

Recurrent petroclival meningiomas: clinical characteristics, management, and outcomes

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Abstract This study seeks to elucidate the prognostic predictors and outcomes of recurrent/progressive petroclival meningiomas (PCMs). We reviewed our cohort of 39 recurrent/progressive PCMs (27 females, 69.2 %) and analyzed the results from the literature. Twenty-three patients underwent reoperations, 2 received radiotherapy alone, and 14 declined any treatment. During a follow-up of 70.4 months, 7 patients experienced a 2nd recurrence/progression (R/P) and 18 patients died. In the 23 patients, gross total resection (GTR), subtotal resection (STR), and partial resection (PR) were achieved in 8, 8, and 7 patients, respectively. The percentage of the 2nd R/P-free survival of GTR, STR, and PR was 88 %, 67 %, and 40 %, respectively. The overall survival following the 1st R/P of GTR, STR, and PR was 88 %, 63 %, and 33 %, respectively. Patients rejecting treatment suffered from significantly poor overall survival (7 %; $p=0.001$) and short survival duration (42.0 months; $p=0.016$) compared with that of the patients receiving treatment (67 % and 86.9 months). The GTR was the only independent favorable predictor. In the 21 included studies with 98 recurrent/progressive PCM patients, 17 patients presented with a 2nd R/P and 10 died of a 2nd R/P; patients undergoing observation had a significantly poor tumor regrowth control rate compared with patients undergoing surgery ($p=0.004$) or radiotherapy alone ($p<0.001$). Proactive treatment should be performed for patients with recurrent/progressive PCMs. Observation can lead to relentless outcome. GTR as a preferential therapeutic strategy should be pursued as far as possible on the condition of minimal functional impairment.

Keywords Meningioma · Petroclival region · Radiosurgery · Recurrence · Skull base

Introduction

Approximately 20 % of all primary intracranial tumors are meningiomas, of which only 2 % develop in the petroclival region [43]. Petroclival meningiomas (PCMs) were once considered to be inoperable, formidable, and technically challenging with tremendous surgical morbidity and mortality (>50 %) because of their deep-seated location, limited surgical exposure, and complex relationships between the tumor and neurovascular structures (Fig. 1) [68]. With the development of neuroradiography, microsurgical techniques, and electrophysiologic monitoring, desirable outcomes of surgically treated PCMs have been reported in several recent studies compared to studies published in the past few decades [12, 13, 17, 21, 26, 30, 35, 37, 44, 50, 51, 55, 57]. The recurrence/progression (R/P) rate of surgically treated PCMs has been reported to be approximately 4–50 %, and the prognosis of these PCMs is not completely understood [1, 2, 4, 8, 43–45]. Because these masses are rare, few studies have been published regarding the clinical characteristics, prognostic factors, or outcomes of recurrent/progressive PCMs. Literature regarding the recommendation of a preferential therapeutic strategy or different outcomes between various treatments for recurrent/progressive PCMs is limited. The validity of reintervention over a long period on improving the 2nd R/P-free survival and the overall survival following the 1st R/P remains undefined.

Because the pathology is often benign and the surgery for recurrent/progressive PCMs is very difficult, the confirmation of an optimal treatment strategy is important. In this study, we retrospectively reviewed our cohort of 39 recurrent/progressive PCMs and the results from the literature to

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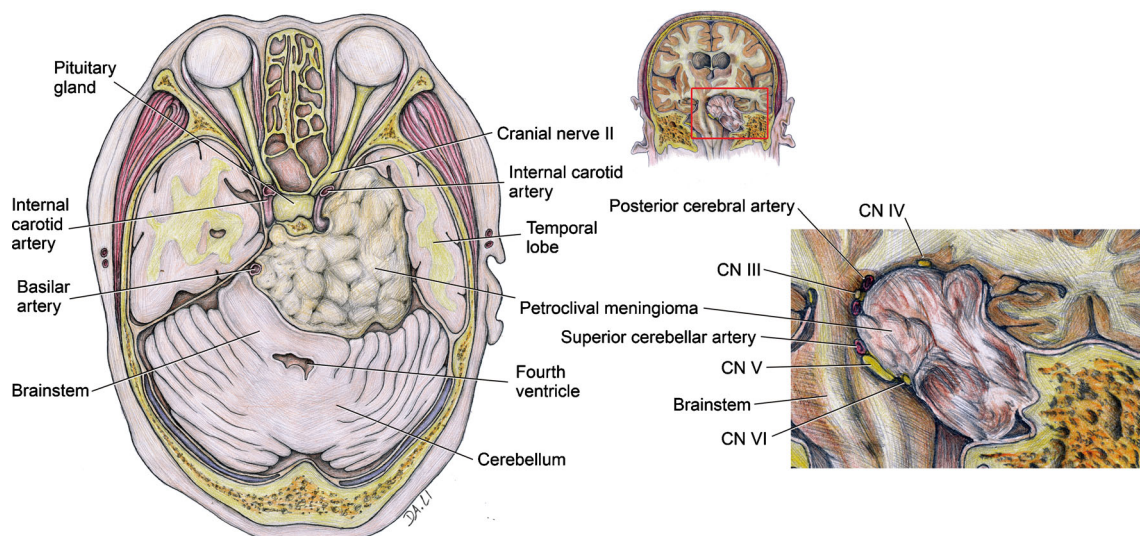


Fig. 1 Illustration of the relationships between a petroclival meningioma and the surrounding neurovascular structures. Transverse section through the pons and eyeball (*left*). The lesion partially encased the basilar artery and the left carotid artery, involved the cavernous sinus, and significantly compressed the brainstem with a noticeable space-occupying effect. A

coronal section through the lesion and the brainstem (*right upper*) and dislocation of CNs III–VI, posterior cerebral artery, superior cerebellar artery, and anterior inferior cerebellar artery (*right inferior*). Neurovascular encasement might occasionally exist

complement the knowledge of the clinical demographics and outcomes, to assess the risk predictors, and to determine a reasonable treatment modality.

Material and methods

Patient population

The clinical charts of 39 patients diagnosed with recurrent/progressive PCMs in Beijing Tiantan Hospital between May 1995 and May 2012 were retrospectively reviewed (Table 1). Patient flow is depicted in Fig. 2a. The neurological functional status was evaluated by two authors (Li and Hao) independently according to Karnofsky Performance Scale (KPS) score. The Beijing Tiantan Hospital Research Ethics Committee approved this study.

All preoperative and postoperative magnetic resonance imaging (MRI) scans were extensively reviewed by two independent neuroradiologists (Fig. 3; Table 2). The tumor size was calculated as the tumor equivalent diameter $(abc)^{1/3}$, where a , b , and c represented the three diameter measurements obtained on axial, sagittal, and coronal MRI, respectively [27, 35, 44]. The radiographic information and intraoperative findings were recorded (Table 2), including the regions of the skull base involved with recurrent/progressive lesions, the presence or absence of brainstem edema, the subarachnoid space between brainstem and lesion, the tumor boundary, the consistency, the blood supply, adhesion of the tumor to the brainstem, and neurovascular encasement; definition of these characteristics were defined in a prior study [35].

Reintervention strategy

The therapeutic strategy was tailored to the individual patient in all the cases. The patients' quality of life and neurological function were prioritized. The treatment was selected depending on the patients' neurological status, wishes, and goals, on the surgeons' expertise, experience, and preferences, and on the radiographic characteristics (tumor location, extent, size, and regrowth pattern). In this study, surgery was preferentially recommended. Gamma knife surgery (GKS) to control tumor regrowth was reserved for patients with one or more of the following conditions: poor neurological status; declining surgery due to surgical risk or older age; asymptomatic small-sized lesions; lesions mainly involving the cavernous sinus with a size less than 3 cm; lesions presenting with multiple recurrent sites or en plaque regrowth pattern along the skull base dura but without compressing the brainstem.

The goal of the reoperation was to maintain or improve the patients' neurological function and to prolong the 2nd R/P-free survival time and life span. In addition to the tumor characteristics and the surgeons' experience, the former surgical approach was considered when selecting the reoperative approach. A gross total resection (GTR) was attempted in all patients. The goal evolved when the lesion presented with aggressive biological behavior with extensive dural attachment, rapid regrowth with brainstem penetration, or extracranial invasion that did not warrant a GTR. The maximal decompression of the brainstem, vital vessels, and cranial nerves (CNs) was proposed. Lesions involving the cavernous sinus were removed or left behind depending on the tumor consistency and adhesions to the carotid artery and CNs. If

Table 1 Demographics of the 39 recurrent/progressive petroclival meningiomas

| No. | Sex/age, years | Initial surgery before the 1st R/P | | | | 1st R/P-free duration, m | | | | Treatment for the 1st R/P | | | | 2nd R/P | | Survival duration after 1st R/P, m | Recent KPS | Cause of death | | |
|-----|----------------|------------------------------------|--------------------|------------------|-----------------|--------------------------|-----------------|-----|------------------|---------------------------|--------------------|---------|-----------------|---------|------------------|------------------------------------|------------|----------------|---------|-------|
| | | TED, cm | Approach/extent | KPS ^a | WHO Grade | TED, cm | Approach/extent | RT | KPS ^a | Pre- | Post- | TED, cm | Approach/extent | RT | KPS ^a | | | | Pre- | Post- |
| | | | | | | | | | | | | | | | | | | | | |
| 1 | F/38 | 3.8 | Presigmoid/GTR | 70 | I | 70 | I | LA | 87.6 | 2.3 | Presigmoid/STR | LA | 60 | 60 | No | 125.7 | 128.5 | 70 | | |
| 2 | F/32 | 5.5 | ATPA/STR | 70 | I | 60 | I | GKS | 60.5 | 4.5 | Frontotemporal/STR | GKS | 70 | 70 | No | 43.6 | 49.9 | 70 | | |
| 3 | F/42 | 3.6 | Retrosigmoid/PR | 90 | I | 80 | I | | 83.9 | 5.6 | Presigmoid/GTR | | 70 | 70 | No | 151.2 | 175.6 | 80 | | |
| 4 | F/35 | 3.0 | Presigmoid/STR | 70 | I | 60 | I | GKS | 152.4 | 5.2 | Presigmoid/STR | GKS | 90 | 80 | No | 9.1 | 14.5 | 90 | SM | |
| 5 | F/39 | 5.3 | Retrosigmoid/STR | 70 | I | 80 | I | | 24.8 | 5.9 | Presigmoid/STR | | 60 | 0 | | 0.0 | 7.9 | 0 | | |
| 6 | F/35 | 3.1 | ATPA/STR | 70 | I | 60 | I | | 39.1 | 6.2 | ATPA/STR | | 70 | 60 | No | 21.2 | 23.8 | 60 | | |
| 7 | M/40 | 4.4 | Presigmoid/GTR | 80 | I | 70 | I | GKS | 34.5 | 4.2 | Presigmoid/STR | | 80 | 70 | Yes | 5.5 | 20.8 | 70 | | |
| 8 | F/29 | 3.8 | ATPA/GTR | 70 | I | 60 | I | | 43.5 | 2.6 | ATPA/STR | | 70 | 70 | Yes | 74.0 | 119.7 | 0 | 2nd R/P | |
| 9 | F/52 | 4.3 | Presigmoid/GTR | 70 | I | 70 | I | | 77.4 | 3.6 | Presigmoid/PR | | 80 | 80 | Yes | 62.8 | 118.1 | 0 | 2nd R/P | |
| 10 | F/42 | 3.3 | Presigmoid/PR | 80 | I | 80 | I | | 35.3 | 3.4 | Presigmoid/GTR | | 80 | 80 | No | 147.0 | 148.8 | 80 | | |
| 11 | F/67 | 6.8 | Retrosigmoid/STR | 70 | II ^b | 60 | II ^b | GKS | 19.8 | 4.9 | ATPA/PR | | 70 | 40 | Yes | 3.3 | 8.9 | 0 | 2nd R/P | |
| 12 | F/54 | 3.8 | ATPA/STR | 70 | I | 70 | I | | 61.4 | 4.8 | Presigmoid/PR | | 40 | 0 | | 1.9 | 4.5 | 0 | SM | |
| 13 | F/48 | 3.8 | ATPA/GTR | 80 | I | 80 | I | | 28.9 | 3.2 | ATPA/PR | | 80 | 80 | No | 202.0 | 204.7 | 100 | | |
| 14 | F/70 | 2.5 | Presigmoid/PR | 50 | I | 50 | I | | 133.6 | 1.8 | Far lateral/PR | | 50 | 50 | No | 57.3 | 69.8 | 50 | | |
| 15 | F/38 | 3.6 | ATPA/GTR | 70 | I | 60 | I | GKS | 43.6 | 3.3 | Frontotemporal/PR | | 70 | 70 | Yes | 4.3 | 10.8 | 0 | 2nd R/P | |
| 16 | M/33 | 3.9 | Far lateral/STR | 70 | I | 60 | I | | 47.3 | 4.8 | NA/PR ^c | | 70 | 60 | | 0.6 | 1.6 | 0 | OULD | |
| 17 | F/46 | 4.6 | Presigmoid/GTR | 80 | I | 50 | I | | 78.3 | 4.6 | Retrosigmoid/GTR | LA | 60 | 60 | No | 41.2 | 43.5 | 50 | | |
| 18 | F/46 | 4.1 | Presigmoid/PR | 50 | II | 70 | II | | 6.8 | 3.0 | Presigmoid/GTR | GKS | 60 | 60 | Yes | 126.0 | 158.6 | 0 | 2nd R/P | |
| 19 | M/32 | 5.6 | Presigmoid/STR | 70 | I | 60 | I | | 131.0 | 2.0 | Presigmoid/STR | | 60 | 30 | | 6.8 | 7.0 | 0 | SM | |
| 20 | M/46 | 4.3 | ATPA/STR | 70 | I | 80 | I | | 107.2 | 3.1 | ATPA/GTR | | 60 | 60 | No | 141.9 | 144.4 | 90 | | |
| 21 | F/54 | 3.4 | Presigmoid/PR | 60 | I | 80 | I | | 24.4 | 4.3 | Presigmoid/GTR | | 60 | 60 | No | 92.4 | 94.0 | 60 | | |
| 22 | F/34 | 4.2 | Presigmoid/GTR | 80 | I | 60 | I | | 44.9 | 3.9 | Presigmoid/GTR | | 70 | 70 | No | 163.1 | 167.9 | 80 | | |
| 23 | F/42 | 6.6 | Retrosigmoid/PR | 80 | I | 80 | I | | 15.7 | 2.7 | ATPA/GTR | | 80 | 60 | No | 202.2 | 203.8 | 80 | | |
| 24 | M/48 | 3.5 | Presigmoid/GTR | 70 | I | 80 | I | | 39.6 | 3.8 | | GKS | | | No | 107.0 | 107.4 | 90 | | |
| 25 | F/30 | 4.9 | Presigmoid/STR | 50 | I | 50 | I | | 12.4 | 3.2 | Observation | | | | Yes | 11.9 | 53.1 | 60 | 1st R/P | |
| 26 | F/54 | 4.3 | Presigmoid/GTR | 60 | I | 60 | I | | 153.6 | 4.6 | Observation | | | | | 27.6 | 27.6 | 0 | 1st R/P | |
| 27 | M/39 | 4.3 | Presigmoid/GTR | 60 | I | 70 | I | | 43.7 | 4.1 | Observation | | | | | 50.7 | 50.7 | 0 | 1st R/P | |
| 28 | M/36 | 3.6 | Presigmoid/PR | 70 | I | 70 | I | | 10.7 | 2.9 | Observation | | | | | 128.0 | 128.0 | 0 | 1st R/P | |
| 29 | F/53 | 3.6 | Presigmoid/STR | 60 | I | 60 | I | GKS | 23.6 | 4.4 | Observation | | | | | 11.0 | 11.0 | 0 | 1st R/P | |
| 30 | F/58 | 4.3 | Presigmoid/STR | 60 | I | 60 | I | GKS | 53.2 | 4.2 | Observation | | | | | 11.0 | 11.0 | 0 | 1st R/P | |
| 31 | M/51 | 5.6 | Frontotemporal/STR | 80 | I | 80 | I | GKS | 67.2 | 6.7 | Observation | | | | | 70.6 | 70.6 | 0 | 1st R/P | |
| 32 | M/61 | 5.7 | Frontotemporal/STR | 50 | I | 60 | I | | 25.8 | 3.2 | Observation | | | | | 6.2 | 6.2 | 0 | 1st R/P | |
| 33 | F/68 | 3.2 | Presigmoid/PR | 60 | I | 50 | I | | 86.6 | 5.2 | Observation | | | | | 6.0 | 6.0 | 0 | 1st R/P | |
| 34 | F/37 | 5.3 | Presigmoid/GTR | 60 | I | 70 | I | | 172.4 | 3.1 | Observation | | | | | 40.1 | 40.1 | 0 | 1st R/P | |
| 35 | F/45 | 4.5 | Presigmoid/GTR | 50 | I | 60 | I | GKS | 122.2 | 5.2 | Observation | | | | | 41.3 | 41.3 | 0 | 1st R/P | |

Table 1 (continued)

| No. | Sex/age, years | Initial surgery before the 1st R/P | | 1st R/P-free duration, m | | Treatment for the 1st R/P | | 2nd R/P | | 2nd R/P-free duration, m | Survival duration after 1st R/P, m | Recent KPS | Cause of death |
|-----|----------------|------------------------------------|-----------------|--------------------------|-----------|---------------------------|---------|-----------------|----|--------------------------|------------------------------------|------------|----------------|
| | | TED, cm | Approach/extent | KPS ^a | WHO Grade | Post-RT | TED, cm | Approach/extent | RT | | | | |
| 36 | M/26 | 4.4 | Presigmoid/PR | 60 | I | 23.8 | 4.4 | Observation | | 24.9 | 0 | 1st R/P | |
| 37 | F/62 | 3.6 | Presigmoid/GTR | 70 | I | 205.3 | 1.3 | Observation | | 18.2 | 60 | | |
| 38 | M/24 | 5.1 | ATPA/STR | 60 | II | 20.0 | 3.8 | Observation | | 21.6 | 0 | 1st R/P | |
| 39 | M/40 | 5.0 | ATPA/GTR | 60 | I | 56.0 | 7.7 | Observation | | 130.5 | 0 | 1st R/P | |

GKS gamma knife surgery, GTR gross total resection, LA linear accelerator, m months, NA not available, OUD other unrelated disease, post- postoperative, PR partial resection, pre- preoperative, R/P recurrence/progression, RT radiotherapy, SM surgical mortality, STR subtotal resection, TED tumor equivalent diameter, y years

^aThe postoperative KPS was evaluated at discharge

^bIn case 11, WHO Grade II was assigned at the first surgery and changed to Grade III at the second surgery

^cThe operation was performed in a local hospital and some information was not available

aggressive resection risked functional impairment, the attempted GTR was abandoned and the patients were referred for adjuvant radiotherapy. The extent of tumor removal was classified into 3 degrees, depending on the postoperative MRI scans which was performed within 72 h after surgery: GTR (Simpson Grades I/II), subtotal resection (STR; Simpson Grades III/IV, with 90–99 % excision of the lesion), and partial resection (PR; Simpson III/IV, with less than 90 % excision of the lesion).

Scheduled radiographic examinations at 6 and 12 months, and then once per year were recommended to the patients, especially for those patients rejecting adjuvant radiotherapy after a non-GTR. Patients with potential R/P risks were closely monitored. Periodic MRI scans were essential for the early detection of morphological changes in the residual lesions, without which patients commonly presented with mild to moderate symptoms but with medium to large size recurrent/progressive PCMs because the regrowth proceeded prior to functional aggravation.

Follow-up and statistical analysis

Follow-up was obtained in the clinic, by telephone, or by questionnaires regarding the neurological function status, dysfunctions, follow-up treatment and pertinent responses, and the most recent MRI scan examination. If the patient was deceased, the cause of death was obtained from his/her relatives. The statistical analysis was performed with the IBM SPSS Statistical Package v. 19.0 (SPSS Inc., Chicago, IL). For analysis, the age and lesion size after R/P were stratified into <50 or ≥50 years and <4 or ≥4 cm, respectively. The risk factors of 2nd R/P-free survival and the overall survival were analyzed with the Cox regression method (univariate and multivariate analysis) and further illustrated by the Kaplan–Meier survival method. A *P* value <0.05 was considered significant.

Literature search

A literature search using the online database PubMed was performed by two authors independently (Li and Wang) from January 1986 to July 2013 with the search terms “petroclival” and “meningiomas” (Fig. 2b). Meningiomas of the clivus or clival meningiomas without a specific lesion origination or the dural basement were excluded. The search was limited to studies in the English language and specific to humans. We further reviewed all the references provided in our identified studies and incorporated all the pertinent citations. We included surgical series with at least three cases. Studies without long-term outcome information concerning the patients with recurrent/progressive PCMs were excluded from our review of the management and pertinent prognosis of relapsed cases. Studies of interest included those that provided information

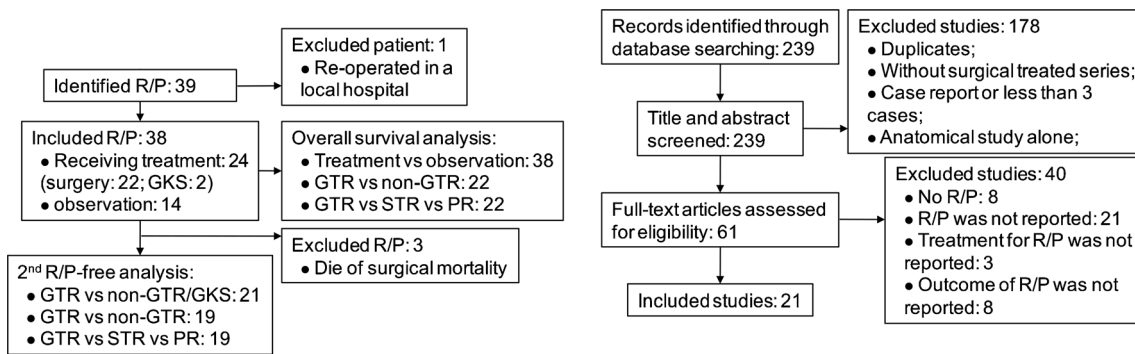


Fig. 2 Flowchart of participants (*left*) and literature search for surgical series of petroclival meningiomas with recurrence/progression (*right*). GKS gamma knife surgery, GTR gross total resection, PR partial resection, R/P recurrence/progression, STR subtotal resection

regarding the treatments before and after surgery, the final outcomes, and factors related to the prognosis.

Results

Brief review of patient demographics before R/P

The study included 39 patients (27 female, 69.2 %) with a mean and median age of 44 ± 12 and 42 years (range 24–70 years), respectively, and the mean duration of symptoms was 29.1 ± 31.8 months (range 2.9–144.5 months; Table 1). The mean preoperative tumor size was 4.3 ± 1.0 cm (range 2.5–6.8 cm). Five patients experienced a history of treatment before being referred to our institute: 3 had incomplete surgical resections, 1 had an operation with GKS, and 1 had an operation with GKS and a linear accelerator. Spermatocytoma and multiple intracranial meningiomas were noted in 1 patient each.

The surgical approaches selected for resecting the lesions included the retrolabyrinthine presigmoid transpetrosal approach ($n=23$) [29], the anterior transpetrosal–transtentorial approach ($n=9$) [70], the retrosigmoid approach ($n=4$), the frontotemporal approach ($n=2$), and the far lateral approach ($n=1$). GTR was achieved in 15 patients (38.5 %), STR in 15 patients, and PR in 9 (23.1 %) patients after the first operation. Surgical morbidities were noted in 16 patients (41.0 %), including tracheostomy ($n=7$), intracranial infection ($n=7$), pneumonia ($n=3$), and cerebrospinal fluid leak ($n=2$). The means of the pre- and postoperative KPS scores were 67.2 ± 10.0 and 65.6 ± 9.9 , respectively. Ten patients received postoperative adjuvant radiotherapy (GKS, $n=9$; linear accelerator, $n=1$). Postoperative histopathological examination identified WHO Grade I and II in 36 and 3 patients, respectively. The mean of the 1st R/P-free duration was 64.1 ± 49.5 months (range 6.8–205.3 months).

Clinical chart after 1st R/P

The mean and median ages at the 1st R/P were 50 ± 13 and 48 years (range 26–81 years), respectively (Table 1). All but two patients (cases 24 and 37) experienced symptomatic R/P. The MRI scans after the R/P were reviewed (Table 2). None of the lesions were limited to the petroclival region, and all the lesions involved other regions with extensive dural basement involvement. Diffuse and multiple R/P loci, a large mass effect, and extracranial regrowth were noted. Brainstem edema was present in 21 patients (53.8 %), subarachnoid space between the brainstem and the lesion was absent in 24 patients (61.5 %), and hydrocephalus developed in 8 patients (20.5 %). The mean and median lesion sizes were 4.0 ± 1.4 and 4.1 cm (range 1.3–7.7 cm), respectively.

Treatment for 1st R/P

After the R/P, 23 patients (59.0 %) (cases 1–23) underwent surgery and 8 of the 23 patients had GTR by the first surgery. Because in the 23 patients, 17 patients had lesions of at least 3 cm in size and 1 patient had radiotherapy after the first surgery, we did not recommend radiosurgery to these patients. Two patients (cases 24 and 25) received GKS alone and 14 patients (35.9 %; cases 26–39) declined any treatment and were followed-up with observation (Tables 1 and 3).

Of the 23 patients, the surgical information of patient 16 (Table 1), who received a reoperation in a local hospital and died of an unrelated disease, was not available. In the remaining 22 patients, the mean preoperative KPS score was 67.7 ± 11.5 (range 40–90), and the surgical approaches included the retrolabyrinthine presigmoid transpetrosal approach ($n=12$) [29], the anterior transpetrosal–transtentorial approach ($n=6$) [70], the retrosigmoid approach ($n=1$), the frontotemporal approach ($n=2$), and the far lateral approach ($n=1$). Thirteen patients (56.5 %) underwent the same approaches that were for the 1st surgery. The intraoperative findings associated with the extent of the resection are detailed in Table 2. GTR was achieved in 8 patients (36.4 %), STR in 8 patients, and PR in 6

Fig. 3 Case illustration of patient 4 (Table 1) with a left petroclival meningioma. The preoperative T2-weighted (a) and fluid-attenuated inversion-recovery (b). MRI scans showed brainstem compression and cavernous sinus involvement. Postoperative axial (c) and sagittal (d) MRI scans with contrast enhancement after a presigmoid approach. The residual tumor was treated with gamma knife radiosurgery. Axial (e) and sagittal (f) MRI scans at the 1st recurrence 12.7 years after the initial operation. Axial (g) and sagittal (h) MRI scans after reoperation using the same surgical approach. Tumor involving the cavernous sinus was left behind. Gamma knife radiosurgery was performed again to control the residual tumor. *MRI* magnetic resonance imaging

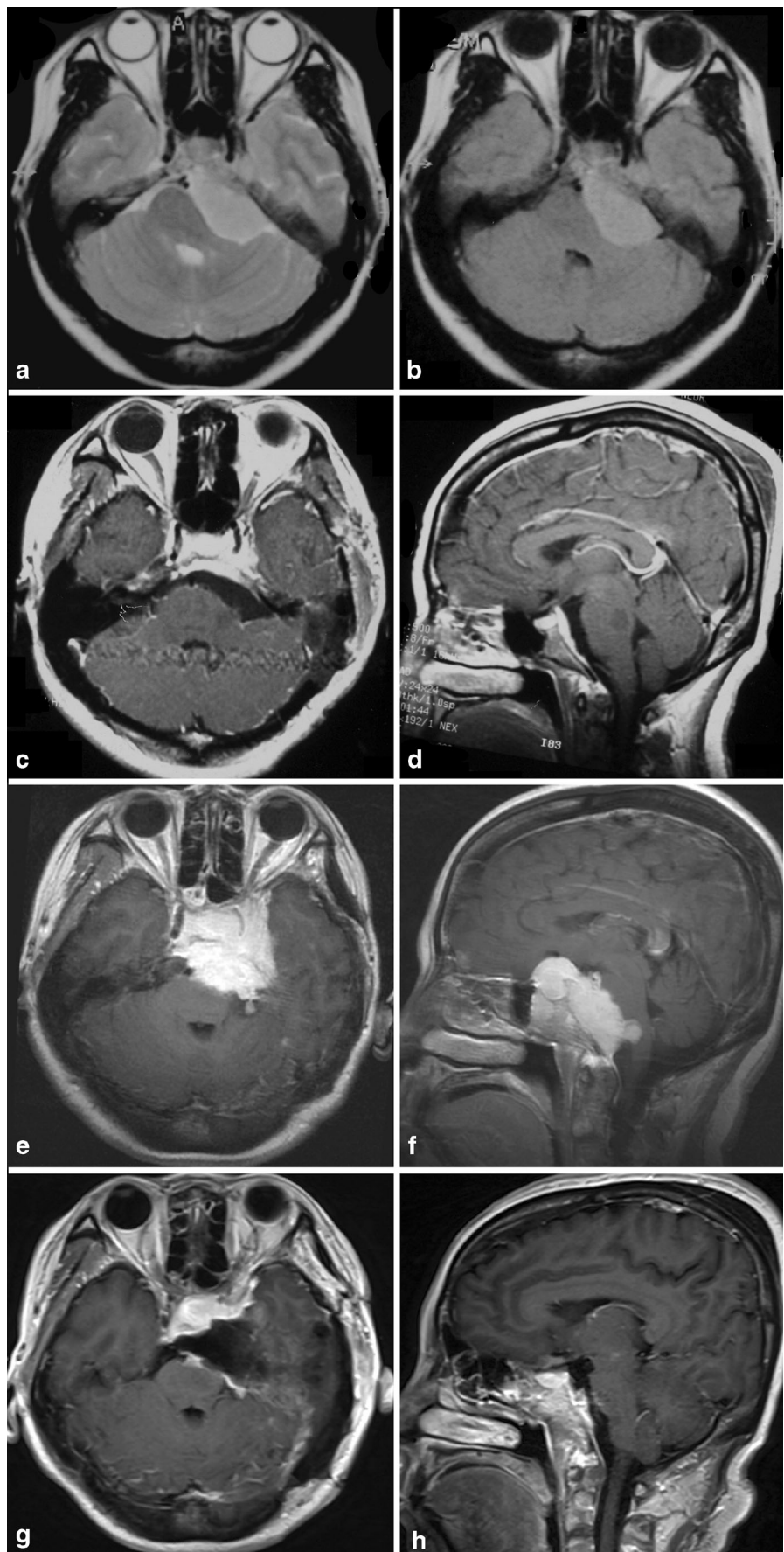


Table 2 Radiographic and intraoperative findings of petroclival meningiomas after the 1st R/P

| Variable | No. of pts. (%) |
|--------------------------------------|-----------------|
| Radiographic characteristics | Total, 39 |
| Involved regions ^a | |
| Limited to petroclival | 0 |
| Cavernous sinus W/O Meckel cave | 35 (89.7) |
| Middle fossa | 23 (59.0) |
| Saddle area W/O sphenoid sinus | 21 (53.8) |
| Contralateral clivus | 18 (46.2) |
| Cerebellopontine angle | 27 (69.2) |
| Foramen magnum | 14 (35.9) |
| Jugular foramen | 16 (41.0) |
| Contralateral cavernous sinus | 11 (28.2) |
| Orbit | 5 (12.8) |
| Brainstem edema | |
| Presence | 21 (53.8) |
| Absence | 18 (46.2) |
| Subarachnoid space | |
| Absence | 24 (61.5) |
| Presence | 15 (38.5) |
| Intraoperative findings ^b | Total, 22 |
| Tumor blood supply | |
| Abundant | 11 (50.0) |
| Moderate | 10 (45.5) |
| Lack | 1 (4.5) |
| Tumor consistency | |
| Hard | 4 (18.2) |
| Tough | 13 (59.1) |
| Soft | 5 (22.7) |
| Tumor boundary | |
| Unclear | 14 (63.6) |
| Clear | 8 (36.4) |
| Adhesion of tumor to brainstem | |
| Tight | 12 (54.5) |
| Moderate | 10 (45.5) |
| Absence | 0 |
| Neurovascular encasement | |
| Severe | 15 (68.2) |
| Moderate | 3 (13.6) |
| No | 4 (18.2) |

R/P recurrence/progression, W/O with or without

^a The majority of the lesions were involved more than 1 region

^b Intraoperative findings were available in 22 patients receiving reoperations in our institute after R/P

patients (27.3 %). The reasons for failure of GTR included one or more of the following: tight adhesion of the tumor to the brainstem ($n=10$), cavernous sinus involvement ($n=9$), extensive dural basement involvement ($n=8$), severe neurovascular

encasement ($n=7$) [35], unclear tumor boundary ($n=7$), and hard tumor consistency ($n=4$).

Surgical morbidities occurred in 8 patients (36.4 %; 5 with GTR, 2 with STR, and 1 with PR), including hydrocephalus ($n=4$), tracheostomy ($n=3$), pneumonia ($n=2$), motor weakness ($n=2$), intracranial hematoma ($n=2$), consciousness disorder ($n=1$), intracranial infection ($n=1$), cerebrospinal fluid leak ($n=1$), and CN III and VI deficits in two patients each. A ventriculoperitoneal shunt was performed in the 4 patients suffering from hydrocephalus from surgical morbidities. Three patients died 1 day, 1.9 months, and 6.8 months after surgery due to either intracranial hematoma ($n=2$) or respiratory failure ($n=1$). The mean postoperative KPS score at discharge was 58.2 ± 22.6 (range 0–80), which was significantly poorer than the preoperative KPS score ($t=2.719$, $p=0.013$). Five patients received postoperative radiotherapy (GKS, $n=3$; linear accelerator, $n=2$).

Long-term outcome of multi-treatment

During the follow-up period of 70.4 ± 63.3 months (range 5–205 months) for 38 patients, 7 patients experienced a 2nd R/P with a 2nd R/P-free duration of 41.1 ± 47.7 months. Eighteen patients died of either the 1st ($n=13$) or the 2nd R/P ($n=5$) with a mean survival duration following the 1st R/P of 54.8 ± 52.1 months (Table 3). The most recent KPS score of the overall patients was 32.6 ± 38.0 ; in the remaining 17 survivors, the KPS was 72.9 ± 14.9 with a mean follow-up duration of 98.2 ± 67.2 months.

In the 22 surgically treated patients, a 2nd R/P occurred in 6 patients, and 5 of the 6 patients died of the 2nd R/P of the tumor. The recent KPS score was 46.8 ± 38.1 (range 0–100) for all 22 patients but was 73.6 ± 15.0 (range 50–100) for the remaining 14 survivors. The data categorized by the extent of the resection are shown in Table 3. The percentage of a 2nd R/P-free survival was 88 % for GTR, 67 % for STR, and 40 % for PR. The R/P rate among the patients who underwent GTR was 12.5 % (1/8). The percentage of overall survival following the 1st R/P was 88 %, 63 %, and 33 % for GTR, STR, and PR, respectively. The GTR group had a longer 2nd R/P-free duration than that of the STR and PR groups ($p=0.031$; Table 3). The overall survival duration of the GTR group after the 1st R/P was longer than that of the other 2 groups ($p=0.013$; Table 3).

In two patients receiving GKS alone because of the perceived surgical risk, patient 24 had an asymptomatic R/P detected by scheduled MRI reexamination and underwent GKS (two times) at another hospital; at the recent follow-up evaluation, the lesion was stable with a KPS score of 90. The other patient (patient 25) suffered from a remarkably rapid R/P 12.4 months after the 1st surgery, and GKS was performed immediately, but the lesion was out of control and maintained regrowth, and a 2nd GKS was performed 12 months after the

Table 3 Clinical data categorized by treatment modalities^a

| | Overall | Treatment modalities | | | Resection extent (total 23) | | | |
|---|--------------|----------------------|-------------|-------------------------------|-----------------------------|------------|------------|---------------------------|
| | | Surgery or GKS | Observation | <i>p</i> value | GTR | STR | PR | <i>p</i> value |
| Number of patients | 39 | 25 | 14 | | 8 | 8 | 7 | |
| Male to female ratio | 12:27 | 5:20 | 7:7 | 0.075 ^d | 1:7 | 2:6 | 1:6 | 0.784 ^f |
| Lesion size at diagnosis (cm) | 4.3±1.0 | 4.2±1.1 | 4.5±0.8 | 0.472 ^e | 4.3±1.1 | 4.3±1.1 | 4.1±1.3 | 0.933 ^g |
| GTR at 1st surgery (no. of patients) | 15/39 (39 %) | 9/25 (36 %) | 6/14 (43 %) | 0.740 ^d | 2/8 (25 %) | 3/8 (38 %) | 3/7 (43 %) | 0.749 ^f |
| 1st R/P-free duration (months) | 64.1±49.5 | 57.4±39.9 | 76.0±63.1 | 0.330 ^e | 49.6±36.2 | 71.7±47.6 | 58.9±38.1 | 0.567 ^g |
| Age after 1st R/P (yr) | 50±13 | 48±11 | 53±16 | 0.223 ^e | 48±6 | 41±5 | 57±15 | >0.05 ^h |
| Lesion size after 1st R/P (cm) | 4.0±1.4 | 3.9±1.2 | 4.4±1.6 | 0.307 ^e | 3.8±1.0 | 4.1±1.6 | 3.8±1.1 | 0.857 ^g |
| 2nd R/P-free survival (no. of patients) ^{bc} | | 14/21 (67 %) | | | 7/8 (88 %) | 4/6 (67 %) | 2/5 (40 %) | |
| 2nd R/P-free duration (months) ^{bc} | | 85.4±66.5 | | | 133.1±48.4 | 46.5±46.4 | 65.9±81.1 | 0.031 ^g |
| Overall survival after 1st R/P (no. of patients) ^b | 17/38 (45 %) | 16/24 (67 %) | 1/14 (7 %) | 0.001 ^d | 7/8 (88 %) | 5/8 (63 %) | 2/6 (33 %) | |
| Overall survival duration after 1st R/P (months) ^b | 70.4±63.3 | 86.9±68.5 | 42.0±41.2 | 0.016 ^e | 142.1±50.6 | 46.5±49.8 | 69.5±80.0 | 0.013 ^g |
| Most recent KPS score ^b | 32.6±38.0 | 49.2±37.5 | 4.3±16.0 | <0.001 ^e | 65.0±29.3 | 45.0±38.2 | 25.0±41.8 | 0.149 ^g |

GTR gross total resection, KPS Karnofsky Performance Scale, PR partial resection, R/P recurrence/progression, STR subtotal resection

^a Means are provided with standard deviations and statistically significant values are shown in bold type

^b One patient who died of unrelated disease was excluded

^c Patients dying of surgical mortality were excluded

^d Fisher exact test

^e Independent-sample *t* test

^f Likelihood ratio

^g One-way ANOVA

^h Games-Howell

1st GKS [23]. At the recent evaluation, she lived dependently with poor neurological function and a KPS score of 60.

In the 14 patients (cases 26–39) without any treatment, only 1 patient (case 37) was alive with a recent KPS of 60. The overall survival duration after the 1st R/P was 42.0±41.2 months, which was significantly worse than that of the patients receiving surgery/GKS ($p=0.016$; Table 3).

Statistical analysis

For the 2nd R/P-free survival analysis: a univariate analysis identified GTR as a favorable predictor (OR 3.018, 95 % CI 1.113–8.183, $p=0.030$) compared with STR or PR (Fig. 4a), but sex (OR 1.071, 95 % CI 0.129–8.917, $p=0.950$), age (OR 0.685, 95 % CI 0.132–3.547, $p=0.652$), lesion size (OR 1.090, 95 % CI 0.203–5.853, $p=0.920$), or preoperative status or co-morbidities were not associated with the 2nd R/P-free survival. There was no significant difference between STR and PR (log rank chi-square=0.810, $p=0.368$). A multivariable modeling with adjustment for sex and age demonstrated that only GTR remained a favorable predictor (OR 8.087, 95 % CI 1.421–46.027, $p=0.018$). A Kaplan–Meier analysis showed that WHO grade II/III ($p=0.048$) further predicted

R/P (Fig. 4b) and that the patients with GTR obtained favorable R/P-free survival compared to the patients with non-GTR ($p=0.027$; Fig. 4c) or non-GTR/GKS alone ($p=0.028$; Fig. 4d). WHO grade II/III was not used in the multivariable analysis due to the small number of patients with Grade II/III.

For the overall survival analysis: a univariate analysis showed that the patients with treatment had better overall survival compared to the patients declining treatment (OR 4.739, 95 % CI 1.850–12.142, $p=0.001$; Fig. 5a); the patients with GTR had significantly favorable overall survival compared with the patients with non-GTR (OR 8.797, 95 % CI 1.011–76.515, $p=0.049$; Fig. 5b) or the patients with STR or PR (OR 2.743, 95 % CI 1.118–6.730, $p=0.028$; Fig. 5c). Sex (OR 0.602, 95 % CI 0.246–1.475, $p=0.267$), age (OR 1.779, 95 % CI 0.739–4.285, $p=0.199$), lesion size (OR 2.349, 95 % CI 0.958–5.760, $p=0.062$), WHO grade (OR 1.946, 95 % CI 0.565–6.704, $p=0.291$), or preoperative status or co-morbidities were not significantly associated with the overall survival. The difference between STR and PR was insignificant (log rank chi-square=0.695, $p=0.404$). In the multivariable modeling with adjustment for sex and age, the patients receiving treatment (OR 4.739, 95 % CI 1.850–12.142, $p=0.001$) had significantly better overall survival than the

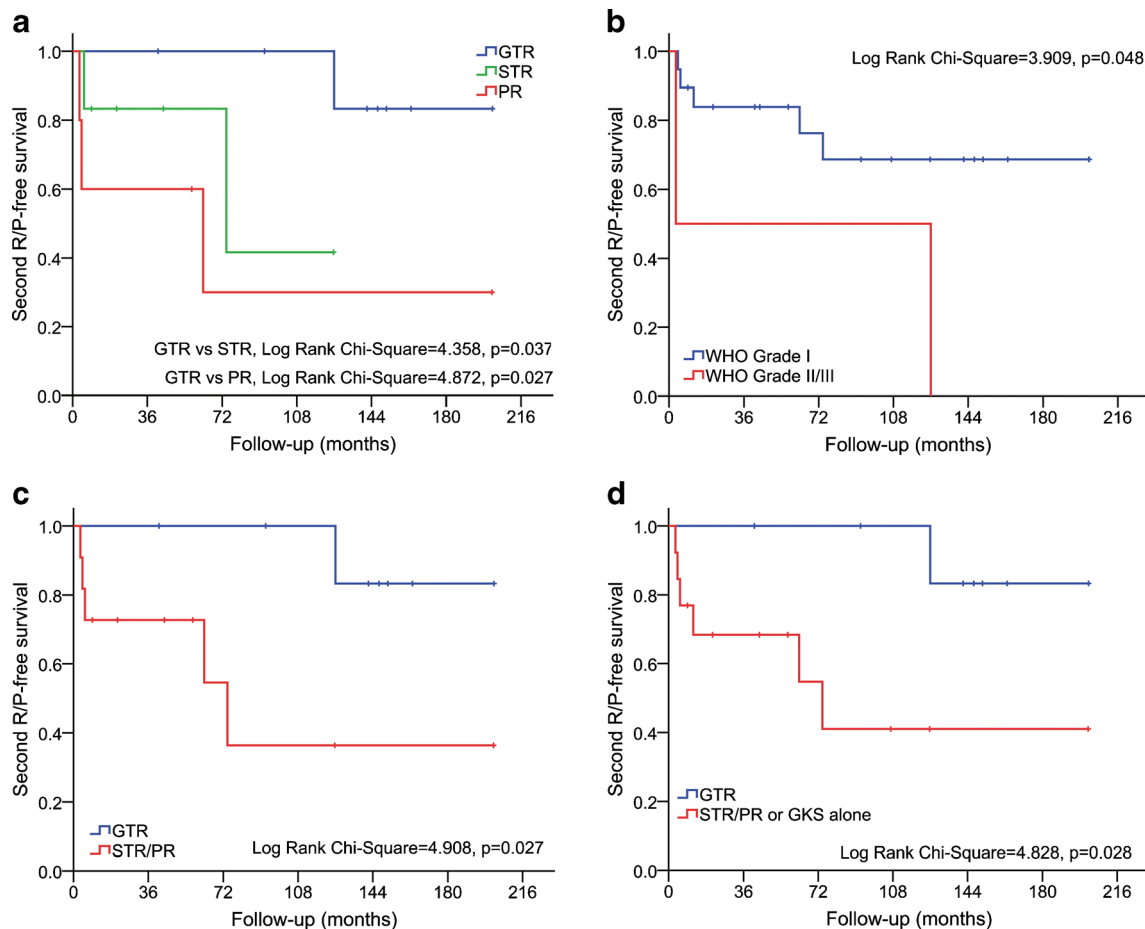


Fig. 4 Kaplan–Meier analysis illustrating the 2nd R/P-free survival of various treatment modalities. **a** The 2nd R/P-free survival of GTR was significantly better than that of STR ($p=0.037$) or PR ($p=0.027$). **b** WHO grade II/III presented with a poorer 2nd R/P-free survival than WHO

grade I ($p=0.048$). Patients with GTR had a better 2nd R/P-free survival than patients with STR/PR ($p=0.027$; **c**) and patients with STR/PR or GKS alone ($p=0.028$; **d**). GKS gamma knife surgery, GTR gross total resection, STR subtotal resection, PR partial resection

patients declining treatment. GTR contributed to a favorable overall survival compared with STR or PR (OR 2.743, 95 % CI 1.118–6.730, $p=0.028$). The 2nd R/P-free survival rate was 80.7 % at 1 year, 80.7 % at 5 years, 67.2 % at 10 years, and 57.6 % at 15 years; the overall survival rate following the 1st R/P was 76.3 % at 1 year, 67.3 % at 3 years, 57.8 % at 5 years, 44.9 % at 10 years, and 28.3 % at 15 years (Fig. 5d).

Literature review

Up to now, 2,393 surgical-treated PCMs have been reported in 59 series (2 of the 61 series were excluded due to duplicates; Fig. 2) [1–10, 12–22, 24–28, 30, 31, 33–38, 40–45, 47, 49–51, 55–60, 62–64, 66, 67, 69, 71–73]. A total of 898 (45.1 %, 95 % CI 43.0–47.3) of 1,990 PCMs were documented as GTR in 44 series that provided specific information regarding the resection rates. Patients who died of surgical mortality or did not have available follow-up information were excluded from the calculation of the R/P rate. In 40 series with R/P information, 177 (11.2 %, 95 %

CI 9.7–12.8) of 1,582 cases experienced an R/P. In 35 series with detailed information on the R/P rate of GTR or non-GTR, 26 (3.4 %) of 768 patients with GTR and 118 (18.0 %) of 654 patients with non-GTR experienced an R/P; the patients with non-GTR suffered from a significantly higher risk of R/P (Pearson chi-square test, OR 6.283, 95 % CI 4.051–9.745, $p<0.001$).

In the included 21 series (Fig. 2), a total of 126 (11.3 %) of 1,115 PCMs were documented with an R/P (Table 4). Of the 126 patients, 28 patients were excluded from further analysis due to either death from unrelated disease ($n=1$) or unavailability of information regarding treatments ($n=7$) or outcomes ($n=20$). Information of the 2nd R/P-free survival and persistent tumor progression in the remaining 98 patients stratified by surgery, radiotherapy alone, or observation are detailed in Table 5: 17 patients suffered from a 2nd R/P including 3 from the reoperation group, 3 of the radiotherapy alone group (all 3 patients treated with GKS), and 11 of the observation group. Ten patients died of either the 1st R/P ($n=7$) or a 2nd R/P ($n=3$). The patients with observation had significantly poor tumor

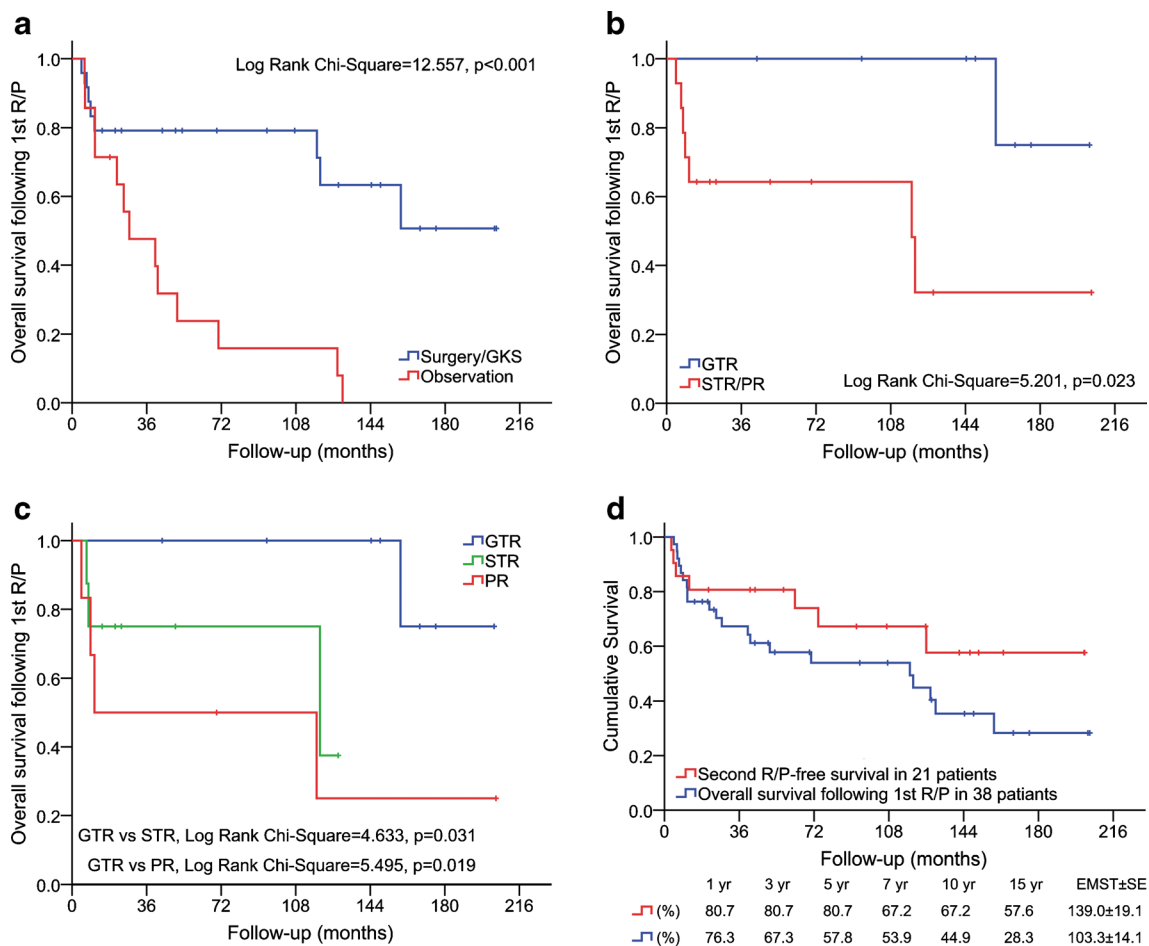


Fig. 5 Kaplan–Meier analysis illustrating the overall survival of different treatment modalities. The patients with observation suffered from malignant overall survival compared with the patients receiving surgery/GKS ($p<0.001$; **a**). In the surgically treated patients, patients with GTR had better overall survival than patients with STR/PR ($p=0.023$; **b**) or patients with STR ($p=0.031$) or PR ($p=0.019$; **c**). Kaplan–Meier curve illustrates

the overall survival following the 1st R/P and 2nd R/P-free survival (**d**). The percentage of overall survival declined rapidly because of the 13 patients who died of the 1st R/P without any treatment. *GKS* gamma knife surgery, *GTR* gross total resection, *STR* subtotal resection, *PR* partial resection

growth control compared with the patients with surgery (OR 7.333, $p=0.004$) or radiotherapy alone (OR 11.564, $p<0.001$). The difference between the patients with surgery or radiotherapy alone was not significant ($p=0.591$).

Discussion

Although extensive research has characterized the R/P risk factors and the surgical outcome of PCMs, the overall R/P rate is 11.2 % (range 4–50 %) and accounts for a certain percentage of PCMs [2–4, 7, 8, 13, 21, 27, 28, 30, 32, 35, 36, 40, 44, 45, 50, 55, 57, 69, 71]. The management of recurrent/progressive PCMs has been demonstrated to be a remarkable and intractable challenge [30, 35]. In the present study, we evaluated the

outcomes of 39 recurrent/progressive PCMs based on the treatment modalities, assessed the risk predictors of the 2nd R/P-free survival and overall survival, and reviewed the outcomes of 98 recurrent/progressive PCMs. We found the following: (a) the patients declining treatment harbored malignant overall survival compared with the patients receiving treatment; (b) the patients with GTR could obtain a favorable 2nd R/P-free survival and overall survival compared with the patients with STR or PR; and (c) in the 98 patients from the 21 series, the outcomes of surgery or radiotherapy alone were significantly better than that of observation. These results suggested the following: (a) a proactive attitude towards treatment is important for recurrent/progressive PCMs and the negative effectiveness of observation leads to disastrous prognosis; (b) GTR was preferentially selected to achieve satisfactory

Table 4 Twenty-one series of surgically treated petroclival meningiomas reported from January 1986 to July 2013^a

| Series | <i>n</i> | GTR | | | NTR, R/P | Mean FU, m | R/P | | Reintervention for R/P | Outcome |
|------------------------|-----------------|----------|----|-----|----------|-------------------|----------------|----|--|--|
| | | <i>n</i> | % | R/P | | | <i>n</i> | % | | |
| Al-Mefty et al. [2] | 13 | 11 | 85 | 0 | 2, 1 | 26 | 1 | 8 | RT | Alive |
| Angeli et al. [3] | 16 | 14 | 88 | 2 | 2, 1 | 36 | 3 | 19 | Surgery in 1; Observation in 1; NA in 1 | 2nd R/P free in 1; alive in 1; NA in 1 |
| Bambakidis et al. [4] | 44 | 21 | 46 | 0 | 23, 6 | 43 | 7 ^f | 16 | GKS in 2; Surgery in 1; GKS and surgery in 1; Observation in 3 | Tumor under control in 4; Progression in 3 |
| Brandt et al. [7] | 4 | 0 | 0 | 0 | 4, 2 | 22 | 2 | 50 | RT in 2 | Both alive |
| Bricolo et al. [8] | 30 | 25 | 79 | 3 | 5, 4 | 52 | 7 | 23 | Surgery in 2; Observation in 1; NA in 4 | Death in 3 ^c ; NA in 4 |
| Couldwell et al. [13] | 109 | 75 | 69 | 2 | 34, 12 | 73 | 14 | 13 | EBRT in 6; surgery in 6; Surgery and RT in 2 | All 2nd R/P free |
| Goel and Muzumdar [21] | 26 | 19 | 75 | 1 | 7, 0 | 48 | 1 | 4 | Observation | Alive |
| Ichinose et al. [27] | 62 | NA | NA | NA | NA | 95 | 11 | 18 | SRS in 7; none in 4 | Stable in 10; R/P in 1 |
| Javed and Sekhar [28] | 52 | 38 | 73 | 2 | 14, 0 | 4-83 ^b | 2 | 4 | Surgery in 1; Surgery and EBRT in 1 | Dependent in 1; NA in 1 |
| Jung et al. [30] | 38 ^d | 0 | 0 | 0 | 38, 16 | 48 | 16 | 42 | Surgery in 4; EBRT in 5; Surgery and EBRT in 2; None in 5 | 2nd R/P in 1; Stable in 10; NA in 5 |
| Kawase et al. [32] | 42 | 32 | 76 | 0 | 10, 3 | 54 | 3 | 7 | Surgery in 1; RT in 1; NA in 1 | Alive in 2; Death in 1 |
| Li et al. [36] | 55 | 31 | 58 | 7 | 24, 0 | 34 | 7 | 13 | RT in 7 | Stable in 7 |
| Li et al. [35] | 256 | 135 | 53 | 1 | 121, 10 | 55 | 11 | 4 | Surgery in 5; RT in 1; Surgery and RT in 2; Observation in 3 | Death in 5 ^e ; Alive in 6 |
| Matsui [40] | 15 | 10 | 67 | 0 | 5, 3 | 120 | 3 | 20 | RT and surgery in 1; RT in 2 | Social independence in 2; NA in 1 |
| Natarajan et al. [44] | 150 | 48 | 32 | 2 | 102, 5 | 102 | 7 | 5 | STR in 2; GKS in 5 | Alive in 2; Stable in 2; progression but alive in 2; death in 1; |
| Nishimura et al. [45] | 22 | 15 | 71 | 1 | 7, 7 | 60 | 8 | 36 | Observation | Death in 3; Asymptomatic in 5 |
| Ramina et al. [50] | 18 | 17 | 94 | 0 | 1, 1 | 42 | 1 | 6 | RT (LA) | Stable |
| Samii et al. [53] | 12 | 9 | 75 | 0 | 3, 1 | 68 | 1 | 8 | Observation | Independent |
| Seifert [57] | 93 | 34 | 37 | 2 | 59, 13 | NA | 15 | 16 | Surgery in 2; RT in 7; Observation in 6 | Stable in 2; NA in 13 |
| Watanabe et al. [69] | 26 | 11 | 42 | 0 | 15, 3 | 74 | 3 | 12 | Radiosurgery in 2; NA in 1 | Independent in 3 |
| Yamakami et al. [71] | 32 | 19 | 59 | 0 | 13, 3 | 66 | 3 | 9 | GKS in 3 | Good tumor control in 3 |

CI confidence interval, EBRT external-beam radiation therapy, FU follow-up, GKS gamma knife surgery, GTR gross total resection, LA linear accelerator, m months, NA not available, PR partial resection, R/P recurrence/progression, RT radiotherapy, SRS stereotactic radiosurgery, STR subtotal resection

^a Patients dying of surgical mortality or without available follow-up evaluation were excluded

^b Range of the follow-up duration

^c One died of surgical mortality during the reoperation and 2 died of R/P

^d All 38 patients underwent STR

^e One patient died of an unrelated disease, 1 died of a 2nd R/P after reoperation, and 3 died of 1st R/P

^f Resection extent was not available in 1 patient

outcomes; and (c) radiotherapy was an alternative option for patients who rejected surgery. To improve the outcomes of recurrent/progressive PCMs, the untreated clinical course, optimal management strategy, and outcomes of various treatments of recurrent/progressive PCMs should be understood.

Untreated clinical course

The natural history of PCMs was undefined and was commonly described as slow growth with benign histopathology and asymptomatic presentation at early clinical stages, but unmercifully progressive growth was complicated by

Table 5 Outcomes of the 98 recurrent/progressive petroclival meningiomas from the 21 series categorized by treatment modalities

| No. of patients | Overall | Surgery ^a | RT alone ^b | Observation |
|--------------------------|-----------|----------------------|-----------------------|-------------|
| Overall | 98 | 30 | 44 | 24 |
| 2nd R/P-free or stable | 80 (83 %) | 26 (90 %) | 41 (93 %) | 13 (54 %) |
| 2nd R/P or progression | 17 (18 %) | 3 (10 %) | 3 (7 %) | 11 (46 %) |
| Surgical mortality | 1 | 1 | | |
| Death due to R/P | 10 | 2 | 1 | 7 |
| Odd ratio | | 7.333 ^{cd} | 11.564 ^{ce} | Reference |
| 95 % confidence interval | | 1.738-30.945 | 2.793-47.884 | Reference |
| <i>p</i> value | | 0.004 | <0.001 | |

Statistically significant values are shown in bold type

R/P recurrence/progression, RT radiotherapy

^a Nine patients received postoperative adjuvant RT (RT, *n*=5; external-beam radiation therapy, *n*=3; and gamma knife surgery, *n*=1)

^b This group included gamma knife surgery (*n*=13), external-beam radiation therapy (*n*=11), RT (*n*=12), stereotactic radiosurgery (*n*=7), and linear accelerator (*n*=1)

^c Pearson chi-square test

^d Surgery versus observation

^e RT alone versus observation

hydrocephalus and led to poor outcomes [11, 35, 48, 54, 57, 61, 63, 65, 68]. In a series of 15 asymptomatic PCMs, after a median follow-up period of 40 months, 9 lesions (60 %) showed radiological tumor growth and 7 patients (47 %) developed functional deterioration, based on which Terasaka et al. [65] considered that growing tumors were unpredictable and variable [68]. In an early study of 21 PCMs under observation, 16 patients (76 %) showed radiological tumor growth with functional deterioration occurring in 10 patients (48 %), and Van Havenbergh et al. [68] concluded that a change in the growth pattern often preceded functional deterioration. In another series of 24 PCMs with observation for 82 months, tumor progression occurred in 11 PCMs (46 %) [57]. Sughrue et al. [61] reviewed 42 PCMs and identified symptom progression in 28 % of patients. These studies demonstrated an asymptomatic latent period during which the lesions grew gradually and resulted in functional deterioration and decompensation of the intracranial pressure, which finally justified surgery. Small to medium-sized tumors tended to grow more rapidly than larger tumors [68]. Due to the relatively short-term follow-up duration for benign tumors compared to the life span, we assumed that the eventual outcome would be more disastrous with extension of the follow-up period in the absence of intervention.

In a series of 38 PCMs with non-GTR, lesion progression developed in 16 PCMs (42 %) during a mean follow-up period of 47.5 months [30]. This study found that the mean growth rate was 0.37 cm/year in diameter and 4.94 cc/year in volume and the mean doubling time was 8 years. Jung et al. [30] confirmed that the growth rate of residual tumors was low. These growth rates differed substantially from those reported by Van Havenbergh et al. [68], which indicated that the

remnants of incompletely surgically treated PCMs grow faster than the initially untreated PCMs; this result was verified by another study [23]. In the present study, only 1 (7.1 %) of 14 recurrent/progressive PCMs with observation (Table 3) survived following the 1st R/P, and 11 (45.8 %) of 24 recurrent/progressive PCMs from 9 studies (Tables 4 and 5) presented with persistent progression until 7 of the 11 died [3, 4, 8, 21, 27, 35, 45, 55, 57]. The outcomes of observation were worse than previously expected. Because of the low incidence and variable biological behavior of PCMs, few studies paid attention to the outcomes of untreated recurrent/progressive PCMs; understanding these studies is important and necessary for clinicians and their patients to compare these results with other studies and to select a reasonable and individual treatment. Based on our series and prior studies, it was assumed that after R/P was identified by radiographic evidence, lesions most likely continued to grow with a slow growth rate if no interventions were performed. The final outcome remained to be seen, and the follow-up should be continued.

Treatment philosophy

Surgery was preferentially selected to remove the PCMs in most experienced institutes, and GTR was the optimal strategy to achieved favorable R/P-free survival and overall survival [12, 13, 17, 21, 26–28, 30, 35–37, 43, 44, 50, 51, 55, 57]. It was challenging and difficult to achieve a high rate of GTR with minimal surgical morbidity. If the cleavage plane and arachnoid membrane were intact in the first surgery, GTR was possible. Additionally, although the cleavage plane and arachnoid membrane were intact, GTR might be occasionally compromised during the first surgery if the tumor had complete

neurovascular encasement (with or without tight adhesion to neurovascular structures), cavernous sinus involvement, or extensive dural basement involvement that could not be exposed completely via a single surgical approach. GTR should be attempted in all patients, but it was not necessarily performed in each patient when considering the beneficial ratio of neurological function versus a lower R/P risk. The prevalent opinion for the surgical treatment of PCMs was STR with or without adjuvant radiotherapy to control tumor progression that warranted desirable postoperative neurological function, minimal surgical complications, and patients' early return to normal daily life and social activity [12, 13, 30, 35, 37, 44]. Because of unfavorable intraoperative findings and high technical requirements, GTR was only achieved in 45.1 % of patients (898/1,990) [13, 35, 37, 44, 51]. GTR was associated with higher rate of surgical morbidities, but non-GTR increased the risk of an R/P in the future [37, 48].

Until now, the appropriate treatment for recurrent/progressive PCMs remains controversial and undefined. Few studies have validated the superiority of any treatment for recurrent PCMs. Multidisciplinary consultation (including both neurosurgery and radiotherapy) was necessary to determine the treatment. Recurrent/progressive PCMs have increased surgical difficulty because of the indistinguishable anatomical structure and surgical planes resulting from the manipulation in the prior operation, organization or close adhesions due to reactions to radiation, various growth patterns, and common cavernous sinus involvement.

Patients declining treatment were subject to progression and were more likely to have a malignant outcome; these results were significantly different than the outcomes of patients receiving treatment (either surgery or radiotherapy) in our study. To our knowledge, a lack of data had been published regarding whether GTR outweighed STR and PR for recurrent/progressive PCMs. The extent of the resection of surgically treated recurrent/progressive PCMs was not available in most previous studies [3, 4, 8, 13, 28, 30, 32, 40, 44]. We confirmed that GTR was superior to STR and PR (Figs. 4a and 5c), and the surgical morbidities of patients with GTR were acceptable (transient in 4 patients; permanent but mild in 1). The importance of GTR should be emphasized and it should be achieved as much as possible by experienced hands to prevent additional functional deterioration.

The aim of radiotherapy was to control the progression of recurrent/progressive PCMs instead of cytoreduction. The effectiveness of radiotherapy had been described in several studies [30, 44, 52]. In these studies, radiotherapy was typically reserved for older patients or those with certain indications. The morbidity from radiotherapy should be stressed. Because only two patients (case 24 and 25) underwent GKS alone in our series, we did not compare the outcomes of patients with surgery or GKS alone. We indirectly compared the 2nd R/P-free survival between the patients with surgery or

radiotherapy alone based on 17 series and determined that the difference was nonsignificant ($p=0.591$) and that only 3 (7 %) of 44 patients with radiotherapy alone were documented to have progression [2–4, 7, 8, 13, 27, 28, 30, 32, 35, 36, 40, 44, 50, 69, 71]. Despite the heterogeneous types of radiotherapy administered in these 44 patients (Table 5), radiotherapy presented with favorable tumor regrowth control and should be recommended on a routine therapeutic schedule. These findings showed the need for a future study to confirm the validity of radiotherapy over a long-term period.

Recurrent/progressive risk

Risk predictors for the R/P of PCMs have been demonstrated in several studies [13, 35], including WHO grade II/III [13, 35, 39], large tumor size (≥ 5 cm) [35], non-GTR [30, 35, 37, 39, 55], and cavernous sinus involvement [13, 39, 53]. Significant factors predicting a rapid growth rate were the occurrence of menopause and younger age (<50 years) [30, 44]. The R/P rate might be underestimated when it was defined as symptomatic R/P, assessed by computed tomography with or without contrast, or without periodic radiographic examination. PCMs frequently extended in a thin layer and were not necessarily globular or invaded into the cranial nerve foramina, and this might be overlooked by computed tomography with low resolution [30].

Based on the 35 prior studies, we found that the R/P rate of non-GTR (18.0 %) was significantly higher than that of GTR (3.4 %; $p<0.001$), and this result indicated the need for GTR, despite diverse definitions of GTR and various follow-up durations among these studies. In the present study, WHO grade II/III predisposed patients to a 2nd R/P, but age, sex, or tumor size were not significant. After we subdivided the surgically treated patients into the three groups of GTR, STR, or PR, non-GTR predicted a noticeably poor 2nd R/P-free survival and a shorter 2nd R/P-free period. We did not consider the proliferating cell protein or mitotic index in the analysis of the 2nd R/P-free survival, but this was identified in a prior study [46].

Outcomes of multiple treatment modalities

The second R/P-free survival and neurological function were two important aspects of interest when evaluating the outcomes of recurrent PCMs treated by surgery or radiotherapy. Most patients with functional impairments developed coping mechanisms to continue with their lives, and the neurological deficits rarely influenced the overall survival duration [4, 35, 44]. Repeated R/P increased the risk of shortening the life span. Patients occasionally presented with progressive growth of an already surgically treated PCM that could not be inhibited by repeated surgeries or radiotherapies; this ultimately resulted in fatal disease progression [23, 44]. In the 30

patients (Table 5) treated by surgery from 10 series [3, 4, 8, 13, 28, 30, 32, 35, 40, 44], 9 patients received postoperative adjuvant radiotherapy, a 2nd R/P occurred in 3 patients (10 %) who did not receive postoperative adjuvant radiotherapy, and 2 of the 3 patients died of tumor progression. In the 44 patients (Table 5) with radiotherapy alone from 14 studies [2, 4, 7, 13, 27, 30, 32, 35, 36, 40, 44, 50, 69, 71], GKS ($n=13$, 29.5 %) was the most frequently selected method, followed by radiotherapy ($n=12$, 27.3 %) and external-beam radiation therapy ($n=11$, 25.0 %); 3 patients were refractory to GKS, and 1 of the 3 patients died from tumor progression [44]; others were presented with radiographic stabilization. In our series, 6 (31.6 %) of 19 patients presented with a 2nd R/P after reoperation, and we assumed that these patients might have inherent R/P potentiality, although the genetic characteristics were not analyzed. Patient 25 (Table 1) with GKS alone was detected to have a mutation in exon 18 of the WRN gene, which was an insertion at nucleotide 2806 and led to a frame shift and premature stop codon (TGA) [23]. This insertion mutation was supposed to be related with malignant transition of the PCMs and rapid progressive regrowth.

Limitations of the present study

The small sample size and retrospective nature of this study limit the validity and generalizability of our findings. The heterogeneity of the initial treatment algorithm introduced further discrepancies in the cohort of patients analyzed for 2nd R/P free survival. The small number of patients in the radiosurgery arm and the likely selection bias precludes a meaningful comparison between the radiosurgery group and the other two. Because of the small patient number with each type of radiotherapy among the 44 patients (Table 5), we could not identify the optimal radiotherapy modality. To improve the understanding of outcomes of recurrent/progressive PCMs, patients of each series need to be followed-up for a longer period of time. Further investigation is needed to justify the preciseness and utility of the results derived from prior studies and the results of the present study. A prospective multi-center randomized controlled study, which is the theoretically optimal study design with minimal confounding factors and referral bias, is suggested to determine the reasonable and individual therapeutic strategies in future research and to identify whether the outcome of radiotherapy/radiosurgery was better than surgery in some select patients. Considering the wide variability of PCMs, the comparison should be stratified by associated variates further (including sex, age, lesion size, brainstem edema, growth patterns, regions involved etc.); but this type of study is time consuming and difficult because of the low incidence rate of PCMs and their benign histopathology.

Conclusions

Recurrent/progressive PCMs that were treated with observation ultimately led to fatal outcomes. Favorable outcomes of recurrent/progressive PCMs could be obtained by GTR, which we advocated as a preferential strategy. Although our results failed to define the efficacy of radiotherapy in treating R/P PCMs, based on prior studies, radiotherapy, which was comparable to surgery, was recommended to patients who rejected surgery or with non-GTR. These findings were somewhat useful for clinicians and patients in clinical practice to select a suitable and individual method of treatment.

Conflict of interest The authors report no conflict of interest.

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Comments

Atul Goel and Manu Kothari, Mumbai, India

All meningiomas, like finger prints or a pinna, are different. They are different in terms of clinical presenting features, radiological imaging characters, and histological subtleties, and more importantly, in the pattern of their behavior. All meningiomas can be classified into good or bad only in retrospect. Petroclival meningiomas are as benign or as aggressive as meningiomas elsewhere. Suffice to say at the very outset that a petroclival meningioma, but for its proximity to the brainstem, is as ordinary as a convexity meningioma or a neurofibroma under the skin. Both do not and cannot differ in their essential behavior. The ‘malignant’ fault of a petroclival meningioma is its proximity to the brainstem and its occasional proclivity to ensnare it. Petroclival meningioma should be christened as benign microscopically, malignant behaviorally, or rather positionally.

Between the idea (of benignancy)

And the reality (of behavior),

Between the scene (under the microscope)

And the seer (the pathologist)

Falls the shadow (of ambiguity).

(modified from *The Hollow Men* by T.S. Eliot)

A meningioma is a fibrocellular mass that in a ‘predetermined’ fashion starts somewhere in the meninges and remains ‘discreetly silent’ before being detectable or impinging on the consciousness of the patient. A plethora of theories speculate on its *cause*, to no avail. The cause/course/cure of any meningioma is not known and is unlikely to be known.

The *course* is totally unpredictable, ranging from sheer indolence to accretional aggressiveness. In a way, the meningioma is not *causal*, but is *coursal*, being an integrated predetermined part of the biological trajectory of the person dictated by time or age. The so-called surgical *cure* or more truly *care*, for any tumor anywhere and of any type, is debulking by the swipe of a surgical blade. You can only debulk, for the dream of total removal is one of a mirage. Even if it were removed totally, the next normal meninx can throw a meningiomatous tantrum.

A meningioma

Tells a tale

A normal meninx

Is waiting to tell

The surgical philosophy for all tumors, benign or malignant, is to remove the tumor radically and then fold the hands and wait for it to recur. The term radical resection has to be defined and clearly understood. One must realize that ‘once a meningioma always a meningioma’. The aim of surgery can never be ‘cure’ of the meningioma. Surgery can be summarized to be ‘space creating solution;’ for a ‘space occupying lesion’, albeit accompanied by the more meaningful debulking of the tumor. The success of surgery will be maximum space creation, minimal bulk, and safe outcome. Any complication or neurological deficit is related to inadequate understanding and evaluation or less than perfect execution of operation. The difficult terrain of a petroclival meningioma makes the likelihood of complications higher. The recurrences depend more on the growth pattern of the tumor than with the extent of resection. The radicality of resection will also depend on the aggression and extensions of the meningioma. The more extensive is the presence of the tumor, the more difficult is the resection and the likelihood of recurrence is higher. More circumscribed meningiomas are easier to remove and the long term outcome is better.

The aim of surgery for recurrent meningiomas remains the same. Create maximal space and debulk and then again wait for the tumor to recur. The possible difficulties during surgery make the issues more challenging for the surgeon. It is, therefore, mandatory for the surgeon to assess the lesion, its location, and the difficulties that can be associated with surgery in a recurrence situation and then take appropriate decision. It is right that the authors have resorted to treat recurrent petroclival tumors surgically and have resorted to radiotherapy only when the knife

could not be wielded on the meningioma. Surgery per se is lesion far and no further, unless it hurts vessels/nerves/brain on its way. Radiotherapy has necessarily a field impact, charring not only the tumor but also many a vessel or nerve, and for that reason, is to be deployed only under compulsion. Chemotherapy has no role for a meningioma is too dull to be affected by the best chemotherapy. A good neurosurgeon is one who knows when NOT to operate. A good meningioma surgeon is one who will prefer to leave a bit or more of meningioma rather than risk damage to a nerve or a blood vessel.

Much as a normal diploid dividing cell is potentially malignant so is any part of any normal meninx is potentially a meningioma, meningioendothelioma, and meningiosarcoma, all mercifully rare in a crescendo order. Most meningiomas, ‘benign’ to the microscope, make noise late in life and lend themselves to partial or ‘total’ surgical ablation, promising to come back the way it did to start with. Each meningioma is unique and unamenable to any genetic analysis, prevention, chemotherapy, or radiation. It is best lived with, ablated when diseasing and re-ablated when it recurs to disease again.

Volker Seifert, Frankfurt, Germany

There is no question that petroclival meningiomas are correctly considered to be the most difficult skull base tumors to be treated by neurosurgeons.

Petroclival meningiomas are almost exclusively operated on by very experienced and excellent skull base neurosurgeons with an exceptional high experience in complex brain tumor surgery. Despite these facts, it is obvious from the modern data on petroclival meningioma surgery that in general, in only one third to one fourth of the patients the tumor could be removed gross totally, that surgical mortality still occurs in a number of patients, and that especially the permanent quality of life reducing morbidity remains high.

During the last two decades of advanced skull base surgery, it has become clear from increasing experience during surgery of petroclival meningiomas that the clinical result and the radicality of surgery is not, or only to a lesser extent, defined by the surgical approach chosen to explore the tumor but by the biological behaviour of this treacherous subgroup of meningiomas especially in regard to the tumor–brain stem interface.

The reasons for incomplete tumor removal are multiple and have been defined in recent articles on petroclival meningiomas, including hard or fibrous structure of the tumor, no, as mentioned, clear arachnoid interface between tumor and pia of the brain stem and encasement of cerebral vessels and cranial nerves.

This has led over the years to the now generally accepted treatment concept in petroclival meningiomas consisting of an attempt of not over aggressive surgical tumor removal with decompression of the brain stem and judicious intraoperative judgement of the “safe” amount of tumor resection with preservation of vital cerebral vessels and cranial nerves especially lower cranial nerves. The author of this comment has, over the years, together with other experienced skull base surgeons, been a strong proponent of this patient oriented concept, integrated into a modular approach of PCM treatment.

Despite the fact that the majority of surgically treated PCM patients are consequently left with a tumor remnant, the percentage of patients with a relentlessly growing, and in the end, life threatening remaining tumor is, according to the author’s experience and the literature, small, the majority of tumor remnants being stable over a long observation period.

However, no doubt, there are patients with a continuously growing tumor remnant and this exceptionally deep and well written article by Li et al. from the Beijing Tian Tan Hospital, for which the authors are to be commended, deals with this very problematic, albeit small group of patients.

This article is by far too extensive and too multi-faceted to be touched on in detail during this comment; however, I agree and also disagree with the final and generalizing conclusion of the authors that “Proactive treatment should be performed for patients with recurrent/progressive PCM.”

In my opinion, the main aspect which should guide the decision making process in these patients should be the amount of the initial tumor resection and the postoperative clinical outcome.

If, like in the case presented in their article (Fig. 3), the tumor could be almost completely removed during the first surgery, it can be assumed that the tumor was soft, that there was a perfect arachnoid interface as dissection plane, and that there was no relevant cranial nerve or vessel encasement. Relying on some surgical luck, it can be assumed that these conditions will remain the same for the second surgery, and therefore, surgery should be undertaken.

However, the circumstances are completely different if during the initial surgery, the surgeon had been forced to restrict his surgery to subtotal or even only partial removal. Assuming he was a surgeon with high expertise then there was a reason or better several reasons why he used his thoughtful intraoperative judgement and left tumor behind, and again, as already pointed out, these reasons would have been hard tumor texture, no reliable dissection plane, and vessel and nerve encasement !

Why should this have changed after surgery and during the period in which regrowth of the tumor remnant had occurred. The surgeon will face exactly the same problems during recurrent surgery as during the initial surgery only with an even more complex and higher magnitude, because now the scaring induced by the previous surgery will increase the surgical difficulties as every surgeon knows, thereby rendering any attempt at radical removal of the recurrent tumor impossible and also dangerous as the results of the authors clearly demonstrate.

So in this scenario, which surely applies to the majority of recurrent PCMs, repeated surgery should definitely not be the way to go.

The surgeon should be able to make a clear judgement whether repeated treatment in any specific case of recurrent PCM is really indicated considering a large variety of patient specific aspects, e.g. growth speed of the recurrent tumor, clinical picture, and neurological deficits of the patient, age, life expectancy, concomitant disease, and patients expectation.

If he comes to the conclusion that the patient should or must be treated, he should be aware of the above mentioned surgical aspects: radical initial surgery, incomplete initial surgery because of relevant intraoperative aspects preventing complete removal.

In the first scenario, repeated surgery can be attempted; in the second scenario modern, expert guided, paradigms of radiosurgery or repeated radiosurgery should be tried eventually in conjunction with the experimental application of modern chemotherapy methods, with which, for example, convincing preliminary results have been achieved in recurrent, vestibular schwannomas.

So, notwithstanding the excellent work of Li and coworkers, the treatment of recurrent petroclival meningiomas can definitely not be guided by generalized recommendations, but should be the result of an intensive discussion of a board of experienced experts of neurosurgery, radiosurgery, and neurooncology, considering the individual patient and his preservation of quality of life as the ultimate target of treatment.