Title: Extent of resection predicts risk of progression in adult pilocytic astrocytoma

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Abstract

Object Pilocytic astrocytomas are rare tumours in adults. Presentation, management and prognostic factors are poorly characterised. ***Methods*** Retrospective single centre study from 2000 - 2016. ***Results*** 50 cases were identified (median age 29 years; range 16–76). Symptoms at presentation were neurological deficit (n=21), headache (n=18) and seizures (n=6). Five were incidental findings. Five patients had hydrocephalus at presentation and required emergent management, two by endoscopic third ventriculostomy and three by external ventricular drain. Symptoms were present for a median of 16 weeks (range 1 week to 34 years). Surgery consisted of gross total resection (n=23), subtotal resection (n=21) or biopsy (n=6). Progression occurred in 20 patients at a median time of 7 years following surgery and was asymptomatic in just over half of these cases. A greater degree of resection (complete vs. subtotal) was associated with longer time to progression (Kaplan-Meier analysis, log rank test = 3.58, p=0.059). At their first progression 12 patients underwent re-resective surgery and the remainder received radiotherapy. The median 5-year survival was 80%. ***Conclusions*** In adult patients with a pilocytic astrocytoma, a macroscopic resection should be the aim at the first resective operation. Emergency management of hydrocephalus may be required in the first instance.

Key words: Pilocytic astrocytoma, adult, outcome, resection, hydrocephalus

Introduction

Pilocytic astrocytoma is the most common childhood glioma but is infrequently seen in adults. They are described by the 2016 WHO Classification of Tumours of the Central Nervous System as borderline benign/malignant entities with uncertain behaviour patterns [7,11,12]. Derived from neuroepithelial tissue these astrocytic tumours are assigned grade I status

to denote their well circumscribed nature [11]. They tend to be slowly growing, cystic and preferentially located in cerebral midline structures such as the cerebellum, hypothalamus, brain stem and optic pathways [11]. Histologically they are characterised by a biphasic pattern with varying proportions of compacted bipolar cells with Rosenthal fibres and loose textured multipolar cells with microcysts and granular bodies [3]. Whilst surgery may be curative, complete resection is not always feasible and due to the relative rarity of this disease in adults, there are few publications on the most effective management strategies and subsequent patient outcomes [7,19]. The aim of this study was to investigate the clinical presentation, management and outcomes in adults with pilocytic astrocytoma.

Methods

Patients with a diagnosis of pilocytic astrocytoma were identified from histopathology records at a single institution. The histology was classified according to the WHO criteria in use at the time of diagnosis. Patients aged over 16 years are treated at the adult service in our region and therefore such patients treated between January 2000 and February 2016 were included. Medical records, operative notes, imaging reports and correspondence were examined and data gathered on age, gender, presenting symptoms and neurological signs. Tumour location, size and presence of hydrocephalus were determined from computed tomography and magnetic resonance imaging scans. Surgery, indication and extent of resection were obtained from the operative notes and post-operative imaging. Extent of resection was categorised as gross total resection, subtotal resection or biopsy. Patient management and adjuvant therapy was discussed at weekly multidisciplinary tumour meetings (or tumour boards). Complications were recorded from medical notes.

Tumour progression was defined radiologically by RANO criteria and confirmed clinically by review and discussion at MDT. Progression free survival (PFS) was measured as time

from diagnosis to first progression and overall survival (OS) was taken as time from diagnosis to tumour death. Cases where the patient died before progression were censored at the last brain scan and those who were lost to follow up or died of other causes were censored at the last clinic appointment recorded. Data were analysed using SPSS version v22 (IBM co., 2011). For analysis of PFS and OS, the Kaplan-Meier product limit method was used and survival curves plotted. Log rank tests were applied to detect differences between paired groups. For multivariate analysis Cox's method was used to compare competing hazards. Standard tests were used for comparisons of means and analysis of variance. The level of significance was set at 95% to reject the null hypothesis and all p-values and confidence intervals are stated.

Results

Presenting features

Fifty patients were identified with a median age of 29 years (range 16–76). There were 29 male and 21 female patients. Symptoms at presentation were neurological deficit (n=21), headache (n=18), seizures (n=6) and five were incidental. Five patients had hydrocephalus at presentation and required emergency management, two by endoscopic third ventriculostomy (ETV) and three by external ventricular drain (EVD). Symptoms were present for a median of 16 weeks (range 1 week to 34 years). Tumours were located in cerebellar hemisphere (n=14), intraventricular (n=13), brainstem (n=10), lobar (n=9) and hypothalamus (n=4).

Surgical treatment

Surgery consisted of gross total resection (GTR) (n=22), subtotal resection (STR) (n=20) or biopsy (n=8). No hypothalamic tumours and only one brainstem tumour underwent GTR

although there was no statistical association of location with degree of resection (Fisher's exact test 17.8, p = 0.324). Surgical complications included three cases of transient neurological deficits (two upper limb weakness and one 6th nerve palsy) and two permanent neurological deficits (one permanent loss of visual acuity, one permanent cognitive impairment). Other surgical morbidity included two superficial and four deep wound infections which required antibiotic treatment and 5 CSF leaks that required suturing but not temporary or permanent CSF diversion. Patients with permanent neurological deficit were significantly older (t-test 2.08, p=0.043) at the time of surgery but had not had more extensive resection (Fisher's exact test 2.48, p=0.292) nor were their tumours in different locations (Fisher's exact test 3.60, p=0.774) compared to those with no complications.

Adjuvant therapy

All 22 patients who underwent GTR were observed with serial MRI scans at 6-12 month intervals at the operating neurosurgeon's discretion. None of these patients received adjuvant post-operative radiotherapy or interstitial radiosurgery. After biopsy or subtotal resection the decision to treat with adjuvant radiotherapy was made by the neuro-oncologist after multidisciplinary discussion based on imaging findings, patient's performance status and age. Of those 28 patients, 18 were monitored with 6-12 monthly MRI as for gross total resection cases and six received fractionated radiotherapy (50 - 54 Gy in 30 fractions). Three patients were treated with interstitial radiosurgery by iodine-125 seeds inserted at the time of biopsy (one seed with activity of 9.4mCi to cover the tumour with 60Gy isodose line implanted for 14 days, one seed of 14.2mCi to cover the tumour with 60Gy isodose and one with regime not specified but likely to be similar).

Progression and survival

Tumour progression occurred in 20 patients at a median of 7 years (95% CI 4.5 – 9.5) following surgery (Figure 1a). Only 4 of the 22 patients who underwent GTR progressed, at a median of 1 year (maximum of 3 years) following surgery. By comparison 12 of 20 patients who underwent STR progressed at a median of 7 years for those who received adjuvant radiotherapy versus 5 years for those who were simply observed. GTR was associated with a trend to longer progression free survival (PFS) than STR although this did not reach significance (Kaplan-Meier analysis, log rank test = 3.58, p=0.059), illustrated in figure 1b. Post hoc we further divided the STR group by assessment of the available post op scans, MDT reports and operation notes into two groups, dependent on how much residual was left, >25% of the original tumour (n=10) or <25% (n=7). There was no significant difference in PFS between these subgroups (log rank test = 1.49, p = 0.222) although both had significantly longer PFS than biopsy cases (p=0.022 and 0.005 respectively). Even dividing STR into just two subgroups there were only 3 events (the rest were censored) in one group so further subdivision of this category was not deemed statistically justified. Of the other factors assessed, age (HR=1.02, p=0.557), tumour location (pooled log rank = 3.864, df = 6, p = 0.695) and adjuvant therapy (pooled log rank = 0.96, df = 2, p=0.619) were not significantly associated with PFS after surgery. For those patients receiving biopsy only, interstitial radiosurgery at the time of biopsy was not associated with the incidence of progression (Fisher's exact test 1.494, p=0.51).

At first progression, seven patients who had undergone STR or biopsy at their first presentation, including two who had received adjuvant radiotherapy, underwent resection then observation with serial scans. Three were originally STR but achieved GTR and three were originally biopsy but achieved STR (with at least 75% tumour resection looking at the imaging). In this group there was one patient with a major surgical complication (intraventricular haemorrhage and permanent neurological deficit) and three with minor

complications (wound leak, infection, and hospital acquired pneumonia). Five patients who had undergone GTR or STR followed by observation at their first presentation underwent a further subtotal resection to the progressive tumour followed by fractionated radiotherapy (54 Gy / 30#). There were no major surgical complications in this group, minor complications were wound infection and DVT. One patient did not receive adjuvant radiotherapy because of tumour proximity to the optic nerve. One patient's treatment after progression was unknown as surgery was performed elsewhere.

Two patients who had undergone biopsy and interstitial radiosurgery and one who had undergone biopsy only went on to have a further biopsy (to confirm no change in histology) and interstitial radiosurgery with radioiodine seeds when they progressed and one of those developed radiation necrosis. One patient with STR initially who then progressed rapidly had radiotherapy (50.4 Gy in 28 #). One patient underwent palliative shunt insertion and was not fit for further therapy.

Second progression occurred in four patients out of 20 at a median of 1 year from their first progression and only two of these went on to have another craniotomy. Patient flow is seen in Figure 2. The 5-year overall survival for this series was 80%; median follow up varied greatly and was 3.5 years in the whole cohort (range 0 – 21 years) but 4 years (range 0 – 12 years) in the group with GTR at first operation

Discussion

Introduction – presentation/symptomatology/tumour location

Pilocytic astrocytomas are benign tumours, occurring mainly in children, which have the potential for cure. They are described pathologically as as exhibiting nuclear

abnormalities in all cases and endothelial proliferation in many and are World Health Organisation (WHO) grade I [2,12]. Adults are also affected, and previous reports demonstrate a median adult age of 31 years[7,8,17], similar to our series. More males than females develop the tumour[7,8,17]. Presentations of headache and or incidental finding predominate in the current study rather than previous series which report neurological deficit[7], which may be due to the increased availability of MRI, and the drive for earlier scanning in patients with potential symptoms of a brain tumour [4,6]. They are typically T2 hyperintense enhancing nodular lesions in the cerebellum or periventricular area[18].

Tumour location dictates the surgical strategy and the extent of resection that can be achieved. Complete resection is difficult in some locations, particularly deep midline locations, so may promote the use of non-invasive or less aggressive interventions [19]. Tumours in the cerebellar hemisphere and intraventricular regions predominated, although previous studies have described cerebral lobes, brainstem, and spinal cord[8]. The current study excluded spinal cord tumours.

Therapeutic intervention

Pilocytic astrocytoma is amenable to a range of therapeutic interventions including surgery, radiotherapy and chemotherapy, yet there are no randomised trials and allowing for the idea of maximal safe resection, there is little consensus on how they should be employed to ensure optimal patient outcomes. The emergency management of hydrocephalus may be required in the first instance, but once stable, the present study suggests that the best outcomes for patients are obtained with complete resection. Use of image guidance, Multidisciplinary Team Meetings (MDT or tumour boards) to aid in surgical decision making, intraoperative ultrasound and / or intraoperative MRI by surgeons routinely performing cranial oncology surgery should be considered[20]. If residual disease is found on an early post op scan, early

reoperation should be considered as long as surgical risks allow. Otherwise, patients with residual disease may be observed, and only offered radiotherapy or radiosurgery after evidence of progression [2]. Defining the degree of residual disease is problematic and we found disagreement depending on sequences and techniques used. We therefore binned surgical treatment into only 3 categories: gross total resection, subtotal and biopsy. Ideally, some formal regime of imaging would allow comparison of pre and post-operative enhancing tumour volume and the volume of tumour resected should be calculated in order to characterise the relation of degree of residual to progression and survival. This is particularly useful if there is a cut-off past which the risk of progression greatly increases.

Operative risks are higher at surgery following progression. Few repeat surgeries achieve complete resection (although a small number did here for reasons that are not discernible by retrospective review only), and most ultimately have radiotherapy[7]. Previous authors have suggested that fit individuals should be offered appropriate salvage therapies in anticipation of long term survival and proven good neurological outcomes[1,7], although the current series suggests interventions on those who progress are relatively unsatisfactory. As most patients are observed, and radiation treatment reserved for progression, reports on the outcome after radiotherapy are rare and include only small numbers of patients. Adjuvant radiotherapy as first line treatment is reported as significantly increasing progression-free survival rates over observation alone, although overall survival is not altered [7,10]. Malignant transformation following radiotherapy of pilocytic astrocytomas is reported [5,15,17]. The role of chemotherapeutic agents, proton beam therapy, and other newer novel treatments is not clear.

Overall survival

Five and 10 year progression free rates of 63% and 35% and overall survival rates 95% and 85% respectively are reported[13 7]. The current study reports a slightly lower 5-year survival of 80% possibly reflecting differences in demographics, therapeutic interventions, and the fact that advances in medical technology and practice occurring over large study time frame may confound data. Long term follow up beyond that reported in the recent SEER database study confirms that recurrence after 10, 15 or 20 years is rare[8] therefore it is argued that if there is no residual enhancing disease at 5 years after complete resection then patients can be safely discharged; this study confirms this is problematic in practice and many patients in this series were followed up for longer than this, up to a maximum of 12 years even after GTR.

Future directions

Molecular tumour charecteristics are being developed. Standardized assessment of proliferating cell nuclear antigen (PCNA) to investigate tumour cell growth kinetics in pilocytoc astrocytomas may be a useful, independent indicant of biological behaviour [14]. Whole genome interrogation has shown single point aberrations of the mitogen-activating protein kinase (MAPK) pathway in nearly all cases[9]. The most commonly observed mechanism gives rise to a transforming fusion protein with BRAF kinase domain[9]. Whilst not yet commonplace, array comparative genomic hybridization (aCGH) analysis is being used to identify a variety of novel, subtle genomic changes which may liberate clinically useful diagnostic and therapeutic biomarkers [16]. Although specific to supratentorial tumours, the histological characteristis of adult pilocytic astrocytomas are known to include nuclear abnormalities, mitoses and endothelial proliferation[2].

The importance of optimal pilocytic astrocytoma management in increasing patients' quantity and quality of life is clear. However there is an apparent lack of

progression/recurrence predictors and modern, consistent, authoritative evidence on the matter, especially in terms of histological or genetic factors and appropriate therapeutic interventions. As such, national, prospective, adult specific future clinical studies are warranted to determine the role of adjuvant radiotherapy and chemotherapy.

Conclusion

This single centre series supports the growing consensus that in adult patients with a pilocytic astrocytoma, a macroscopic resection should be the aim at the first resective operation and early second look surgery for any residual on postoperative imaging should be considered. Patients with no residual enhancing disease at 5 year follow up may be discharged but this does not appear to routinely happen in clinical practice.

Disclosure of interest

The authors report no conflict of interest concerning the funding, materials or methods used in this study or the findings specified in this paper. The study follows the principles of the Declaration of Helsinki.

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Figure 1a – Progression free survival plot

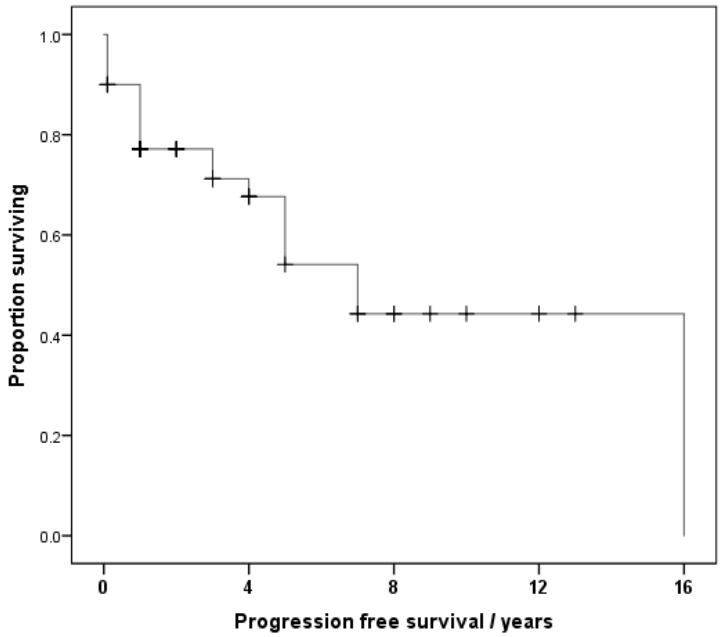


Figure 1b – Progression free survival plot by degree of resection

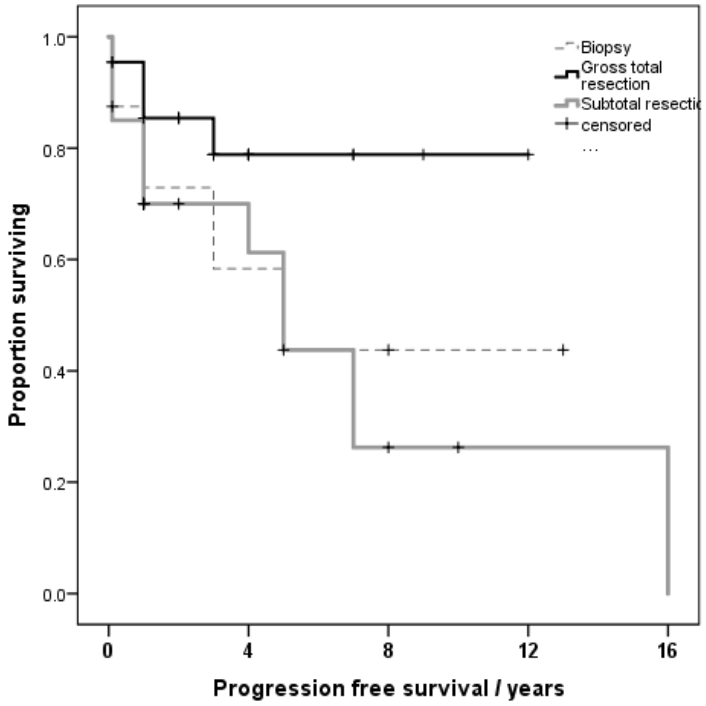
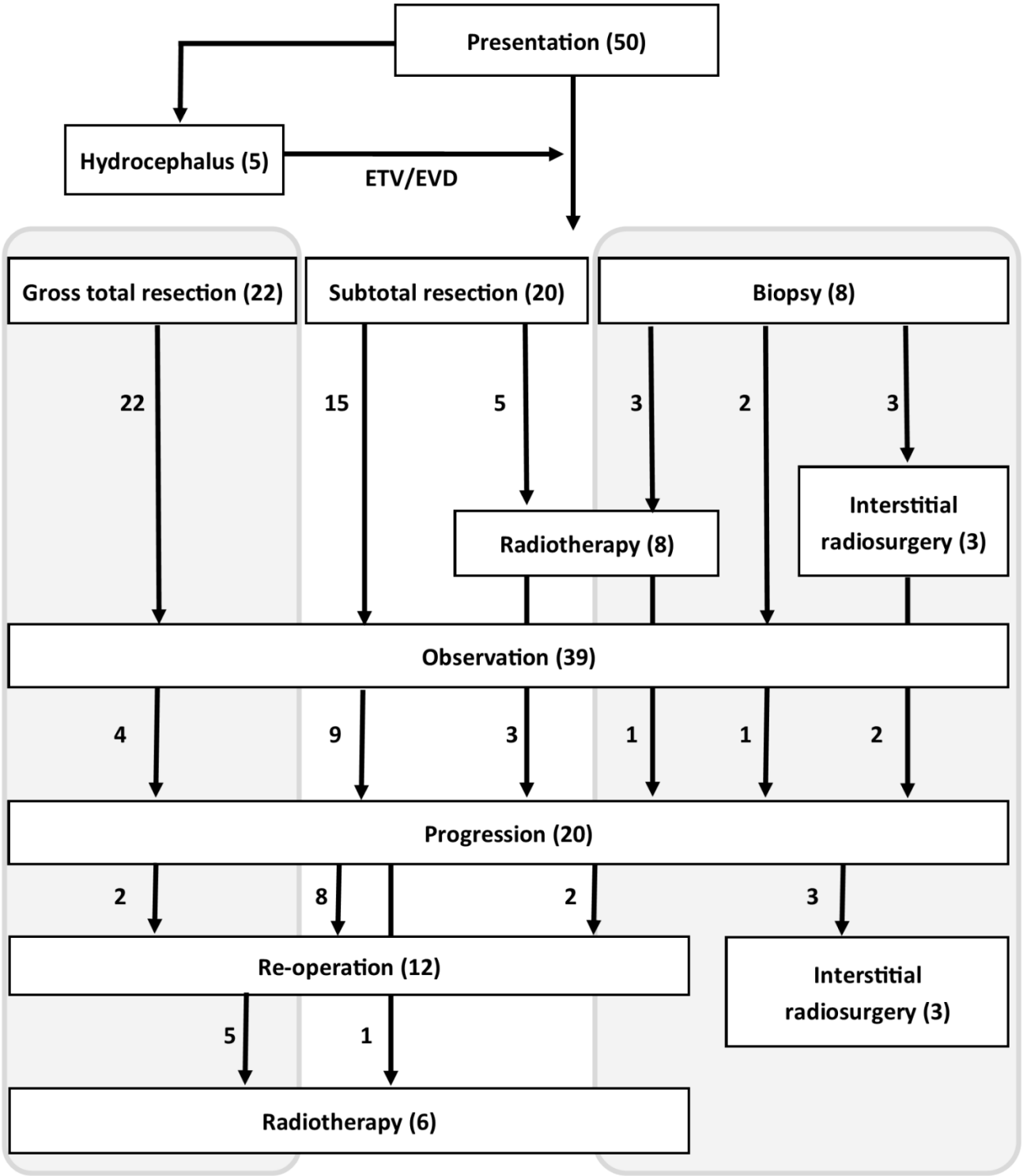


Figure 2 - Patient flow



ETV - *Endoscopic Third Ventriculostomy*

EVD - External Ventricular Drain