Low rates of recurrence and slow progression of pediatric pilocytic astrocytoma after gross-total resection: justification for reducing surveillance imaging

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OBJECTIVE Pilocytic astrocytomas (PAs) are common brain tumors in children. Optimal management of PA is gross-total resection (GTR), after which event-free survival (EFS) is excellent. The tempo of recurrences, when they do occur, is relatively sparsely reported, and there is no agreed upon surveillance recommendation for patients in this category. It has been suggested that surveillance MRI is performed too frequently and could be safely reduced in both frequency and duration. The authors conducted a retrospective review of pediatric patients with PA who underwent GTR at a single institution over an 18-year period and who had documented recurrences.

METHODS All patients under 18 years of age who had undergone GTR of a PA between 1996 and 2013 were included in the study. Clinical, radiological, and tumor characteristics were recorded.

RESULTS Sixty-seven patients met the criteria for GTR over the period studied. The 5-year EFS rate was 95% (95% CI 89%–100%) and overall survival was 100%. Recurrences showed a nonsignificant trend of occurring more commonly in patients with persistent nonenhancing FLAIR abnormalities after surgery, but there was no difference with regard to tumor location. All recurrences occurred before 3 years postresection, all were asymptomatic, and all patients were observed for at least one additional scan after the initial detection during routine surveillance MRI before further therapy was undertaken.

CONCLUSIONS EFS and overall survival are excellent after GTR in this population with PAs. Progression after recurrence occurs slowly and is asymptomatic. A less intensive schedule of MRI surveillance in this group of patients would result in time and cost savings, without compromising safety. The authors suggest a schedule of 6 MRI scans to be obtained postoperatively, at 3–6 months, then at 1, 2, 3.5, and 5 years.

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years and at clinician discretion thereafter. This regimen probably over-utilizes resources for a low-risk group of patients. We report the experience at our institution over the past 18 years in the treatment of 67 consecutive pediatric patients with PA in whom GTR was achieved.

Methods

All patients (age 0–18 years) at our institution who were diagnosed with PA between 1996 and 2013 were identified, and the relevant clinical, diagnostic, and treatment data were abstracted from the clinical record. The review was conducted with the approval of the institutional ethics review board. We identified patients who underwent surgical treatment alone and for whom recorded MRI scans, follow-up, and recurrence data were available.

GTR was defined by the radiologist report as the absence of enhancing nodular elements and was determined on the immediate postoperative MR scan or, if there were elements present that could represent residual disease, on the subsequent scan. We recognize that on some postoperative scans, postsurgical change can be difficult to differentiate from residual disease.

The information obtained for our cohort was used as an independent data set on which the proposed reduction in surveillance by Kim et al.⁶ was tested. Statistical analysis was completed using the “survival” package (version 2.38–2) in the R language (version 3.1.3). A Kaplan–Meier analysis of survival was performed, and p values were generated using the chi-square test. Event-free survival (EFS) pertained to the time from surgery to the last MRI (censored) or time to MRI that showed categorical evidence of disease recurrence.

We performed a cost analysis for all patients with follow-up to at least 5 years by recording the total number of MRI scans obtained with and without general anesthesia (GA) for all patients with this length of follow-up. The cost of MRI scans and GA was obtained using the government rebate provided to the hospital, and the cost analysis per patient and per event was calculated.

Results

A total of 268 children aged 0–18 years were diagnosed with low-grade gliomas at our institution over the 18-year period from 1996 to 2013. Of these, 69 patients had histology consistent with PA and met the criteria for GTR outlined above. Two children were excluded as they had adjunctive therapy after resection. One of these patients showed evidence of metastatic disease and was started on chemotherapy after resection. The other patient had a tumor that exhibited some concerning histological features and was started on radiotherapy. The remaining 67 patients (37 males, 30 females) were included in the review and had a mean age at diagnosis of 6.9 years (range 1–16 years); 58 patients had posterior fossa tumors, and 9 patients had supratentorial tumors.

There were 3 recurrences throughout the period studied, yielding a 5-year EFS rate of 95% (95% CI 89%–100%) (Fig. 1). Progressions occurred at a mean of 23 months from diagnosis (range 9–33 months) and all were asymptomatic at the time of detection. Recurrences in all 3 patients were detected on routine surveillance MRI, and all recurrences were observed for between 2 and 4 subsequent MRI scans over a period of 6–15 months for evidence of ongoing progression before second-line therapy was employed. Recurrences in 2 of the patients were treated with chemotherapy and in the third patient by radiotherapy; none of the patients underwent further resection.

The overall survival rate of the cohort was 100%. There was no difference in recurrence rate with regard to tumor site (p = 0.37). Six children initially had contrast-enhancing tumors and had persistent nodular FLAIR signal (non-enhancing) in the postoperative period, one of whom later had a recurrent tumor; however, there was no statistically significant association between persistent FLAIR signal and an increased risk of recurrence in this series (p = 0.194) (Fig. 2).

Thirty-three patients had follow-up to at least 5 years from diagnosis. A total of 399 MRI scans were acquired in these 33 patients (mean 12 scans per patient [range 7–20 scans]), with 102 of the scans carried out under GA. Only 1 of 33 patients experienced recurrence. All of the MRI scans were government funded at a cost of AU $450 per scan or AU $584 for a scan performed under GA. The total cost for this cohort was AU $193,218 (AU $5855 per patient), which detected only 1 recurrence. Under a more restricted schedule, as suggested by Kim et al.,⁶ the cost would be substantially reduced to AU $2700 per patient without GA or AU $3504 per patient where GA is required. Assuming, as demonstrated in this cohort, that approximately one-quarter of MRI scans are acquired under GA and assuming an EFS rate of 95%, the cost per event detected would be AU $58,020.

Discussion

In a large cohort of patients with PA who had GTR confirmed by MRI, we have demonstrated an excellent 5-year EFS rate of 95% and no deaths. This figure concurs with large prospective studies from Europe and North America, which showed EFS rates of between 85%⁴ and 93%⁹ for
up to 8\textsuperscript{9} to 10-year\textsuperscript{4} follow-up. Based on the findings, current surveillance MRI procedures are too intensive, resulting in higher health care cost as well as inconvenience for patients and families. This becomes even more important considering the recent literature on cumulative gadolinium deposition in CNS structures over multiple MRI scans,\textsuperscript{5} and concerns about exposure to multiple episodes of GA\textsuperscript{3} in early childhood for those patients who require it for accurate scanning.

The schedule suggested by Kim et al.\textsuperscript{6} consists of a contrast-enhanced MRI brain scan in the immediate postoperative period and at 3 months, followed by scans at 1, 2, 5, and 10 years from diagnosis. There was 1 case of late relapse in their cohort, but it has been shown in many other series that although late relapse occurs, it is rare.\textsuperscript{4,5,10} If it does occur, there is no particular reason it would occur at or around the time when a 10-year postdiagnosis scan would detect it. Had the suggested schedule been applied to our patients, the average latency of detection of recurrence would have been 21 months (range 3–34 months).

We believe that the interval between the 2- and 5-year scans offers much greater value in terms of recurrence detection. One-third of the recurrences in the Kim et al. cohort occurred in this time period, and 2 of 3 recurrences in our study also occurred between these times. We propose a slight modification to their suggested schedule, with scans in the immediate postoperative period, at 3–6 months postoperatively, and at 1, 2, 3.5, and 5 years postoperatively. Patients with very late relapse will only be detected when clinical symptoms become apparent, which would likely be the case if using the Kim et al. schedule.

Should our suggested schedule be applied to our cohort, the average latency of detection compared with the current scanning protocol would be 8 months (range 3–16 months). All of our patients were observed for at least one additional scan before instituting further therapy, and the latency in adopting our suggested schedule would have exceeded the observation period for our patients in only 1 patient, and then by less than 6 months. The potential clinical impact of this latency is unknown. Although some have advocated no surveillance for PA after GTR,\textsuperscript{2} this practice has not been widely adopted, and we believe that reducing, rather than eliminating, surveillance may be more palatable for clinicians and families.

It has been suggested that persistent FLAIR signal in the postoperative period may be a predictor of recurrence.\textsuperscript{6} In our cohort, the association was not statistically significant (p = 0.194), but the patient numbers were small. There is some difficulty in determining what constitutes a GTR. Before the routine use of MRI, a surgical report of the extent of resection was the best available measure. This may have occurred with CT scan correlation, a modality not well suited for the purpose, particularly in the posterior fossa. Even where MRI is used, the hardware and software of MRI has improved considerably over time, which may have improved the sensitivity of detection of residual disease.

The EFS in our cohort is higher than that reported in other series.\textsuperscript{4,6} The most likely reason for this is that the criteria for categorizing surgery as GTR in our series were relatively strict. There is frequent difficulty in interpreting immediate postoperative scans in light of postsurgical changes. To meet criteria for GTR in our series, if there was any question that residual disease may be present in the immediate postoperative scan, a further scan demonstrating no enhancing residual tissue was required before inclusion in the series. This all but eliminates the recurrences detected less than 6 months after resection described in other series. As discussed earlier, before the routine use of MRI, the sensitivity for detecting residual disease was significantly lower, which may be responsible for the higher recurrence rates noted in older series.

There are some potential limitations of our study. There was no central review for radiology or pathology, which may interfere with the accuracy of classification. Our record capture methods have ensured a complete data set, so selection bias is unlikely, and the study is not prone to recall bias. Transfer bias is possible but seems unlikely as relapse is unlikely to be related to adherence with recommended follow-up programs. The extremely small number of recurrences limits the ability to comment on predictors of recurrence with any certainty. Lastly, our series captures patients who had resection only and specifically excluded children who had adjunctive therapy. Since there were only 2 children excluded for this reason, neither of whom are representative of the group for whom reduced surveillance would be appropriate, this is unlikely to influence the results.

Conclusions

We report a large series of patients with PAs in whom GTR has been achieved. The cohort had a very low rate of progression, and all progressions in the series were first detected before 4 years. All progressions were detected on surveillance MRI scans, with no clinical symptoms apparent, and all were observed for at least one additional scan before receiving further treatment. This suggests that recurrences after GTR are rare and progress slowly.
We concur with the recommended schedule of surveillance MRI suggested by Kim et al., with the slight alteration of omitting the 10-year scan and replacing it with a scan between 3 and 4 years after resection. Adopting this schedule will result in significant time and cost savings for this group of patients at very low risk of tumor recurrence, while preserving their safety.

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References

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