their demographic characteristics are summarized in Table 1. Patient outcomes and resource utilization are stratified by tumor histopathology in Table 2 and further divided by resection extent in Table 3.

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Table 2: Summary information for patients included in this study

	Pilocytic astrocytoma	Non-pilocytic astrocytoma	p-value
N	15	13	
Age	7 ± 4 yrs	7 ± 5 yrs	0.43
Gender (% female)	53%	54%	1.00
CSF Diversion	1	3	0.20
MRIs / patient	7 ± 2	8 ± 4	0.43
Fraction of MRIs with GA	45%	40%	0.75
Follow-up	6 ± 3	7 ± 5	0.61
Re-operation	13%	31%	0.28

GA=general anaesthetic; N=number of patients; CSF=cerebrospinal fluid

Patients with Total Resection

The first craniotomy provided for total resection in 19 patients aged 7 ± 4 years at surgery, 42% of whom were female. These were divided as 11 of 15 (73%) pilocytic astrocytoma patients and 8 of 13 (62%) non-pilocytic astrocytoma patients. A total of 146 surveillance MRIs were performed among these patients, of which 75 (51%) required general anesthetic, for an average follow-up of 7.0 years. All of these studies were negative for recurrent disease with an average time interval between studies of 11 months. Given the absence of any tumor recurrences in this series, the NMS ratio as defined yields values of 1.0 for each of pilocytic and non-pilocytic astrocytoma subtypes (χ^2 test, p = 1.0), with an overall NMS ratio of 1.0.

Patients with Subtotal Resection

The first craniotomy provided for subtotal resection in nine patients aged 8 ± 4 years at surgery, 78% of whom were female. These were divided as 4 of 15 (27%) pilocytic astrocytoma patients and 5 of 13 (38%) non-pilocytic astrocytoma patients. One of these patients exhibited disease regression by surveillance neuroimaging after 18 months. Two of the four patients with residual pilocytic astrocytoma and four of the five patients with non-pilocytic astrocytoma underwent subsequent operation (χ^2 test, p = 0.34) with averages of 3.5 and 2.8 surveillance MRIs (Analysis of variance (ANOVA), p = 0.56) between the first and second craniotomies. Among these six patients undergoing re-operation, four had stable disease by neuroimaging whereas two (one of each pathological subtype) had progressive disease both within six months of the index operation. A total resection was achieved in five of these six patients. The calculated NMS ratios for disease progression are 0.75 and 0.80 for pilocytic and non-pilocytic astrocytomas respectively, and were not different by histological subtype (χ^2 test, p = 0.86), with an overall NMS ratio of 0.78.

A total of 70 surveillance MRIs were performed among these patients, for which 25 (36%) required general anesthetic, with an average follow-up of 4.4 years and an average time interval between studies of six months. All of these studies demonstrated residual disease, with the exception of those performed after the second operation provided for complete resection.

Discussion

Postoperative neuroimaging surveillance of patients after brain tumor resection is done to identify recurrent or progressive disease prior to onset of symptoms. The unproven benefit in that hypothesis is that earlier identification implies more treatable disease and superior patient outcomes with more timely second operation or implementation of adjuvant therapy. Surveillance neuroimaging, particularly in children, has many important considerations that have been introduced in this work. The low yield observed for disease recurrence and progression among low-grade cerebellar astrocytomas is consistent with the natural history of this disease. Nevertheless, 216 surveillance MRIs were performed for these 28 patients, with more than 40% of studies requiring the use of general anesthetic. Such intervention is not without risk, with highest event rates between 1 and 5% described for adverse effects of hypoxemia, central apnea, and airway obstruction.[13,14] Unexpected admission to hospital was required in fewer than 0.1% of patients. Other considerations include the resource utilization costs of surveillance MRI and the anxiety caused to the patient and family surrounding each followup with low physician expectation of asymptomatic recurrence.

Patients with total resection of low-grade cerebellar astrocytomas have recurrence rates between 0 and 13% with mean follow-up between three and six years, whereas

Table 3: Follow-up for patients in this study stratified by extent of resection

	Pilocytic Astrocytoma			Non-pilocytic Astrocytoma		
Resection	Total	Subtotal	p-value	Total	Subtotal	p-value
N	11	4		8	5	
Age	7 ± 3 yrs	7 ± 5 yrs	0.95	7 ± 6 yrs	8 ± 4 yrs	0.63
Gender (% female)	45%	75%	0.57	38%	80%	0.27
MRIs / patient	7 ± 2	7 ± 2	0.55	8 ± 5	9 ± 4	0.82
Fraction of MRIs with GA	42%	55%	0.57	47%	30%	0.49
Recurrent or progressive disease	None	25%	N/A	None	20%	N/A
Re-operation	None	50%	N/A	None	80%	N/A

GA = general anaesthetic; N=number of patients

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significantly higher rates of disease progression are described for those patients with subtotal resection.[3,7,11,15,16] Sutton and coworkers[11] used multivariate analysis to conclude that age, cystic morphology, and histological subtype do not affect likelihood of recurrence among 93 patients with cerebellar astrocytomas, but that surveillance strategy should be stratified by extent of resection. The results presented herein are consistent with this literature with no patient experiencing recurrence after total resection, whereas two-thirds of those patients with subtotal resection required subsequent surgical intervention.

Growth arrest can occur among patients with cerebellar astrocytoma after incomplete resection, observed in one of our nine patients. Palma and coworkers[17] describe 31 children having 22 pilocytic astrocytomas and 9 diffuse astrocytomas, with symptomatic recurrence occurring in 17 after a range of 25 to 450 months and 14 patients remaining asymptomatic after a range of 84 to 516 months. Smaller series looking specifically at surveillance neuroimaging provide variable evidence regarding the benefit of this strategy. Schneider and coworkers[18] describe 8/12 patients with subtotal resection experiencing no CT evidence of tumor progression with a mean of five year follow-up. Sutton and coworkers[11] describe 11 of 14 patients with subtotal resection experiencing asymptomatic disease progression by MRI with a mean of eight year follow-up. Dirven and coworkers[16] describe 8 of 25 patients as having stable disease and 2 of 25 patients exhibiting regression by MRI with a mean of 4.5 year follow-up. Disease stabilization occurs from devascularization of residual tumor[19] or transformation of residual cells to quiescent state with reduced concentration of pro-proliferative growth factors.[2,18,20] Indeed, the proliferative potential of cerebellar tumors is decreased at second operation following initial partial resection.[21,22]

The NMS ratio is calculated as the total number of years with negative MRIs divided by the total years of follow-up. This parameter is sensitive to the interval selected between neuroimaging studies, expected to decrease in magnitude for aggressive tumors that frequently recur as well as for surveillance strategies with imaging studies spaced too far apart. The higher NMS ratio reflects a longer median interval until recurrence is detected, with values of unity observed for both pilocytic astrocytomas (NMS ratio = 1.00) and non-pilocytic astrocytomas (NMS ratio = 1.00) after total resection. Any recurrence decreases this ratio, occurring more frequently with more aggressive tumors and to lesser fractional extent with longer followup for benign disease. For those patients in whom subtotal resection was achieved, the NMS ratios were 0.75 and 0.80 for pilocytic and non-pilocytic astrocytomas respectively, reflecting the one patient in each group in whom disease progression occurred. These lower values are consistent with more frequent disease progression after subtotal resection.[3,5,11] Comparison between populations of subtotal resection patients, four with pilocytic astrocytoma and five with non-pilocytic astrocytoma, is too small to draw meaningful comparison between histological subtypes (power of 0.66 to detect a difference of two standard deviation). The goal of a surveillance neuroimaging strategy would be to maximize the interval between sequential MRI studies while not compromising the NMS ratio.

The similarity of surgical outcomes and incidence of disease progression between the pilocytic and non-pilocytic subtypes of low-grade cerebellar astrocytoma may reflect the small numbers in this study. However, other work describes spurious interobserver variability in histological subclassication with no survival difference among 107 patients stratified by World Health Organization (WHO) grade (I or II), histological subtype (pilocytic or diffuse), or Kernohan grade (I or II).[23] Grouping all of the low-grade cerebellar astrocytoma patients together, stratified by resection extent, the calculated NMS ratios for total and subtotal resection NMS ratios were 1.0 and 0.78 respectively (χ^2 test, p = 0.03).

While the low recurrence rate among pediatric cerebellar astrocytomas may negate the value of the negative MRI string ratio in this series, such benign behavior has not always been the case in other reported series. One application of the NMS ratio is to permit comparison between different centers with different surveillance strategies. This would create insight into both asymptomatic recurrence rates and potential future national MRI surveillance recommendations. Consequently, we introduce but have not yet exhaustively explored the full extent and utility of this metric, with forseeable applications to include characterizing NMS ratio by tumor aggressiveness and by surveillance strategy.

Our results are consistent with the low rates of recurrence following total resection and the modest rates of progression following subtotal resection. No clear benefit exists for routine surveillance neuroimaging after the initial post-operative MRI defines complete tumor removal. Conversely, early disease progression may be observed for those patients with partial tumor removal and close follow-up may be required. There is little data in the literature to support a specific schedule of surveillance neuroimaging for low-grade cerebellar astrocytomas of pilocytic or non-pilocytic differentiation. The literature remains diverse regarding the likelihood of disease recurrence or progression, and the experience at our centre has lead the senior author to adopt routine post-operative MRI followed by surveillance at 6 months, 18 months, 3 years, and 5 years. These recommendations definitely require validation in larger scale studies with even longer follow-up as the benign nature of these pathologies may make early conclusions about disease recurrence or progression spurious.

Limitations

The retrospective nature of this study and the prolonged period of time over which patients were identified required the NMS ratio to normalize outcomes between variable protocols used by different neurosurgeons in this work. No patients were excluded for incomplete chart information, though duration of the study may introduce treatment bias from evolving adjuvant chemotherapy and radiotherapy. Further work must include expanding the scope of this analysis to wider range of tumor types with more variable aggression to evaluate the validity of the NMS ratio in comparing surveillance neuroimaging strategies.

In conclusion, the results of this study support that pediatric patients with either pilocytic or non-pilocytic cerebellar astrocytomas who have undergone gross and radiologic total resection may not benefit from routine surveillance neuroimaging, primarily because of low recurrence likelihood. Those patients in whom subtotal resection is obtained are expected to benefit from surveillance of the residual disease, with two-thirds in this series requiring further surgical intervention after a median of three surveillance studies. The benefits of developing a more stringent surveillance program following complete resection of low-grade astrocytic tumors include more cost-effective health care delivery and lesser exposure of pediatric patients to general anesthesia. However, if such strategy is to be implemented, then thorough clinical examination at follow-up is mandatory to raise suspicion of disease recurrence.

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