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The role of reoperation in pediatric cerebellar pilocytic astrocytoma

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OBJECTIVE Cerebellar pilocytic astrocytomas (cPAs) in childhood have long been recognized to have a good prognosis after total resection, but the outcome after incomplete resective surgery remains largely unpredictable, with the incidence of radiological progressive disease ranging from 18% to 100%. It has been traditionally thought that gross-total resection was required for long-term survival, and small residuals were classically resected in a subsequent operation.

METHODS The authors analyzed their pediatric low-grade glioma (PLGG) database for cases treated between 1985 and 2020 and filtered for intracranial PAs, to determine what clinical or radiological factors precipitated revisional resective surgery in their single quaternary care center cohort.

RESULTS Using the pediatric low-grade glioma database, 283 patients were identified to have a histopathological diagnosis of intracranial PA between 1985 and 2020, of which 200 lesions were within the cerebellum (70.7%). The majority of patients with cPA were between 1 and 10 years of age (n = 145, 72.5%) without gender predominance (M/F = 99:101), usually presenting with 1 lesion (n = 197, 98.5%). Gross-total resection was achieved in 74.5% (n = 149) of initial surgeries for cPA. In patients with subtotal resection, the mean largest diameter of the postoperative residual tumor was 1.06 cm (range 0–2.95 cm). Seven patients with subtotal resection did not require a second resective intervention. In 31 patients the neuro-oncology multidisciplinary team recommended a second resection at a mean time interval of 22.9 months (range 0.13–81.6 months) from the initial surgery. Proportionally, the children who underwent multiple resections were also more likely to receive adjuvant chemo/radiotherapy. Functionally, the children in the multiple operation cohort experienced more complications of therapy including ongoing endocrinopathy, treatment-associated hearing deficit, and neurocognitive deficits.

CONCLUSIONS Residual disease in cPA should be maintained under clinicocoradiological surveillance postoperatively with adoption of a more conservative approach when residual disease is not significantly changing over time.

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KEYWORDS pediatric pilocytic astrocytoma; recurrent; residual; reoperation; oncology

Cerebellar astrocytoma in childhood has long been recognized as having a good prognosis after total resection,[1–8] but the final outcome after incomplete surgery remains largely unpredictable, with the incidence of radiological progressive disease ranging from 18% to 100%.[1,2,4,6–18] Symptomatic progression in pilocytic astrocytomas (PAs) that have been subtotally resected was much lower, however, ranging from 1% to 45%.[17,19] Surgery for PAs in the cerebral hemispheres or cerebellum resulting in gross-total resection (GTR) or subtotal resection (STR) can result in long progression-free survival (PFS) without further adjuvant therapy.[20] Tools to aid the pediatric neurosurgeon to achieve safe maximal resection of lesions have significantly evolved in recent decades, including intraoperative microscopes, image guidance, ultrasonography, and fluorescent tumor markers. For hemispheric cerebellar pilocytic astrocytoma (cPA), intraoperative MRI tended to leave less residual tumor and result in fewer reoperations.[21]

The prognosis for PA is very good, with a 10-year overall survival (OS) and PFS of 94% and 40%–44%, respec-

ABBREVIATIONS cPA = cerebellar pilocytic astrocytoma; GTR = gross-total resection; NF1 = neurofibromatosis type 1; OS = overall survival; PA = pilocytic astrocytoma; PFS = progression-free survival; PLGG = pediatric low-grade glioma; STR = subtotal resection.

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TABLE 1. Descriptive data of pediatric PA cohort

Description	All Patients, n = 283	cPA, n = 200
Age at Dx		
Mean age in yrs (SD)	7.41 (4.26)	7.14 (4.16)
<1	7 (2.5%)	2 (1.0%)
1–5	90 (31.8%)	70 (35.0%)
6–10	106 (37.5%)	75 (37.5%)
>10	80 (28.3%)	53 (26.5%)
Gender		
Female	142 (50.2%)	101 (50.5%)
Male	141 (49.8%)	99 (49.5%)
Dx of NF1	11 (3.9%)	5 (3.0%)
Total no. of lesions		
1	275 (97.2%)	197 (98.5%)
2	5 (1.8%)	2 (1.0%)
3	3 (1.1%)	1 (0.5%)
Tumor location		
Cerebral hemisphere	23 (8.1%)	0
Exophytic brainstem	33 (11.7%)	0
Cerebellum	200 (70.7%)	200 (100%)
Other, not otherwise specified	6 (2.1%)	0
Tectal plate	3 (1.1%)	0
Deep midbrain, thalamus/BG	16 (5.7%)	0
Disseminated disease at Dx	7 (2.5%)	0
Resection, excludes Bx only, n = 2*	261 (92.2%)	200 (100%)
Upfront primary resection	255 (97.7%)	200 (100%)
STR	70 (26.8%)	39 (19.5%)
GTR	185 (70.9%)	149 (74.5%)
Unknown	13 (5.0%)	12 (6.0%)
CSF diversion at presentation	37 (14.2%)	16 (8.0%)
CSF diversion after tumor resection	28 (10.7%)	10 (5.0%)

BG = basal ganglia; Bx = biopsy; Dx = diagnosis.
* Values may vary because of missing data.

tively.[22,23] These numbers highlight the principle that PAs represent a chronic lifelong disease with multiple potential recurrences.[1,9] Unfortunately, recurrent tumor growth is highly variable among patients with the same histological tumor subtype, and as many as one-third of individuals with partially resected cPAs show no sign of progression.[19] Tumor recurrence has been observed in 23%–40% of cases,[10,23] with 27% of residual growth[9] occurring within 5 years of the initial surgery.[23–25] Generally, progression after recurrence occurs slowly and is often asymptomatic,[24] leading some authors to suggest a less intensive schedule of MRI surveillance.[24] Although rare, recurrence after 25 years or more has been observed.[26–30]

Methods

We analyzed our pediatric low-grade glioma (PLGG) database for cases treated between 1985 and 2020, and filtered for intracranial PAs to determine what clinical or radiological factors precipitated revisional resective surgery in our single quaternary care center cohort. The initial data pull excluded optic pathway gliomas. In analyzing the study cohort, supratentorial, cervicomedullary, and brainstem PAs were excluded from the final analysis. Optic pathway gliomas were excluded from the cohort. Where data were limited, clinical data was extracted for surgical and radiological variables. In all cases, MRI was obtained within 72 hours of surgery.[31] GTR was defined as MRI-verified complete tumor removal on postoperative scans performed within 72 hours of surgery. Reoperation was defined as a further resective surgery (i.e., not including biopsy). Further treatment was defined as interval treatment to include reoperation, adjuvant chemotherapy, and/or radiotherapy.

Categorical variables were reported using counts and proportions and compared using the chi-square or Fisher test. Continuous variables were reported as the mean (SD or range as most clinically relevant) and compared using the independent samples t-test or Mann-Whitney U-test as appropriate. SPSS software (IBM Corp.) was used for analysis. Statistical significance was set at 0.05. Multivariate Cox regression analysis was conducted. A Kaplan-Meier analysis was performed for survival in the context of progressive disease.

Results

Pediatric PA Cohort

Within the PLGG database, over this period, 283 patients were identified who had a histopathological diagnosis of an intracranial PA. Their mean age was 7.41 years (4.26 years), with most children ≥ 1 year of age (97.5%), and there was no gender predominance. Optic nerve gliomas were excluded. A total of 97.2% presented with 1 lesion and 7 (2.5%) children presented with disseminated disease at diagnosis. Only 3.9% of the children with PA had a diagnosis of neurofibromatosis type 1 (NF1), and in the reoperation group only 1 patient had a diagnosis of NF1. This child had a residual tumor on the right cerebellar peduncle and medulla that progressed, requiring 1 further resection 2.5 years later—achieving a GTR with no residual at last surveillance scan 8 years later. Within the PA cohort, 200 patients' tumors were cerebellar in location (70.7%) (Table 1). Herein we will discuss with reference to the cPA cohort.

Pediatric cPAs

The 200 children within the cPA cohort had a mean age of 7.14 years (4.16 years) at diagnosis. All of these children were treated with a resective surgical procedure. In the children in this cohort presenting with 1 cerebellar lesion, GTR and STR was achieved in 149 (74.5%) and 39 (19.5%) children, respectively (Fig. 1). CSF diversion was required at presentation in 16 (8%) children and in a further 10 (5%) after tumor resection. After GTR, subsequent treatment was only required in 2 patients in the form of reoperation for a new progressing lesion within the resection cavity. In the STR group, however, proportionally more patients underwent further therapy in the form of reoperation (n = 29, 74.4%), chemotherapy (n = 4, 10.3%), and/or radiotherapy

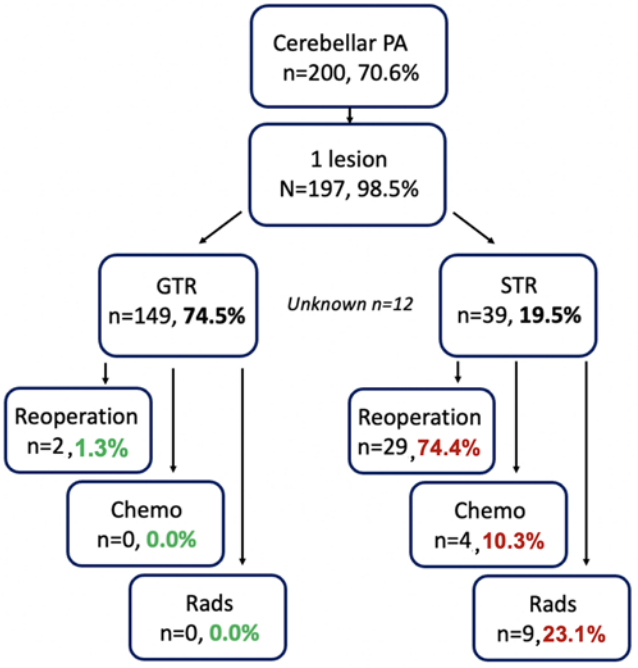

FIG. 1. Pediatric cPA cohort flowchart. Rads = radiation therapy. Figure is available in color online only.

(n = 9, 23.1%) (Fig. 1, Table 2). There was a significant difference between undergoing further treatment between the single and reoperation cohorts (Fig. 2).

Reoperation in cPA

Analyzing the multiple operation (i.e., reoperation) cohort further, it was observed that the majority (87.1%) underwent only 1 further resective procedure, with 4 (12.9%) undergoing a third resective operation (Table 3). In the entire reoperated cohort (n = 31), GTR was achieved in 9.7%, with the majority (74.2%) achieving varying degrees of STR, and with extent of resection unknown in 12. The location of the reresected residual was in the cerebellar hemisphere in 45.2%, whereas the remainder were sited in more eloquent areas including the fourth ventricular floor (16.1%), cerebellar peduncle (16.1%), and vermis (3.2%). The mean largest diameter for postoperative tumor residual after the initial surgery was 1.06 cm (0–2.95 cm). The second resective procedure was undertaken at a mean interval of 22.9 months (0.1–81.6 months). Seven patients with an STR after initial surgery did not require any further reresection surgery. The majority of second resective procedures were undertaken for either postoperative residual (38.7%) or significant growth of residual (38.7%) on interval imaging. Only 1 patient was deemed to be symptomatic for tumor residual (i.e., described as unwell after index STR procedure). The increase in mean diameter before the second operation as compared to the index postoperative imaging was 1.16 cm (0–4.71 cm). This second surgery achieved GTR in 19 (61.3%) of patients and STR in 11 (35.5%). A third resective operation was performed in 4 children at a mean time interval of 22.7 months for a mean change in residual size of 1.92 cm as compared to

TABLE 2. Outcomes for GTR versus STR in 200 patients with a single cPA

Description	GTR	STR
cPA w/ 1 lesion*	149/200 (74.5%)	39/200 (19.5%)
Proportion undergoing reop	2/149 (1.3%)	29/39 (74.4%)
Chemotherapy only	0 (0.0%)	4/39 (10.3%)
Radiotherapy only	0 (0.0%)	9/39 (23.1%)

* Including 12 unknown extent of resection in patients with a single cerebellar lesion (n = 197).

the imaging obtained after the 2nd operation. Extent of resection was GTR in all 4 cases. In the reoperation group, 8 of 31 (25.8%) historical children's notes did not have a pathology report available. Of the available reports, only 11 reported a Ki-67 immunoreactivity that was qualitative (all described as low) or miconducted.

Outcomes After cPA Resection and Reoperation

The mean follow-up was 186.4 months in all children with cPA and 172.9 months in children undergoing reoperation (Table 4). The 5-year and 10-year PFS was 0.71 and 0.67, respectively, in the entire cPA cohort as compared to 0.15 and 0, respectively, in the reoperation cohort. Three deaths occurred in our cohort. At 20 and 30 years after management of pediatric PA and after transition into the adult service, 1 patient at each time interval died of unknown causes, with no documentation found in the medical records. The remaining child died secondary to disease progression to gliomatosis cerebri 18 months after the debulking procedure and diagnosis. This child had presented initially with multifocal disease (3 lesions; i.e.,

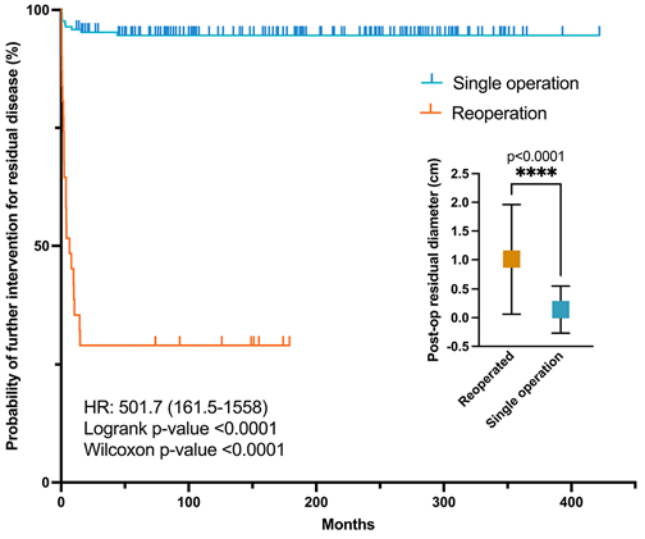

FIG. 2. Postoperative residual disease and likelihood of further intervention. Kaplan-Meier curve showing the probability of further intervention for residual disease and paired t-test showing significantly higher postoperative residual diameter in the reoperated cohort (n = 31, ****p < 0.0001). Excludes patients returning to operating theater shortly after index procedure for significant residual. HR = hazard ratio. Figure is available in color online only.

TABLE 3. Multiple resection cohort analysis of factors associated with decision to undergo subsequent resective treatment

Description	Multiple cPA Resection, n = 31
No. of reresections	
1	27 (87.1%)
2	4 (12.9%)
Surgical interventions	
Initial surgery	
STR	23 (74.2%)
GTR	3 (9.7%)
Unknown	5 (16.1%)
Location of postop residual	
Cerebellar hemisphere	14 (45.2%)
4th ventricular floor	5 (16.1%)
Cerebellar peduncle	5 (16.1%)
Vermis	1 (3.2%)
Unknown	5 (16.1%)
Mean postop residual largest diam in cm (range)	1.06 (0–2.95)
2nd resective surgery	
Reason for reresection	
Significant growth of residual	12 (38.7%)
Significant postop residual	12 (38.7%)
Significant growth of new recurrent disease	3 (9.7%)
New enhancement of residual	1 (3.2%)
Not mentioned	3 (9.7%)
Symptomatic for tumor residual/progression	
Yes	1 (3.2%)
No	30 (96.7%)
Mean difference in size of residual in cm (range)	1.16 (0–4.71)
Extent of resection	
STR	11 (35.5%)
GTR	19 (61.3%)
Not mentioned	1 (3.2%)
Mean postop residual largest diam in cm (range)	0.23 (0–1.64)
Time from 1st surgery to 2nd resective surgery in mos (range)	22.9 (0.1–81.6)
3rd resective surgery*	
Reason for reresection	
Significant growth of residual	2 (50.0%)
Significant postop residual	1 (25.0%)
Clinical deterioration despite radiological stability	1 (25.0%)
Symptomatic of tumor residual/progression	
Yes	0 (0.0%)
No	4 (100%)
Mean difference in size of residual in cm (range)	1.92 (0–2.89)
Extent of resection	
STR	0 (0.0%)
GTR	4 (100.0%)
Mean postop residual largest diam in cm (range)	0.09 (0–0.36)
Time from 1st surgery to 3rd resective surgery in mos (range)	22.7 (3.8–61.3)

Diam = diameter.
Unless otherwise indicated, values are expressed as the number of patients (%).
* A third resective surgery was performed in 4 patients.

cerebellum, pons, and medulla) at the age of 2.1 years. She also had a *BRACA2* mutation, and received treatment with vincristine and carboplatin and with 54 Gy radiotherapy in 1.8-Gy fractions, followed by maintenance temozolamide. After extensive symptomatic disease progression, the child received palliative care to alleviate discomfort, nausea, and vomiting, passing away peacefully at home in the presence of her parents.

Functionally, from the limited data available, treatment-induced hearing loss, endocrinopathy, and neurocognitive deficits were proportionally more frequent in the cohort with multiple cPAs. Excluding the children who received biopsy only (n = 2), 19 children were managed with adjuvant therapy—with 3, 14, and 2 children receiving chemotherapy only, radiotherapy only, and chemoradiotherapy, respectively. Proportionally more children in the chemoradiotherapy cohort (i.e., endocrinopathy 50%, hearing deficit 50%, neurocognitive deficit 50% [1 death]), followed by radiotherapy only (i.e., endocrinopathy 57.1%, hearing deficit 14.2%, neurocognitive deficit 50%) and chemotherapy only (i.e., endocrinopathies 33.3%, hearing deficit 0.0% [neurocognitive deficit not assessed in this cohort]) groups developed treatment-related endocrinopathies, hearing deficits, and neurocognitive deficits. Both children receiving chemoradiotherapy presented with 3 discrete lesions, with the largest lesion located in the cerebellum. No significant difference was observed between the 5-year and 10-year OS between all cPA and multiple reoperation groups.

TABLE 4. Clinical outcome of posterior fossa cPA

Description	All Patients w/ cPA, n = 200	Multiple cPA Resections, n = 31
Mean FU duration in mos (SD)	186.4 (104.9)	172.9 (102.5)
5-yr PFS	0.71	0.15
10-yr PFS	0.67	0.00
Mean PFS in mos (SD)	32.4 (30.8)	27.9 (25.2)
Neurocognitive effect of treatment		
Treatment-induced hearing loss	2 (1.0%)	1 (3.2%)
Endocrinopathy	5 (2.5%)	3 (9.7%)
Attended mainstream school	191 (95.5%)	27 (87.1%)
Highest educational achievement		
GCSE	1 (0.5%)	0
A-levels	5 (2.5%)	0
Undergraduate degree	10 (5.0%)	3 (9.7%)
Postgraduate degree	0	0
College course/diploma	4 (2.0%)	0
No formal qualifications	1 (0.5%)	0
Not available	180 (90.0%)	28 (90.3%)
Neurocognitive deficiency	21 (10.5%)	8 (25.8%)
OS		
Mean FU in yrs (SD)	15.6 (8.6)	14.4 (8.5)
Dead	3 (1.5%)	1 (3.2%)
Mean time from Dx to death in mos (SD)	189.3 (173.0)	364
Mean age at death in yrs (SD)	17.7 (13.6)	30
Cause of death		
Disease progression	1 (33.3%)	0
Malignant transformation	1 (33.3%)	0
Unknown	1 (33.3%)	1 (100.0%)
5-yr OS	0.99	0.97
10-yr OS	0.99	0.97

FU = follow-up; GCSE = General Certificate of Secondary Education.
Values may vary because of missing data.

Discussion

Current Standard of Care for PLGGs

Management options in subtotally resected or progressive PLGGs include systemic chemotherapy, radiotherapy, surgery, and observation. Standard chemotherapeutic agents include carboplatin and vincristine, or vinblastine monotherapy.[32] Radiotherapy is typically reserved for children older than 5 years, to minimize the side effects of neurocognitive sequelae of ionizing radiation. After the second resection, some institutions offer radiation and/or chemotherapy to patients, with a small proportion experiencing progressive disease despite adjuvant therapy.[25] Risks associated with recurrence or tumor progression were extent of resection, invasion of eloquent tissue as evaluated on T2-weighted MRI scans, predominantly solid lesions, presence of an exophytic component, opticochiasmatic location, and pilomyxoid variant.[17,23,33–35] Furthermore, complete removal of the cystic lesions has been controversial, although the outcome in cystic tumors was not significantly different between GTRs and STRs.[8]

Reoperation in Posterior Fossa PAs

Large case series of pediatric posterior fossa astrocytomas report repeat surgery in 9%–36%[25,36,37] of patients due to progressive tumor recurrence, with time to secondary resection ranging between 1 month and 10 years, with an even smaller cohort (2%–28.5%) undergoing a third resection.[10,36] Some authors report second-look surgery in patients whose initial resection was partial, at rates of 40.9% of their STR subgroup or 15.8% of their total cohort.[35] In Austin and Alvord's series in 1988,[10] 19/21 recurrences were treated surgically. In the literature there is a trend for higher thresholds for reresection with increasing understanding of the indolent biological behaviors of the majority of PAs. Recurrence after GTR ranged between 5.7% and 5.9%,[17,35] with a PFS rate reported between 71.3% and 75%.[17,33] Furthermore, the 10-year PFS of cPA is 32% with adjuvant chemotherapy and 65% with adjuvant radiotherapy.[22] In our cohort, the finding of a 5- and 10-year PFS for the entire cohort was 0.71 and 0.67, respectively, as compared to the cPA multiple resections cohort's PFS of 0.15 and 0.00, respectively, suggesting that some patients experience an initial radiological progression after 5 years of surveillance. This observation has obvious implications for long-term surveillance. Given that this was a historical cohort dating back 35 years, genetic data were not available to determine whether there were lesions that were a more aggressive genotype than the majority of the cPAs requiring no further intervention. Moreover, lesions

involving the floor of the fourth ventricle or superior cerebellar peduncle, in patients undergoing multiple surgeries and adjuvant therapy, may represent a biologically distinct (i.e., brainstem interface) or difficult to resect group of tumors, requiring adjuvant therapy.

Clinical Outcome of cPAs

In the literature, the OS in surgically resected cPA has been reported to be 92.6%–100%.[38] The 10-year OS in our entire cohort and for the reoperated cerebellar was 0.99 and 0.97, respectively, in keeping with the international experience. Because we have yet to identify subgroups within cPA that will progress and behave with a more aggressive phenotype, there is an understandable trend for neuro-oncology multidisciplinary teams to pursue a policy of GTR wherever possible. In our series, tumor residuals were commonly identified in the postoperative scans at the interface of the brainstem (i.e., floor of the fourth ventricle, superior cerebellar peduncle) and the superior anteromedial border of the resection cavity. Although changes in radiological appearance occurred either as an interval increase in size or in enhancement pattern, we reassure the reader with our large cohort series that, similarly to Gorodezki et al., we observed a subset of patients (i.e., 12.9% of children undergoing one operation received adjuvant therapy in the form of focal radiotherapy only to the residual tumor [n = 5] or chemotherapy only [n = 4]), with smaller residuals undergoing regression on interval imaging, corroborating these authors' residual tumor senescence hypothesis.[39] In fact, radiographic follow-up has revealed arrested growth in 16%–45% or spontaneous regression of benign cerebellar astrocytoma remnants in 14%–42.8% of cases in the literature.[9,11,14,17,19,40–42] Moreover, in one series of 4 patients, residual tumors involving the brainstem did not show tumor enlargement or progression in up to 6 years of clinicoradiological follow-up,[25] providing further evidence of the indolent natural history of tumor residuum in many cases. One Canadian report cited a history of cannabis smoking with regression of a histologically proven tumor residual.[43] Death of recurrent disease has been reported to be as high as 29.4% at 2–38 years after initial resection[19]—although this was not our institutional experience, with a 10-year OS of 99%.

On balance, a less aggressive watch and wait approach with clinicoradiological follow-up will identify the children likely to require additional input from specialty neuro-oncology multidisciplinary teams. Whereas traditionally our group undertook a more aggressive approach to cytoreduction of disease burden, this cohort demonstrates the need for a more conservative approach with residual and recurrent tumors. Given the excellent OS for cPA, the onus is now on clinicians to ensure that future management paradigms appropriately prioritize functional outcome along with radiological complete resection.

Conclusions

When a GTR is achieved after the index surgery, it is unlikely that any further treatment will be required. However, residual disease in cPA should be maintained under clinicoradiological surveillance postoperatively, following a more conservative approach when residual disease is not significantly changing over time.

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Author Contributions

Conception and design: Kameda-Smith, Green, Jeelani, Aquilina. Acquisition of data: Kameda-Smith, Green, Hutton, Hargrave. Analysis and interpretation of data: Kameda-Smith, Thompson, Aquilina. Drafting the article: Kameda-Smith, Thompson, Aquilina. Critically revising the article: Kameda-Smith, Jeelani, Thompson, Hargrave, Aquilina. Reviewed submitted version of manuscript: Kameda-Smith, Green, Hargrave, Aquilina. Approved the final version of the manuscript on behalf of all authors: Kameda-Smith. Statistical analysis: Kameda-Smith. Administrative/technical/material support: Kameda-Smith, Aquilina. Study supervision: Aquilina.

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